

SIGNIFICANT ITEMS (Sis)

FY 2010 House Appropriations Committee Report 111-220
and

FY 2010 Senate Appropriations Committee Report 111 -66

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**National Cancer Institute
(NCI)**

House Significant Items

Item

Adult Acute Leukemia - The Committee is encouraged by ongoing research on adult acute leukemia particularly in understanding how changes in a person's DNA can cause bone marrow cells to develop into leukemia, the detection of minimal residual disease which can indicate a relapse in the disease, and the discovery of more effective chemotherapy drugs. The Committee encourages NCI to expand current studies and support promising new research through all available mechanisms. (p.108)

Action taken or to be taken

NCI is funding research on the epigenetic regulation of gene expression that may contribute to progression and survival in acute leukemia. Recent studies show that there may be a distinct type of acute leukemia associated with a profound epigenetic silencing (DNA methylation) of genes suppressing the expression of important developmentally related transcription factors (HOX genes). This type of acute leukemia may have a longer survival time and greater responsiveness to chemotherapy. In addition, NCI researchers are developing agents that target epigenetic mechanisms to treat acute myeloid leukemia (AML). An NCI team reported combining two inhibitors (3-Deazane-planocin A and panobinostat) might be an effective and selective epigenetic therapy for AML.

To identify DNA changes predictive of disease stage and progression in myelogenous leukemia and acute lymphocytic leukemia, NCI sponsored a high-resolution analysis of total gene expression. Important changes in the expression of the number of gene copies of specific genes and significant chromosomal abnormalities were detected in cells during disease progression. These striking genetic differences were detected in the progression of both lymphoid and myeloid leukemias to their most serious and dangerous stages. These findings will assist in developing targeted therapies.

NCI is supporting a Specialized Program of Research Excellence (SPORE) that has been studying leukemia/bone marrow microenvironment interactions. The group previously reported that cells arising from bone marrow inhibit chemotherapy's ability to cause cell death in acute myeloid leukemia. A new study shows that targeting the bone marrow cells' specific inhibitors makes leukemic cells more likely to be destroyed by chemotherapy.

In a collaborative effort, NCI investigators evaluated survival patterns of ~9,700 registered AML patients diagnosed in Sweden in 1973 to 2005 and found AML survival has improved during the last decades. However, the majority of AML patients die of their disease and age remains an important predictor of prognosis.

The NCI-sponsored Eastern Cooperative Oncology Group reported that higher dose daunorubicin as part of standard therapy for AML resulted in improved overall survival, compared to standard dose daunorubicin, with no increase in toxicity.

An important component for curative therapy in AML is allogeneic bone marrow transplantation. Since more than half of those who develop AML are generally deemed not eligible for transplant due to advanced age, the NCI-sponsored Cancer and Leukemia Group-B (CALGB) has explored the use of transplant for individuals with AML. The initial clinical trial results appear favorable. Efforts to improve this treatment modality in the older patient population with AML are ongoing.

An international collaboration led by the NCI-sponsored CALGB is focusing on a rare type of AML with extremely poor survival. This clinical trial utilizes a novel agent targeting a molecular defect (FLT3) and will determine if this approach improves the survival of these patients.

Item

Blood Cancers- The Committee is aware that there are currently over 800,000 blood cancer patients living in the United States, and that the incidence of certain blood cancers has increased in recent decades. Public Law 107-172 directed NIH to expand, intensify, and coordinate programs for the conduct and support of research with respect to blood cancer, and particularly with respect to leukemia, lymphoma, and multiple myeloma. These diseases constitute one of the leading causes of cancer deaths. In addition, the Committee urges NCI to increase its focus on more rare forms of blood cancer such as Waldenstrom's macroglobulinemia. (p.108)

Action taken or to be taken

NCI is promoting research on the development and validation of biomarkers for the early detection, prediction, and recurrence of blood cancers, especially in high-risk individuals, as well as for risk assessment of primary and secondary hematopoietic malignancies. In addition, development and improvement of technologies and methods for quantitative detection of novel biomarkers is ongoing. An international effort led by NCI is focused on identifying biomarkers, novel targets, and combination therapies for the development of early phase clinical trials for multiple myeloma (MM) patients.

Ongoing genome-wide association studies are examining the effects of common genetic variants in relation to non-Hodgkin lymphoma susceptibility and survival as well as key genes that may contribute to lymphomagenesis. NCI researchers are investigating the causes of blood cancers in the general population by large-scale epidemiological studies with biomarkers to uncover lifestyle and environmental risk factors, gene-environment interactions, the role of immunity and infection, and precursor lesions. In addition, NCI is actively recruiting new families to participate in its ongoing research investigating familial occurrences of blood cancers. The goal of these studies is to identify both genetic and environmental components of familial risk.

This year, NCI expanded the number of hematologic malignancy SPOREs by two: leukemia and lymphoma. The existing SPOREs reported new advances in genomic characterization of hematologic diseases, the development of new treatment strategies, and insights in risk assessment. A novel, high-resolution genomic approach was used to better characterize the recurrent chromosome abnormalities associated with Waldenstrom's macroglobulinemia (WM) pathogenesis.

NCI has made significant efforts to expand and intensify treatment-changing clinical research in blood cancers, including rare conditions, in the past year. Current clinical trial efforts include three complimentary phase III studies in MM, a phase III trial in the rare and lethal blood cancer primary amyloidosis, several ongoing clinical trials enrolling patients with WM focused on specific pathways, and a new bone-marrow transplant protocol.

NCI investigators recently reported the following significant findings in blood cancer:

- Abnormal white blood cells can be present in patients' blood more than six years prior to the diagnosis of chronic lymphocytic leukemia;
- Sets of genes were identified in diffuse large B-cell lymphoma that influence the effectiveness of treatment and contribute to patient survival;
- Monoclonal gammopathy of undetermined significance was shown to precede MM;
- Several studies reported the impact of gene deregulation and genetic mutations in blood cancers, some of which are linked to immune responses;
- A case-control study showed that obesity at all ages was an independent risk factor for chronic myeloid leukemia with a significant dose-response effect;
- Several promising anticancer agents and immunotherapy treatments have been shown effective in animal models and clinical trials (including: BL22, bortezomib, alemtuzumab, rituximab, Romidepsin, siplizumab)

Item

Gastrointestinal (GI) Cancer - The Committee is concerned that early diagnosis of most GI cancers is difficult or impossible, especially aggressive GI cancers in young people, and curative treatment options are non-existent at later stages. The Committee encourages NCI to study GI cancers in people age 40 and under, giving emphasis particularly to late-stage cancers for whom curative treatment options are unavailable. In addition, the Committee requests NCI to consider developing an interconnected gastrointestinal cancer biorepository with consistent, interoperable systems for collection, storage, annotation, and information sharing. (p.108)

Action taken or to be taken

In 2009, NCI co-sponsored a workshop on the biology of colon and other cancers in adolescent and young adult populations. Participants examined the biological underpinnings of the rising incidence of colon cancer in this age group and why these young patients often have poorer outcomes than older ones. NCI is developing a study that will accrue patients from both pediatric and adult clinical trial groups that study gastrointestinal (GI) disorders. In addition, adult phase III treatment trials routinely include participants down to age 18 and the data are examined according to patient age.

Individuals with a family history of colorectal cancer (CRC) are at increased risk of the disease: having a first-degree relative with CRC approximately doubles the risk, which increases further with the proportion of relatives affected, particularly if they are diagnosed at an early age. The NCI-established Colon Cancer Family Registry (C-CFR) is an international research infrastructure for investigators interested in conducting studies on hereditary CRC. The C-CFR has biospecimens from more than 11,300 families across the

spectrum of risk for colon cancer and is centralizing these samples so that researchers can use the biospecimens for further study.

NCI intramural researchers have started a clinic to study gastrointestinal stromal tumor in children and young adults. The clinic collects tumor tissue, which is tested for known mutations associated with this cancer. In addition to the samples, information from patient histories, physical examinations, and imaging studies is used to develop new treatment regimens for patients who currently have limited options for cure.

An NCI initiative known as the cancer Human Biobank (caHUB) is establishing a centralized specimen bank that will collect high-quality, standardized samples from GI cancers, including colon, pancreatic, and stomach tumors. Using state-of-the-art informatics tools, caHUB will allow data from biospecimens to be paired with other clinical information. NCI-sponsored phase III trials collect other biospecimens and an interconnected GI biorepository inventory summary is being planned. All of these resources will aid investigators in the GI field.

NCI-funded studies are pursuing methods in all age groups to detect early GI cancers, which may be more amenable to treatment than advanced cancers. Scientific reports this year indicate that small molecules known as microRNAs, which can be detected in blood samples, have the potential to help identify patients with early pancreatic cancer and may provide useful biomarkers for colon cancer and predict survival. Another study suggests that mutations in certain genes associated with adding sugar molecules to proteins may cause a predisposition to colon cancer.

Screening for one of the most common types of liver cancer, hepatocellular carcinoma (HCC), may be able to be improved, particularly if the patient has a history of hepatitis. By combining two screening tests, researchers reported this year that they were able to accurately identify more early stage HCC cases.

Item

Gynecologic Cancer SPORES The Committee is encouraged by the success of the gynecological cancer SPORE program. At present there is no available screening test for ovarian cancer to identify the disease at an early stage and improve survival. Given the inadequacies of current tools, there is a pressing need for new effective screening technologies, as well as for the development of new targeted therapies to decrease the mortality and morbidity of this disease. In addition, there is a need for research that is focused on endometrial and uterine cancer, The Committee encourages NCI to support existing gynecologic cancer SPORES as well as to consider increasing their overall number. (p.108, 109)

Action taken or to be taken

This year, researchers from NCI's SPORE program, the Early Detection Research Network, and the Prostate, Lung, Colorectal and Ovarian cancer screening trial reported on a rigorous validation study of more than 50 potential markers for detecting early signs of ovarian cancer in blood. The study found that the most accurate marker is CA-125, a protein that is already routinely monitored in women with the disease. Panels of markers

tested in the study offered, at best, only marginal improvements in the ability to detect the disease over CA-125 alone although several other candidate markers showed promise, including HE4. This latter protein was discovered in a SPORE program and has recently been approved by the FDA for monitoring cancer recurrence. Other NCI early detection studies include measuring a blood panel of methylation markers and a compound called claudin-4.

Another SPORE is exploring mass ovarian cancer screening by studying biomarkers in urine. Currently, the researchers are testing 10 proteomic urine markers in a large validation study.

Research also continues with biomarkers for endometrial cancer. For example, about two to six percent of endometrial cancers are inherited and NCI-supported investigators are developing regimens for better identifying those women carrying the associated mutation. A biomarker called synuclein-3 may serve as a useful tool for the diagnosis and prediction of treatment response in women with one form of uterine cancer.

Certain agents called matrix metalloproteinase (MMP-2) inhibitors have been studied to deter the metastasis of ovarian cancer. A new report shows that to improve efficacy, the drugs must be given immediately following resection of ovarian cancer.

Another study of a receptor called GPR30 confirms in ovarian cancer what has already been seen in endometrial and breasts cancers: higher levels of the receptor are associated with lower survival. This information suggests that GPR30 may be a potential target for therapy in these cancers.

Extensive clinical research is underway to identify, develop, and evaluate new targeted therapies for ovarian, endometrial, uterine, and cervical cancer. The NCI has worked closely with the academic community to integrate research on targeted therapies conducted in the ovarian and gynecologic SPOREs with the NCI-funded Clinical Trials Cooperative Groups. The Gynecologic Oncology Group, for example, has recently completed accrual to a large phase III trial evaluating the addition of bevacizumab, a novel agent targeting the development of new blood vessels in cancers, to standard therapy among women with advanced ovarian cancer. Similar trials are underway among women with endometrial and cervical cancer.

Item

Gynecologic Oncology Clinical Trials - The Committee is concerned that the gynecology clinical trials network has not been able to fully fund an institution's research costs when it enrolls patients in a trial. This may have the impact of limiting access for patients to these trials which are offering cutting edge cancer treatments. This may also negatively impact the pace with which these clinical trials can be completed and results evaluated and published. The Committee encourages NCI to reconsider the per patient research costs of these clinical trials. (p.109)

Action Taken or to be Taken

NCI has worked closely with our clinical trials networks, including the Gynecologic Oncology Group, to identify all the institutional costs associated with trials as well as design a framework for increased per-case reimbursement for more complex trials. In addition, the NCI has set aside funds to pay for the additional costs of such items as biomarkers and quality-of-life studies integral to the design of specific trials. The NCI is also working with our clinical trials networks to ensure that our clinical trials are conducted as efficiently as possible to most effectively utilize available resources and maximize patient benefit.

Item

Hematology -The Committee is aware of efforts being made by the Institute's Office of Latin American Cancer Program Development to train physicians and scientists in the development of clinical trials and collaborative research networks focused on blood cancers. The Committee encourages NCI to support these international programs, which will improve research mechanisms and access to novel treatments for cancer patients. (p.109)

Action taken or to be taken

The Office of Latin American Cancer Program Development was established in 2008 to promote and facilitate research efforts to reduce the increasing cancer burden in Latin American countries and in due course, impact the cancer trends observed in the U.S. Hispanic population. These efforts have the potential to improve cancer medicine and control and will ultimately drive improved health and healthcare in this region.

It has been estimated that global cancer will climb to 12.9 million new cases this year, and the worldwide toll is predicted to rise to 27 million new cancer cases and 17 million deaths by the year 2030. Cancer is ranked among the top three causes of death in Latin America; and, among the top two in the U.S. The trend of cancer incidence and mortality in Latin America is very similar to what is observed in the U.S. Hispanic population which is destined to become the largest minority by 2020. Based on these trends and the projected impact of cancer burdens, it is critically important to consider initiating trans-Latin American research programs.

The National Cancer Institute and the American Society of Hematology sponsored the *NCI-ASH Hematology Clinical Trials Workshop* held in Sao Paulo, Brazil in May 2009. This educational workshop encouraged clinical research collaborations to better understand hematological malignancies as a means to improve medical management and treatment of patients. The curriculum was designed to increase the number of hematologists trained in clinical trial design and conduct by drawing on the resources and expertise of the NCI and ASH which were adapted to address needs specific to Latin America. Based on the results of this workshop, NCI and ASH intend to sponsor a two- to three- day workshop, *Molecular Diagnosis Standard Practices for Hematologic Malignancies*, in June 2010 to be held in Mexico City, Mexico. This workshop will identify areas for standardizing and harmonizing molecular diagnosis to improve oncologic epidemiology data on Latin American populations. The program will be designed to initiate and discuss potential research concepts and to evolve into proposals for research projects.

The intent of this workshop is to generate a research project to develop clinical protocols that result in findings that will enhance cytogenetic methodology and result in optimizing diagnosis.

Item

HPV Vaccine and Cervical Cancer - The Committee encourages NCI to study clinical and cost analysis benefits of prospectively tracking cytologic screening and HPV test results and outcomes in communities where HPV vaccines are being implemented. The Committee encourages NCI to fund research, including registry-based tools, that will permit identification of the most cost-effective management strategy for cervical cancer screening in the era of HPV vaccines and will identify the circumstances where current screening protocols fail. (p.109)

Action taken or to be taken

HPV vaccines have shown near complete protection against new infections and lesions caused by HPV types targeted by the vaccine. To understand the long-term impact of HPV vaccination and determine the most cost-effective, evidence-based screening strategies for vaccinated populations, NCI has extended follow-up of women enrolled in a 7,500-woman community-based trial of an HPV-16/18 vaccine in Costa Rica. This follow-up will provide important information on the long-term impact of HPV vaccination and on the effect of vaccination on cytologic and virologic screenings. Results from this trial will provide much needed data for cost-benefit analysis and to inform changes in cervical cancer screening protocols and policies.

To obtain data directly applicable to the United States, NCI is also considering efforts by groups proposing to create prospective, population-based, cervical cancer screening registries that can fully monitor screening and prevention programs among vaccinated and unvaccinated individuals and provide data for cost-benefit analyses. Furthermore, NCI researchers are continuing collaborations with health decision analysts and economists to examine strategies for integrating the HPV vaccine into current screening algorithms. NCI also supports research efforts aimed at validating low cost screening tools as well as developing vaccines that are less costly and more easily stored. Currently, researchers are developing more efficient techniques to determine treatment options for women with abnormal Pap smears, thereby improving patient care.

Published modeling data suggest that targeting vaccination among women at younger ages before initial HPV infection may be more effective. In addition, the data indicate that the cost-effectiveness of HPV vaccination depends on duration of immunity, requires high vaccine coverage, and declines as age at vaccination increases. New data on screening technology performance, the impact of type-specific HPV infections, multiple HPV infections, duration of infection, vaccine efficacy in older women and males, and sexual behavior and transmission will be added to current models which will contribute to further policy-relevant effectiveness analyses.

A new project, Population-based Research Optimizing Screening through Personalized Regimens (PROSPR), aims to develop the capacity for multi-site, coordinated, transdisciplinary research to evaluate and improve the screening process for cervical,

breast, and colorectal cancer. PROSPR will provide the necessary infrastructure to collect population-level data that will allow researchers to assess the comparative effectiveness of alternative approaches to the diagnosis of cervical abnormalities, screening intervals, and protocols for treating common cervical abnormalities. NCI also continues to track knowledge and awareness of the HPV vaccine using the Health Information National Trends Survey (HINTS). Researchers and public health officials can use this information to identify how public information campaigns influence attitudes about cervical cancer screening and the HPV vaccine.

Item

Liver Cancer -The Committee urges NCI to focus research efforts on liver cancer, which continues to be one of the fastest growing cancers in the U.S. The committee encourages NCI to pursue new interventions and treatments, as well as new methods for early detection and prognosis. (p. 109)

Action taken or to be taken

NCI continues to focus efforts on liver cancer to research its etiology; develop animal models; find novel approaches to prevent malignancy; create therapeutic and diagnostic tools for reliable prognostic indicators; and develop therapeutic approaches to minimize morbidity and mortality associated with this cancer.

NCI scientists have identified over 50 genes with significant prognostic relevance for liver cancer. Several genes are associated with signaling pathways, revealing a number of new potential therapeutic targets for liver cancer. Other biomarkers identified may also be used to identify:

- Aggressive disease and who might benefit from interferon treatment;
- Tumor initiating activity of liver cancer cells;
- Tumor progression and metastasis or tumor cell survival; and
- A gene signature, identifying those who may benefit from epigenetic therapy.

NCI continues to look for new genetic associations, biomarkers, and risk factors for liver cancer through:

- The investigation of the role of chemical carcinogens;
- A collaboration with the Thai Chulabhorn Research Institute to study cellular and molecular alterations in liver cancer;
- The NCI Surveillance, Epidemiology, and End Results (SEER) Program which is identifying at-risk groups and the impact of risk factors;
- Support for a Gastrointestinal (GI) SPORE liver cancer project investigating hepatitis C virus proteins and hepatocellular carcinoma (HCC) development; and
- Support for a multi-institutional team of researchers from the NCI's Early Detection Research Network (EDRN) comparing the efficacy of using various biomarkers for HCC detection.

NCI also has focused efforts to study the host immune response to generation and development of tumors. Genetic risk factors in the T-cell receptor locus have been identified and two interleukins have been found to induce anti-tumor activity while another

interleukin has been linked to liver cancer promotion. Studies also include analysis of virus host interactions, genetic variation, and viral escape mutants.

The NCI continues to sponsor clinical development of new investigational agents and treatments for liver cancer. One NCI grant is investigating an Oncolytic rVSV(MD51)-M3 gene/viral therapy approach. NCI is recruiting for a trial that aims to minimize chemotherapy side effects for those with inoperable liver cancer. NCI is also supporting a trial to determine whether treatment with the nutritional supplement, SAME, reduces levels of alpha-fetoprotein, a cancer biomarker. New NCI-supported trials include a phase III trial to evaluate liver cancer treatment in children and two phase III studies evaluating different treatment combinations--sorafenib/doxorubicin and sorafenib/Trans-Arterial Chemoembolization (TACE)—in adults. NCI partners with NIDDK on investigations based within the Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial and to work with the Hepatobiliary Cancer Task Force on developments in the field, new collaborations, and the progress of existing trials.

Item

Lung Cancer - The committee remains concerned about increased lung cancer rates among women and urges NCI to support research for lung cancer diagnosis and treatment. (p.109)

Action taken or to be taken

In 2008, NCI reported that while lung cancer rates are dropping for men, they continue to rise in women. NCI is committed to advancing lung cancer research to reverse this trend and has instituted several initiatives specifically targeting women while still funding many studies that are informing the diagnosis and treatment of both genders. NCI's sustained support for research on lung cancer includes the following activities, studies, and advances:

- NCI, in collaboration with others, launched Women.Smokefree.gov to help women quit smoking and remain smoke free. The interactive site provides relevant topics to women such as weight management and pregnancy, and uses tools such as a step-by-step cessation guide and self-quizzes to actively engage users;
- A clinical study of the anti-estrogenic drug, fulvestrant, plus an anti-EGFR (epidermal growth factor receptor) agent, gefitinib, showed promising results, particularly in lung cancer of post-menopausal women with high levels of estrogen receptor (ER) beta;
- An NCI supported case-series study in men and women with lung cancer will evaluate gender differences in lung cancer risk by looking at molecular markers of susceptibility, exposure, and tumor tissue alterations;
- Using an animal model of small cell lung cancer (SCLC), researchers suggest the immune response detected that may offer methods for early detection of SCLC;
- NCI is investigating the commonalities between lung cancer and chronic obstructive pulmonary disease (COPD) including shared pathways in the origin and progression of each disease and to define characteristics that may determine individual risk. These results will help physicians tailor the therapies to the treatment or prevention of both diseases;

- A recent study suggests that increased expression of microRNA (miR-21) may play a significant role in lung carcinogenesis in never-smokers, as well as in smokers, and is a potential therapeutic target for this disease;
- Study shows a distinct 72-gene signature is closely associated with survival in early-stage non-small cell lung cancer (NSCLC) patients and may become a tool for patient selection for therapy;
- An international genome-wide analysis of NSCLC identified 5 markers that might be prognostic of overall survival;
- Investigators validated multiple EGFR pathway-related biomarkers in NSCLC patients;
- In a SPORE study, proteins identified by a novel detection approach may predict the outcome of NSCLC patients treated with EGFR inhibitors;
- Data combined from 5 trials assessed the impact of mutations in two genes (EGFR and KRAS) on clinical outcomes and the results suggest that advanced NSCLC patients with EGFR mutations should receive the drugs erlotinib or gefitinib
- NCI has more than 25 on-going active early phase clinical trials in lung cancer using novel molecular targets or cancer vaccines including one to validate genetic-guided therapy in early stage lung cancer;
- NCI is evaluating the therapeutic activity of the combination of chemotherapy, bevacizumab, and cetuximab in advanced NSCLC, incorporating biomarkers with the intent to better define the patient population who will benefit from this combination; and
- NCI is developing novel radiation therapy techniques for patients who are not candidates for surgery such as stereotactic body radiation therapy, and imaging studies integrated with therapeutic protocols.

Item

Melanoma - The Committee is encouraged by the collaboration between NCI and the advocacy and research community on prioritizing NIH-funded melanoma research that resulted in a community-oriented strategic action plan for melanoma research. The Committee encourages NCI to support the areas of research identified by the strategic research plan. Furthermore, the Committee encourages NCI to include melanoma in the Cancer Genome Atlas consortium to help identify new markers for classification, detection and risk-assessment, particularly in high-risk populations. (p.109)

Action taken or to be taken

NCI has made critical discoveries regarding the role of genes in melanoma causation and characterizing melanoma types associated with different genetic and environmental risk factors. Since more than 60 percent of melanomas have mutations in a gene called BRAF, NCI has collaborated with industry to obtain compounds that inhibit targets in this pathway, which increases the risk for melanoma independent of sun exposure. The institute then provides the potential drugs for clinical testing by NCI-supported researchers. NCI has four ongoing phase I and phase II clinical trials using one such compound--AZD6244. Mutations also occur in melanoma that may prove to be the targets for new therapies. In a personalized medicine approach, one trial screens patients for c-Kit mutations and those with this alteration receive imatinib, which hones in on c-Kit. Molecular markers to determine cancer aggressiveness are being sought.

ARRA funds also allowed two large, phase III clinical trials to start this year. It is believed that the results of these trials will change clinical practice for melanoma treatment.

The Cancer Genome Atlas (TCGA) will expand over the next five years to include 500 melanoma cases, including primary and metastatic tumors. These samples will be molecularly characterized to provide the statistically significant data required for TCGA-type bioinformatic analysis, which will enable the discovery of prognostic, diagnostic, and therapeutic targets for melanoma. Already, through other research, NCI has found some genes that are related to high and low risk of melanoma and developed a web-based melanoma risk assessment tool.

TCGA is anticipated to generate more ways to identify individuals who are at risk for melanoma as well as tumor subtypes that can lead to personalized treatment. Using data from the Surveillance, Epidemiology, and End Results Program, NCI identified a recent increase in melanoma in young women, specifically, those born after 1965. To follow up, researchers are examining differences in rates, risk factors, age, sex, and anatomical sites of lesions, and thereby identifying distinctive patterns of disease.

NCI continues to investigate important associations linking environmental exposures with genetic alterations and melanoma risk in ongoing case-control, family-linkage, and genome-wide association studies.

NCI intramural investigators have made several significant melanoma findings:

- A study showing how skin cells regulate drug resistance of melanoma cells.
- Finding a biomarker for intratumoral regulatory T cells in metastatic melanoma lesions.
- A study that provides strong evidence that exposure to UV radiation leads to mutations that contribute to the formation of melanomas in xeroderma pigmentosum patients.

Item

Mitochondrial DNA and Cancer - The Committee is aware that mitochondrial DNA mutations are associated with numerous cancers and that NCI has increased its efforts to better understand this relationship. The Committee encourages the Institute to continue its involvement in this area of research. (p.109)

Action taken or to be taken

The NCI supports basic, translational, and clinical research programs focused on understanding the contribution of mitochondrial DNA (mtDNA) mutations to the development and dissemination of cancer. NCI's basic research program includes studies focused on the mechanisms by which mtDNA mutations and mitochondrial dysfunction initiate stress signals that lead to global changes in gene expression, cellular morphology, and tumor invasiveness. In one project, the influence of mtDNA mutations on the bone stromal environment in prostate cancer metastasis is studied. Investigators have shown that mtDNA mutations enhance cellular reactive oxygen and prostate tumor growth, especially in the bone stromal microenvironment, and they have begun to identify the

specific signaling pathways responsible for this effect. Other projects seek to investigate the process of mtDNA replication, its role in maintaining genomic integrity, and the mechanisms through which mtDNA communicates with the nucleus, as well as the interplay of these two genomes in cancer.

A number of studies in translational science areas are focused on determining the relevance and predictive potential of mitochondrial mutations as biomarkers for the early detection of cancers. Studies from Early Detection Research Network (EDRN), using high-throughput array-based technologies, indicate that 79% of the lung, 100% of the bladder, and 69% of the kidney tumors examined contained mtDNA mutations. In another study, investigators have identified a specific mtDNA deletion that may aid in the diagnosis prostate cancer. These studies are likely to provide new opportunities in the area of biomarker development.

One study examines the ability of chemopreventive agents to reduce nuclear and mtDNA damage in cancer models. Other investigations focus on understanding how certain therapeutic agents inflict mitochondrial toxicity, how mitochondrial metabolism and DNA repair can be used to enhance the effectiveness of existing treatments, and whether acceleration of mtDNA damage and alterations in oxidative stress contribute to the deleterious effects of chemotherapy.

Investigators involved in drug discovery are focusing on mechanistic studies of mitochondria to identify suitable molecular drug targets to aid in designing compounds to induce cell death by apoptosis, a death process using pathways controlled by mitochondrial enzymes. New delivery strategies, some involving nanotechnology or special targeting sequences, are also being created to deliver drugs selectively to mitochondria. In one example, an investigator found a promising new way to kill tumor cells by administering compounds that penetrate mitochondria by means of a special sequence. Once inside, the compounds inhibit a heat shock protein that controls the folding of proteins in multiple signaling networks that drive tumor growth. These compounds cause tumor cell death and inhibit human tumors grown as xenografts.

In population studies supported by NCI, investigators examine the association between mtDNA copy number and risk for cancers such as breast, colorectal, ovary, uterine, and pancreatic. Another study investigates the frequency of mtDNA variants and acquired mutations in pancreatic cancer and yet another examines whether there is a higher frequency of mtDNA mutations associated with prior anthracycline treatment for pediatric ALL.

Item

National Disparities - NCI has developed and supported a national network of designated cancer centers at academic medical centers across the nation as a premier vehicle for promoting cancer research and outreach. These centers are particularly valued in their regions and States for their role in supporting all facets of cancer research, prevention, control and education. The Committee notes the incidence of national disparities in cancer prevalence, diagnosis, treatment, and control, particularly within regions with large underserved and minority populations with poor access to these centers.

In order to reach these populations and extend the benefits of designated cancer centers, the Committee recommends that NCI consider supporting developing centers through the renewal of the NCI planning grant program. This grant mechanism will support the development of additional designated cancer centers that will bring the benefits of cancer research, prevention, control, and outreach fostered at these centers to those populations most in need. (p.109, 110)

Action Taken or to be Taken

Through the planning grant mechanism NCI will continue to expand opportunities to advance established cancer research networks and to encourage translational efforts to impact the reduction of cancer in communities with an excess burden from cancer. The three major pillars of the NCI-designated cancer centers program are the institutionalization of a critical mass of researchers to conduct collaborative studies in basic, clinical, and population-based research, the integration of a comprehensive cancer research training program, and the incorporation of a strong and sustainable community-based research program that supports activities in outreach and education, provides information on advances in health care for both health care professionals and the community, access to primary and secondary prevention, and state-of-the-art cancer services. NCI continues to develop new ways to encourage the development of collaborative networks that strengthen programs designed to aid in building capacity to address the needs of the underserved and minority populations. For example, the NCI Minority Institution/Cancer Center Partnership Program – links Minority-serving institutions (MSI) with NCI-designated Cancer Centers (or groups of centers) to develop comprehensive partnerships in cancer research, cancer training, cancer outreach programs and cancer education that will achieve the following goals: (1) build and stabilize independent competitive cancer research capacity at the MSI; (2) improve the effectiveness of the NCI-designated Cancer Center activities specifically designed to address the cancer disparities in underserved, and racial and ethnic minorities and the socio-economically disadvantaged; and, (3) create stable, long-term collaborative relationships between the MSI and the Cancer Center in all areas of cancer research, training, education, and outreach. These Partnerships were developed initially through an NCI planning grant program.

The NIH Centers for Population Health and Health Disparities (CPHHD) seeks to advance understanding of social determinants of health and health disparities using multilevel, trans-disciplinary team science approaches. The Centers support research on health disparities by integrating approaches from the basic, clinical, and population sciences. CPHHD research informs our understanding of how the social and built environments interact with biological processes, such as inherited susceptibility, epigenetic modifications, gene expression, endocrine function, inflammation, tumor growth, and aggressiveness to affect cancer outcomes. This kind of scientific information is crucial in developing appropriate interventions in prevention, early detection, and treatment to lessen cancer disparities.

Using planning grants NCI plans to strengthen and expand these research and training partnerships to broaden the NCI Cancer Center model to address cancer health disparities and training by developing other transdisciplinary, multi-component networks of NCI-

supported cancer research institutions and programs, including minority-serving institutions, majority academic institutions, NCI-designated cancer centers, the NCI Community Cancer Center Program (NCCC), and other health disparities research programs like the Community Networks Program and Patient Navigation Research Program. A major focus of the NCCCP, for example, is on improving access to care among underserved populations with unusually high cancer rates. The NCCCP offers more access to research-based cancer care in home communities, and makes it easier to receive the latest, research-driven cancer screening, prevention, treatment, and palliative care services in a community setting.

Item

Neuroblastoma - The Committee continues to encourage NCI to accelerate support for neuroblastoma research, with a focus on clinical trials for high-risk patients. Given the poor survival rates for children with advanced disease, the Committee encourages NCI to prioritize support for all promising neuroblastoma (NB) research, both intramural and extramural. (p.110)

Action taken or to be taken

NCI recognizes the need for more effective treatments for children with NB and supports a number of important programs that seek to discover new and more efficacious approaches to treating this disease as well as understanding the biology of the disease.

The International Neuroblastoma Risk Group (INRG) Biology Committee published an international consensus for NB molecular diagnostics which will provide a uniform classification system of NB and will facilitate clinical and translational research studies.

Examples of recent advances in understanding the biology of NB which may lead to development of targeted therapies include the following:

- NCI researchers have demonstrated cytokines IL-27 and IL-2 synergize to combat metastatic NB in an animal model;
- In a collaborative study, NCI researchers discovered NB-derived secretory protein is a novel secreted factor overexpressed in NB; and
- The high expression of the gene MIRHG1 correlates with poor outcome for patients with NB, indicating important oncogenic functions of this microRNA in NB.

The Children's Oncology Group (COG) recently reported that immunotherapy with the chimeric antibody 14.18, manufactured by NCI, plus cytokines (GM-CSF and IL-2) improves event-free survival and overall survival for children with high-risk NB patients when administered following myeloablative therapy and stem cell transplant. This is the first monoclonal antibody that has been shown to be clinically beneficial in children with cancer prior to a demonstration of efficacy in adults with cancer.

NCI also supports the New Approaches to Neuroblastoma Treatment (NANT) Consortium, which consists of a group of 13 university and children's hospitals with strong research and treatment programs for NB. The NANT Consortium focuses on new therapies for patients with NB who no longer respond to standard treatment approaches.

The NCI-sponsored Neuroblastoma TARGET (Therapeutically Applicable Research to Generate Effect Treatments) Project is cataloguing genetic mutations and alterations that occur in high-risk NB. The group recently found the ALK gene is activated through mutation in approximately 10% of high-risk NB cases. Small molecule ALK inhibitors are currently under clinical evaluation, and NCI is supporting the first clinical trial of an ALK inhibitor in children with cancer.

The NCI-supported Pediatric Preclinical Testing Program (PPTP) is a comprehensive program to systematically evaluate new agents against childhood cancers (including NB). To date, over 30 agents have been tested for their activity against the PPTP's NB models. Several agents have shown activity, including an agent that selectively inhibits Aurora A kinase (MLN8237) and a novel agent (oncolytic virus SVV-001). These agents are now in pediatric phase I evaluation through the COG Phase 1/Pilot Consortium.

Item

Pancreatic Cancer - While there has been a continuing decline in mortality rates for many types of cancer, mortality rates for pancreatic cancer have changed little in the past 30 years. Further, survival rates have changed little in the last 30 years. The Committee last year urged NCI to launch a pancreatic cancer-specific research and training initiative. To further these efforts, the Committee encourages NCI to convene a conference of internal program and research staff to jointly assess the current status of the pancreatic cancer research and training initiative and to develop an action plan for the use of fiscal year 2010 funding. The Committee requests a report on the results of that meeting within 60 days of its occurrence. (p.110)

Action taken or to be taken

Since the publication of *Pancreatic Cancer: An Agenda for Action in February 2001*, the NCI has expanded its portfolio of pancreatic cancer research from \$21.8 million in fiscal year (FY) 2001 to \$87.3 million in FY 2008, an increase of 300%. During this same span of years, the total NCI budget increased by about 28%; thus, the growth in the pancreatic cancer portfolio has been approximately tenfold larger than the growth in the total NCI budget. Growth of the NCI pancreatic research portfolio has been seen in: dollars invested (300%), projects funded (up 260% since FY 2000), unique R01 Grant Principal Investigators funded (up 220% since FY 2000), and training/career development awards (up more than 65% since FY 2005). Part of this growth came about through planned actions and funding opportunities specific to pancreatic cancer, and part grew out of an increasingly larger pool of pancreatic cancer researchers successfully competing for general funding opportunities and unsolicited research grants. There are currently 70 NCI-sponsored clinical trials relevant to pancreatic cancer. NCI has developed pancreatic cancer-focused initiatives, including the Pilot Studies in Pancreatic Cancer, the Pancreatic Cancer Cohort Consortium, and pancreatic and GI SPOREs. Pancreatic cancer studies have also been funded within the Cancer Nanotechnology Platform Partnerships, the Early Detection Research Network, the Tumor Glycome Laboratories of the NIH Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, and other initiatives.

In addition to the activities noted above, funding through the American Recovery and Reinvestment Act of 2009 (ARRA) supports projects focused on pancreatic cancer. As of October 2009, at least 35 pancreatic cancer-related projects have received ARRA funding. These projects include some focused on training/career development that are relevant to growing the critical mass of pancreatic cancer investigators, a group of traditional R01 research grants, a Challenge Grant, and a Grand Opportunity or “GO” grant. The NCI Community Cancer Centers Program (NCCCP), which already includes work on pancreatic cancer, is slated for substantial growth with ARRA funds. The ACTNOW initiative includes a clinical trial addressing pancreatic cancer. The Cancer Genome Atlas project (TCGA) is using ARRA funds to rapidly increase the number of cancers covered by the project, with pancreatic cancer on the expansion list.

In response to the Committee's request to convene a conference to assess the current status of the pancreatic cancer research and training initiative, NCI is planning to hold a meeting to develop an action plan for the use of fiscal year 2011 funding and will provide a report on the results of that meeting within 60 days of its occurrence.

Item

Pediatric Cancer The Committee urges NCI to intensify pediatric cancer research, including laboratory research, to identify and evaluate potential therapies, preclinical testing, and clinical trials through cooperative clinical trials groups. This research should include research on the causes, prevention, diagnosis, treatment, and late effects of pediatric cancer. (p. 110)

Action taken or to be taken

NCI supports a comprehensive preclinical and clinical research program for helping children with cancer. This research program extends from basic biology research and preclinical testing used to identify and validate new therapeutic targets to an extensive clinical trials program that determines whether the preclinical discoveries can be translated into clinical benefit.

Pediatric research in the laboratory includes studying the genetic and other mechanisms related to tumor formation and metastasis. Successful mouse and cell-line models have been developed that mimic several pediatric cancers. NCI's Childhood Cancer *Therapeutically Applicable Research to Generate Effective Treatment* (TARGET) Initiative applies high-throughput genomic analysis methods to identify novel therapeutic targets for childhood cancers and is an example of a synergistic and multidisciplinary program that begins in the laboratory and goes beyond. New targets have been identified for acute lymphoblastic leukemia (ALL) and for neuroblastoma, and investigational agents blocking the action of these targets have moved to clinical testing. These successes have led to TARGET's expansion to include pediatric osteosarcoma, acute myeloid leukemia, and high-risk Wilms tumor. The Pediatric Preclinical Testing Program (PPTP) is an NCI-supported research contract begun in 2005 to generate preclinical data to inform decisions about the prioritization of new agents and combinations of agents for study against specific types of childhood cancers. Novel agents with high level activity against childhood cancer preclinical models have been identified and have transitioned to clinical evaluation.

NCI supports several consortia of institutions to perform the initial pediatric phase 1 clinical trials of novel agents and treatments, thereby allowing preclinical discoveries to rapidly move to the clinic and be studied by experienced pediatric oncology investigators. The Children's Oncology Group (COG) develops and coordinates cancer clinical trials that are available at over 200 member institutions, including at the NCI and domestic and international cancer centers. The clinical trials conducted by COG, NCI, and other NCI-supported consortia play key roles in evaluating new treatment approaches. Recent results from COG clinical trials have defined new, more effective treatments for Ewing sarcoma, high-risk neuroblastoma, and high-risk ALL. An example of successful a bench to bedside development is a new agent for high-risk neuroblastoma. Chimeric 14.18, an immunotherapy, was manufactured by NCI and shown in a COG phase 3 clinical trial to reduce relapses and improve survival for children with high-risk neuroblastoma.

Other immunotherapies are under development by NCI intramural researchers and include those that have shown impressive clinical activity in relapsed ALL with minimal toxicity. NCI scientists are also pursuing a new approach incorporating immunotherapy into standard chemotherapy regimens to prevent recurrence of sarcomas in children.

Item

Reproductive Scientists Development Program (RSDP) - The Committee urges NCI to continue its partnership with NICHD with regard to training the next generation of gynecologic cancer researchers. The success of the Reproductive Scientists Development Program Fellows is reflected in the fact that a majority of these individuals receive an investigator-initiated grant and continue to prosper as a career-clinician scientist. (p.110)

Action taken or to be taken

The NCI has continued its partnership with NICHD to co-fund the Reproductive Scientists Development Program (RSDP) for gynecologic oncologist training. Since FY07, NCI has supported two RSDP scholars for Phase I to study Taxol resistance in ovarian cancer cells, growth factors in uterine carcinosarcoma, and endometrial gland formation as it relates to endometrial cancer initiation, growth, and metastasis. In the first phase (Phase I) of the RSDP, scholars spend two or three years in intensive mentored basic science training. Phase I is supported by the co-funding agreement at \$100,000 per scholar per year. Scholars spend an additional three-year period in Phase II establishing their research programs as junior faculty in a Department of Obstetrics and Gynecology. The NCI has reauthorized the co-funding agreement with NICHD to continue supporting gynecologic oncologists through the RSDP in FY 2010.

Senate Significant Items

Item

Asian/Pacific Islanders - The Committee notes that Asian and Pacific Islanders have a high incidence of stomach and liver cancers compared to Caucasians, and it urges the NCI to focus on the special needs of this population. (p. 88)

Action Taken or to be Taken

NCI has created community-based participatory research (CBPR) programs to reduce disparities in these populations. The NCI supports two Community Networks Program (CNP) that target Asian populations—a national program called the Asian American Network for Cancer Awareness, Research and Training (AANCART), and a second program called the Asian Community Center Network (ATECAR). These programs use specific Asian languages to communicate with Chinese, Vietnamese, Cambodians, Filipinos, Koreans and Hmong communities as well as developing culturally appropriate educational interventions to promote use of beneficial medical procedures, such as smoking cessation, mammography, PAP smears, and colorectal cancer screening. There are three CNP programs that specifically address the cancer issues in Pacific Island populations. One CNP, the Imi Hale – Native Hawaiian Cancer Network located in Hawaii, has a Native Hawaiian oncologist as its the principal investigator. The other two programs, Weaving an Islander Network for Cancer Awareness, Research and Training (WINCART) located in California and The American Samoa Community Center Network located in American Samoa develop culturally appropriate educational interventions for Hawaiians, Samoans, Tongans, and Chamorro to promote the use of beneficial medical procedures and address the cancer prevention needs of the communities they serve.

Item

Cancer Metabolism - The Committee encourages the NCI to support more research on cancer metabolism, specifically how cancer cells become addicted to using more nutrients than normal cells to ensure their survival and growth. Research targeting these metabolic pathways could have a profound and broad effect on cancer cell survival and tumor growth, and ultimately cancer treatment. (p. 88)

Action taken or to be taken

NCI supports a growing number of research programs studying cancer metabolism and recognizes that these pathways have a profound effect on cancer cell survival and tumor formation. In a dramatic example of the link between metabolism and cancer, up to 80% of human gliomas harbor mutations in isocitrate dehydrogenases (IDHs) gene, which reduce the activity of a key metabolic enzyme and in turn help cancer cells survive and grow. This finding raises the possibility that providing cancer cells with the metabolite lost subsequent to the IDH1 mutation could modulate their growth. Also, mutations in phosphoinositide 3-kinase (PI3K) are among the most common events in solid tumors and PI3K has been shown to regulate cell growth and glucose uptake. Targeting glucose uptake or other aspects of glycolytic metabolism may be a viable approach to novel therapeutics for cancer.

TSC1 and TSC2, two tumor suppressor genes in a signaling pathway that regulates cell growth and proliferation, are mutated in tuberous sclerosis. Numerous studies are underway to examine the molecular effects of dysregulated TSC1 and 2 in cancer and how targeting this pathway can be exploited therapeutically. Importantly, treatment with metformin, the well-established anti-diabetes II therapeutic which targets glucose responsive components of the TSC1/2 pathway, has been linked to a lower breast cancer incidence in diabetes patients. Its effect on tumor growth is not fully understood and is the object on intense investigation. The TSC1/2 pathway also control signals from the

hypothalamus regulating appetite and obesity. This novel finding connects organismal biology with cellular nutrient uptake and opens up a new avenue for research to understand the links between organism behavior and cellular metabolism for future study.

An NCI-supported SPORE is studying certain metabolic pathways that may contribute to the anticancer effects of dietary fat modulations in prostate cancer. In preclinical models, they demonstrated that dietary fat reduction and decrease in the ratio of omega-6 to omega-3 fatty acids affect the development and progression of prostate cancer. A clinical trial is underway to determine if altering dietary fat affects prostate cancer biomarkers.

NCI is supporting new research on metabolomics, the systematic study of small-molecular-weight substances in cells, tissues and/or whole organisms as influenced by multiple factors including genetics, diet, lifestyle and pharmaceutical interventions. These substances may directly or indirectly interact with molecular targets and thereby influence the risk and complications associated with cancer. Knowledge regarding genetics, susceptibility factors, timing, and degree of exposure to a drug or food component is fundamental to understanding the metabolome and its potential use for predicting and preventing early phenotypic changes. Understanding the metabolome will assist in identifying intermediate or surrogate cancer biomarkers.

A workshop on cancer cell metabolism sponsored jointly by NCI and the National Institute of Neurological Disease and Stroke was held July 9-10, 2009 brought together prominent investigators in the fields of cancer biology, metabolomics, and cell energetics to discuss research needs and opportunities in cancer cell metabolism and metabolic reprogramming that could lead to more effective cancer therapeutic, diagnostic, and preventive strategies. A report is being prepared for publication which is expected to be an important resource for this emerging field.

Item

Gastrointestinal (GI) Cancer - The Committee encourages the NCI to put a higher priority on GI cancers in people age 40 and under, giving emphasis particularly to late-stage cancers for which curative treatment options are unavailable. In addition, the Committee requests the NCI to consider developing an interconnected gastrointestinal cancer biorepository with consistent, interoperable systems for collection, storage, annotation, and information sharing. (p. 88)

Action taken or to be taken

Please refer to page 3 of this document for NCI's response to this item.

Item

Hematology - The Committee is aware of efforts being made by the Institute's Office of Latin American Cancer Program Development, in conjunction with the American Society of Hematology, to train physicians and scientists in the development of clinical trials and collaborative research networks focused on blood cancers. The Committee encourages international programs such as this, which will improve research mechanisms and access to novel treatments for cancer patients. (p. 88)

Action taken or to be taken

Please refer to page 6 of this document for NCI's response to this item.

Item

Human Papillomavirus [HPV] Vaccine and Cervical Cancer- The Committee urges the NCI to fund research, including registry-based tools, that will allow for the identification of the most cost-effective management strategies for cervical cancer screening in communities where HPV vaccines are being implemented and to identify the circumstances where current screening protocols fail. (p. 88)

Action taken or to be taken

Please refer to page 7 of this document for NCI's response to this item.

Item

Liver Cancer - The Committee supports a stronger focus on liver cancer, which continues to be one of the fastest growing cancers in the Nation during a time when the overall incidence of cancer has stabilized. The Committee urges that new interventions and treatments, as well as new methods for early detection and prognosis, be aggressively pursued. (p.89)

Action taken or to be taken

Please refer to page 8 of this document for NCI's response to this item.

Item

Lung Cancer - The Committee recognizes that lung cancer survival rates are too low, at 15 percent, and it urges the NCI to expand its research into improving lung cancer diagnosis and treatment. (p. 89)

Action taken or to be taken

Please refer to page 9 of this document for NCI's response to this item.

Item

Melanoma - The Committee encourages the NCI to work with advocates and researchers to fund the areas of research identified by the recently developed strategic research plan on melanoma and to use all available mechanisms to target research in those areas. The Committee is aware of recent successes in the therapy of rare forms of melanoma that were the result of basic research on the genetic signature of melanomas, and encourages NCI to include melanoma in The Cancer Genome Atlas consortium to establish a comprehensive map of genetic changes that will point to new therapies for the most common types of melanoma and help identify new markers for classification, detection and risk assessment. The Committee also urges the NCI to promote alliances between industry and academia in the field of melanoma research to foster laboratory and clinical trial consortia that will develop individualized therapies that target pathways or stimulate the patients' own defense system. The continuing increase in melanoma incidence should spur new efforts to prevent melanoma among high-risk individuals and reach populations at risk for early diagnosis when melanoma is still curable by surgery. (p. 89)

Action taken or to be taken

Please refer to page 10 of this document for NCI's response to this item.

Item

Neuroblastoma - The Committee urges continued support for research on high-risk neuroblastoma, particularly as it relates to the development and clinical testing of new therapies for relapse patients. (p. 89)

Action taken or to be taken

Please refer to page 14 of this document for NCI's response to this item.

Item

Neurofibromatosis (NF) - NF is an important research area for multiple NIH institutes. Recognizing NF's connection to many of the most common forms of cancer, the Committee encourages the NCI to substantially increase its NF research portfolio in pre-clinical and clinical trials by applying newly developed and existing drugs. The Committee also encourages the NCI to support NF centers, virtual centers, SPORE programs, pre-clinical mouse consortiums, patient databases, and tissue banks, and to work together with other NIH institutes and Government agencies in doing so. The Committee also urges additional focus from the NHLBI, given NF's involvement with hypertension and congenital heart disease. The Committee encourages the NINDS to continue to aggressively explore NF's implications for conditions such as spinal cord injury, learning disabilities and memory loss. In addition, the Committee continues to encourage the NICHD to expand funding of clinical trials for NF patients in the area of learning disabilities, including the creation of NF centers involved with treating and curing these disabilities. NF2 accounts for approximately 5 percent of genetic forms of deafness; the Committee therefore encourages the NIDCD to expand its NF2 research portfolio. (p. 118)

Action taken or to be taken

Please refer to page 218 in the Office of the Director's section of this document for the response to this item.

Item

Pancreatic Cancer - While there has been a continuing decline in mortality rates for many types of cancer, the number of Americans dying of cancer of the pancreas continues to rise. Despite its highly lethal nature, less than 2 percent of NCI's budget is devoted to what is now the fourth leading cause of cancer-related death. The Committee last year urged the NCI to launch a pancreatic cancer specific research and training initiative. This will require a sustained and targeted effort designed to foster prioritized research immediately as well as build a cadre of researchers over the longer term. To further these efforts, the Committee strongly urges the NCI to develop an action plan for the use of fiscal year 2010 funds and to describe its progress in the fiscal year 2011 congressional budget justification. (p. 89)

Action taken or to be taken

Please refer to page 15 of this document for NCI's response to this item.

Item

Pediatric Cancer - The Committee urges the NCI to further expand and intensify pediatric cancer research, including laboratory research to identify and evaluate potential therapies, preclinical testing, and clinical trials through cooperative clinical trials groups. Such research should include research on the causes, prevention, diagnosis, recognition, treatment, and late effects of pediatric cancer. (p. 89, 90)

Action taken or to be taken

Please refer to page 16 of this document for NCI's response to this item.

Item

Reproductive Scientists Development Program (RSDP) The Committee urges the NCI to continue its partnership with the NICHD with regard to training the next generation of gynecologic cancer researchers. (p. 90)

Action taken or to be taken

Please refer to page 17 of this document for NCI's response to this item.

Item

Social Psychological Research - The Committee applauds the NCI's efforts to incorporate innovative social psychological theories into cancer prevention research, and it encourages additional work in this area. (p. 90)

Action taken or to be taken

NCI continues efforts to encourage and incorporate innovative social psychological theories into cancer prevention research. An overarching emphasis of NCI's behavioral research program is in the development and evaluation of health behavior theories and facilitation of their use in interventions to promote healthy behavior. Research is underway to examine how people use and attach meaning to health-related numeric information, and to determine how cognitive and affective processes underlie decision-making that is involved in initiation and long-term maintenance of healthy behaviors. Additionally, NCI sponsors studies to understand how stereotypes, relationships, mortality salience, and group decision-making influence cancer prevention strategies.

NCI sponsors various meetings to advance work in this area. For example, the Summer Institute for Social and Personality Psychology that NCI is sponsored in 2009 focused on cancer prevention and control as a platform to test classic and novel theoretical perspectives from social and personality psychology. NCI is also proposing to fund research to combine existing NIH-funded longitudinal data sets that will allow for new analyses to understand health behavior theory across multiple behaviors, contexts, and populations. The proposed project would both uncover and begin to address the multi-level barriers to combining existing longitudinal datasets.

To help advance theories of health behavior NCI also supports an array of workshops, conferences, and training opportunities collectively called the "Theories Project." The project supports initiatives focused on how health behavior theory can be used in interventions to promote actions individuals can take to prevent cancer and speed its early

detection. One component of the Theories Project is the Advanced Training Institute on Health Behavior Theory (ATI). The ATI offers in-depth instruction on the use, development, and evaluation of health behavior theory. NCI has obtained support from five NIH Institutes and Centers for the upcoming 2010 ATI.

NCI also funds research to identify and reduce cognitive biases created by decision aids (booklets, websites, or videos), and to improve communication and understanding of cancer risk. For example, NCI is currently investigating women who are aware of their positive status for either BRCA1 or BRCA2 (mutations that increase breast/ovarian cancer risk) during young adulthood to study how this knowledge shapes decision-making about couple relationships, family formation, tolerability of cancer screening technologies, and risk-reduction strategies. By continuing to test new and existing theories, NCI research will increase understanding of which psychosocial variables are influential in genetics-related decision making.

Understanding gained through social psychological research can greatly improve the health status of our nation. Developing and implementing new psychosocial and behavioral interventions in medical treatment can increase positive health behaviors—such as proper eating and exercise—and reduce behavior—such as tobacco use—that will greatly contribute to improved health.

**National Heart, Lung, and Blood Institute
(NHLBI)**

House Significant Items

Item

Atrial Fibrillation- The Committee encourages NHLBI to convene a scientific workshop to identify evidence-based best practices for identification and management of AFib, and to disseminate the findings of the workshop to the patient and healthcare provider community. (p. 111)

Action taken or to be taken

On April 28-29, 2008, NHLBI convened the Workshop on the Prevention of Atrial Fibrillation (AFib) to both review evidence associated with the development of AFib and its progression to a persistent state and to identify opportunities for prevention. The Workshop Executive Summary is published at <http://www.nhlbi.nih.gov/meetings/workshops/prevent-af.htm>, and a more comprehensive article on the proceedings was published in the widely read journal *Circulation* (volume 119, pp. 606-18, February 3, 2009). The NHLBI has updated its Web-based patient education portal on the diagnosis and treatment of AFib (http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html). The Workshop also spurred a number of research grant applications, including one for a clinical study on risk prediction of AFib.

A collaboration of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology has issued Practice Guidelines, most recently updated in 2006, for the Management of Atrial Fibrillation, that are based on expert consensus of the clinical evidence (http://www.acc.org/qualityandscience/clinical/guidelines/atrial_fib/pdfs/AF_Exec_Sum.pdf) Several studies supported by the NHLBI, such as the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial, form the basis of that evidence. In addition, the ACC/AHA Physician Consortium, in collaboration with the Heart Rhythm Society, recently published Clinical Performance Measures for physicians treating patients with AFib to improve quality of care and encourage the use of guideline-based therapy (<http://content.onlinejacc.org/cgi/content/full/51/8/865#SEC6>).

In 2009, the NHLBI began multi-year funding that will total \$18 million for the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial and two industry partners contributed an additional \$30 million. CABANA is designed to determine whether catheter ablation is more effective than drug therapy for the treatment of AFib. Although this procedure is widely performed, the evidence for its use is based on smaller studies with somewhat limited follow-up. The trial will be conducted at about 140 U.S. and international sites.

Item

Cardiovascular Disease - The Committee urges NHLBI to strengthen current studies, support new research, and continue to implement priorities outlined in its Division of Cardiovascular Diseases Strategic Plan. (p. 111)

Action taken or to be taken

The NHLBI is actively advancing the priorities outlined in its Strategic Plan in the areas of basic, clinical, and population research in cardiovascular diseases (CVD). Although CVD mortality declined markedly over the past four decades, CVD remains the leading cause of death in the United States and other industrialized countries. Moreover, the rising prevalence of obesity and related metabolic disorders, including diabetes, threatens to slow or even undo this progress. The Institute is funding several large programs addressing the prevention and treatment of diabetes and obesity. Two major clinical trials in patients with diabetes, the ACCORD and BARI 2D studies, were recently completed and a major initiative on the prevention of obesity is being launched.

While many NHLBI CVD trials have traditionally fallen under the heading of comparative effectiveness research, this area has recently emerged as a major priority and an integral approach to address the translational goals of the Strategic Plan. An Institute of Medicine review of research opportunities in comparative effectiveness noted that Cardiovascular and peripheral vascular disease ranks second as primary research areas, after the health care delivery system, in terms of the number of recommended research projects. Diseases of the heart were the leading causes of deaths in the United States in 2006, and such conditions are associated with multiple coexisting conditions, such as diabetes and obesity, that are becoming increasingly prevalent. The CER priority list includes eight topics related to ischemic heart disease, heart failure, and cardiac arrhythmias and two topics focused on the treatment and management of peripheral vascular disorders.

We are currently launching major studies addressing the effectiveness and cost-effectiveness of imaging techniques in real-world settings to screen patients with signs of heart attack or chronic coronary heart disease to reduce unnecessary hospitalizations and invasive procedures.

Item

Diabetic Cardiovascular Disease - Research has shown that heart disease begins as early as childhood or adolescence in type 1 diabetes patients, and leads to a higher fatality and shorter survival. As much as 10 percent of premature cardiovascular disease morbidity and mortality in the general population is due to type 1 diabetes. Several clinical trials have demonstrated the benefit of statin therapy in Type 2 diabetes. However, there is little data regarding statin therapy in young (below 45 years of age) people with type 1 diabetes. The Committee encourages NHLBI to develop clinical research to determine the benefits of statin therapy for those with type 1 diabetes. (p. 111)

Action taken or to be taken

The NHLBI supports a portfolio of basic and clinical research for the prevention of macrovascular complications of both type 1 and type 2 diabetes. Statins and other lipid-modifying agents offer potent utility in patients with type 1 diabetes, but the processes that

lead to atherosclerotic complications in type 1 diabetes may be different from those involved in type 2 diabetes. Therefore, the NHLBI is focusing on understanding the mechanisms responsible for the pathogenesis of diabetic macrovascular diseases in patients with type 1 diabetes. However beneficial statins may be, they also pose a risk of side effects very much related to their mechanisms of action. More research is needed before conducting large-scale clinical studies in the young to ensure patient safety and wellbeing.

Although the NHLBI does not currently have a clinical trial of statin therapy in patients with type 1 diabetes, it funds a number of clinical studies that seek new therapies for such patients. Since 2006 the Institute has been supporting a multinational team of biologists, biochemists, clinicians, and geneticists who are studying progression of cardiovascular disease (CVD) and potential new treatments in a cohort of 5,000 patients with type 1 diabetes. The NHLBI also supports a large program project grant in this area.

The Coronary Artery Calcification in Type 1 diabetes (CACTI) Study has been funded by the NHLBI for the past 10 years. It provides data on potential biomarkers that are predictive of CVD in type 1 diabetes. This data, which will help in designing new clinical studies by identifying which patients might benefit from statins or other lipid-lowering agents and when treatment should be initiated. In addition, the NHLBI is supporting investigators looking at potential new treatments for prevention of atherosclerosis. For example, researchers are looking at monoclonal antibodies targeted at the insulin-like growth factor-I that has been implicated in the development of atherosclerotic lesions in patients with type 1 diabetes.

Finally, the NHLBI and the NIDDK have initiated a series of meetings to discuss the need for clinical trials related to the prevention of CVD complications in both type 1 and type 2 diabetes. The design of clinical studies addressing the effectiveness of statin therapy in the prevention and treatment of CVD in patients with type 1 diabetes will be one of the topics of discussion.

Item

Gender Differences - The Committee requests NHBLI to focus research on several key questions about women and heart disease, including research on gender differences. These questions include: the best tools and methods for assessing women's risk of heart disease; the best strategies for preventing heart disease in women; which treatments for heart disease work best for women; what are the most effective treatments for diastolic heart failure, which is the most common form of congestive heart failure in women; what is the role of inflammation in heart disease in women; and why women aged 50 and younger are more likely to die following a heart attack than men of the same age. (p. 111)

Action taken or to be taken

NHLBI-supported investigators are currently exploring all of the key areas identified by the Committee. To determine the best tools for assessing the risk of heart disease in women, the Institute has funded a large study within the Women's Health Initiative (WHI). It will validate the Reynolds and Framingham risk scores in women and identify new biomarkers of risk for coronary heart disease, including indicators of inflammation. While a better

understanding of the relative importance of various risk factors in women will enable us to fine-tune preventive efforts, strong evidence already exists that maintaining normal blood pressure, treating dyslipidemia, and abstaining from smoking are effective preventive strategies in women.

Heart failure has become as common as coronary heart disease, and diastolic heart failure is prevalent in older persons, among whom women predominate. The accurate diagnosis of heart failure in research studies remains problematic. Therefore, the NHLBI is focusing efforts in several of its cohort studies, including the Atherosclerosis Risk in Communities (ARIC) and the Women's Health Initiative, on better identification of heart failure and clearer understanding of factors that lead to its subtypes (systolic or diastolic). The Institute-supported Treatment Of Preserved Cardiac function heart failure with an Aldosterone antagonist (TOPCAT) study is evaluating the salutary effects of the drug spironolactone in a cohort of heart failure patients—predominantly women—with diastolic heart failure. Prevention of diastolic heart failure is of paramount importance; however, current treatment options are quite limited.

The reason that women have poorer outcomes after a heart attack than men was clarified in a recent analysis of 136,000 patients (including 38,000 women) who had experienced a heart attack. Women in this cohort were nearly twice as likely as men to die within the first 30 days. Their higher death rate was attributable not only to older age, but also to a higher prevalence of high blood pressure, high blood cholesterol, diabetes, and heart failure in the women. After adjustment for differences in cardiovascular risk factors, there was no difference in the survival between women and men.

These findings suggest that among younger people, gender differences in survival after heart attack may also be explained by differences in the traditional cardiovascular risk factors common to both men and women.

Item

Hematology - With the rising incidence in the U.S. of Myelodysplastic Syndrome (MDS), an increasingly common and often fatal bone marrow failure disorder that primarily affects individuals over 60 years of age, a vigorous research program into the causes of this disorder and the development of effective treatments is needed. In 2008, a panel of outside experts, in collaboration with several NIH institutes, recommended a research agenda for MDS. The Committee encourages NHLBI, working with NCI, NIDDK, and NIA, to develop a plan to implement the MDS research agenda beginning in 2010. (p.111)

Action taken or to be taken

The NHLBI remains firmly committed to collaborate with other NIH components, including NCI, NIDDK, and NIA, to support research in MDS.

In November 2008, outside experts and staff from NHLBI, NIDDK, NCI, and NIA participated in a workshop sponsored by the American Society of Hematology (ASH) to address a research agenda for MDS. The meeting focused on identifying research questions for the field, determining where gaps exist in the research, pinpointing the windows of opportunity for further investigation, and establishing a list of priorities as a

potential basis for future grant opportunities. The ASH workshop report is forthcoming and will be considered as the basis on which NIH's research agenda for MDS is developed further. As soon as the report is received, NHLBI, in collaboration with NCI, NIDDK, and NIA, will evaluate whether research initiatives should be developed to address the research priorities identified at the meeting. Additional trans-Institute and trans-agency meetings will be held in 2010 to highlight knowledge gaps and research needs and to discuss opportunities for cooperative and coordinated efforts to support research in MDS.

Item

Lymphatic Research and Lymphatic Disease — The Committee again commends the NHLBI for taking a leadership role in the Trans-NIH Coordinating Committee and for engaging consultative expertise, and it encourages the continuation of these efforts in concert with the other relevant institutes and centers. (p. 118)

Action taken or to be taken

Please refer to page 213 in the Office of the Director's section of this document for the response to this item.

Item

Lymphangioliomyomatosis (LAM) - The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease of women with no effective treatment. The Committee supports both intramural and extramural means of expanding research on LAM and urges NHLBI to use all available mechanisms as appropriate, including support of state-of-the-science symposia, requests for applications, and facilitation of access to human tissues, to stimulate a broad range of clinical and basic LAM research. The Committee understands that recent scientific findings have presented new treatment approaches for clinical testing, and that experimental trials have begun. The Committee commends NHLBI for supporting the multicenter inter-national trials, and further encourages the support of intramural and extramural phase I and phase II clinical treatment trials to capitalize on the LAM patient populations that NHLBI has assembled. The Committee is also aware of the potential benefit of establishing regional LAM centers, and suggests NHLBI consider supporting these activities. (p. 110)

Action taken or to be taken

NHLBI-funded scientists examined cellular pathways affected by genetic abnormalities in tuberous sclerosis complex (TSC) and LAM cells and found that sirolimus (rapamycin) mimics the function of missing or abnormal proteins needed to control LAM cell growth and movement. The Multicenter International Lymphangioliomyomatosis Efficacy of Sirolimus (MILES) trial is currently under way. However, sirolimus is unlikely to be the only therapeutic approach needed. Patients with LAM appear to vary in their sensitivity to sirolimus, and the view that LAM behaves like a "cancer" suggests that multiple drug therapy may be required. The role of estrogen is also being explored to help understand how the hormone promotes cell growth and metastasis and why LAM, but not TSC, affects women almost exclusively. Intramural and extramural investigators are collaborating on procedures to isolate LAM cells from body fluids for diagnosis and research. They are studying molecular markers on the surface of LAM cells similar to those found in breast cancer and melanoma that may target LAM cells to different tissues in the body, and they

have shown that hypoxemia (a low blood oxygen level) is associated with accelerated disease progression.

The NHLBI continues to support the collection, processing, and distribution of LAM tissue through the National Disease Research Interchange (NDRI), a not-for-profit corporation that provides human cells, tissues, and organs needed to facilitate research on rare diseases. Improving access to LAM databases is being explored with the NDRI and patient advocacy organizations. The Institute continues to co-fund the annual LAM scientific conference and to participate in trans-NIH TSC coordinating committee meetings.

Several mechanisms of support are available for increasing research efforts on LAM, including investigator-initiated regular research grants, exploratory/developmental research grants, and the NHLBI ancillary studies initiative. In addition, a new translational program project grant is available to encourage collaborative high-risk/high-impact research involving translation of research results from basic to clinical research. A second new program solicits applications for Phase II clinical trials of novel therapies for lung diseases. These mechanisms need to be fully used to build the appropriate research base before consideration can be given to LAM centers.

Item

Marfan Syndrome – The Committee commends NHLBI for its strong support of research on Marfan syndrome, particularly the pediatric heart network clinical trial focused on the drug losartan. The Committee encourages the institute in, 2010, to work to advance additional research related to aortic aneurysms, including studies of surgical outcomes for procedures to repair compromised aortas and valves. (p. 112)

Action Taken or to be Taken

The most serious manifestation of Marfan syndrome is enlargement of the aorta, the large artery that carries blood from the heart. The NHLBI Pediatric Heart Network (a multicenter, collaborative, clinical research group; www.PediatricHeartNetwork.com) is conducting a clinical trial to determine whether atenolol (a type of beta-blocker) or losartan (an angiotensin II receptor blocker) is better at slowing the progression of aortic root enlargement in patients with Marfan syndrome. The study is also looking closely at the kinds of side effects that can occur when taking either of these medicines. It will enroll 604 individuals aged 6 months to 25 years, and will take approximately six years to complete. Recruitment is occurring at the eight Pediatric Heart Network sites and 13 auxiliary sites. The trial is also supported by the National Marfan Foundation, which is providing funds for investigator and patient travel and ancillary studies, and the FDA's Orphan Drug Program, which is providing grant assistance.

Thoracic aortic aneurysms (TAA) generally occur in older individuals because of hypertension or atherosclerosis and in young adults who have rare genetic disorders, such as Marfan syndrome. The NHLBI-supported Genetically Triggered Thoracic Aortic Aneurysms Registry (GenTAC) serves as a resource to advance treatment of patients with TAA that appears to result from a genetic susceptibility. It will provide valuable information, such as phenotype and unique biomarkers associated with TAA, especially in Marfan patients, that will help to improve treatments and outcomes for patients. Two

recent , NHLBI-supported studies provide evidence that a unique biomarker for Marfan syndrome—transforming growth factor-beta (TGF- β)— may be useful in monitoring a patient’s response to treatment and that phenotypic differences in TAA appear to be related to different mutations in the genes for the TGF- β receptors. The GenTAC registry has also characterized current therapy, including surgery, for these patients. A recent report demonstrated that more than half of the patients in the registry had undergone at least one operation, most commonly to treat aortic aneurysm, valve dysfunction, or aortic dissection. Significant differences were found in the age at surgery and indications and types of surgery based on a patient’s particular genetic syndrome.

Item

Obesity - NHLBI, along with NIDDK, first published guidelines on the identification, evaluation, and treatment of overweight and obesity for the adult population in 1998. In the 11 years since the guidelines were published, a great deal of scientific advancement has occurred in the areas of identification, prevention, management, and treatment of this disease. Yet the obesity guidelines have not been updated to reflect new evidence and practice. The Committee believes NIH's obesity guidelines should be updated and re-issued. Although NHLBI began the process of updating the clinical guidelines in September, 2008, it remains unclear when the guidelines will actually be published. The Committee encourages NIH to update the obesity guidelines to ensure the most up-to-date, effective management and treatment of overweight and obesity are available to help healthcare professionals, as well as families and communities, address the challenges associated with the obesity epidemic confronting the nation. (p. 112)

Action taken or to be taken

The NHLBI recognizes the tremendous public health burdens of overweight and obesity and the critical need for up-to-date guidelines for healthcare practitioners and the public on the identification, evaluation, and treatment of these conditions. Staff of the NHLBI and other NIH components are working with an outside panel of medical and research experts in overweight and obesity, diet and nutrition, physical activity, bariatric surgery, clinical trials, and other disciplines to develop a high-quality set of guidelines. The first expert panel meeting was held on September 24, 2008. The obesity guidelines-development process is using an evidence-based-medicine strategy that includes the formulation of critical questions and very specific criteria to determine which studies will be considered following a search of the scientific and medical literature published since the release of the 1998 guidelines. Subgroups of the expert panel have been organized to: 1) spearhead the literature review in critical topic areas, 2) determine the best format for presenting the evidence to the full panel, and 3) consider key issues that will require specific recommendations.

The obesity guidelines are being developed in conjunction with two other expert panels convened to update the guidelines on high blood cholesterol and high blood pressure. In addition, a separate panel is developing an integrated adult cardiovascular guideline that will include critical recommendations from all three topical guidelines. This step was recommended by numerous external medical advisors to ensure that clear guidance is provided to medical practitioners who treat individuals with multiple risk factors for cardiovascular disease. Moreover, several working groups composed of participants in the

three topical guidelines panels have been convened to address cross-cutting issues such as lifestyle change, risk reduction, and effective dissemination of the guidelines. All guidelines are scheduled to be completed by the summer of 2011.

Item

Pulmonary Hypertension (PH) - The Committee commends NHLBI for its leadership on PH. The Committee encourages the institute to work with the PH community to support the establishment of a PH clinical research network that could provide for expanded clinical trials and facilitate collaboration and data sharing among PH investigators. (p. 112)

Action taken or to be taken:

Development of new treatments for PH is a high priority of the NHLBI. The Institute has engaged in discussions with the PH community about establishing a PH clinical network. Concerns exist regarding the feasibility of doing so at this time because of the relatively rare nature of this disease, the large numbers of clinical centers that would be required to enroll sufficient numbers of patients into network protocols, and the substantial competing investment by industry in supporting clinical trials in PH. An upcoming workshop in March 2010 will include a discussion with investigators from the PH community on the best directions NHLBI can take to further PH clinical research.

One NHLBI-supported clinical trial on PH is currently recruiting patients and will be continued with oversight by an independent data and safety monitoring board. This trial is not renewable, but the Institute welcomes new applications for clinical trials in PH.

We are pleased that the new NHLBI translational research initiatives have attracted investigator-initiated applications in PH. The Institute is open to exploring other opportunities with the community to advance clinical research in pulmonary vascular diseases of children and adults.

Item

Sickle Cell Disease - The NHLBI research program on sickle cell disease is a core program that has advanced physicians' understanding of how to diagnose, treat, and manage this chronic blood disease. The Committee encourages NHLBI to strengthen its funding for the Basic and Translational Research Program in sickle cell disease. The Committee takes note of NHLBI's Request for Information to identify sites with sufficient research infrastructure and patient population to undertake clinical studies in hemoglobinopathies with an emphasis on sickle cell disease and thalassemia. This research network, along with the surveillance system and disease registry under development with CDC, will improve knowledge and lead to better treatments for sickle cell disease and other hemoglobinopathies. (p. 112,113)

Action taken or to be taken

In February 2009, the NHLBI issued a Request for Information (RFI) to identify investigators and institutions interested in participating in collaborative clinical research studies in hemoglobinopathies. The response was excellent, with input from over 40 institutions well distributed across the country and in several foreign locations. Respondents described their access to both children and adults with hemoglobinopathies,

their inpatient and outpatient infrastructure, and their clinical research experience and capabilities. Many also noted their association with the new NIH network of Clinical and Translational Research Award (CTSA) institutions, which could offer them access to an integrated and organized resource for conducting research in community settings. This significant response to the RFI will help the Institute to identify and characterize sites having access to appropriate populations and a potential infrastructure that will facilitate development of a multi-center clinical study platform for future clinical research activities.

The Institute continues to support the Basic and Translational Research Program, which emphasizes fundamental investigations and their translation into initial studies in humans, as well as community translation to promote evidence-based clinical practice. Complementing efforts under way to enhance clinical and translational research in sickle cell disease, the NHLBI and the CDC are working to develop the first national surveillance and registry system for hemoglobinopathies (RuSH) to enhance the research agenda and improve care for patients with sickle cell disease and the thalassemias.

Item

Sleep Disorders - The Committee applauds the Institute's investment in sleep-related research through the National Center on Sleep Disorders Research. The Committee notes the growing understanding of the link between sleep and cardiovascular health and encourages further research to better understand and modify the link between sleep disorders and cardiovascular disease. (p. 113)

Action taken or to be taken

NHLBI research has provided the strongest evidence to date linking insufficient sleep and untreated sleep apnea to an increased risk of cardiovascular disease (CVD) and diabetes. Sleep deprivation is a pervasive characteristic of modern urban lifestyles that is estimated to affect about 30 percent of the U.S. adult population. More than 12 million adult Americans have sleep apnea, a disorder in which the upper airway is intermittently narrowed during sleep causing breathing to be difficult or completely blocked.

The NHLBI continues to support research on the relationship between sleep and cardiovascular health. In fiscal year 2010, NHLBI will fund research to assess the CVD risks associated with sleep in the ongoing Hispanic Community Health Study and the new NHLBI study of Health Behavior in School-Age Children. New NHLBI initiatives include the first U.S.-based clinical trials and pilot studies to compare the effectiveness of various apnea treatment strategies in reducing CVD risk in adults. In addition, a clinical trial is under way to determine whether adenotonsillectomy is an effective surgical treatment for sleep apnea in children.

The Institute also continues to coordinate its sleep research program with other agencies. In partnership with the CDC, new, nationally representative health surveillance data have been released from an NHLBI-sponsored module on the prevalence of sleep problems and sleep disorder treatment among U.S. adults (National Health and Nutrition Survey, 2005-2008). The NHLBI, in partnership with NICHD, will also launch the Health Behavior in School-Age Children study in fiscal year 2010 with the first objective assessment of adolescent sleeping behavior and developmental changes in CVD risk factors. The NHLBI

will continue to explore opportunities for coordination and partnership with other NIH Institutes to improve the evidence base needed to inform medical practice and improve public health.

Item

Thalassemia - Thalassemia, or Cooley's anemia, is a fatal genetic blood disease. NHLBI has operated the Thalassemia Clinical Research Network for nine years to advance the science of treating this disease. The Committee strongly encourages NHLBI to renew its focus on thalassemia, which has implications for other blood-related disorders. (p.113)

Action Taken or to be taken

The Thalassemia Clinical Research Network is continuing its efforts in clinical research. Ongoing trials include the Thalassemia Network Longitudinal Follow-up Study, use of decitabine to increase hemoglobin F levels, treatment of pulmonary hypertension with sildenafil, and investigation of the etiologies of pain in thalassemia and treatments to alleviate it.

In May 2009 the NHLBI held a conference, open to the healthcare community and advocacy groups, to discuss the future direction of NHLBI-sponsored clinical trials in thalassemia. Areas of particular focus were iron overload, fetal hemoglobin, endocrine disorders, stem cell transplantation, and gene therapy. The feasibility of clinical research, including opportunities and obstacles, was examined. The use of a global approach was discussed, with contributions from attendees from Thailand. The Cooley's Anemia Foundation presented a patient and family perspective.

Senate Significant Items

Item

Atrial Fibrillation - The Committee urges the NHLBI to convene a scientific workshop to identify evidence-based best practices for the identification and management of atrial fibrillation, and to disseminate the findings of the workshop to the patient and healthcare provider community. (p. 90)

Action taken or to be taken

Please refer to page 24 of this document for NHLBI's response to this item.

Item

Cardiovascular Disease - The Committee believes that an increased investment in funding and resources to combat cardiovascular diseases is important to capitalize on progress when scientific discoveries are on the horizon and to help prepare for the increased prevalence of these diseases in aging populations. The Committee recommends that a significant portion of the additional funds provided for the NHLBI be devoted to cardiovascular research and to continue to implement priorities outlined in its Division of Cardiovascular Diseases Strategic Plan. (p.90)

Action taken or to be taken

Please refer to page 25 of this document for NHLBI's response to this item.

Item

Chronic Obstructive Pulmonary Disease (COPD) - The Committee is pleased that the CDC has taken initial steps to collect COPD-related data in the National Health and Nutrition Examination Survey and in the National Health Interview Survey. (p.72) The Committee continues to applaud the NHLBI's efforts to raise public awareness of COPD. The Committee notes that only 15 States have developed COPD Action Plans, and it urges the NHLBI to continue to work with the remaining states to develop plans as appropriate. (p. 90)

Action taken or to be taken

On March 3, 2009, the NHLBI's *COPD Learn More Breathe Better* campaign convened its community partners for a capacity-building workshop in Bethesda, Maryland. Participants included representatives of sites that have either instituted statewide COPD plans or otherwise participated in COPD awareness and education. They are independent lung health organizations and local and regional chapters of national organizations representing California, Florida, Virginia, Arizona, Colorado, Illinois, Indiana, Texas, Hawaii, Minnesota, Nebraska, New Hampshire, Maine, North Carolina, Kentucky, and Wisconsin. The representatives provided important input to inform strategies for advancing the campaign's community-based efforts. Participants overwhelmingly supported the development of a formalized community-based partner program. Further more indicated that continued support from the NHLBI would be needed to enable further development of state-based coalitions and increased dissemination of consistent public health messages on COPD. They also recommended an increased focus on data and evaluation to guide state strategies and track the progress of state and national efforts.

The NHLBI has taken action on these major recommendations. In June 2009, the campaign instituted the Breathe Better Network as a key strategic component of the campaign. In September, the Institute awarded 15 contracts to community organizations for developing state plans and conducting COPD outreach and education. The solicitation for these contracts yielded 35 proposals representing 29 States and the District of Columbia, which indicates that the national campaign has inspired strong local and regional interest and that many more states are now in the process of developing COPD action plans.

In addition, the NHLBI has partnered with colleagues in the CDC's Division of Adult and Community Health to support the addition of a module on COPD to the Behavioral Risk Factor Surveillance System survey of all U.S. states and territories beginning in 2011. The COPD module includes one question about COPD history that, if answered affirmatively, prompts additional questions about health care usage and quality of life. The resulting state-state and state-nation comparisons will inform the NHLBI's campaign programming and support the development of state COPD plans throughout the country.

Item

Diamond-Blackfan Anemia (DBA) - The Committee understands that DBA's recent identification as the first human disorder linked to a ribosomal protein deficiency has led to breakthrough discoveries indicating that decreased expression of ribosomal proteins can have pathogenic consequences within bone marrow and during development of other tissues. The Committee commends the NHLBI for its attention to this important area of disease research and encourages efforts to further investigate the role of ribosomal proteins in DBA and related marrow failure diseases. (p. 90)

Action taken or to be taken

In September 2004, the NHLBI awarded 16 grants supporting the research initiative "Molecular Mechanisms Underlying Diamond-Blackfan Anemia (DBA) and Other Congenital Bone Marrow Failure Syndromes." Its goal was to encourage research on the genetics and basic mechanisms of rare bone marrow failure disorders. Through this initiative, numerous new genes (ribosomal proteins) have been identified for DBA and other related marrow failure syndromes. More important, this was the first time a human disorder had been linked to a ribosomal protein deficiency or defect. These breakthrough discoveries indicate that decreased expression of ribosomal proteins can have pathogenic consequences within bone marrow and during development of other tissues. Investigators funded via the RFA had their fifth and final meeting in May 2009, at which they presented impressive work of their respective laboratories on rare bone marrow failure disorders. Many of them have successfully competed for new R01 grants, continuing their work in DBA and other bone marrow failure disorders.

Recently, the executive summary of the NHLBI and NIDDK workshop "Ribosomes and Their Role in Diseases" was released. The NHLBI has again joined forces with the NIDDK to release the program announcement "Erythropoiesis: Components and Mechanisms." Its goals are to assemble a collection of genes expressed during blood cell development and differentiation and describe how and where they are expressed. The results will be used to understand the structure–function relationships that exist in blood cells from normal and diseased states, with possible application to other cell types.

Item

Heart Rhythm Disorders - The Committee notes that more research is needed to understand the causes of heart rhythm disorders and to develop more effective treatments. The Committee urges the NHLBI to intensify its investments in basic research, clinical investigations and trials. (p. 91)

Action taken or to be taken

The NHLBI has a longstanding commitment to supporting basic, translational, and clinical research in heart rhythm disorders. The Institute's extramural investment in this area currently comprises 141 investigator-initiated research project grants totaling more than \$60 million in annual expenditures and spanning a range of topics. Of these, 27 awards were made in FY 2009 using funds made available through the American Recovery and Reinvestment Act (ARRA) for a total of approximately \$8 million dollars. The NHLBI also supports small business enterprises through its funding opportunity announcements ([PA-07-031](#) and [PA-07-032](#)) to develop improved methods for arrhythmia detection, treatment,

and prevention. Examples of clinical studies supported include the VEST Prevention of Early Sudden Death Trial, a multicenter clinical trial funded with industry co-sponsorship to determine whether a wearable defibrillator vest can save lives in the first few months following a heart attack. The associated PREDICTion of ICD Therapies Studies will examine a battery of tests to improve identification of those who are at risk for sudden (i.e. arrhythmic) cardiac arrest for patients who have had a heart attack. Such information could better refine the indications for wearable or implantable defibrillators.

In 2009, the NHLBI began multi-year funding that will total \$18 million for the Catheter Ablation Versus Anti-arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial, with two industry partners contributing an additional combined \$30 million. CABANA is designed to determine whether catheter ablation is more effective than drug therapy for the treatment of atrial fibrillation. Although this procedure is widely performed, the evidence for its use is based on smaller studies with somewhat limited follow-up.

In partnership with the Heart Rhythm Society (HRS), the NHLBI planned and supported the Workshop on the Prediction and Prevention of Sudden Cardiac Death on September 29-30, 2009, to explore emerging approaches for improved prediction and prevention of sudden death.

Item

Hematology---Myelodysplasia (MDS) - The Committee strongly urges the NHLBI, working with the NCI, NIDDK, and NIA, to develop a plan to implement the MDS research agenda that was developed in November 2008. (p. 91)

Action taken or to be taken

Please refer to page 27 of this document for NHLBI's response to this item.

Item

Lymphatic Research and Lymphatic Disease - The Committee again commends the NHLBI for taking a leadership role in the Trans-NIH Coordinating Committee and for engaging consultative expertise, and it encourages the continuation of these efforts in concert with the other relevant institutes and centers. (p.126)

Action taken or to be taken

Please refer to page 213 in the Office of the Director's section of this document for the response to this item.

Item

Lymphangiomyomatosis (LAM) - The Committee supports both intramural and extramural means of expanding research on LAM and urges the NHLBI to use all available mechanisms as appropriate, including facilitating access to human tissues, to stimulate a broad range of clinical and basic LAM research. The Committee commends the NHLBI for supporting the multicenter international LAM efficacy of sirolimus [MILES] trial, and further encourages the support of intramural and extramural phase I and phase II clinical treatment trials to capitalize on the LAM patient populations that the NHLBI and the Rare Lung Disease Consortium have assembled. The Committee is also aware of the potential

benefit of establishing regional LAM centers, and suggests the NHLBI consider supporting these activities. (p. 91)

Action taken or to be taken

Please refer to page 28 of this document for NHLBI's response to this item.

Item

Marfan Syndrome - The Committee encourages the Institute to continue its support for the Pediatric Heart Network study of the drug Losartan, and advance research on surgical outcomes for Marfan syndrome patients who undergo different procedures to repair compromised aortas and valves. (p. 91)

Action taken or to be taken

Please refer to page 29 of this document for NHLBI's response to this item.

Item

Obesity and Asthma/Allergy - Studies have documented that the incidence of asthma is 50 percent more common among those who are overweight or obese. More recently, obesity has been linked to food allergies as well. The Committee is pleased that the NHLBI is collaborating with the NICHD in support of a consortium to evaluate methods to treat and prevent obesity. The Committee believes that the link between obesity and food allergy/asthma should be explored through this resource and that additional investigator initiated research should be fostered through other institutes and centers, including the NIAID, NIEHS, NIDDK, NHGRI and NCMHD. (p. 119)

Action taken or to be taken

The links between obesity, asthma, and food allergies are of considerable interest and concern. Research has found an increased onset of asthma in people, particularly young women, who gain excessive weight. Moreover, overweight people with asthma tend to have more trouble controlling asthma symptoms. Asthma and food allergy have been linked to obesity in recent epidemiological studies. It is hypothesized that chronic inflammation in the obese state contributes to symptoms of food sensitization and asthma. In particular, abdominal fat may play a significant role due to its heightened metabolic activity in systemic inflammation.

The NHLBI is exploring the relationship between obesity and asthma through longitudinal cohort studies that examine associations between BMI (body mass index, a measure of weight in relation to height) and development of allergies and asthma, through ancillary studies in NHLBI-supported asthma clinical research networks, and through inclusion of BMI measures in a range of projects that include asthma populations. Such approaches will enable correlative analyses to enhance understanding of mechanisms of obesity and asthma and identify potential therapeutic targets. Further, the NHLBI participates in several NIH and interagency committees that meet regularly to exchange information and explore possible collaborations. The Institute will encourage the Federal Liaison Group on Asthma and the NIH Obesity Research Task Force to examine how investigator-initiated research on potential links between obesity and asthma might best be advanced.

The new Childhood Obesity Prevention and Treatment Consortium, a collaboration between the NHLBI and the NICHD, is scheduled to start in July 2010. It will conduct clinical trials of innovative interventions to prevent excess weight gain in overweight and non-overweight youth and/or to reduce weight in young people who are obese. The ultimate goal is to improve children's health by preventing obesity-related morbidity and mortality from chronic diseases. The NHLBI will explore the feasibility of collaborations with consortium investigators to obtain data on lung function and asthma outcomes.

The NICHD has been a champion of a systems-oriented approach to addressing childhood obesity. It connects macrosocial factors with biological mechanisms to understand how their dynamic interactions influence obesity-related behaviors and outcomes and how interventions can be made both more effective and sustainable. The NICHD plans to lead a major initiative in FY2011 to establish U.S.-global centers of excellence on systems-oriented pediatric obesity research and training. The roles of inflammation, stress pathways, and other mechanisms may be examined as potential "regulators" that connect socio-environmental influences and biological predispositions to obesity-related outcomes.

Item

Pulmonary Hypertension (PH) - The Committee acknowledges the difficulties in establishing a pulmonary hypertension [PH] Clinical Research Network and encourages the NHLBI to prioritize support and renewal of the two PH clinical trials currently funded by the Institute. (p. 91)

Action taken or to be taken

Please refer to page 31 of this document for NHLBI's response to this item.

Item

Sarcoidosis - . The Committee is concerned that little progress has been made in understanding the cause of Sarcoidosis for which there is no effective treatment option. The Committee strongly encourages the NHLBI to place a high priority on Sarcoidosis by intensifying its investments in basic research, clinical investigations and trials. (p. 91)

Action taken or to be taken

Sarcoidosis remains an enigmatic disease affecting most of the major organs in the body. Although its cause is unknown, recent findings suggest that in approximately one-third of patients the disease may result from an abnormal response of the immune system to a persistent bacterial protein in tissue, most likely reflecting a special genetic susceptibility in those individuals. No treatment is consistently helpful, but agents are available that can help to reduce the symptoms of acute illness and control disease progression.

Currently, the NHLBI supports 11 grants in sarcoidosis. They include projects investigating the cause of sarcoidosis, genes that may predispose to the disease, and more efficacious ways to administer immunosuppressive therapy. The NHLBI intramural program is conducting a clinical trial of atorvastatin as a disease-modifying agent in pulmonary sarcoidosis. The Institute remains interested in receiving and supporting meritorious research grant applications in sarcoidosis. New initiatives are being developed to encourage research into the etiology and pathogenesis of sarcoidosis and to explore

cardiac manifestations of sarcoidosis. The NHLBI will continue to work with the Trans-NIH Sarcoidosis Coordinating Committee to share research progress and identify future areas for new collaboration. Announcements under the American Recovery and Reinvestment Act (ARRA) yielded several new research applications related to sarcoidosis, the most meritorious of which have been awarded support.

Item

Severe Asthma - Research funded by the NHLBI has led to dramatic improvements in the treatment of mild asthma, but severe asthma remains poorly understood. The European Union has undertaken a major initiative on severe asthma, and the Committee believes that the NHLBI should expand its focus on severe asthma as well, especially among women and African-Americans. The Committee encourages the NHLBI to work with the National Center for Minority Health and Health Disparities and the Office of Research on Women's Health to solicit investigator-initiated research on this topic and to pursue initiatives that will complement and encourage collaboration with the European Union consortium on severe asthma. (p. 91)

Action taken or to be taken

The NHLBI Severe Asthma Research Program (SARP) is investigating the mechanistic basis for severe asthma and the elements that distinguish it from mild-to-moderate asthma. Since the start of the program in 2001, SARP has recruited a well-characterized and diverse cohort of 1,200 individuals (64% female and 27% African American) who have mild-to-severe asthma. A recent and important finding from SARP is that severe asthma is heterogeneous in several dimensions, including age of onset, sex, allergic response, comorbidities, patterns of inflammation, and response to treatment. Ongoing research using data from this cohort promises to refine our understanding of demographic, clinical, physiologic, genetic, and pathobiologic characteristics in relation to pharmacologic therapy. The ultimate aim is to enable prediction of therapeutic efficacy and identify novel treatments for severe asthma.

SARP investigators are actively involved with the European Union's severe asthma project called the U-BIOPRED study (Unbiased BIOMarkers used for PREDicting disease progression and medication efficacy in severe asthma). The SARP manual of procedures is being used in the design of that study. SARP investigators participated in the 2009 U-BIOPRED Taskforce "Understanding Severe Asthma" and are developing additional international research collaborations.

To promote further investigator-initiated research in severe asthma, especially in vulnerable populations, the NHLBI will invite representatives of the National Center for Minority Health and Health Disparities and the Office of Women's Health to an upcoming meeting of the Federal Liaison Group on Asthma to exchange information on Federal government programs in severe asthma and explore opportunities for collaboration.

Item

Sickle Cell Disease - The Committee supports NHLBI's request for information to identify sites with sufficient research infrastructure and patient population to undertake clinical studies in hemoglobinopathies with an emphasis on sickle cell disease and thalassemia.

This research network, along with the surveillance system and disease registry under development with the CDC, will improve knowledge and lead to better treatments for sickle cell disease and other hemoglobinopathies. The Committee requests that NHLBI provide an update on the network in the fiscal year 2011 congressional budget justification. (p. 91,92)

Action taken or to be taken

Please refer to page 31 of this document for NHLBI's response to this item.

Item

Sleep Disorders - The Committee applauds the Institute's investment in sleep-related research through the National Center on Sleep Disorders Research. The Committee notes the growing understanding of the link between sleep and cardiovascular health, and it encourages further research to better understand and modify the link between sleep disorders and cardiovascular disease. The Committee is also aware that NHLBI research has demonstrated that adolescents who get too little sleep are at greater risk of high blood pressure. The NHLBI is encouraged to partner with other institutes to expand research on the benefits of sleep to learning and healthy development of young people. (p. 92)

Action taken or to be taken

Please refer to page 32 of this document for NHLBI's response to this item .

Item

Specialized Centers of Clinically Oriented Research [SCCOR] - The Committee encourages the continued use of Specialized Centers of Clinically Oriented Research [SCCOR] as a mechanism to foster the translation of multidisciplinary basic research to improve clinical care. (p. 92)

Action taken or to be taken

The primary objective of the SCCOR program was to foster multidisciplinary research on clinically relevant questions and thereby facilitate rapid application of basic science findings to clinical problems. It had been expected that the SCCOR grants would provide an avenue for extraordinary progress in prevention, diagnosis, and treatment of the particular diseases under study. However, over the years, it became apparent that studies supported via the SCCOR program were not as successful in the discovery of new therapies as had been envisioned. Thus, the NHLBI has instituted several new approaches for supporting translational research that would realize the benefits of basic discovery and deliver new diagnostics and therapeutics to the public.

One example is the upcoming Science Moving towards Research Translation and Therapy (SMARTT) program, which is designed to assist translation to the clinic of new synthetic, natural, or biologic therapeutic interventions arising in the scientific community for the treatment of heart, lung, and blood diseases. The program will include several components to serve NHLBI investigators. Two production facilities will support translational research by producing biologic, non-biologic, and small molecules intended for clinical use. A center will be established to conduct pharmacology and toxicology analyses on therapeutics. A coordinating center will handle the organizational and

regulatory aspects of the SMARTT Program. Awards are expected to be made in September 2010.

A second new initiative is the NHLBI Translational Research Implementation Program (TRIP), a two-stage program designed to translate fundamental research ideas to proof-of-concept efficacy testing in patients. In Stage 1, supported by ARRA funds, the NHLBI will fund two-year awards for preliminary studies intended to culminate in the development of clinical trials. The awards will enable investigators to complete activities that are necessary to take recent exciting and promising ideas for heart failure and arrhythmia treatment and prevention derived from fundamental research to the point of safety and efficacy testing in people. In the ensuing five-year Stage 2 portion of the TRIP, the NHLBI will use regularly appropriated NHLBI funds to support the most meritorious safety and efficacy trials developed under Stage 1.

A comprehensive translational effort, *From Bench to Bassinet*, has succeeded the NHLBI Pediatric SCCOR Program. It includes the new Cardiac Development Consortium, a cooperative research group that will pursue an integrated approach to the investigation of cardiovascular development. Its purpose is to support basic collaborative research leading to a comprehensive understanding of the regulatory networks controlling cardiovascular development. The consortium will consist of up to four research centers, scientific cores as necessary, and a steering committee. The research centers will select key regulatory pathways, identify the components of the pathways and targets, and rapidly disseminate data to the scientific community. The new NHLBI translational effort also includes the companion NHLBI Pediatric Cardiac Genomics Consortium and Administrative Coordinating Center. Both consortia will interact with each other and the NHLBI Pediatric Heart Network to encourage translation of results from basic science to clinical research and to provide clinical input on pressing needs for basic research.

Item

Thalassemia - Thalassemia, or Cooley's anemia, is a fatal genetic blood disease. NHLBI has operated the Thalassemia Clinical Research Network for 9 years to advance the science of treating this disease. The Committee strongly encourages NHLBI to renew its focus on this disease, which has implications for other blood-related disorders and assure that research continues to advance treatments and find a cure. (p. 92)

Action taken or to be taken

Please refer to page 33 of this document for NHLBI's response to this item.

**National Institute of Dental and Craniofacial Research
(NIDCR)**

House Significant Items

Item

Temporomandibular Joint Disorders (TMJDs) - A range of comorbid conditions are associated with TMJDs. Many are captured in ongoing longitudinal studies funded by Institutes and Centers other than NIDCR. In order to advance the knowledge of the degree of overlap between TMJDs and the associated comorbidities, the Committee requests that NIH-funded population-based research projects, where appropriate and in consultation with the NIH Pain Consortium co-chairs, add measures to characterize the TMJD phenotype to permit the development of a sound basis for research into the underlying mechanisms driving the TMJD phenomenology and its comorbid conditions. (p. 138, 139)

Action taken or to be taken

TMJDs are a complex set of diseases involving one or more tissues of the face and the temporomandibular joint (TMJ). The primary symptoms of TMJD may include chronic pain in facial muscles and limited and painful movement of the jaw. In addition, these and other symptoms of TMJD may occur together with other chronic disorders such as fibromyalgia; trigeminal neuralgia; chronic fatigue syndrome; irritable bowel syndrome; sleep disorders; migraine headache; speech, hearing, swallowing, balance, smell, and taste disorders; affective disorders; and certain cardiovascular diseases. The NIDCR supports research leading to the discovery of possible etiological and pathophysiological mechanisms underlying this set of chronic disorders that overlap with TMJDs. These studies support the characterization and measurement of TMJD phenotypes in the context of common, overlapping phenotypes associated with other comorbid conditions as well as phenotypes specific to TMJDs. The results of this work provide a basis for follow-up preclinical laboratory research that will further characterize these mechanisms and identify potential novel targets for therapeutic interventions. The NIDCR recently sponsored a workshop on *Genetics of Temporomandibular Joint Disorder and Comorbid Chronic Pain Conditions: Current Status and Next Steps*. Recommendations from this workshop include the necessity to identify robust pain phenotypes that are both common among these conditions comorbid with TMJD and specific for each disease. Ensuring that these phenotypes are incorporated into genetic studies will allow for identification of entirely new genes and molecular pathways that may be involved in the mechanisms underlying the development of TMJDs.

The NIDCR continues to participate in trans-NIH efforts on pain research. The NIDCR was an initial co-sponsor of the NIAMS Osteoarthritis Initiative, a public-private partnership aimed at finding biological markers in the human population for the onset and progression of osteoarthritis, primarily of the knee. Incorporated into the study protocol, however, are assessments relating to the presence of pain localized to the TMJ and to the muscles surrounding the joint. Information garnered from this study is likely to provide insight into mechanisms responsible for development and sustained presence of TMJD in a subset of patients with other inflammatory joint conditions. The Pain Research Consortium recently expanded its leadership expertise, and the Directors of NIDA and NCCAM joined the

Directors of NIDCR, NINDS, and NINR as co-chairs of the NIH Pain Consortium. The Pain Consortium played a critical role in preparing research initiatives for the NIH Roadmap for Medical Research Transformative R01 program and the NIH Blueprint for Neuroscience Research Grand Challenges. Each of these programs has a component addressing chronic pain conditions that are of interest to many NIH Institutes. The results from this funded research are likely to impact our understanding of pain phenotypes common to TMJDs and other overlapping conditions.

Senate Significant Items

Item

Saliva - The Committee is pleased to see the progress that continues to be made in the field of salivary diagnostics, especially regarding the creation of an online data sharing network for saliva biomarkers. (p. 92)

Action taken or to be taken

The NIDCR appreciates the note from the Committee, and assures the Committee that we continue to support several projects that seek to apply salivary diagnostics technology for the detection and diagnosis of HIV, oral cancer, cardiovascular or respiratory diseases. Investment from the American Recovery and Reinvestment Act of 2009 allows us to expand this program on several fronts, including the development of an additional nano-biochip device for rapid detection of oral premalignant and malignant lesions. This technology has the potential to provide clinicians with a new non-invasive tool to identify and manage persons at highest risk for oral cancer.

Item

Oral Health Disparities - The Committee commends NIDCR for continuing a progressive health disparities research portfolio. (p. 92)

Action taken or to be taken

The NIDCR appreciates the Committee's commendation. The NIDCR assures the Committee that NIDCR continues its commitment, as articulated in the 2009-2013 NIDCR Strategic Plan, to eliminating the disproportionate burden of oral diseases and conditions experienced by vulnerable segments of the U.S. population. We continue to place a priority on intervention research that is tailored, practical and sustainable in communities. Collaborative Research Centers to Reduce Oral Health Disparities Research are focused on comparing the effectiveness of varied approaches that address Early Childhood Caries – a particular devastating form of dental caries experienced by very young children. Oral and pharyngeal cancer as well as maternal and child oral health are the focus of additional Centers for Research to Reduce Oral Health Disparities. A wide range of disadvantaged subgroups of the U.S. population participate in these intervention studies. Investment from the American Recovery and Reinvestment Act 2009 allows us to expand the health disparities research program on several fronts, including support for research focused on new models for oral health promotion in community settings and on children with special health care needs.

Item

Future of Dental Science- The Committee has learned that US dental schools now receive less than half of the NIDCR extramural budget. The Committee encourages NIDCR to work closely with schools of dentistry to foster a more intensive research component to dental education, with the goal of cultivating and retaining dental students who have an interest in research. (p. 92)

Action taken or to be taken

To increase the capacity of US dental schools to conduct research, the NIDCR is participating in the American Recovery and Reinvestment Act of 2009 (ARRA) funded Request for Application (RFA-OD-09-005) -- Limited Competition: Supporting New Faculty Recruitment to Enhance Research Resources through Biomedical Research Core Centers (P30) -- and has awarded funding to seven dental schools. This program provides funding to hire new tenure-track research faculty at dental schools, and requires joint appointment(s) with other academic unit(s) at the applicant institution, allowing new faculty to access University-wide research resources and core facilities, and to serve as mentors for graduate programs affiliated with other academic unit(s). This program is designed to improve the research infrastructure in these schools, encourage interdisciplinary collaboration between the dental schools and other academic departments, and augment specific research focus areas.

The NIDCR has also developed the NIDCR Dentist Scientist Pathway to Independence Award (K99/R00). This program is a variation on the regular Pathway to Independence Award, and specifically provides dentist scientists with funding for intensive postdoctoral research training followed by independent research support for a tenure track position with the option of concurrent dental specialty training. The intent is to better prepare the recipient dentists for long-term successful research careers, and to encourage dental schools to offer independent research faculty positions to these dentist scientists. The NIDCR continues to monitor its research training and career development programs and is shifting more resources to individual fellowships and career development awards, as these mechanisms have been shown to be more successful than institutional training grants in identifying and preparing investigators for careers in research. We also plan to introduce changes to the institutional training grant program to focus on recruiting and providing specific opportunities to dentist scientists.

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

House Significant Items

Item

Digestive Diseases — Diseases of the digestive system continue to affect more than one-half of all Americans at some time in their lives. The Committee urges NIDDK to prioritize and begin to implement the recommendations of the recently completed Long-range Research Plan for Digestive Diseases produced by the National Commission on Digestive Diseases. The Committee is pleased that irritable bowel syndrome has been included in the action plan. The Committee also encourages NIDDK to establish an advisory body to guide the implementation of the recommendations of the Commission on a long-term basis. (p. 113)

Action taken or to be taken

The research plan of the National Commission on Digestive Diseases, broadly released in final form in 2009 (<http://NCDD.niddk.nih.gov>), was designed to be a dynamic source of goals and opportunities for advancing digestive diseases research. The plan contains basic, clinical, translational, and behavioral research recommendations for areas of future research relevant to the wide variety of digestive conditions, including irritable bowel syndrome and other functional gastrointestinal disorders. While the NIDDK provided leadership and support for this planning effort, it addresses all stakeholders across NIH, as well as in the broader digestive disease research community.

The Commission concluded at their public meetings that prioritizing the plan's numerous research goals would detract from its inclusiveness of opportunities relevant to all areas of digestive diseases research. Instead, the plan includes four major themes and additional strategies for implementation that transcend specific disease or research areas, representing important foci for future research with great potential to synergize and advance many areas of digestive diseases research. Research partners outside the NIH were also encouraged to use the research plan as a tool for identifying their priorities for digestive diseases research and optimal approaches to achieving them.

The NIH continues to solicit broad stakeholder input as it oversees implementation of the plan's recommendations for digestive diseases research, in response to scientific opportunity, and within available resources. As a report directed to the NIH Director and to Congress, the plan's implementation is being carried out by coordinated efforts of NIH and other Federal agencies through existing advisory bodies such as the National Advisory Councils to the NIH Institutes and Centers, as well as through the efforts of investigators and research partners outside the NIH. Implementation of the plan's recommendations has already begun through mechanisms such as research project grants, research consortia, small business/technology transfer grants, digestive disease research center projects, career training, NIH Roadmap studies such as the Human Microbiome Project, and new initiatives such as the Intestinal Stem Cell Consortium. The plan's recommendations are also informing distribution of funds in the American Recovery and

Reinvestment Act of 2009 programs, such as NIH Challenge Grants, which include applications focusing on the gut microbiome and digestive diseases.

Efforts to promote the research plan's goals within the scientific, healthcare, and patient advocacy communities are also important to ensure that they move from words in a report into the research laboratories, and ultimately are translated into clinical and community settings. For example, Dr. Stephen James, Director of NIDDK's Division of Digestive Diseases and Nutrition, who chaired the Commission, presented information on the Commission's research plan and its implementation at the May 2009 Digestive Disease Week meeting of four major professional societies. Additionally, scientists and patient advocates serving on the Commission were provided slides to promote implementation of the research plan's goals to the wider professional and patient advocacy communities. Through these collective efforts, the Commission's research plan is helping to guide NIH and other partners in pursuing research opportunities that enrich our knowledge and lead to ways to reduce the burden of digestive diseases.

Item

Genetics of Diabetic Kidney Disease — The Committee recognizes NIDDK for supporting studies to identify the genetic factors that make some diabetic patients more susceptible to kidney disease. The Committee encourages NIDDK to develop programs to translate this new knowledge into therapies to treat and prevent kidney disease. (p.114)

Action taken or to be taken

One approach to identifying the genetic factors underlying the risk people with diabetes have of developing kidney disease is genome-wide association studies (GWAS), which examine genetic variation across the entire human genome to try and identify genetic differences that are associated with a particular disease. GWAS have been completed recently for two cohorts of patients with type 1 diabetes—the Genetics of Kidneys in Diabetes (GoKinD) Study, and Epidemiology of Diabetes Interventions and Complications (EDIC) Study—and the data are being shared through the NIH's dbGAP database. In 2007, three investigators received funding to carry out an analysis of these data over three years. In 2009, samples from the NIDDK's Family Investigation of Nephropathy and Diabetes (FIND), a cohort of patients with kidney disease primarily due to diabetes, were tested using GWAS; analysis of these data is ongoing. Finally, the NIDDK recently used American Recovery and Reinvestment Act funds to support GWAS in the NIDDK-funded Chronic Renal Insufficiency Cohort (CRIC), where a substantial fraction of the participants suffer from kidney disease due to diabetes. The goal of the GWAS is to identify gene variants that contribute to the variable progressive loss of renal function in subjects with established chronic kidney disease, including that caused by diabetes. As with the data from the GoKinD and EDIC, the FIND and CRIC GWAS data will be available through dbGAP <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap>) in 2010-2011 for sharing with the broader research community. The data and samples from GoKinD, EDIC and FIND studies are also available for sharing *via* the NIDDK repository. The genetic analyses being carried out currently, and that will be carried out by the researchers who access the shared data and samples, may lead to the identification of genes that influence susceptibility to and treatment of diabetic kidney disease, as well as new targets for approaches aimed at preventing or treating this serious condition.

Although the risk of developing diabetic kidney disease is influenced by genetics, environmental factors also play a role. The NIH Genes and Environment Initiative (GEI) aims to improve understanding of the interaction between genes and the environment and the impact on health and disease. The NIDDK plays a leading role in the “Translation” component of the GEI, and is thus well-positioned to capitalize on insights arising from ongoing GWAS—or other—studies of diabetes and kidney disease.

There has also been progress in our understanding of kidney disease not caused by diabetes. In 2008, two teams of researchers identified variations in the *MYH9* gene that are strongly associated with kidney diseases disproportionately affecting African-Americans. To build upon this insight, the NIDDK recently used American Recovery and Reinvestment Act funding to support a Challenge Grant that will generate mouse models in which *MYH9* variants are inserted into the mouse genome. These model systems will provide an opportunity to study the physiological consequences of human *MYH9* variants under precisely controlled genetic and environmental conditions in order to understand their contributions to the development of kidney injury. Another recently funded grant will examine the genetic and environmental factors that affect the development of kidney disease in subjects with a high risk *MYH9* genotype. In addition, the NIDDK will host a scientific meeting in the spring of 2010 to discuss the potential implications of this discovery on the prevention and treatment of kidney disease in patients at risk.

Item

Genetics of Type 1 Diabetes — The Committee commends NIDDK for its management of the International Type 1 Diabetes Genetics Consortium, which has taken a lead role in providing data and samples to investigators for studies to understand the genetic causes of type 1 diabetes. (p. 114)

Action taken or to be taken

The NIDDK appreciates the Committee’s commendation of its management of the Type 1 Diabetes Genetics Consortium (T1DGC). As recently as 2003, just three type 1 diabetes genes were known. The T1DGC has now identified at least 40 different genetic regions that influence a person’s risk of developing the disease. Thus, the T1DGC has led to unprecedented new knowledge about the genetic underpinnings of type 1 diabetes. The NIDDK is building on these exciting results and has launched a new initiative to pinpoint the exact genes that are involved and to understand their function in health and disease. Understanding the genetic contributors to type 1 diabetes can aid the ability to predict risk, as well as to inform the development of new prevention and treatment strategies.

Item

Glomerular Disease Research — Focal segmental glomerulosclerosis and nephrotic syndrome are serious glomerular diseases that have a disproportionate impact on children and young adults. The Committee urges NIDDK to continue to strengthen the glomerular disease research portfolio through collaboration with other NIH institutes and centers. The Committee continues to be interested in the establishment of a national patient registry on glomerular disease. (p. 114)

Action taken or to be taken

The NIDDK, along with the NIH Office of Rare Diseases Research, has established a Nephrotic Syndrome Rare Disease Clinical Research Network. It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy. The researchers will investigate the underlying disease mechanisms and assess the responsiveness of these diseases to various treatment approaches. This Consortium will provide a readily accessible research and education resource that will significantly advance the study, classification, characterization, diagnosis, and treatment of these diseases. It will also bring clinical and translational scientists together with lay research and patient foundations to educate patients with these diseases. This study was funded in collaboration with the NIH Office of Rare Diseases Research through its Rare Diseases Clinical Research Network (RDCRN). The RDCRN's Data and Technology Coordinating Center has developed a unique voluntary patient registry that provides ongoing contact with approximately 5,000 individuals from over 60 countries representing 42 diseases—including the kidney diseases minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy—that alerts them when new studies are opened in the network or when ongoing studies expand to new sites.

Additionally, the NIDDK has funded an NIH Challenge Grant related to IgA nephropathy (IgAN), a significant cause of kidney disease and failure. IgAN is a genetically complex trait, and genetic basis for this disease is not known. This project proposes the first genome-wide association study (GWAS) of IgAN to provide insights into the underlying disease processes in IgAN, thereby providing novel opportunities for the potential development of new diagnostic and therapeutic tools for this disease.

Item

Hemophilia and Hepatitis C — The Committee understands that hepatitis C (HCV) continues to have a devastating impact on the hemophilia population, with nearly half of all persons with hemophilia having contracted HCV, and many of these individuals co-infected with HIV. The Committee encourages NIDDK to pursue research initiatives on co-infection and the progression of liver disease in this population. (p. 114)

Action taken or to be taken

Consistent with the research goals of the trans-NIH *Action Plan for Liver Diseases Research* (<http://liverplan.niddk.nih.gov>) and the research plan of the National Commission on Digestive Diseases (<http://NCDD.niddk.nih.gov>), the NIDDK and other NIH Institutes will continue to support research on liver disease associated with Hepatitis C (HCV) infection, with or without human immunodeficiency virus (HIV) co-infection, in highly affected patient populations. Such populations include individuals with hemophilia who were infected by contaminated blood transfusions prior to the institution of a general screening program for these pathogens in donor blood.

Several research advances have been made toward reaching the goals addressing HCV/HIV co-infection. For example, the AIDS Clinical Trials Group funded by the National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring a clinical trial, entitled

“Suppressive Long-term Antiviral Management of Hepatitis C Virus (HCV) in HIV-1 Co-infected Subjects,” to evaluate the safety and efficacy of long-term antiviral treatment in slowing liver disease progression in people infected with both HCV and HIV. NIAID is also sponsoring a clinical trial, called “Pioglitazone for Hepatic Steatosis in HIV/HCV Co-infection,” which will evaluate the potential benefits of pioglitazone—an FDA-approved diabetes drug—for reducing fatty liver disease in co-infected individuals. In addition, NIH is funding several prospective studies that are actively assessing factors associated with progression of liver diseases in patients with HIV/HCV co-infections, including: the Natural History of HCV infection in HIV disease study, sponsored by the National Institute on Drug Abuse (NIDA); the HIV/HCV-Coinfection, Antiretroviral Therapy and Fibrosis study, sponsored by NIDA; and the Women’s Interagency HIV Study, sponsored by the NIAID, NIDA, the *Eunice Kennedy Shriver National Institute of Child Health and Human Development* (NICHD), and the *National Cancer Institute* (NCI). Additionally, the NIDDK has helped support research on genetic factors contributing to liver disease progression in people with hemophilia who are infected with HCV, many of whom are co-infected with HIV, using data collected through the ongoing Multicenter Hemophilia Cohort Study sponsored by the NCI.

Item

Hepatitis B — The Committee notes that NIDDK has responded to the challenges surrounding the management of chronic hepatitis B by establishing a Hepatitis B Clinical Research Network and by conducting a Consensus Development Conference on the management and treatment of Hepatitis B. The Committee encourages the Hepatitis B Clinical Research Network to increase its focus on pregnant women and pediatric cases of Hepatitis B and further urges that a research plan be developed to address the research priorities identified by the Consensus Development Conference. In particular, better understanding of the nature of the different clinical categories of Hepatitis B and of fibrosis and cirrhosis are needed. New medical interventions for management of Hepatitis B and the diseases, with which it is associated, including fibrosis and cirrhosis, are also needed. (p.114)

Action taken or to be taken

The NIDDK supports a robust research portfolio, as well as consensus-building workshops amongst experts, aimed at improving management of chronic Hepatitis B.

The NIDDK established the Hepatitis B Clinical Research Network in fall 2008 to promote translational research on hepatitis B by elucidating disease processes and natural history, as well as developing means of treatment and control. The Network consists of 12 clinical centers, a data coordinating center, and an immunology center. Currently in the final planning stages, the Network’s centers are on the verge of engaging in multiple clinical trials in both adults and children. Research planned at some of the centers will focus on such projects as collecting information on individuals with chronic hepatitis B for studies of such issues as risk of transmission from pregnant women to their infants during childbirth. Another focus of research at some of the Network sites will be investigations of children with hepatitis B, including natural history and comparative effectiveness studies of different therapies, as well as proposed ancillary studies to address the limited treatment options for children with hepatitis B by conducting a pilot study of the pharmacokinetics and optimal

dosing of a drug already used in adults. Many of the Network sites will investigate different clinical features of chronic hepatitis B currently used to categorize patients in terms of prognosis and treatment response, including effects on fibrosis and cirrhosis development using various means such as liver biopsy, biomarkers, and transient elastography (a measure of liver stiffness). New therapeutic approaches to chronic Hepatitis B and its associated conditions will also be tested at several sites through this Network.

Research conducted by the Network is addressing Hepatitis B research questions and goals identified in recent research plans, such as the trans-NIH *Action Plan for Liver Disease Research* (<http://liverplan.niddk.nih.gov>) and the research plan of the National Commission on Digestive Diseases (<http://NCDD.niddk.nih.gov>), as well as through NIH-sponsored meetings in recent years on hepatitis B management. For example, research recommendations from the NIH Consensus Development Conference on management of hepatitis B, held in October 2008, are directly informing research conducted by the Network. The NIDDK convened this Conference together with the NIH Office of Medical Applications of Research and The Johns Hopkins University School of Medicine, with additional support from the NCI, NIAID, CDC, and FDA. The purpose of this 3-day Conference was to examine important issues in hepatitis B therapy, including hepatitis B management related to current burden, disease development, benefits and risks of current treatment options, which groups of patients benefit from currently available treatments (including infants born to women with hepatitis B), appropriate measures to monitor treatment, and the greatest challenges and opportunities for future research on hepatitis B. The recommendations from this Conference were made available to the research community and the public following the Conference. The panel's full statement and additional information about this conference are available at: <http://consensus.nih.gov/2008/2008HepatitisBCDC120main.htm>

Item

Hepatitis C — The Committee urges a continuing focus on the development of new treatments for hepatitis C and notes that without new medical interventions the projected direct and indirect costs of hepatitis C will be more than \$85,000,000,000 (\$85 billion) over the next 10 years. (p. 114)

Action taken or to be taken

Consistent with research goals recommended in the trans-NIH *Action Plan for Liver Disease Research* (<http://liverplan.niddk.nih.gov>) and updated in the research plan of the National Commission on Digestive Diseases (<http://NCDD.niddk.nih.gov>), the NIDDK continues to support robust extramural and intramural research programs on liver disease associated with hepatitis C virus (HCV) infection. The research portfolio includes basic and clinical research studies, as well as early-stage translational research to evaluate effectiveness of available forms of HCV therapy, to inform better patient care in terms of outcomes and healthcare costs. For example, the NIDDK has supported clinical research on hepatitis C, with co-sponsorship by the NIAID and the NCI, through a multi-center clinical study of long-term therapy of chronic hepatitis C known as the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis trial (HALT-C). The randomized clinical trial phase of HALT-C was completed in 2007, providing clear evidence that long-term treatment with low-dose peg-interferon was ineffective in preventing liver disease progression due to

hepatitis C. The HALT-C trial has been extended until 2010 in order to complete the final phase of the trial, including follow-up of patients for their outcomes after treatment; publication of papers; and preparation of datasets for public use.

Although many of the recent NIDDK-sponsored clinical studies of hepatitis C, such as HALT-C, have been largely completed, several pharmaceutical companies are in the late stages of conducting clinical trials to develop new treatments for this disease. The NIDDK is following the results of these trials with great interest, with an eye toward potential opportunities to support mission-related research based on the outcomes of the trials.

Item

Incontinence — The Committee is pleased that NIDDK collaborated with NICHD and the Office of Medical Applications of Research on a state-of-the-science conference on incontinence. The Committee urges the Institute to prioritize and begin to implement the recommendations of this conference. (p. 114)

Action taken or to be taken

The December 2007 NIH State-of-the-Science conference on Incontinence in Adults, sponsored by NIDDK in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and the Office of Medical Applications of Research, identified a variety of gaps and opportunities in the prevention and treatment of incontinence. Following a series of scientific presentations by experts and open public discussions, an independent panel concluded that fewer than half of individuals experiencing incontinence report their symptoms to healthcare providers without being prompted. In response to the recommendation of the conference to raise public awareness of incontinence, the NIDDK, in consultation with advocacy organizations and external experts in the field, has developed a detailed action plan for an awareness campaign for fecal incontinence, which will be launched in 2010. Regarding urinary incontinence, the NIDDK supports the Urinary Incontinence Treatment Network (UITN) to conduct rigorous, long-term clinical trials of therapies for incontinence in women. The UITN has completed three trials and NIDDK anticipates that the results of the third trial will be available in spring 2010. A new UITN study is designed to determine the appropriate amount of pre-surgical urinary testing that is necessary for a patient. The UITN is also developing a patient sample repository that can be used in future research studies. The UITN addresses a recommendation of the State-of-the-Science conference to determine the effects of interventions in women with urinary incontinence. NIDDK has also been working with the research and advocacy communities to identify new directions and next steps in research for prevention and improved treatment of incontinence in adults, through efforts such as a January 7-9, 2009, international scientific meeting it sponsored on urinary incontinence. NIDDK will continue to be guided by recommendations of the extramural community as it moves incontinence research forward.

NICHD-supported investigators from the Pelvic Floor Disorders Network (PFDN) recently published results on the prevalence of these disorders in women in the United States. In women ranging from 20 years to over 80, 23.7 percent were affected by one or more pelvic floor disorder, with the most common problem being urinary incontinence. Finding also that these conditions increase with age and the changing demographics of the U.S.

population, the number of women seeking treatment for a pelvic floor disorder will become an increasing burden on our nation's health care system. In response to the rising need for prevention and treatment, NICHD, with support from ORWH, recently issued a solicitation to attract more basic scientists into this field, and a number of outstanding applications were funded. In addition, the PFDN received a portion of NICHD's stimulus funding to test an innovative treatment for over-active bladder, a major cause of urinary incontinence that disproportionately affects women.

Item

Inflammatory Bowel Disease (IBD) — The Committee commends NIDDK for its leadership on inflammatory bowel disease (IBD) and encourages the institute to strengthen its support for genetic and clinical IBD research and other opportunities outlined in the research agenda, Challenges in inflammatory Bowel Disease. The Committee particularly encourages NIDDK to support pediatric IBD research. (p. 114)

Action taken or to be taken

The NIDDK continues to maintain a significant and productive IBD portfolio designed to address the most pressing issues facing the IBD community of clinicians, researchers, patients, and stakeholders. The Institute is committed to continuing its valuable partnership with the IBD community and remains attentive to the research goals outlined in the Crohn's and Colitis Foundation of America's research plan, "Challenges in Inflammatory Diseases," as they align with the research goals set out in the recommendations of the National Commission on Digestive Diseases (NCDD)

<http://www2.nidk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/FinalResearchPlanPosting.htm>). The NIDDK IBD Genetics Consortium continues to be a major

strength of the research program, providing support and resources to enhance gene discovery and uncover the roles that genes play in this complex disease, which impacts the lives of both children and adults. The Consortium is working with pediatricians to develop new projects that specifically involve children. The genome-wide association studies (GWAS) supported by the Consortium have been particularly successful. For example, two genomic regions associated with pediatric IBD have recently been identified using GWAS technology. This discovery includes the linking of pediatric ulcerative colitis susceptibility with the MHC chromosomal region, a region that contains many important immune system genes. Pediatric IBD susceptibility was also associated with a genomic region that has been identified with TNF, a protein that plays a key role in the inflammation that is characteristic of IBD. TNF is the target of drug therapies that have been shown to effectively treat IBD. A gene previously linked to adult IBD, involved in a process that breaks down cellular debris such as bacteria has now been linked to pediatric IBD. In addition, another GWAS project has identified regions in two chromosomes that are associated with adult ulcerative colitis. A study co-funded by the NIDDK, NIAID, the Canada Foundation for Innovation, the Canada Research Chair Program, the Research Institute of the McGill University Health Centre and the Crohn's and Colitis Foundation of Canada has shown that the gene for cryopyrin, an intracellular bacterial sensor which plays a role in initiating the immune response, is a gene that increases susceptibility to Crohn's disease. The NIH Roadmap's new Transformative R01 program, created to support exceptionally innovative and creative projects, is funding a pediatric IBD study. The aim of this research is to develop a prototype social network for teenagers with IBD,

their parents, and physicians that will encourage them to interact more freely, taking advantage of internet communication, in an effort to improve drug compliance and self-management for better patient outcomes.

Item

Kidney Disease — The Committee urges NIDDK to prioritize research on the disease's relationship with its leading causes, particularly diabetes, hypertension, and obesity; methods for prevention; and effective therapies that improve mortality statistics. In particular, the Committee also urges NIDDK to prioritize investigator-initiated research that studies: acute kidney injury, diabetic nephropathy, glomerular disease, hypertension, transplantation, and kidney-related cardiovascular toxicity. Additional work is required to (1) develop new disease biomarkers and imaging technologies which are critical for the management of kidney diseases, (2) implement necessary infrastructure for disease-specific registries and clinical trials networks to better allow investigators to bridge the gap from the bench to the bedside, and (3) track data on patient race and ethnicity to understand the disparities related to morbidity and mortality of kidney disease among underrepresented minority patients. (p. 115)

Action taken or to be taken

The NIDDK supports a strong, diverse portfolio of solicited and investigator-initiated research into the causes of and treatments for chronic kidney disease. Within this program, the NIDDK has just initiated a Chronic Kidney Disease Biomarker Consortium that seek to identify and validate biomarkers, which should stimulate bench to bedside translation and may enhance researchers' ability to evaluate promising new therapies. A robust portfolio of research projects is focused on improving existing imaging techniques and developing novel ways to observe kidney structure and function non-invasively. The Nephrotic Syndrome Rare Disease Clinical Research Network provides a readily accessible research and education resource that will significantly advance the ability to characterize, diagnose, and treat non-inflammatory glomerular diseases. Additionally, the NIDDK has funded approximately \$14 million in Challenge Grants for research related to the causes, prevention, and treatment of chronic kidney disease. One will create a national registry of so-called "incompatible" kidney transplant recipients that will link data from multiple centers to improve and expand this form of kidney transplantation.

Cardiovascular disease is the leading cause of death among patients with chronic kidney disease. The Systolic Pressure Intervention Trial (SPRINT)—jointly funded by the NIDDK and the National Heart, Lung, and Blood Institute—is examining the impact of lowering systolic blood pressure on cardiovascular disease and on chronic kidney disease. SPRINT was recently expanded to include a cohort of elderly patients.

Acute kidney injury (also called acute renal failure) is a relatively common complication in hospitalized patients. A study of the natural history of patients with acute kidney injury, ASSESS AKI, will provide important information about the natural history of acute kidney injury and recovery. A solicitation for ancillary studies to this trial has been issued, and a biomarker consortium focused on acute kidney injury is being considered.

Data related to chronic kidney disease and kidney failure is tracked by the United States Renal Data System (USRDS), a national data system that collects, analyzes, and distributes information about kidney disease in the U.S. In 2008, the USRDS Annual Data Report was expanded to include a new atlas devoted to chronic kidney disease. The USRDS also produces a Researcher's Guide, fulfills data requests, provides standard analysis files and specialized datasets to researchers, and presents the results of its research at national conferences and in peer-reviewed journals. The USRDS is funded by the NIDDK and the Centers for Medicare and Medicaid Services.

Item

Polycystic Kidney Disease (PKD) — The Committee encourages NIDDK to work via the NIH Program on Public-Private Partnerships to support the establishment of PKD diagnostic and clinical treatment centers for treating PKD patients and overseeing clinical trials. These centers should work in collaboration with clinical and translational science awards and PKD Centers of Excellence to ensure that PKD patients can participate in promising clinical trials and pilot studies. The Committee encourages NIDDK to also facilitate the establishment of a centralized facility for the volumetric analysis of kidney images, PKD genotyping and surrogate marker analysis.

The Committee urges NIDDK to maintain its support of clinical trials and the PKD Diagnostic and Clinical Treatment Centers. The Committee encourages NIDDK to convene a blue ribbon panel to plan the future strategic direction of PKD research, to expand the number of PKD researchers, and implement best practices in order to strengthen current efforts. The Committee also encourages NIDDK to consider the feasibility of establishing a core repository of laboratory animals for renal cystic diseases like PKD, which will help lower research costs and enhance scientific discoveries in this area of translational research. (p. 115)

Action taken or to be taken

The NIDDK welcomes additional partners who wish to join its PKD research efforts. One way to do so is through the NIH Public-Private Partnership (PPP), which allows Institutes to leverage their resources and work collaboratively with partners who have similar goals. Other avenues for cooperation exist as well. For example, the NIDDK is currently collaborating with the PKD Foundation and the Food and Drug Administration to establish standards for clinical trial data collection through the *Clinical Data Interchange Standards Consortium*, a global, multidisciplinary, non-profit organization that supports the acquisition, exchange, submission, and archiving of clinical research data and metadata.

Two large NIDDK-funded studies of PKD—HALT-PKD and CRISP—are focused on identifying better monitoring and imaging approaches as well as improvements in patient care for individuals with the most common form of PKD. The HALT-PKD study is testing whether optimum blood pressure management, in combination with drugs that target the renin-angiotensin system, will slow disease progression. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments. This valuable cohort of patients has been monitored through two extensions of the original study: CRISP II and the recently-approved CRISP III. The image analysis methods

developed in CRISP are currently being implemented in HALT-PKD and have been implemented by industry-sponsored trials for patients with PKD. The NIDDK has supported extensive and ongoing data collection related to volumetric analysis of kidney images, PKD genotyping, and surrogate marker analysis in the CRISP studies and HALT-PKD. These data and samples will be available to the research community through the NIDDK Repository. The NIH also supports Mutant Mouse Regional Resource Centers, which distribute and cryopreserve scientifically important, genetically engineered mouse strains and mouse embryonic stem cell lines that are of value to the broad research community. Use of this facility fulfills an investigator's obligation to share biomedical research resources, reduces animal housing costs, and eliminates the need to ship mice to multiple requesting investigators.

In addition, a new NIDDK initiative is encouraging identification and validation of biomarkers and risk assessment tools for kidney function, injury, and disease progression in people with chronic kidney disease. Improved biomarkers for screening, monitoring kidney function, and managing chronic kidney disease would be of benefit to people with PKD. The NIDDK has also funded four NIH Challenge Grants on PKD that relate to genetic analysis in mouse models to discover mechanisms underlying PKD; to develop novel assays to diagnosis PKD early in the disease process; to test microRNA-based therapeutics as a way to treat PKD; and to translate new discoveries into potential therapies, diagnostics, or research tools.

Item

Thalassemia — The Committee urges NIDDK to play a significant role in the Thalassemia Clinical Research Network because the iron chelation and non-invasive iron measurement issues addressed by the institute are important to the quality of life of thalassemia patients. (p. 115)

Action Taken or To Be Taken

The NIDDK remains committed to developing more effective ways to treat iron overload resulting from repeated blood transfusions used to treat patients with severe chronic thalassemias, including Cooley's anemia. As part of recent efforts, the Institute co-sponsored the NIH-NHLBI/NIDDK Thalassemia Workshop with the National Heart, Lung, and Blood Institute in May 2009. The workshop served as a forum to discuss important issues concerning future clinical trials and provided assistance to NHLBI in planning the next generation of thalassemia clinical studies.

Item

Type 1 Diabetes Clinical Trials — The Committee urges NIDDK to continue to expand the pipeline of new therapies being tested by the Type 1 Diabetes TrialNet. Implementing the sharing of study samples and data fosters mechanistic and clinical research aimed at understanding how these drugs work, so they can be optimized to reduce side effects and to benefit all patient populations. (p. 115)

Action taken or to be taken

The NIDDK's Type 1 Diabetes TrialNet (TrialNet) is a clinical trials network focused on testing promising new strategies to prevent, delay, or reverse progression of type 1

diabetes. TrialNet recently demonstrated that the drug rituximab delayed progression of type 1 diabetes in newly-diagnosed patients. In addition to this success, there is a robust pipeline of potential new therapies to be tested. Recruitment has completed for a clinical trial to determine whether the agent CTLA-4 Ig (abatacept) can preserve insulin production in newly-diagnosed type 1 diabetes patients. Another study, to determine whether administration of glutamic acid decarboxylase (GAD) can preserve insulin production, has started recruitment. In collaboration with the NIAID-led Immune Tolerance Network (ITN), TrialNet is recruiting for clinical trials to test whether the agent thymoglobulin or a combination of the immune system modifying drugs IL2 and sirolimus can halt progression of type 1 diabetes in newly-diagnosed patients.

TrialNet is also testing or will soon begin testing several new therapies—including oral insulin, GAD, anti-CD3, and omega-3-fatty acid docosahexaenoic acid—to prevent type 1 diabetes in people at high risk for developing the disease. TrialNet has also partnered with the NICHD-led Diabetes Research in Children Network (DirecNet) to study the value of near normalization of glucose immediately after diagnosis using continuous glucose monitoring and insulin pump therapy. To accelerate transition of promising agents from the laboratory to clinical trials, the NIDDK supports the Type 1 Diabetes-Preclinical Testing Program (T1D-PTP) and, in collaboration with NCI, the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program. T1D-PTP provides investigators with resources and expertise to validate promising new therapeutics in preclinical studies and T1D-RAID provides resources for preclinical development of agents to be tested in clinical trials. Thus, in addition to the studies currently under way or in development, TrialNet is considering and prioritizing the testing of other therapies that are in the pipeline for future study.

The NIDDK encourages researchers to apply for access to samples generated from TrialNet studies and provides information about available samples and the application process. For example, the NIDDK developed a public website (www.T1Diabetes.nih.gov) that has information on research resources, including data and samples, available through research consortia supported by the Special Statutory Funding Program for Type 1 Diabetes Research, including TrialNet. In addition, the NIDDK uses the NIH Guide for Grants and Contracts to broadly advertise the availability of samples from TrialNet type 1 diabetes clinical research studies.

Item

Type 1 Diabetes Research Biosamples — The Committee commends NIDDK for establishing biorepositories to house data and biological specimens collected by studies such as the international Type 1 Diabetes Genetics Consortium [TIDGC], the Environmental Determinants of Diabetes in the Young [TEDDY] Study, and the natural history study of TrialNet. The Committee urges NIDDK to widely advertise the availability of samples to the diabetes research community, ensure that the biorepositories implement efficient procedures to rapidly disseminate those samples to qualified researchers, and develop policies to expedite the availability of samples from other clinical trials in type 1 diabetes. (p. 115)

Action taken or to be taken

The NIDDK appreciates the Committee's commendation for establishing biorepositories and the desire to make available samples and data from clinical research studies to accelerate research progress. To facilitate sharing of samples and data, the Central NIDDK Repositories created a website dedicated to type 1 diabetes studies (www.niddkrepository.org/niddk/jsp/public/diabetes.jsp). Data from several genome-wide association studies focused on type 1 diabetes and its complications, such as the Type 1 Diabetes Genetics Consortium (T1DGC), the Epidemiology of Diabetes Interventions and Complications study, and the Genetics of Kidneys in Diabetes study, are being made available through the Repository in collaboration with the National Library of Medicine's database of Genotype and Phenotype. The website also includes policies and procedures for requesting samples and data.

The NIDDK developed a public website (www.T1Diabetes.nih.gov) that has information on research resources, including samples and data that are available through research consortia supported by the Special Statutory Funding Program for Type 1 Diabetes Research. The NIDDK is enhancing this public website to include information on timeframes when additional data and samples are expected to become available and consortia access policies. The enhanced website will include information on the T1DGC, The Environmental Determinants of Diabetes in the Young, Type 1 Diabetes TrialNet, and other type 1 diabetes clinical research studies.

The NIDDK uses various methods to advertise availability of samples, data, and other research resources to the scientific community. For example, in June 2009, the NIDDK distributed a flyer to attendees of the American Diabetes Association's annual meeting to advertise the Institute's type 1 diabetes website and availability of research resources. Several thousand scientists studying diabetes were in attendance, so this meeting provided a venue to advertise broadly to the research community. The NIDDK also uses the NIH Guide for Grants and Contracts to advertise the availability of samples. For example, a May 2008 notice announced the availability of serum, RNA, and peripheral blood mononuclear cell samples from people enrolled in the Natural History Study of Type 1 Diabetes TrialNet, for the purpose of validating new molecular markers of type 1 diabetes. Through these types of approaches, the NIDDK will continue to ensure that the research community is aware of samples and data available through its type 1 diabetes clinical research studies.

Senate Significant Items

Item

Chronic Hepatitis B — The Committee commends the NIDDK for establishing a Hepatitis B Clinical Research Network and conducting a consensus development conference on the management and treatment of hepatitis B. The Committee urges that the Hepatitis B Clinical Research Network increase the focus on pregnant women and pediatric cases of hepatitis B and further urges that a research plan be developed to address the research priorities identified by the consensus development conference, especially in understanding the nature of the different clinical categories of hepatitis B and of fibrosis and cirrhosis, and

developing new medical interventions for the management of hepatitis B and the diseases with which it is associated, including fibrosis and cirrhosis. (p. 93,99)

Action taken or to be taken

Please refer to page 49 of this document for NIDDK's response to this item.

Item

Chronic Hepatitis C — The Committee urges a continuing focus on the development of new treatments for hepatitis C. (p. 94)

Action taken or to be taken

Please refer to page 50 of this document for NIDDK's response to this item.

Item

Chronic Pediatric Kidney Disease — The Committee appreciates NIDDK's support of two prospective multicenter pediatric nephrology studies, as requested by the Committee in fiscal year 2009. Beginning in fiscal year 2010, the Committee urges NIDDK to initiate two additional prospective multicenter pediatric nephrology translational studies or treatment trials over the next 2 years. These collaborative studies offer the best opportunity to systematically gain new knowledge about children being treated for kidney disease, and to use this knowledge to improve care and reduce future costs. (p. 94)

Action taken or to be taken

The NIDDK, along with the NIH Office of Rare Diseases, has established a Nephrotic Syndrome Rare Disease Clinical Research Network. It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, focal and segmental glomerulosclerosis, and membranous nephropathy. The researchers will investigate the underlying disease mechanisms and assess the responsiveness of these diseases to various treatment approaches. This group will provide a readily accessible research and education resource that will significantly advance the study, classification, characterization, diagnosis, and treatment of these diseases. It will also bring clinical and translational scientists together with two lay research and patient foundations to educate patients with these diseases.

The NIDDK has also established a Consortium for Hereditary Causes of Nephrolithiasis and Renal Failure to study primary hyperoxaluria, cystinuria, APRT deficiency, and Dent disease. These four diseases are characterized by deposition of crystals in the kidneys that often lead to kidney stones. This consortium will focus on the discovery of biomarkers of disease risk, disease activity, and response to therapy for these four rare diseases that share similar mechanisms and severe disease manifestations.

Both of these consortia were funded under the NIH Rare Diseases Clinical Research Network. Sponsored by the NIH Office of Rare Diseases Research in conjunction with multiple NIH Institutes and Centers, this program facilitates the identification of biomarkers for disease risk, disease severity and/or activity, and the identification of measures of

clinical outcomes appropriate for applicability to clinical trials. It encourages the development of new approaches to diagnosis, prevention, and treatment of rare diseases.

Additionally, the NIDDK has funded an NIH Challenge Grant related to pediatric kidney injury. This project addresses acute kidney injury, a life-threatening condition seen commonly in the pediatric intensive care unit. The researchers aim to create and test a pediatric-specific kidney support device that could be used to treat these critically ill children.

Item

Diabetes Prevention Program — The Committee encourages the NIDDK's efforts to expand community research applications of the successful diet and exercise interventions of the Diabetes Prevention Program trial. The NIDDK is encouraged to partner with other institutes and centers to enhance similar community research networks. (p. 94)

Action taken or to be taken

The landmark Diabetes Prevention Program (DPP) clinical trial demonstrated that a lifestyle intervention aimed at reducing weight through diet and exercise was an effective means to prevent or delay type 2 diabetes in people at risk. While the lifestyle intervention as delivered in DPP was cost-effective, efforts are underway to find lower cost ways to test for pre-diabetes, and to deliver the lifestyle intervention more broadly in communities and at lower cost. Therefore, the DPP continues to drive discovery through follow-up studies and new trials that benefit from the experience and findings from the DPP.

To maximize benefits from its investment in the DPP, and to investigate the long term health outcomes of the interventions, the NIH is currently following the cohort of DPP patients through the DPP Outcomes Study (DPPOS). This study is following DPP participants for an additional 10 years to assess the durability of the effect of the lifestyle intervention on weight loss, cardiovascular disease risk factors, and development of diabetes. Examining longer term benefits, beyond average treatment period of 2.8 years in DPP, has important implications for the cost effectiveness of the intervention. Other critical ongoing research is aimed at translating the result of the DPP into more general practice, and at lowering the cost of the already cost-effective intervention. For example, one study seeks to test whether the intervention can be effectively and inexpensively delivered through YMCA programs. The NIDDK is also working with the Centers for Disease Control and Prevention (CDC) state diabetes programs to help translate the DPP. CDC and NIDDK also co-sponsored a conference on policy issues related to DPP translation. Strategies to optimize translation of key scientific advances including the DPP are being addressed in a diabetes research strategic plan currently in preparation by NIDDK.

Because the diet and exercise component of the DPP achieved goal levels of weight loss (7 percent of body weight in the first year of the study among participants who were all overweight or obese at the beginning of the study), the intervention has been adapted and used in other studies. For example, Look AHEAD, a collaborative effort between the NIDDK and NHLBI which seeks to reduce cardiovascular disease complications in obese people with type 2 diabetes, adapted the DPP lifestyle intervention to achieve even greater

average weight loss (8.6 percent of initial body weight) after 1 year. Notably, the Look AHEAD adaptation also delivers portions of the lifestyle intervention in group settings, to lower costs, and make the approach even more cost-effective. Other ongoing research includes testing delivery of similar weight loss interventions via an internet-based approach.

Item

Digestive Diseases — The Committee urges the NIDDK to prioritize and implement the recommendations of the National Commission on Digestive Diseases' recently completed Long-Range Research Plan for Digestive Diseases. (p. 94)

Action taken or to be taken

Please refer to page 45 of this document for NIDDK's response to this item.

Item

Endoscopy and Obesity-Related Research — While bariatric surgery is an important option for patients with medical complications from obesity, the Committee notes the emergence of less-invasive, endoscopic techniques to induce weight-loss without the risk of surgery. The Committee urges the NIDDK to fund studies comparing bariatric surgery with endoscopic interventions and support the development of novel endoscopic therapies for diabetes management through weight reduction. (p. 94)

Action taken or to be taken

Bariatric surgery is an important component of the NIDDK research effort to address obesity. The Institute would welcome investigator-initiated applications for pilot studies concerning novel endoscopic techniques to induce weight loss. NIDDK has a number of mechanisms to support pilot projects, including centers and exploratory and developmental research grants.

The Institute is conducting several research projects to determine the safety and efficacy of bariatric surgery. A prominent NIDDK program focused on this topic is the Longitudinal Assessment of Bariatric Surgery (LABS), a consortium that plans, develops, and conducts coordinated clinical, epidemiologic, and behavioral research in bariatric surgery. *Teen-LABS*, an ancillary study to LABS, is a prospective observational cohort study with the goal of collecting similar data in adolescent patients. The NIDDK also supports research comparing the effectiveness of various approaches to bariatric surgery to one another, and to intensive lifestyle interventions for weight loss. Aside from programs and projects that are supported using traditional grant mechanisms, the NIDDK is also funding three American Recovery and Reinvestment Act Challenge Grants on bariatric surgery as a potential therapy for type 2 diabetes.

Item

Fatty Liver Disease (Nonalcoholic Steatohepatitis) — The Committee commends the NIDDK's recent efforts to address fatty liver disease and urges the Institute to convene a consensus development conference to confirm best practices and to identify additional research priorities. (p. 94)

Action taken or to be taken

The NIDDK continues to sponsor the multi-center Nonalcoholic Steatohepatitis (NASH) Clinical Research Network to study the causes, contributing factors, natural history, complications, diagnosis, prevention, and therapy of this form of non-alcoholic fatty liver disease in both adults and children. Funding for this Network has been extended through 2014.

This Network of eight clinical centers and a data coordinating center is investigating the nature and management of NASH and is conducting two clinical trials of potential therapies. One of the clinical trials is in adults, evaluating the safety and efficacy of two potential treatments for NASH—the drug pioglitazone, or vitamin E—as compared to a placebo. The other clinical trial is in children and is comparing the drug metformin, vitamin E, and placebo in the treatment of non-alcoholic fatty liver disease. Renewal of funding for the Network has enabled expansion of a database to collect samples from additional adult and pediatric participants.

Although NIDDK is vigorously committed to supporting the NASH Clinical Research Network and other research opportunities to better our understanding of fatty liver disease, the Institute believes that the current status of knowledge and practice in the field does not warrant a Consensus Development Conference at this time. However, as the aforementioned clinical trials are completed over the coming years, NIDDK foresees a future opportunity to hold a Conference to confirm best practices and identify additional research priorities in light of new and emerging evidence.

Item

Fecal Incontinence — The Committee is pleased with NIDDK's actions to establish a public and professional awareness campaign for fecal incontinence in collaboration with patient organizations. (p. 94)

Action taken or to be taken

The NIDDK is pleased with the Committee's commendation of its commitment to establish a Fecal Incontinence Awareness Campaign. The campaign is based on recommendations of the panel of experts 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. The NIDDK plans to launch the campaign in 2010.

Item

Glomerular Disease Research — The Committee urges the NIDDK to collaborate with the NCMHD to support expanded research on glomerular disease and its effects on minorities and the specific implications of the link between the MYH9 gene and the high prevalence of focal segmental glomerulosclerosis among African Americans. (p. 94)

Action taken or to be taken

In 2008, two teams of researchers identified variations in a single gene, *MYH9*, that are strongly associated with kidney diseases disproportionately affecting African-Americans. *MYH9* risk variants account for nearly all of the increased risk for idiopathic FSGS and

HIV-associated FSGS among African Americans compared to European Americans and a portion of the increased risk for hypertensive kidney disease. Surprisingly, however, these variants were not associated with kidney failure arising from diabetes. Diabetes is the major cause of kidney failure.

To build upon this insight, the NIDDK has recently funded a Challenge Grant to generate a mouse model in which *MYH9* variants are inserted into the mouse genome. This model system would provide an opportunity to study the physiological consequences of human *MHY9* variants under precisely controlled genetic and environmental conditions in order to understand their contributions to the development of kidney injury. These animal models will be powerful tools for identifying new strategies for preventing kidney disease and kidney failure in African Americans.

In addition, the NIDDK is convening a scientific meeting on *MYH9* in the spring of 2010. NIDDK and NCMHD staff, and researchers from academic medical centers, will serve on the planning committee. It is envisioned that the conference will review genetic, public health, and ethical and social implications of these new findings, and that conference participants will provide feedback to the NIH regarding future research directions.

Item

Inflammatory Bowel Disease (IBD) — The Committee encourages support for the IBD research agenda detailed in the National Commission on Digestive Diseases report. The committee also encourages NIDDK to prioritize and expand research in the area of pediatric disease in collaboration with the IBD patient and professional community. (p. 94)

Action taken or to be taken

Please refer to page 52 of this document for NIDDK’s response to this item.

Item

Interstitial Cystitis (IC) — The Committee is concerned by the significant drop in overall funding for interstitial cystitis, with both the ending of the IC Clinical Trials Network [ICCRN] and the conclusion of an IC-specific basic science initiative. The Committee notes that this drop occurs at a time when a RAND epidemiology study of IC concluded that the prevalence of this disease is close to 4 million Americans, nearly fourfold the original estimates. Therefore, the Committee urges the NIDDK to resume the ICCRN as well as a dedicated IC-specific investment in basic science. (p. 94, 95)

Action taken or to be taken

NIDDK remains committed to improving our understanding of the underlying causes of interstitial cystitis, also referred to as painful bladder syndrome (IC/PBS), and ultimately improving patient care, through the active support of basic, translational, and clinical research. Regarding funding for IC/PBS, NIH’s shift to a new computer-based process—requested by the Congress—to report on its portfolio for over 200 diseases and conditions, called the Research, Condition, and Disease Categorization (RCDC) system, has led to changes in reported funding levels for a variety of conditions, including IC/PBS. There are a number of reasons for these differences, including more or less restrictive “definitions” for some disease reporting categories under the new system; more information is available

at <http://report.nih.gov/rcdc/reasons/> . NIH began using RCDC to report actual funding levels in FY 2008. While the change in reported IC/PBS funding during the transition to the RCDC system can be disconcerting, it is important to note that it does not reflect a change in NIDDK's commitment to research on IC/PBS. For example, in September 2008, following several meetings with the research and advocacy community, NIDDK launched a new and novel collaborative research network to address key questions of clinical relevance in IC/PBS and another urologic pain syndrome, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), including the potential relationship of IC/PBS with a number of urologic and non-urologic pain conditions often found in patients. NIDDK's Multidisciplinary Approach to the Study of Urologic Chronic Pelvic Pain (MAPP) Syndromes Research Network has now developed several collaborative scientific studies designed to uncover the underlying causes of IC/PBS and to characterize the disease profiles (phenotypes) in patients. Patient recruitment was initiated in fall 2009. The goals and approaches of the MAPP Research Network reflect the most current thinking on IC/PBS pathology and involve significant new advancements in how IC/PBS is studied over previous basic and translational approaches. All efforts are designed to provide insights that can be translated to improve the clinical care of IC/PBS patients. It is anticipated that MAPP findings will help guide NIDDK's future basic and clinical research efforts in IC/PBS.

NIDDK has committed \$37.5 million dollars over five years to the MAPP Research Network, beginning in FY 2008. In addition, through the American Recovery and Reinvestment Act of 2009 (ARRA), NIDDK provided in FY 2009 an additional \$1.5 million to the MAPP Network to expand its scientific efforts, specifically to enhance its ability to recruit appropriate patient and control groups. These funds are being provided as administrative supplements to the MAPP Research Network sites. In addition, the NIDDK has recently funded an ARRA Challenge Grant to test a novel nanoparticle "Trojan horse" method of delivering novel therapeutics to the bladder. Other steps NIDDK is taking to advance basic and clinical research on IC/PBS include a scientific meeting planned for spring 2010 through which it hopes, in part, to foster the cadre of investigators in the field and thereby strengthen the pool of applicants for research funding. In addition, NIDDK continues to work with other NIH Institutes and Centers in collaborative efforts to advance IC/PBS research. This includes NIDDK recently joining the Trans-NIH Pain Consortium and participation in drafting future basic and translational science funding initiatives developed by the Consortium, which will include language promoting studies specific for IC/PBS. (p. 100)

Item

Irritable Bowel Syndrome — The Committee commends NIDDK for its expansion of the research portfolio on irritable bowel syndrome. (p. 95)

Action taken or to be taken

The NIDDK is pleased with the Committee's commendation of its irritable bowel syndrome (IBS) research portfolio. The Institute's portfolio includes a strong basic research program in IBD. The Center for Neurovisceral Sciences and Women's Health, supported by the NIDDK, Office of Research on Women's Health, National Center for Complementary and Alternative Medicine, National Institute of Nursing Research, National Institute of Arthritis

and Musculoskeletal and Skin Diseases, and the VA Medical Research Program, conducts valuable research on understanding of how stress, pain and emotion interact in health and disease with the aim of discovering more cost effective ways to prevent chronic disorders, such as IBS. An NIH Challenge grant has recently been awarded to study IBS-diarrhea.

Item

Kidney Disease — The Committee urges the NIDDK to prioritize research on: the relationship between kidney disease and its leading causes, particularly diabetes, hypertension, and obesity; methods for prevention; and appropriate and effective therapies that improve disheartening mortality statistics. In particular, the Committee urges the NIDDK to emphasize research support for acute kidney injury, diabetic nephropathy, glomerular disease, hypertension, transplantation, and kidney-related cardiovascular toxicity. Additional resources are needed to support the development of new disease biomarkers and imaging technologies, which are critical for the management of kidney diseases; implement the necessary infrastructure for disease-specific registries and clinical trials networks to better allow investigators to bridge the gap from the bench to the bedside; and track data on patient race and ethnicity to understand the overwhelming disparities related to morbidity and mortality of kidney disease among underrepresented minority patients. The Committee requests an update on these priorities in the fiscal year 2011 congressional budget justification. (p. 95)

Action taken or to be taken

Please refer to page 53 of this document for NIDDK's response to this item.

Item

Liver Disease — The Committee urges the NIDDK to redouble its efforts to address the recommendations in the Action Plan on Liver Research developed in 2005. (p. 95)

Action taken or to be taken

The trans-NIH *Action Plan for Liver Disease Research* was developed under the auspices of the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee, based on input from a broad range of external investigators involved in liver disease research, staff of the NIH, other Federal agencies, industry, health care providers, and concerned lay persons. The NIDDK provided leadership and support for this trans-NIH effort. The NIH remains committed to the primary purpose of the Action Plan, which is to advance research on liver and biliary diseases, with the ultimate aim of decreasing their burden in the U.S. and worldwide, and to its specific research goals for the decade.

Since the Action Plan's release in 2004 (<http://liverplan.niddk.nih.gov>), the Liver Disease Subcommittee has taken an active and collaborative approach to its implementation. Implementation activities include Subcommittee meetings and annual progress reviews with input from researchers external to the NIH. Larger meetings are planned for the 5-year and 10-year marks to encourage public participation and input for realizing the *Action Plan's* goals. The progress reviews developed each year by the Subcommittee summarize progress made during the previous year toward achieving each of the goals in the *Action Plan*, based on input from Federal and external experts who participated in the *Action Plan's* development. The progress reviews are available for public input on the *Action*

Plan's website. Additionally, in 2006, the NIDDK submitted a requested report to Congress on “Activities and Future Plans for Implementing the *Action Plan for Liver Disease Research*.” The *Action Plan* also directly informed development of liver and biliary disease-related goals in the research plan developed by the National Commission on Digestive Diseases released in 2009 (<http://NCDD.niddk.nih.gov>).

The NIDDK continues to provide leadership and support for the Liver Disease Subcommittee’s active monitoring of research progress and implementation of research activities addressing the *Action Plan’s* goals. In developing its own research programs related to liver and biliary diseases, the NIDDK continues to be guided by the *Action Plan’s* goals and utilizes it as a resource for developing new initiatives, awarding grants that address research goals, and identifying opportunities for collaborating with other NIH Institutes and Centers, as well as external research partners.

Item

Pelvic Pain — The Committee recognizes that there is a growing population of patients with chronic pelvic pain, chronic prostatitis and urogenital pain, and it urges the NIDDK to collaborate with the ORWH, NIAID, NIAMS, NINDS, and NICHD to establish a dedicated center for research and education on urologic/urogenital chronic pelvic pain and chronic prostatitis syndromes that will focus specifically on interstitial cystitis and vulvodynia, and related co-morbid disorders. (p. 95)

Action taken or to be taken

NIDDK and NIH are committed to research that can help understand, prevent, and improve treatment for pelvic pain conditions. In 2008, NIDDK launched a new and novel collaborative research network to address key questions of clinical relevance in the most common forms of chronic urologic pelvic pain, interstitial cystitis/painful bladder syndrome (IC/PBS), and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)—including the potential relationship of these conditions with a number of urologic and non-urologic pain conditions often found in patients. In exploring this relationship, scientists in the Multidisciplinary Approach to the Study of Urologic Chronic Pelvic Pain (MAPP) Research Network are focusing on conditions most strongly associated with IC/PBS and CP/CPPS in scientific studies thus far—chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. Opportunities also exist for MAPP investigators to propose additional, ancillary studies that capitalize on the Network’s research resources, which may be funded following review by an external scientific advisory committee. NIDDK has worked with NINDS, NICHD, and ORWH in developing the MAPP research focus. NIH is also conducting focused efforts to promote research and education on the poorly understood urogenital pain condition, vulvodynia. The lead Institute for vulvodynia research, the NICHD, has collaborated with the ORWH to promote studies and raise awareness of this condition. In fall 2007, ORWH, in partnership with NICHD, NINDS, and the NIH Pain Consortium, as well as the National Vulvodynia Association, the American College of Obstetricians and Gynecologists, and other professional groups, launched the Vulvodynia Awareness Campaign to inform the public about this condition and NIH research efforts to combat it. This campaign has also been highlighted on the NIH Pain Consortium website. The NIH will continue to foster and support research on vulvodynia, and to coordinate educational efforts for patients and physicians based on research and scientific evidence.

Item

Polycystic Kidney Disease (PKD) — The Committee urges the NIDDK to plan the future strategic direction of PKD research, expand the number of PKD researchers and strengthen current efforts, which include multiple clinical trials and the development of treatments. The Committee also encourages the NIDDK to look at the feasibility of establishing a core repository of laboratory animals for renal cystic diseases like PKD, which will help lower research costs and enhance scientific discoveries in this burgeoning area of translational research. (p. 95)

Action taken or to be taken

Please refer to page 54 of this document for NIDDK's response to this item.

Item

Urological Diseases — The Committee is disappointed that the NIDDK has not established a separate branch for urological diseases research. The Committee requests the Institute to provide an update in the fiscal year 2011 congressional budget justification on how it will move forward to strengthen urological diseases research, and to prepare a trans-NIH Action Plan for Urological Disease Research. (p. 95, 96)

Action taken or to be taken

NIDDK is actively involved in strengthening research on benign urologic diseases through effective use of its current organizational structure. Currently, several senior NIDDK scientific staff direct a multi-faceted urology research program ranging from basic research to epidemiology and clinical trials, and recruitment is under way for a new staff member to lead program efforts in clinical and translational urology research. Through its chairmanship of the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, NIDDK also coordinates trans-NIH urologic diseases research, fostering collaborations across the NIH in this area.

Despite significant progress in basic knowledge and therapeutics made possible through NIDDK supported studies, gaps exist in urologic diseases research that limit the development of future therapies. NIDDK has been working closely with the urology research community to close these gaps. In 2009, NIDDK held its second meeting in two years with leaders in academia and professional societies to identify factors that are hindering research progress, and to develop solutions targeting the respective roles of NIH and the extramural community. Building on these efforts, NIDDK has taken several steps to revitalize the urology research community. For example, NIDDK initiated support for a multidisciplinary career development research training program for urology researchers and revised its George M. O'Brien Urology Research Centers program. NIDDK is also working with the NIH Center for Scientific review to enhance peer review of urology research grant applications to the NIH. Moreover, through the NIH Challenge Grant initiative and other opportunities made available by the American Recovery and Reinvestment Act, NIDDK funded several grants addressing scientific challenges in urology. Moving forward, the Institute will continue to implement recommendations from its strategic planning meetings with the urology research community leadership. NIDDK also continues to work with the American Urological Association (AUA) on issues of research

and research training. In 2009, senior NIDDK scientific staff attended the AUA's National Urology Research Summit as *ex officio* observers. NIDDK staff also contributed ideas to the AUA's new strategic research plan emerging from this meeting.

Finally, NIDDK continues to plan strategically to address current and future challenges and opportunities in NIH-supported urology research. In the past three years, NIDDK has spearheaded strategic plans for research in pediatric urology and prostate disease. Recent scientific meetings on urinary incontinence, benign prostatic hyperplasia (BPH), and the urologic complications of diabetes and obesity, as well as meetings planned for 2010 on neuro-urology and on brain imaging in urologic pelvic pain, will contribute to NIDDK's planning process by identifying gaps in the current knowledge base for these areas. These examples of new and ongoing program enhancements in urology research, strategic planning, and research training, demonstrate NIDDK's continuing commitment to strengthening research that can help reduce the burden of urologic diseases on men, women, and children in the United States now and for the future.

**National Institute of Neurological Disorders and Stroke
(NINDS)**

House Significant Items

Item

Charcot-Marie-Tooth (CMT) - The Committee commends NINDS for its recent efforts to advance understanding and development of therapies for CMT and related neurodegenerative diseases. NIH has undertaken an innovative partnership with a voluntary health association involving high throughput screens to identify candidate treatments that will quickly be brought to clinical trials. The Committee supports this effort and believes that such translational research has the greatest potential to rapidly develop therapies for patients with CMT and other degenerative disorders. The Committee encourages NINDS to develop innovative communications mechanisms to ensure that information on treatments can be shared in an accurate and timely manner with practitioners and patients. (p. 116)

Action taken or to be taken

NINDS continues to support new translational research strategies in CMT and related disorders. In 2009, NINDS used funding from the American Recovery and Reinvestment Act (ARRA) to support a grant to identify new compounds to treat CMT. The results of this grant will lay the groundwork for future studies to develop and test these compounds as potential therapies for CMT. In addition to supporting clinical and translational research focused on the natural history and diagnosis of peripheral neuropathies, NINDS continues to partner with the CMT Association, which uses high throughput screening approaches to identify candidate treatments for neuropathies. NINDS provides expertise and advice on this project, and is encouraging investigators to apply for translational NINDS grants.

NINDS-funded researchers have recently created the Hereditary Neuropathy Consortium (HNC), consisting of clinical researchers from around the world with demonstrated expertise in CMT. Through this consortium, researchers will develop a Pediatric Scoring System for CMT patients, as well as undertake a natural history analysis of different CMTs caused by a variety of genetic mutations. The scoring system will be used around the world to measure impairment and progression of disability in children with CMT. In addition, these projects will provide insights into disease mechanisms as well as help to develop therapies for CMT and other inherited neuropathies.

NINDS, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), released Funding Opportunity Announcements (FOAs) in August 2008 to promote translational research in neuromuscular diseases, including CMT. The first announcement was designed to encourage preclinical therapy development of candidate therapeutics. The companion FOA was established to catalyze the development of drugs and devices to aid in the treatment of neuromuscular disorders.

NINDS places a high priority on developing communications mechanisms to share information on treatments with the public. The website of NINDS contains links to over 400 disorders, including CMT with each link containing up-to-date information on

treatment, prognosis, research advances, organizations, links to patient groups, and related publications. In 2008, NIH launched the website, Research Portfolio Online Reporting Tool (RePORT), which allows the public to search for relevant grants and strategic plans in many disease areas. In 2009, the RePORT Expenditures and Results (RePORTER) module was launched, which provides access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and results of NIH-supported research. RePORTER also provides links to publication and patent databases. Also, the HNC will develop a website that will allow patients and researchers to learn about the latest information on treatments for CMT.

Item

Dystonia - The Committee continues to support research on treatment regarding the neurological movement disorder, dystonia, and recommends that NINDS consider updating the recent program announcement on dystonia research. (p. 116)

Action taken or to be taken

NINDS continues its strong commitment to dystonia research in both its intramural and extramural programs. To follow up a scientific workshop on dystonia, the NINDS together with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute of Environmental Health Sciences (NIEHS), and in conjunction with the Dystonia Medical Research Foundation (DMRF) and the Bachmann-Strauss Dystonia and Parkinson Foundation, Inc. issued a set of program announcements in 2007 on “Understanding and Treating Generalized and Focal Dystonias.” The announcements invite research grant applications aimed at understanding or treating generalized and focal dystonias and encourage basic, translational and clinical studies. The announcements will be active through July 2010.

In 2009, NINDS solicited research on a key research issue for dystonia, the development of *in vitro* assays (laboratory tests) to assess the potency of Botulinum toxin type A, which is used in the treatment of dystonia. Dystonia researchers are also eligible for all NINDS investigator-initiated grant programs and for several other active NINDS solicitations. In 2009, for example, NINDS and the NIH Office of Rare Diseases Research (ORDR) are cofunding a major grant for a Dystonia Coalition to advance clinical research on dystonia. This multi-investigator grant is part of the Rare Diseases Clinical Research Consortia program. In another effort to promote collaboration and resource sharing, the NINDS Human Genetics Repository expanded to accept clinical samples from dystonia and distribute valuable DNA and other resources to the research community.

As the 2007 program announcement on generalized and focal dystonias nears its termination date in July 2010, NINDS is reviewing the current research program in dystonia. The Institute will assess unmet research needs and determine how best to foster progress against dystonia. The NINDS Intramural Research Program also continues an active research program to understand what goes wrong in the brain during dystonia and to translate those insights into therapies, including clinical trials to test drugs and other treatments.

Item

Dystonia: Intramural- The intramural program at NIH continues to advance research activity in dystonia, and the Committee encourages continued support in this area of study. (p. 117)

Action taken or to be taken

Dystonia is a disorder of the brain circuits that control movement. In dystonia, brain signals cause strong and abnormal co-contraction of muscles that produce opposite movements. This can be widespread or localized to certain parts of the body and leads to abnormal postures, impaired movement control, and pain. The NINDS Intramural Research Program's Human Motor Control section has a strong research program to understand how abnormal movement control in the brain results in dystonia and to translate those insights into therapies. Recent research from the intramural program has shown abnormal function of certain types of nerve cells in the cerebral cortex that normally inhibit the activity of other nerve cells, which may represent the fundamental problem that underlies dystonia. The intramural program is continuing its clinical research efforts to understand how abnormal movement control circuits in the brain lead to dystonia using imaging of brain activity, measurements of brain electrical activity, clinical assessments of movement, and genetic analyses.

Intramural investigators are also working to translate new findings into novel therapeutic strategies for dystonia. Studies have included drugs, including botulinum toxin, devices, including transcranial magnetic stimulation and deep brain stimulation, and behavioral interventions that alter abnormal brain circuits. The Intramural group frequently publishes findings from their multiple dystonia studies, and we expect that will continue in the coming year.

Item

Epilepsy – Epilepsy affects the lives of more than 3 million Americans and their families. The Committee applauds NINDS for hosting the "Curing Epilepsy 2007" conference that has resulted in community-determined benchmarks designed to fast-forward the progress of finding a cure for epilepsy. While recognizing that NINDS is working toward advancement of a cure through all of the benchmarks, the Committee is particularly interested in three areas of epilepsy research and encourages NINDS to focus attention on grants and mechanisms that address epileptogenesis, comorbidities, and sudden unexplained death in epilepsy. Epilepsy often occurs as the result of changes in the brain following a head trauma. Such trauma is prevalent in soldiers who suffer traumatic brain injury, which leads to post-traumatic epilepsy in subsequent months. Epileptogenesis research on the origin of this disorder can lead to new approaches to preventing epilepsy and its progression through new insights for treating post-traumatic epilepsy both on and off the battlefield. Epilepsy is often accompanied by other neurological conditions such as stroke, Alzheimer's and autism. By understanding that epilepsy is not just an isolated condition causing seizures but may be the connection among various cognitive disorders, researchers can study co-morbidities and address the problem of senior citizens experiencing seizures for the first time. The Committee encourages researchers to study family history, interactions with medications, and create animal models to help solve the mysteries of sudden unexplained death in epilepsy and prevent death from seizures. The

Committee recognizes that clinical researchers are needed to carry out trials and studies to test findings and further develop the research initiatives from the Curing Epilepsy 2007 conference. The Committee encourages NINDS to provide sufficient support to carry out such clinical research. (p. 116,117)

Action taken or to be taken

In 2007, NINDS released revised Epilepsy Research Benchmarks, first developed in 2000 in collaboration with epilepsy researchers, clinicians and patient advocacy groups, as a set of shared goals for the epilepsy community. While research is actively ongoing in many Benchmarks areas, a shared implementation strategy may further accelerate advances. NINDS will develop such a strategy with the participation of the Interagency Epilepsy Working Group, which NINDS has chaired since 2003 and will now expand to include representatives from across NIH and from advocacy groups, the research community, and additional government agencies. In developing an implementation strategy based on the Benchmarks, the group will emphasize efforts to address epileptogenesis, comorbidities, and Sudden Unexplained Death in Epilepsy (SUDEP).

Many current projects supported or conducted by NINDS focus on epileptogenesis, including an ongoing longitudinal study to clarify the relationship between prolonged febrile seizures in childhood and the development of chronic temporal lobe epilepsy. A range of other studies are investigating epileptogenic mechanisms associated with brain malformations, genetic defects, and precipitating insults like traumatic brain injury (TBI), neonatal oxygen deprivation, stroke, or infection. These studies are identifying changes in brain circuits and signaling pathways that may be targeted to prevent escalation into chronic epilepsy. The NINDS Anticonvulsant Screening Program, which has long played a major role in developing antiepileptic drugs, also presents opportunities for greater emphasis on epileptogenesis and anti-epileptogenic therapeutics. Regarding post-traumatic epilepsy, NINDS recently organized the Federal Interagency TBI Research (FITBIR) network to facilitate communication, coordination, and collaboration in TBI research and will seek opportunities to include a focus on post-traumatic epilepsy in military and civilian populations in FITBIR activities and other collaborations.

To identify needs and directions for research to understand and prevent SUDEP and ways to increase awareness, NINDS held a workshop in November 2008. NINDS is actively considering mechanisms for targeted research and participates in a SUDEP coalition along with the American Epilepsy Society and patient advocacy groups. NINDS also supports and conducts research on cognitive deficits, depression, and other comorbid conditions in epilepsy as well as on epilepsy associated with other disorders including Alzheimer's disease (AD), autism, and disorders like tuberous sclerosis that can present with both epilepsy and autism. Shared mechanisms across such conditions may provide new insights into the causes of epilepsy and targets for intervention. The 2008 NINDS workshop "Dementia of Alzheimer's Disease (AD): Converging Mechanisms" focused on seizure incidence in AD, shared features with temporal lobe epilepsy, and the potential for antiepileptic drugs to treat seizures and cognitive impairment in AD.

NINDS remains committed to supporting and conducting basic, translational and clinical research to understand the many forms of epilepsy and to develop interventions, and

ultimately cures. NINDS also provides training and career development support for new epilepsy investigators, including clinical researchers. As another way to support clinical research, NINDS is developing a set of common data elements for epilepsy that will facilitate data sharing and comparisons and analyses across clinical studies.

Item

Familial Dysautonomia (FD) — The Committee commends NIH for supporting research that has led to progress in FD-related genetic therapy and animal models, and encourages NINDS to place a high priority on basic, clinical and translational research that could lead to advances in medical outcomes for people suffering from FD. The Committee is concerned that people suffering from rare autonomic disorders, and specifically people suffering from FD, continue to face premature mortality and severe morbidity. Despite recent advances in FD life expectancy, the Committee believes that more research is needed to better understand the underlying mechanisms of this disease, to develop more effective treatments, and to prevent or slow down the degenerative effects of FD. (p. 117)

Action taken or to be taken

Familial dysautonomia is a rare and fatal genetic disease that causes a progressive degeneration of nerve cells, leading to widespread dysfunction of the sensory and autonomic nervous systems. Because of the key role of the nervous system in regulating the body, the disease causes problems with every major organ system. Among the many serious consequences are impaired temperature and pain sensation and inability to produce tears, as well as problems with the regulation of heart, blood pressure, respiration, digestion, and swallowing. Although advances in care have extended life expectancy, children with the disease still suffer from many serious problems that affect quality of life. With the discovery of gene defects that cause familial dysautonomia in 2001, the prospects for understanding the underlying causes and developing definitive therapies has improved. NIH continues to support an active investigator-initiated program of research to understand exactly how the identified genetic defects cause the problems of familial dysautonomia and to develop therapies. New and ongoing grants enabled by knowledge of the gene are, for example, using cell and animal models of the disease to test specific hypotheses about how alterations in a molecule that regulates polarized cell growth, reductions in a natural nerve growth and survival molecule called NGF, and alterations in RNA splicing, which is part of the process by which cells read out the blueprint coded by genes, lead to the devastating manifestations of familial dysautonomia. Researchers are using what they learn in experiments like these to develop and test drugs designed to alter the disease process, including, for example, drugs that correct the RNA splicing problem.

In addition to these continuing efforts, NIH announced in October 2009 a major addition to the research effort related to autonomic nervous system disorders in general. As part of the expansion of the Rare Diseases Clinical Research Network (RDCRN), which is led by the NIH's Office of Rare Diseases Research (ORDR), the ORDR and the NINDS are co-funding the "Autonomic Rare Diseases Clinical Research Consortium." The Consortium brings together researchers at Vanderbilt University, the Mayo Clinic, New York University, Harvard University, and the NINDS Intramural Research Program. They are taking a multidisciplinary approach to autonomic disorders with the goal of developing treatments that not only improve quality of life, but also alter the course of disease. Consortium

members have ongoing studies related to several autonomic disorders, including familial dysautonomia. A team-based multidisciplinary approach is especially important for diseases like autonomic disorders that have widespread consequences on organ systems of the body. In addition to research itself, the Consortium is committed to training physicians and scientists in the investigation and treatment of rare autonomic disorders, to developing resources that will catalyze research on these diseases, and to enhancing communication and cooperation among scientists, patients and their families, non-governmental organizations, and the general public on autonomic disorders.

Item

Hypoglycemia - The Committee recognizes NINDS's efforts to organize a workshop of leading experts to identify the challenges and opportunities for preventing episodes of dangerously low blood sugar levels (hypoglycemia). Hypoglycemic episodes affect the majority of people with diabetes, and the threat and incidence of hypoglycemia is a major limiting factor in intensive glucose control. The Committee requests that NINDS consider a pilot study to improve the understanding of hypoglycemia. (p. 117,118)

Action taken or to be taken

An adequate brain supply of glucose is typically ensured through a number of nervous, hormonal, and metabolic responses to falling glucose levels. Chronic hypoglycemia, which occurs in Type 1 (T1D) and Type 2 diabetes patients treated with insulin, can lead to hypoglycemia unawareness (HU), where the body cannot tell that glucose levels are falling dangerously low. NINDS supports research to understand the interplay between glucose control and the brain, biological consequences of hypoglycemia, and potential therapeutic approaches.

For example, one study is investigating whether hypoglycemia-induced increases in brain glycogen, a molecule that can be converted to glucose, are responsible for the development of HU and whether transplantation of insulin-secreting pancreatic cells can restore proper glucose regulation to T1D patients. Through human and animal research, another group is exploring the brain metabolic adaptations that are induced by hypoglycemia and that may contribute to HU. A potential source of injury is re-infusion of glucose after a hypoglycemic attack because it may trigger harmful reactive oxygen species and hasten neuronal death. NINDS-funded researchers are studying this mechanism and are trying to identify adjunct treatments to prevent brain injury during glucose infusion. The long-term cognitive effects of a diabetic pregnancy and fetal hypoglycemic events are also being explored through an NINDS-funded study. Results from these studies are expected to be published during the grant period, which generally runs 2-5 years, depending on the type of grant.

Other NIH Institutes also support important research on hypoglycemia. NIDDK has a strong research program on energy metabolism and on interventions to prevent and treat T1D and T2D. It also funds animal studies on the molecular and physiological mechanisms that allow the brain's hypothalamus to sense falling levels of glucose and supports a study following a cohort of T1D youth to determine whether hypoglycemic events have negative cognitive consequences. NICHD supports the Diabetes Research in Children Network (DirecNet), which focuses on non-invasive strategies to monitor plasma glucose levels and

prevent hypoglycemic attacks. Recently, NICHD partnered with NINDS to enhance DirecNet's ability to study the neurocognitive effects of major glucose fluctuations and the phenomenon of nocturnal HU. Researchers in DirecNet and the NIDDK-funded TrialNet recently partnered to study glucose metabolism in T1D patients connected to a glucose sensor, an insulin pump, and a computer. This project will pave the way for a much needed artificial pancreas for T1D patients.

In September 2009, NINDS, NIDDK, NHLBI, NEI, NICHD, and the Juvenile Diabetes Research Foundation hosted a workshop on CNS and Glycemic Control to explore research on how the brain senses glucose levels and helps maintains balance, mechanisms that promote glucose dysregulation, hypoglycemic brain injury, and potential therapeutic interventions. A summary of the meeting and recommendations for how NIH can stimulate new research and interdisciplinary collaborations have been posted on the NINDS website.

Item

Opsoclonus Myoclonus Syndrome (OMS) – OMS is a rare, autoimmune disorder that targets the brain. In childhood it is associated with neuroblastoma of the chest, abdomen or pelvis. Besides the symptoms of involuntary eye movements, tremulousness, muscle jerks, and gait disorder, the patients have rages, inability to sleep, and may become mute and unable to sit or stand. Permanent problems in motor control, language development, behavior and cognition-even mental retardation-are common. The available treatment options for OMS are extremely limited. The Committee urges NINDS to accelerate research efforts to identify OMS susceptibility genes and biomarkers, and to develop innovative immunotherapeutic strategies. The Committee also encourages NINDS to develop grant opportunities to support further research and to work with private associations in NIH sponsored workshops on OMS. (p. 118)

Action taken or to be taken

NINDS supports and conducts basic and clinical research on autoimmune diseases of the nervous system, as well as translational and clinical research to develop interventions to treat or prevent immune-mediated damage to nervous system tissues. Paraneoplastic neurological disorders, such as OMS associated with neuroblastoma, arise when the body's immune response to a tumor cross-reacts with proteins normally expressed in the brain, which then becomes the target of an autoimmune attack. Ongoing research supported by NINDS includes studies on neuronal proteins targeted by such autoimmune attacks in OMS and other paraneoplastic disorders. Understanding how these proteins function in neurons may provide new insights into the causes of OMS and related disorders and could inform new treatment strategies.

Other NIH Institutes also support research relevant to OMS. For example, the Children's Oncology Group, supported by NCI, is conducting a Phase III clinical trial (NCT00033293) to assess and compare the effectiveness of chemotherapy and the steroid prednisone with or without intravenous immunoglobulin for treating patients with OMS associated with neuroblastoma. NINDS also participates with several other NIH Institutes to support a Program Announcement (PA) on "Functional Links between the Immune System, Brain, and Behavior." This PA solicits research on immune molecules, cells, and mechanisms

involved in regulating normal and pathological central nervous system functions. Grant applications to study or develop treatments for OMS would be viewed as highly responsive to this PA. NINDS will also participate in an upcoming research conference, coordinated by ORDR in collaboration with private associations, on OMS planned for spring 2010. A major focus of the conference will be on issues related to sharing patient samples, which would facilitate further research efforts to identify susceptibility genes and biomarkers.

Item

Peripheral and Autonomic Neuropathy - NINDS is urged to consider renewing its focus on methods to prevent and treat nerve damage due to disease, especially diabetes. (p. 118)

Action taken or to be taken

Millions of people in the United States suffer from neuropathy-related pain associated with diseases such as diabetes, acquired immune deficiency syndrome (AIDS), and cancer. Research on the causes, prevention, and treatment of neuropathies continues to be a priority for NINDS.

NINDS is particularly committed to funding research to treat and prevent diabetic neuropathy (DNP), which will develop in more than 50 percent of diabetic patients. For example, NINDS-funded researchers are using high-throughput screening methods to identify useful DNP biomarkers, which could allow for early diagnosis and accurate prediction of the development and rate of progression of the disease. NINDS has several ongoing grants to investigate treatment of DNP. Research is underway to identify and characterize specific proteins that could serve as therapeutic targets for treatment. NINDS-funded researchers are investigating whether low intensity ultrasound treatment can prevent and/or reverse the development of neuropathy, first in rat models and then in individuals with neuropathies. NINDS supports efforts to advance research in the prevention of DNP. For example, NINDS is funding an epidemiological study to identify risk factors for different types and severities of neuropathy. Another NINDS-funded study is developing gene therapy to prevent diabetic neuropathy.

NINDS also places a priority on working with other institutes to further knowledge of neuropathies related to disease. In 2009, NINDS, NIDDK, NHLBI, NICHD, NEI, and the Juveniles Diabetes Research Foundation, held a workshop on the nervous system and its control of blood sugar. The workshop identified research opportunities, key needs of the relevant research communities, and opportunities for collaborations between diabetes and neuroscience researchers.

NINDS supports research on neuropathies associated with AIDS and cancer. NINDS, along with the National Institute on Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Drug Abuse (NIDA), issued a funding opportunity announcement (FOA) in 2006 soliciting applications on preclinical therapeutics development for NeuroAIDS. NINDS is now funding studies to develop novel diagnostic tests for HIV-related peripheral neuropathy. In addition to HIV-related neuropathy, NINDS is funding research to study nerve damage caused by chemotherapy.

While improvements in chemotherapy have increased the cancer patient's life span, these drugs produce severe neuropathic side-effects, such as numbness, tingling, and pain, which can become chronic. NINDS is currently funding research to reproduce neuropathy in rats receiving the drug, paclitaxel (Taxol), in order to better understand the cause of neuropathic pain and to gain insight into its prevention. Results of these studies are expected to be published in the next 2-5 years.

Item

Stroke – The Committee encourages NINDS to expand current stroke studies and related activities, support new stroke initiatives, and to implement priorities in its Stroke Progress Review Group Report. (p. 118)

Action taken or to be taken

The Stroke Progress Review Group's (SPRG) recommendations continue to guide NINDS priorities. Safer and more effective approaches to early diagnosis and treatment of acute stroke patients are being explored through the Specialized Programs of Translational Research in Acute Stroke (SPOTRIAS). Due to its success, a program announcement was released this year to invite new and renewal grant applications for this network. SPOTRIAS and other NINDS-funded investigators are examining the use of statins, hypothermia, tissue oxygenation, intra-arterial therapy, and other interventions, to improve outcomes and extend the acute stroke treatment window.

Translational research is a key recommendation of the SPRG. Several promising pre-clinical ideas are being developed through the NINDS Cooperative Translational Research Program. Strategies for protecting the brain from lack of blood flow by: making it more tolerant to ischemia, inhibiting harmful processes, and protecting different cell types, are being evaluated for therapeutic potential in stroke patients.

Brain hemorrhage is the most lethal form of stroke and was the focus of several SPRG recommendations. Several NINDS-funded animal studies have recently shown that deferoxamine, a drug that removes excess iron from the body, provides protection after brain hemorrhage. A clinical study has been awarded to evaluate this drug's safety in hemorrhagic stroke patients. More immediate options are being explored through a recently-funded phase III trial comparing the medical practice of physically removing a blood clot after hemorrhage to the combination of removal and the clot-buster tPA.

Research on stroke rehabilitation was also a topic of SPRG recommendations. NINDS supports a number of critical rehabilitation studies including a recently-funded phase III trial that will compare an intensive, individualized, task-based arm therapy to two standard types of arm therapy. A recent workshop, "Promoting Generalization in Stroke Rehabilitation," organized by NINDS, NICHD, NIA, NIDCD, the VA and a number of rehabilitation therapy organizations, brought together basic science researchers in motor, cognitive, and social learning, and clinical investigators in rehabilitation to address scientific and clinical issues related to generalization, or the applicability of skills learned in one type of rehabilitation setting to other areas of function. A summary of the meeting will soon be posted on the NINDS website.

Two new studies will further the Institute's goals for stroke prevention. NINDS is co-funding part of the NHLBI's SPRINT trial, which will evaluate whether intensive lowering of blood pressure prevents cardiovascular disease and stroke. NINDS has also recently funded the Platelet-Oriented Inhibition in New TIA (POINT) trial, which is examining whether the drug clopidogrel is effective in the reduction of the risk of stroke after a transient ischemic attack or mini-stroke. Results from these studies are expected to be published during the grant period, which generally runs 2-5 years, depending on the type of grant.

Senate Significant Items

Item

Chiari Malformation - The Committee notes that a research conference titled "Chiari Malformation: State of the Research and New Directions" was convened in November 2008 to identify the current state of knowledge and identify key areas of research. The Committee encourages aggressive measures toward implementing these recommendations, including but not limited to: using advanced engineering and imaging analysis to develop an objective diagnostic test for symptomatic chiari; understanding the genetic basis of chiari; and increasing focus on pediatric patients, including symptoms, optimal treatments, and quality of life issues. (p. 96)

Action taken or to be taken

In November 2008, NINDS, NICHD, and the NIH Office of Rare Diseases Research (ORDR), together with Conquer Chiari, Column of Hope, and the American Syringomyelia Alliance Project, sponsored the conference "Chiari Malformation: State of the Research and New Directions." Sessions focused on current knowledge about Chiari, recent research developments, and recommendations for advancing research and care. NINDS is promoting progress in areas the conference highlighted through research to understand and develop treatments for Chiari and other brain malformations.

Toward improved diagnosis, NINDS supports a research partnership between basic scientists, engineers and clinicians to develop and test the clinical utility of a non-invasive brain imaging method for assessing Chiari malformations and potentially other disorders. Chiari malformations can disrupt the normal flow of cerebrospinal fluid (CSF) through the ventricles and channels of the brain and spinal cord. By measuring multiple dynamic parameters related to this flow and pressure in and around the brain, the imaging technique may allow more accurate diagnosis and more informed treatment decisions. To identify genetic factors contributing to Chiari malformations, NINDS supports extramural research and conducts studies in its intramural program on families affected by Chiari type I malformation, the most common form of the disorder.

More generally, NINDS supports a broad portfolio of basic and clinical research on early brain development and the mechanisms underlying congenital brain malformations, which may also yield insights into the causes of Chiari malformations and appropriate intervention measures. In terms of treatment, NINDS intramural researchers are working to determine the optimal surgical treatment of syringomyelia, a condition often associated with Chiari type I malformation in which a fluid-filled cyst develops in the spinal cord. An

ongoing study evaluates and treats subjects with Chiari type I and syringomyelia who have had unsuccessful surgery elsewhere to identify factors related to treatment outcomes.

In some patients with Chiari and other brain malformations, disrupted CSF flow may lead to hydrocephalus, in which excess CSF accumulates in the brain's ventricles. NINDS and ORDR supported a September 2009 workshop held by the Hydrocephalus Association that focused on understanding the pathophysiology of hydrocephalus in order to advance clinical applications. NINDS also leads a trans-NIH working group (with representatives from NICHD and NIBIB) on hydrocephalus and associated disorders, such as Chiari malformations. This group meets regularly to share information about ongoing research across NIH and to identify new research needs and opportunities, including those of particular relevance to pediatric populations.

For example: NINDS and NICHD recently issued a FOA for small business research to improve the design, operation and monitoring of CSF shunts. Such shunts are commonly used to treat hydrocephalus and syringomyelia but are prone to infection or blockage and fail after one year in as many as a third of pediatric patients.

Item

Dystonia - The Committee is pleased with the Institute's support of additional dystonia research grants through its program announcement mechanism, particularly its collaboration with NICHD, NICDC, and NIEHS. (p. 96)

Action taken or to be taken

In 2007, NINDS together with NICHD, NIDCD, NIEHS, and in conjunction with the Dystonia Medical Research Foundation (DMRF) and the Bachmann-Strauss Dystonia and Parkinson Foundation, Inc. issued a set of program announcements in 2007 on "Understanding and Treating Generalized and Focal Dystonias." The announcements invite research grant applications aimed at understanding or treating generalized and focal dystonias and encourage basic, translational and clinical studies. The announcements were issued for a three year duration and will be active through July 2010. Although it is not possible to anticipate how many meritorious applications these announcements will elicit, NIH funded dystonia researchers frequently publish the results of their studies, and we expect that productivity to continue in the coming year.

Dystonia researchers are also eligible for other investigator-initiated grant programs and active solicitations. In 2009, NINDS solicited research on a key research issue for dystonia, the development of *in vitro* assays (laboratory tests) to assess the potency of Botulinum toxin type A, which is used in the treatment of dystonia. In 2009, NINDS and ORDR are cofunding a major new grant for a Dystonia Coalition to advance clinical research on dystonia. This multi-investigator grant is part of the Rare Diseases Clinical Research Consortia program. In some cases, dystonias can be treated as an abnormal motor and sensory plasticity that can be partially reversed through activity-mediated rehabilitation. Research within the National Center for Medical Rehabilitation Research, within at NICHD has focused on movement strategies involving exercise therapies, robotic devices, and/or electrical stimulation. In another effort to promote collaboration and resource sharing, the NINDS Human Genetics Repository expanded to accept clinical

samples from dystonia and distribute valuable DNA and other resources to the research community. The NINDS Intramural Research Program also continues an active research program to understand what goes wrong in the brain during dystonia and to translate those insights into therapies, including clinical trials to test drugs and other treatments.

Item

Epilepsy – The Committee applauds the work of the Interagency Epilepsy Working Group, led by the NINDS, and recommends that the membership be expanded to include representatives from the many other institutes and centers that fund epilepsy research, as well as representatives from the Department of Defense, Food and Drug Administration and patient advocacy organizations. The Committee also recommends that the Interagency Epilepsy Working Group use the 2007 NINDS Epilepsy Research Benchmarks to develop a strategic plan for multidisciplinary approaches to finding a cure for epilepsy. In particular, the Committee urges the NINDS to focus attention on epileptogenesis, comorbidities, and sudden unexplained death in epilepsy. (p. 96)

Action taken or to be taken

In 2007, NINDS released revised Epilepsy Research Benchmarks, first developed in 2000 in collaboration with epilepsy researchers, clinicians and patient advocacy groups as a set of shared goals for the epilepsy community. While research is actively ongoing in many Benchmarks areas, a shared implementation strategy may further accelerate advances. NINDS will develop such a strategy with the participation of the Interagency Epilepsy Working Group, which NINDS has chaired since 2003 and will now expand to include representatives from across NIH and from advocacy groups, the research community, and additional government agencies. In developing an implementation strategy based on the Benchmarks, the group will emphasize efforts to address epileptogenesis, comorbidities, and Sudden Unexplained Death in Epilepsy (SUDEP).

Many current projects supported or conducted by NINDS focus on epileptogenesis, including an ongoing longitudinal study to clarify the relationship between prolonged febrile seizures in childhood and the development of chronic temporal lobe epilepsy. A range of other studies are investigating epileptogenic mechanisms associated with brain malformations, genetic defects, and precipitating insults like traumatic brain injury (TBI), neonatal oxygen deprivation, stroke, or infection. These studies are identifying changes in brain circuits and signaling pathways that may be targeted to prevent escalation into chronic epilepsy. The NINDS Anticonvulsant Screening Program, which has long played a major role in developing antiepileptic drugs, presents opportunities for greater emphasis on epileptogenesis and anti-epileptogenic therapeutics.

NINDS supports and conducts research on cognitive deficits, depression, and other comorbid conditions in epilepsy. This includes, for example, both clinical research and studies in animal models on shared mechanisms in depression and epilepsy and the consequences of recurrent childhood seizures on neuropsychological and cognitive development. Additional NINDS-supported research focuses on epilepsy associated with other disorders including Alzheimer's disease, autism, and disorders such as tuberous sclerosis that can present with both epilepsy and autism. Shared mechanisms across such conditions may provide new insights into the causes of epilepsy and opportunities for

intervention. To identify needs and directions for research that lead to understanding and preventing SUDEP and ways of increasing awareness, NINDS held a workshop in November 2008. NINDS is now actively considering mechanisms for targeted research and participates in a SUDEP coalition with the American Epilepsy Society and patient advocacy groups to coordinate efforts in research and education.

NINDS remains committed to supporting and conducting basic, translational and clinical research to understand the many forms of epilepsy and to develop interventions and ultimately cures. Other major efforts with NINDS support include a large-scale study to identify the genetic basis of some of the most common forms of idiopathic epilepsy and a subset of rare epilepsies; a clinical trial to compare non-invasive radiosurgery with standard temporal lobectomy for temporal lobe epilepsy; and a clinical trial through the NINDS Neurological Emergencies Treatment Trials Network comparing intramuscular versus intravenous anticonvulsant administration for the treatment of status epilepticus, a sustained and life-threatening type of seizure.

Item

Frontotemporal Dementia - Although FTD is as prevalent as Alzheimer's disease (AD) among individuals younger than 65 years of age, a disproportionately small amount of research funding is devoted to it. The Committee requests the NINDS to help develop a minimum data set for FTD, including clinical, biomarker, genetic, and pathologic data, and a national repository for such data. The Committee further urges the NINDS to initiate funding for drug discovery efforts that focus on specific targets relevant to treating the mechanisms underlying brain degeneration due to frontotemporal dementia. (p. 96)

Action taken or to be taken

NINDS has taken several steps in the past year to accelerate research in frontotemporal dementia (FTD). It is in the process of developing a common clinical data set for FTD, recognizing that standardization of FTD data will facilitate collaborations and data analysis across studies. The National Institute on Aging (NIA) Alzheimer's Disease Centers and the National Alzheimer's Coordinating Center (NACC) will provide the necessary infrastructure for FTD patient recruitment and a national data repository. In late 2009, the NINDS, NIA, and Association for Frontotemporal Dementias hosted a workshop to establish a standard protocol for collecting neurological and psychological data on FTD patients, identifying FTD-specific pathology data elements, and developing a plan to integrate FTD data into the NACC data repository. Workshop participants included experts on clinical diagnosis of FTD, FTD pathology, and the use of neuropsychological, imaging, and other biological markers, or "biomarkers," of FTD.

NINDS is co-funding two projects to develop new biomarkers for FTD. The first project is in collaboration with the NIA and will use brain imaging and blood, urine, and spinal fluid analyses to identify biomarkers of disease progression. 120 FTD patients and age-matched control subjects will be enrolled in the 18-month study. The second project is funded by NINDS, NIA, and NIMH through ARRA. The study will develop standardized ways of collecting and analyzing spinal fluid to identify biomarkers for FTD, Alzheimer's disease, and schizophrenia. Results from these studies are expected to be published during the grant period, which generally runs 2-5 years, depending on the type of grant.

NINDS initiated several new therapy development projects for FTD in FY 2009. With ARRA funding, NINDS awarded two grants to develop new FTD animal models and launched an ambitious project to identify drugs that restore a key protein lost in some forms of FTD. In addition, a cooperative agreement was awarded through the NINDS translational research program to develop drugs that clear toxic clumps of protein from brain cells in FTD patients.

Item

Mucopolysaccharidosis (MPS) - The Committee commends the Institute's efforts to collaborate with the Lysosomal Storage Disease Network by participating in scientific conferences on lysosomal storage disorders, and it encourages continued collaborations with the goal of better understanding and treating MPS disorders. (p. 96, 97)

Action taken or to be taken

NINDS has engaged in a number of productive collaborations with non-profit organizations dedicated to lysosomal storage diseases (LSDs), which include the mucopolysaccharidosis (MPS) diseases. In the past few years, NINDS has helped fund several scientific meetings organized by LSD groups, including the annual symposia of the Lysosomal Disease Network (LDN). The LDN is a consortium of basic researchers, clinicians, pharmaceutical industry professionals, and patient advocates who promote and facilitate LSD research. The 2009 LDN symposium included talks on MPS in the basic, translational, and clinical research sessions. The annual symposium helped solidify a network of investigators and patient advocacy group and develop scientific and operational procedures for network so much so that the LDN was successful in obtaining funding as part of the Rare Disease Clinical Research Network. In FY 2009, NINDS funded an application from the LDN to join the NIH Rare Disease Clinical Research Network. As part of this network, the LDN will conduct 11 clinical projects on LSDs. These include natural history studies of MPS I, II, IV, and VI and a study on the impact of growth hormone treatment in MPS I patients. Understanding the natural progression of the MPS diseases could have a significant impact on the field; currently, it is difficult for researchers and clinicians to assess whether interventions are slowing or halting disease progression. The growth hormone study also has the potential to improve clinical treatment of MPS I.

In 2004, NINDS established a therapy development research program in collaboration with the Lysosomal Storage Disease Research Consortium (LSDRC). The LSDRC is comprised of six LSD groups, including the National MPS Society and the Canadian Society for Mucopolysaccharide and Related Diseases. The NINDS and LSDRC released a joint solicitation for projects aimed at improving the neurological symptoms of LSDs. The NINDS organized peer review of the applications and selected a subset for NINDS funding. Applicants not funded by NINDS could be considered for LSDRC funding. Over the course of the program, the NINDS awarded a total of 12 grants and LSDRC supported 13 grants.

Several of the NINDS grants awarded under the NINDS-LSDRC therapy development program focused on MPS diseases. One supported the testing of a drug candidate in a mouse model of MPS I. Two others advanced the development of DNA-based therapies

for MPS I and MPS VII. One of these grants will lead to an investigational new drug application to be approved by the FDA, while others are still early on from being awarded. A fourth NINDS grant enabled the completion of preclinical studies to test the safety and efficacy of an MPS I enzyme replacement therapy delivered through the spinal fluid. Intravenous enzyme replacement therapy relieves many MPS I symptoms but not the neurological aspects of the disease because the enzyme cannot cross from the bloodstream into the brain. The results of the spinal fluid delivery studies were very promising — the treated animals showed improvements in neurological tests. Clinical trials are now being planned.

Item

SMA Carrier Screening – The Committee encourages NHGRI, NICHD, and NINDS to work collaboratively to develop specific recommendations and guidelines for providers and patients on pan-ethnic carrier screening for SMA. The Committee urges the institutes to partner with the relevant professional societies and the advocacy community in this effort. The Committee expects an update on these activities in the fiscal year 2011 congressional budget justifications. The Committee also encourages the Director to establish a trans-NIH working group on SMA composed of the relevant institutes to ensure ongoing support of SMA research and drug development.

Action taken or to be taken

Please refer to page 225 in the Office of the Director's section of this document for the response to this item.

Item

Stroke - The Committee recommends that a significant portion of the additional funds provided for the NINDS will be devoted to expand current stroke studies, support promising and new stroke initiatives, and to implement priorities in its Stroke Progress Review Group Report. (p. 97)

Action taken or to be taken

Please refer to page 76 of this document for NIND's response to this item.

**National Institute of Allergy and Infectious Diseases
(NIAID)**

House Significant Items

Item

Antimicrobial Resistance - The Committee is encouraged by NIAID's commitment to a wide range of research addressing antimicrobial resistance—the development of antimicrobials and diagnostics for drug-resistant bacteria and parasites, partnerships for development of vaccines for selected pathogens, in vitro assessments for antimicrobial activity, and targeted clinical trials. The Committee encourages NIAID to consider additional opportunities to advance research related to antimicrobial resistance and related product development. (p. 118,119)

Action taken or to be taken

Research to respond to the public health threat posed by antimicrobial-resistant organisms remains a priority for NIAID. Recent NIAID efforts have focused on innovative clinical trials aimed at prolonging the effectiveness of currently available antimicrobial drugs.

For example, in 2008, NIAID launched a new initiative, *Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance*. This solicited research program will target disease areas where there is greater risk of development of antimicrobial resistance, and support the design and conduct of clinical protocols that test the safety and effectiveness of different therapeutic approaches and regimens. The ultimate goal of the studies is to reduce the probability of the emergence of drug resistance by minimizing unnecessary drug exposure. In September 2009, NIAID awarded two contracts under this initiative—one targeting urinary tract infections in children and the other focused on staphylococcal bloodstream infections. In August 2009, NIAID released a similar announcement for funding in FY 2010 focused on acute ear infections in children, as well as pneumonia and bloodstream infections caused by Gram-negative bacteria. NIAID plans to continue to support additional clinical trials of strategies aimed at reducing antimicrobial resistance in a similar initiative in FY 2011. Also, NIAID continues to support two contracts under the *Clinical Trial for Community-Acquired Methicillin-Resistant Staphylococcus aureus (CA-MRSA)* initiative. These contracts support clinical trials to determine the optimal treatment of uncomplicated cases of skin and soft tissue infections caused by CA-MRSA using existing off-patent antibiotics.

In addition, NIAID is supporting the development of rapid diagnostic methods to identify infectious microbes and the drugs which may be active against these microbes. This will allow for targeted treatment with specific antimicrobial drugs, reducing the use of broad-spectrum antibiotics and the use of antibiotics in cases of non-bacterial infections.

NIAID continues to provide a comprehensive set of services for researchers to facilitate the efficient progression of a basic research concept to product development. These preclinical services also provide quality-controlled research reagents, animal models and clinical specimens to accelerate the rate of discovery. The provision of these services to

drug development entities helps to offset the financial risks of drug development and encourage the development of innovative new antimicrobial agents.

In addition to extramural support for antimicrobial resistance research, NIAID conducts a robust intramural research program in this area. Basic research by NIAID scientists is increasing our understanding of drug resistance in MRSA, *Staphylococcus epidermidis* associated with indwelling medical devices, and other important drug-resistant pathogens. NIAID actively seeks opportunities to partner with pharmaceutical companies, academia, and the non-profit sector to encourage further development of discoveries and inventions arising from our research.

Item

Drug-Resistant Tuberculosis - Drug-resistant TB is on the rise globally, with 500,000 cases reported in 2006. Without the development of new diagnostics, drugs and vaccines, the number of people with drug-resistant TB will continue to increase. The Committee encourages NIAID to intensify research into developing new diagnostics, drugs and vaccines to halt the spread of drug-resistant TB. (p. 119)

Action taken or to be taken

NIAID is strongly committed to advancing efforts to combat drug-resistant tuberculosis (TB) infection through research aimed at developing innovative rapid diagnostic tools, improved vaccines, and novel therapeutics. In 2008, the Institute released the *NIAID Research Agenda for Multidrug-Resistance and Extensively Drug-resistant Tuberculosis (MDR/XDR-TB)* to identify current research and resource gaps and to define priorities in basic research, diagnostics, therapeutics, and vaccines as well as cross-cutting research issues related to drug-resistant TB.

NIAID supports a strong foundation of basic research to enhance knowledge of the TB bacteria and disease progression, essential to understanding the causes of resistance. NIAID conducts clinical studies of TB, including a study of XDR-TB-infected patients in South Korea to understand the bacterial and human host factors that contribute to the development of drug resistance. The Institute also provides a broad range of research resources to investigators to facilitate research and to encourage development of new tools against TB.

NIAID supports research on new and improved diagnostics for the rapid identification of TB infection, disease, and drug resistance. For example, a promising new TB diagnostic developed with NIAID support is being evaluated in late-stage clinical studies. Other NIAID-supported studies are identifying biomarkers that could be translated into novel diagnostic tools. In addition, the newly awarded Clinical Diagnostics Research Consortium will facilitate evaluation of early-stage diagnostic candidates in TB-endemic countries.

The development of novel therapeutics and vaccines is critical to combating both drug-sensitive and drug-resistant forms of TB. For example, NIAID is supporting a Phase Ib clinical trial to evaluate the candidate therapeutic SQ109, initially developed in NIAID labs, in populations with drug-sensitive TB. NIAID intramural researchers are collaborating with partners in South Korea to evaluate the safety and efficacy of the licensed antimicrobial

drug linezolid for treatment of drug-resistant TB. Also, NIAID is supporting research to re-evaluate the efficacy of second-line therapies against MDR- and XDR-TB. Through contracts, NIAID provides facilities and resources for screening of TB vaccine candidates in animal models, and through public-private partnerships, the Institute is supporting the development and optimization of advanced-stage vaccine candidates. Recently, NIAID awarded a cooperative research grant to advance the development of adjuvants for use in vaccines for MDR-TB. The NIAID-supported Tuberculosis Research Unit provides researchers with a venue for the conduct of clinical trials of potential new TB therapeutic, preventive, and diagnostic strategies, as well as for answering critical questions on the human immune response to infection.

NIAID continues to collaborate with the global TB research community and the U.S. TB Task Force to coordinate resources, leverage support for fundamental and translational research, and assure that opportunities for the development of new TB interventions are realized.

Item

Hepatitis B Chronic- The Committee supports NIAID's plans to fund experimental models of hepatitis B (HBV) and to continue support for a specialized animal model of hepatitis virus. The Committee notes that NIAID has effectively responded to the challenges surrounding the management of other infectious diseases with specific programs and networks, and suggests the same be done for HBV. The Committee understands that although there are now a number of medications approved for the treatment of HBV, they are of limited therapeutic value since most of them target the same virus functions. The Committee encourages NIAID to support research on different courses of treatment as well as ways to identify new cellular and antiviral targets. In addition, the Committee believes that special attention to the problems associated with co-infections of hepatitis B with hepatitis C and HIV is needed. (p. 119)

Action taken or to be taken

The majority of the global hepatitis burden is due to hepatitis B virus (HBV), which kills more than 4,000 Americans and 1.2 million people worldwide each year. Here in the United States, the implementation of a national strategy to eliminate HBV has coincided with a steady decline in HBV incidence. NIAID remains committed to supporting research on HBV through a combination of targeted research programs and investigator-initiated research, thus allowing for flexibility as new scientific opportunities arise in basic, translational, and clinical HBV research.

Research to develop new classes of drugs that are safe and effective in treating HBV infections remains a priority for NIAID. Currently licensed antiviral drugs for HBV target a single step in the HBV replication cycle. Through both solicited research programs and investigator-initiated research, NIAID-supported researchers are exploring novel viral targets for the development of classes of antiviral drugs for HBV that work by different mechanisms than licensed HBV polymerase inhibitors. The Institute also supports contracts to conduct *in vitro* screening of candidate drugs for HBV as well as hepatitis C virus (HCV). Last year, more than 400 compounds were screened for antiviral activity. Through other contracts, the Institute supports the testing of therapeutics for HBV in

animal models. In addition, through the *Animal Models for Infectious Diseases* initiative, NIAID has solicited the development of new animal models for hepatitis and other infectious diseases. Awards are expected to be made in FY 2010.

NIAID-supported researchers continue to study the virus-host interactions that lead to acute and chronic HBV infection. A better understanding of the early and late stages of HBV infection should facilitate the development of new antiviral drugs. Other research efforts may contribute to the optimization of treatment with currently licensed antiviral drugs. With the National Institute of Diabetes and Digestive and Kidney Diseases, NIAID cosponsored the *Management of Hepatitis B Consensus Development Conference* in October 2008 to review recent developments in the management and treatment of HBV infection.

NIAID also supports research to understand co-infection with HBV and explore treatment options in co-infected individuals. For example, the Institute is supporting a study to examine the outcomes of HIV-HBV co-infected individuals treated with a combination of active drugs against both HIV and HBV compared to therapies that contain only one active drug against HBV.

Item

Pre-exposure Prophylaxis -The Committee is aware there are currently seven clinical trials testing the safety and effectiveness of PrEP, an experimental HIV prevention strategy using antiretroviral drugs in HIV negative people, and that PrEP is considered among the most promising of potential HIV prevention interventions now being studied. These clinical trials are expected to report results starting in 2010. The Committee urges the NIAID to begin developing a research plan to prepare for the range of possible outcomes. (p. 102)

Action taken or to be taken

NIAID is strongly committed to supporting innovative research to prevent HIV infection. One promising HIV prevention strategy involves giving antiretroviral drug regimens to people who are at high risk for HIV to protect them from infection, an intervention known as pre-exposure prophylaxis (PrEP).

Recent mathematical modeling supported by NIAID, the National Institute of Mental Health (NIMH) and the National Institute on Drug Abuse (NIDA) evaluated the potential benefits for PrEP use in U.S. populations at high risk for HIV infection and determined that the prevention strategy, if found to be safe and efficacious, could substantially reduce the lifetime risk of HIV infection.

Currently, NIAID is supporting iPREG, a Phase III study launched in July 2007 to test the preventive effect of Truvada (tenofovir + emtricitabine), in conjunction with safe-sex counseling and condom use, among HIV-negative men who have sex with men (MSM). This study is being conducted in collaboration with the Bill and Melinda Gates Foundation at sites in Peru, Ecuador, the United States, Brazil, South Africa and Thailand. Results from the iPREG study are expected in 2010. Results from a Centers for Disease Control and Prevention (CDC) proof-of-concept study testing tenofovir alone among 2,400 injection drug users in Thailand are also expected in 2010. These two studies will provide the

earliest data regarding the PrEP approach.

NIAID has taken the lead in organizing the U.S. Government's PrEP Sponsors Working Group (PSWG), which also includes the U.S. Agency for International Development and CDC. NIAID serves as the Secretariat for this group, which was established in 2008, and convenes regular meetings to share information about ongoing federally funded HIV PrEP trials. The PSWG has focused on optimizing communications and ensuring coordination among key stakeholders such as collaborating agencies, the State Department and U.S. embassies, the U.S. Food and Drug Administration, the Joint United Nations Programme on HIV/AIDS (UNAIDS), and foreign regulatory bodies. While it is too early to predict the safety, efficacy, and feasibility of PrEP as a prevention tool, the PSWG members, led by CDC, have begun to develop a strategy to implement this intervention in anticipation of its potential viability for use in populations at high risk for HIV infection. NIAID will continue to provide input into this planning process.

NIAID will work with the PSWG to develop a coordinated five-year plan that will evaluate and integrate key research issues. Such research issues include the strength of evidence required to demonstrate efficacy; the safety and resistance profiles for current and new candidate antiretroviral agents; alternative dosing regimens; acceptability, adherence, and risk compensation; and integration of PrEP into comprehensive HIV prevention strategies for specific populations and settings. NIAID anticipates that the PSWG will complete this research plan by mid-2010.

Item

Immune Tolerance Network - The Committee commends NIAID for its oversight of ITN, which designs and conducts clinical trials of new immune-modulating therapies for Type 1 diabetes and other diseases. The Committee encourages NIAID to implement the sharing of samples and data from these trials, in order to expedite the development of new therapies for Type 1 diabetes. (p. 119)

Action taken or to be taken

NIAID supports basic research, translational, and clinical research on the underlying mechanisms of immune tolerance and the evaluation of tolerance-inducing strategies in animal models and clinical trials. The goal of these strategies is to "reeducate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. Advances in the induction of immune tolerance could provide valuable therapeutic strategies to treat type 1 diabetes and other immune-mediated disorders, and eliminate the need for life-long, systemic immunosuppressive therapy for transplant patients.

The Immune Tolerance Network (ITN), the cornerstone of the NIAID clinical research effort in this area, is an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergies, and rejection of transplanted organs, tissues, and cells.

The ITN accepts applications from scientists in academia, industry, and government for novel clinical trials. In addition, the ITN accepts applications for the development of novel

tolerance assays or studies to understand the mechanisms by which a particular intervention works.

The ITN maintains an extensive specimen repository and a repository of clinical data. These resources are available to the community through an application request process. Each request is reviewed for its scientific merit and to ensure that fulfilling the request does not jeopardize other ongoing trials.

Through continuing support of the ITN, the NIAID will maintain its commitment to basic research on immune tolerance and the translational and clinical research that bring basic discoveries to the patient care arena.

Item

Inflammatory Bowel Disease - The Committee encourages NIAID to accelerate its inflammatory bowel disease research portfolio and explore partnerships with the IBD community aimed at fostering additional research on the role of the immune system in the development and progression of IBD in both adult and pediatric populations. (p. 119)

Action taken or to be taken

NIAID continues its commitment to research toward understanding the group of autoimmune disorders known as inflammatory bowel disease (IBD). NIAID is supporting several research programs that directly align with the goals of the National Commission on Digestive Diseases Report, including initiatives on mucosal immunology and microbial-host interactions, identification of genotypic variation with disease risk, characterization of the intestinal microbiome, and understanding basic mechanisms and infectious causes of IBD, which may yield insights into both adult and pediatric disease.

In 2009, NIAID made 52 awards under the *Immune Defense Mechanisms at the Mucosa* initiative. The goal of this program is to gain new insights into immune defense mechanisms and immune regulation at mucosal surfaces, including those in the gastrointestinal tract. NIAID will re compete this program in FY 2011.

A number of research programs are focused on understanding what factors contribute to the development of IBD. For example, NIAID continues to support the Human Leukocyte Antigen Region Genetics in Immune-Mediated Diseases program to define the association between a set of genes or genetic markers in the immune system and immune-mediated diseases, including two research projects to study IBD. Further, NIAID is participating with other NIH Institutes in the NIH Roadmap for Medical Research Human Microbiome Project, which is characterizing the microbial community associated with the human body—or microbiome—and studying whether changes in the microbiome can be correlated with human disease. As part of this project, researchers will study host genes thought to confer risk of IBD in order to investigate an association with the development of necrotizing enterocolitis in premature infants.

The NIAID-supported Food and Waterborne Diseases Integrated Research Network (FWDIRN) facilitates the integration of research programs to develop products to rapidly identify, prevent, treat, and diagnose food and waterborne diseases that threaten public

health. Two of the FWDIRN research units are pursuing research projects on Crohn's Disease, a form of IBD. One unit is exploring the feasibility of developing an animal model of Crohn's Disease, and the other is studying the role of gastrointestinal microbes in the development of the disease. In addition, NIAID has recently released a request for applications (RFA)—Enterics Research Investigational Network (ERIN) Cooperative Research Centers (CRCs)—that will establish a coordinated research program to bridge the gaps in basic, translational, and clinical research on enteric disease microbes. This RFA provides a funding opportunity for researchers studying IBD while also presenting opportunities for collaboration within the enteric diseases research community.

NIAID collaborates and coordinates with other NIH Institutes and Centers as well as other organizations with an interest in digestive disease, including IBD. NIAID participated in the National Commission on Digestive Diseases, which developed a long-range plan for digestive diseases research. NIAID also participates in the Digestive Diseases Interagency Coordinating Committee, which coordinates research on digestive diseases including the immunology, genetics, and role of the environment in IBD pathogenesis.

Item

Lyme Diseases - The Committee encourages the NIAID to sponsor a scientific conference on Lyme and other tick-borne diseases that would represent the broad spectrum of scientific views on Lyme disease and include input from individuals with Lyme disease. The Committee also encourages NIH to intensify research that will increase understanding of the full range of Lyme disease processes and the physiology of *Borrelia burgdorferi*, including the mechanisms of persistent infection, and research that may lead to the development of more sensitive and accurate diagnostic tests for Lyme disease capable of distinguishing between active and past infections.

Action taken or to be taken

Please refer to page 212 in the Office of the Director's section of this document for the response to this item.

Item

Malaria - The Committee encourages NIAID to strengthen its support for public-private partnerships (PPPs) involved in the research and development of antimalarial drugs, and particularly notes the activities of the Medicines for Malaria Venture (MMV). The Committee is aware that NIAID-funded scientists recently decoded the genome of *Plasmodium vivax*, the malaria-causing parasite most common in Asia and Latin America. This achievement is expected to advance scientific understanding significantly in several areas key to malaria control and prevention, including drug resistance. The Committee urges NIAID to continue this work and help to ensure that new tools are available when current interventions begin to lose their effectiveness. (p. 119)

Action taken or to be taken

Consistent with the goals outlined in its *Strategic Plan for Malaria Research and Research Agenda for Malaria*, NIAID is strongly committed to basic, applied, and clinical research toward the development of new tools to prevent, diagnose, and treat malaria. For example, NIAID conducts and supports research to advance the understanding of the

host-parasite-vector interactions associated with malaria, including research on vector biology, malaria pathogenesis, parasite and host genomics, and the immunologic and epidemiological factors that affect disease transmission and progression. NIAID-supported malaria research is conducted by scientists in the United States and over 20 countries, including many malaria-endemic countries.

The Institute coordinates its research activities with other federal agencies and non-governmental organizations involved in malaria research. For example, NIAID participates in the Federal Malaria Vaccine Coordinating Committee and provides support to the Multilateral Initiative on Malaria/Tropical Disease Research Programme to advance peer-reviewed malaria research and strengthen research capacity at African institutions. NIAID also participates in the Malaria Vaccine Advisory Committee, established at the World Health Organization (WHO) Initiative for Vaccine Research, and in the External Scientific Advisory Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds.

NIAID scientists carry out a robust multidisciplinary research program in malaria, including development of malaria parasite genome databases and new resources to study the mechanism of drug resistance and screen for new antimalarial drugs.

In early 2009, NIAID made several awards under a Request for Applications (RFA) entitled *Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors* to encourage the development of novel and more effective interventions and research tools that will advance the discovery and development of novel vaccines, drugs, diagnostics and vector management strategies for malaria and neglected tropical diseases (NTDs).

In 2009, NIAID released an RFA entitled International Centers of Excellence for Malaria Research, which invites grant applications to establish an International Centers of Excellence for Malaria Research program to provide a multidisciplinary research approach to malaria control and prevention through the integration of findings from clinical and field research. Also, the Institute issued the RFA, NIAID Partnerships with Product Development Public-Private Partnerships (PPPs) to support established, not-for-profit product development PPPs and accelerate preclinical research and development of promising preventive, therapeutic, and diagnostic tools, and advance vector management strategies for NTDs, malaria, and tuberculosis. Awards under both RFAs are anticipated in FY 2010.

Item

Microbicides - Encouraging results from a recent NIH Microbicide Trials Network safety and effectiveness study of particular microbicide candidate showed that the product was safe and approximately 30 percent effective in preventing HIV infection. While data from this study are not definitive and results from additional trials are needed to confirm the findings, this study supports the concept that a microbicide could prevent HIV infection. The Committee urges NIH to work with USAID, CDC, and other appropriate agencies to develop processes for coordinated investment and prioritization for microbicide development, approval, and access. (p. 119,120)

Action taken or to be taken

NIH continues its strong support of research to identify and develop safe, effective, and acceptable topical microbicides through a highly collaborative program that provides support for basic research through preclinical development and clinical trials. NIAID, the lead institute in this area, works closely with the Office of AIDS Research (OAR), other NIH Institutes, other governmental agencies and nongovernmental agencies, such as the U.S. Agency for International Development (USAID), the Centers for Disease Control and Prevention (CDC), and CONRAD to coordinate activities and to exchange scientific and technical information. NIAID also maintains a formal partnership with the International Partnership for Microbicides (IPM) to increase sharing of research information, data, and expertise, and to ensure coordination in order to accelerate development of promising topical microbicides. Currently, the Institute is working with the CDC, IPM and CONRAD to coordinate a number of projects of mutual interest that receive support through NIAID's Integrated Preclinical-Clinical Program for HIV Topical Microbicides (IPCP-HTM) and the Microbicide Innovation Program (MIP). These two programs serve to support the development path of products to advance to clinical trials through the Microbicide Trials Network (MTN). The MTN, supported by NIAID, NICHD and NIMH, collaborates with USAID, IPM and CONRAD to test promising microbicides. In addition, NIAID continues to collaborate with academia, industry, and foundations to identify and explore new and existing compounds that may warrant further study as potential topical microbicidal agents.

OAR, part of the Office of the NIH Director, plans and coordinates microbicide research activities across the NIH and the Federal government through a number of activities. For example, OAR develops the annual Trans-NIH Plan for HIV-Related Research, which includes the strategic plan for microbicides and establishes trans-NIH research objectives/priorities. The plan is developed by the Trans-NIH Microbicide Research Coordinating Committee, convened and chaired by OAR, and comprised of the NIH Institutes and Centers that support microbicide research. The CDC, U.S. Food and Drug Administration (FDA), and USAID also participate along with non-government experts from academia and industry and community representatives. The Coordinating Committee fosters information-sharing, trans-NIH collaboration and coordination, identifies scientific opportunities and research gaps, and facilitates innovative approaches to microbicides research,

OAR also established and chairs a Trans-Governmental Microbicide Coordinating committee, comprised of NIH institutes, CDC, FDA, DoD, VA, and USAID, to further facilitate coordination and collaboration in this area. OAR established the Microbicides Research Working Group (MRWG), an independent non-government panel of experts, that advises NIH and other government and non-governmental entities that support microbicide research and development. Relevant NIH Institutes, including NIAID, and other government agencies, including CDC, FDA and USAID, and non-governmental organizations, such as CONRAD, the Population Council, the International Partnership for Microbicides, and international organizations are invited to attend meetings and to submit issues and topics to the MRWG for consideration.

Item

Scleroderma - The Committee is aware of emerging opportunities in scleroderma research and continues to encourage the Institute to partner with the scleroderma patient community in convening a state-of-the-science conference in this important area. (p. 120)

Action taken or to be taken

NIAID remains committed to understanding the causes of and improving the treatment of autoimmune diseases, including scleroderma. As a part of this commitment, NIAID continues to support the Autoimmunity Centers of Excellence (ACE) to conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies. Co-sponsored by NIAID, the National Institute of Dental and Craniofacial Research and the NIH Office of Research on Women's Health (ORWH), the ACEs support close interaction between clinicians and basic researchers to facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. It is anticipated that lessons learned from other autoimmune diseases, such as lupus and multiple sclerosis, may have relevance for the treatment of scleroderma.

NIAID also is supporting a clinical trial to assess the efficacy of autologous hematopoietic stem cell transplantation for the treatment of scleroderma. This clinical trial includes studies of the underlying immune processes that lead to disease and the way treatment changes the immune response.

Furthermore, NIAID continues to support research on autoimmune diseases, including scleroderma, through support of the Immune Tolerance Network (ITN) and the Cooperative Study Group for Autoimmune Disease Prevention (CSGADP). Co-sponsored by NIAID, NIDDK and the Juvenile Diabetes Research Foundation (JDRF), the ITN supports clinical trials and assay development for promising tolerance induction and immunomodulatory strategies to treat autoimmune diseases. Lessons learned from studies of other autoimmune diseases, such as lupus and multiple sclerosis, may have relevance for treatment of scleroderma. The CSGADP, which is also cosponsored by NIDDK and the JDRF, conducts research on the development of new targets and approaches to prevent autoimmune diseases. NIAID plans to renew the CSGADP in FY 2011.

NIAID appreciates the Committee's suggestion to convene a state-of-the-science conference on scleroderma. While NIAID does not currently have plans to organize a state-of-the-science conference, the Institute and other NIH ICs will continue to support scientific meetings in the area of autoimmune diseases, including scleroderma. For example, NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, supported the biennial International Workshop on Scleroderma Research, last held in 2008, which focused on basic research related to the pathogenesis of scleroderma. This workshop covered autoimmunity, genetics, gene expression, vascular injury, animal models, fibrosis, and matrix metabolism and brought together investigators in scleroderma from throughout the world, along with prominent researchers in related disciplines.

Senate Significant Items

Item

Antimicrobial Resistance - The Committee is encouraged by NIAID's commitment to address antimicrobial resistance and related product (antimicrobials, diagnostics, and vaccines) research through its clearance of council-approved concepts in May 2008 and September 2008. The Committee urges the NIAID to quickly translate these concepts into funding mechanisms. (p. 97)

Action taken or to be taken

Please refer to page 83 of this document for NIAID's response to this item.

Item

Drug-Resistant Tuberculosis- The Committee urges the NIAID to expand and intensify research into developing new diagnostics, drugs, and vaccines to halt the spread of drug-resistant TB. (p. 97)

Action taken or to be taken

Please refer to page 84 of this document for NIAID's response to this item

Item

Chronic Hepatitis B - The Committee understands that although there are now a number of medications approved for the treatment of hepatitis B, they are of limited therapeutic value since they mostly target the same virus functions. The Committee urges additional research on different courses of treatment as well as ways to support efforts to identify new cellular and viral antiviral targets and develop new strategies for intervention. In addition, special attention to the problems associated with co-infections of hepatitis B with hepatitis C and HIV is needed. (p. 97)

Action taken or to be taken

Please refer to page 85 of this document for NIAID's response to this item

Item

Inflammatory Bowel Disease - The Committee applauds NIAID for its continued leadership on IBD and encourages support for the IBD research agenda detailed in the NIH National Commission on Digestive Diseases report. The Committee also prioritizes expanded research in the area of pediatric disease in collaboration with the IBD community and NIDDK. (p. 94)

Action taken or to be taken

Please refer to page 88 of this document for NIAID's response to this item.

Item

Lyme Disease - The Committee encourages the NIAID to sponsor a scientific conference on Lyme and other tick-borne diseases that would represent the broad spectrum of scientific views on Lyme disease and include input from individuals with Lyme disease. The Committee also encourages NIH to intensify research that will increase understanding

of the full range of Lyme disease processes and the physiology of *Borrelia burgdorferi*, including the mechanisms of persistent infection, and research that may lead to the development of more sensitive and accurate diagnostic tests for Lyme disease capable of distinguishing between active and past infections. (p. 97-98)

Action taken or to be taken

Please refer to page 212 in the Office of the Director's section of this document for the response to this item.

Item

Malaria - The Committee is aware that NIAID-funded scientists recently decoded the genome of Plasmodium vivax, the malaria causing parasite most common in Asia and Latin America. This achievement is expected to significantly advance scientific understanding in several areas key to malaria control and prevention, including drug resistance. The Committee urges the NIAID to allocate additional resources to malaria research, and by doing so help ensure that new tools are available when current interventions begin to lose their effectiveness. In addition, the Committee encourages NIAID to expand its current support for public-private partnerships involved in the research and development of antimalarial drugs. (p. 98)

Action taken or to be taken

Please refer to page 89 of this document for NIAID's response to this item.

Item

Nontuberculous Mycobacteria - The Committee commends the NIAID for its planning meetings regarding NTM, outreach to the NTM patient community, and leading NTM treatment center. The Committee recommends further collaboration with the NHLBI, CDC, the advocacy community and other Federal agencies to provide leadership that will enhance diagnostic and treatment options as well as medical and surgical outcomes through the stimulation of multi-center clinical trials and promotion of health care provider education. (p. 98)

Action taken or to be taken

In 2009, an NIAID-led research team analyzed hospital discharge data to estimate the prevalence of pulmonary nontuberculous mycobacteria (NTM) hospitalizations and concluded that NTM is an increasing cause of illness in the United States, particularly among women in certain geographic areas. NIAID researchers and collaborators had previously conducted a multi-year study of risk factors associated with NTM which found that pulmonary NTM patients were primarily Caucasian women over 60 years old and that susceptibility to pulmonary NTM infection is likely inherited.

NIAID remains committed to basic and clinical research on NTM to improve the understanding, diagnosis and treatment of NTM infections. As a part of this commitment, NIAID continues to advance diagnostic and treatment protocols for NTM and to promote collaborative efforts to increase the understanding of NTM. For example, NIAID currently supports a clinical trial planning grant to establish an NTM Research Consortium (NTMRC) and to design a Phase II trial to re-assess the safety, tolerability, and efficacy of the

standard three-drug treatment regimen for previously untreated patients with pulmonary *Mycobacterium avium* complex (MAC) infection. MAC accounts for over 75 percent of pulmonary infections caused by NTM. The NTMRC will include clinical sites that care for many NTM patients as well as highly experienced microbiological reference laboratories experienced in NTM culture and identification. The planning grant should allow researchers to finalize the protocol and complete the regulatory and administrative requirements for the Phase II trial.

NIAID intramural researchers remain central collaborators in the NTM consortium and continue in their efforts to understand NTM prevalence and disease. For example, researchers are studying airway epithelial cell dysfunction and its role in predisposition to bronchiectasis, the critical underlying factor in pulmonary NTM infection. They are also studying the role that innate immunity plays in determining susceptibility to mycobacterial infections. Working closely with NHLBI, other NIH colleagues, and collaborators from other federal agencies and the extramural community, NIAID researchers continue to elucidate the underlying causes of NTM infection in order to guide the development of new therapeutic strategies.

NIAID continues to support research that may lead to more effective and accepted prophylactic and therapeutic approaches for preventing and controlling respiratory infections and strongly encourages researchers to submit grant applications on NTM. In addition, NIAID is assisting the research community by including NTMs in its reagent support contracts and is planning to expand all TB-specific research resources to include NTM and other non-TB organisms. NIAID continues to be actively engaged with the NTM advocacy community and is planning a workshop on natural history of NTM pulmonary infections in FY 2010- 2011. NIAID is collaborating with the research community on providing services for whole genome sequencing of major NTM pathogens.

Item

Pre-exposure Prophylaxis (PrEP) - The Committee is aware there are currently seven clinical trials testing the safety and effectiveness of PrEP, an experimental HIV prevention strategy using antiretroviral drugs in HIV negative people, and that PrEP is considered among the most promising of potential HIV prevention interventions now being studied. These clinical trials are expected to report results starting in 2010. The Committee urges the NIAID to begin developing a research plan to prepare for the range of possible outcomes. (p. 98)

Action taken or to be taken

Please refer to page 86 of this document for NIAID's response to this item.

Item

Scleroderma - The Committee commends the NIAID for its support of scleroderma research through the Autoimmune Centers of Excellence program and the Stem Cell Transplantation for Autoimmune Diseases Consortium, and requests an update in the fiscal year 2011 congressional budget justification. (p. 98)

Action taken or to be taken

NIAID remains committed to understanding the causes of and improving the treatment of autoimmune diseases, including scleroderma. As a part of this commitment, NIAID continues to support the Autoimmunity Centers of Excellence (ACE) to conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies. Co-sponsored by NIAID, the National Institute of Dental and Craniofacial Research and the NIH Office of Research on Women's Health (ORWH), the ACEs support close interaction between clinicians and basic researchers to facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. It is anticipated that lessons learned from other autoimmune diseases, such as lupus and multiple sclerosis, may have relevance for the treatment of scleroderma.

NIAID also is supporting a clinical trial to assess the efficacy of autologous hematopoietic stem cell transplantation for the treatment of scleroderma. This clinical trial includes studies of the underlying immune processes that lead to disease and the way treatment changes the immune response.

Furthermore, NIAID continues to support research on autoimmune diseases, including scleroderma, through support of the Immune Tolerance Network (ITN) and the Cooperative Study Group for Autoimmune Disease Prevention (CSGADP). Co-sponsored by NIAID, NIDDK and the Juvenile Diabetes Research Foundation (JDRF), the ITN supports clinical trials and assay development for promising tolerance induction and immunomodulatory strategies to treat autoimmune diseases. Lessons learned from studies other autoimmune diseases, such as lupus and multiple sclerosis, may have relevance for treatment of scleroderma. The CSGADP, which is also cosponsored by NIDDK and the JDRF, conducts research on the development of new targets and approaches to prevent autoimmune diseases. NIAID plans to renew the CSGADP in FY 2011.

**National Institute of General Medical Sciences
(NIGMS)**

Senate Significant Items

Item

Modeling Social Behavior - The Committee is pleased that the NIGMS is supporting research on the modeling of social behavior, which will clarify the process by which individual interactions lead to collective group behaviors. However, the Committee remains concerned that the NIGMS is still not funding investigator-initiated research by behavioral scientists, as it is authorized to do so by way of its statute and multiple congressional requests. (p. 99)

Action taken or to be taken

The National Institute of General Medical Sciences (NIGMS) supports bBSSR and training related to its mission areas. This investigator-initiated research is supported through the following centers/divisions: Bioinformatics and Computational Biology; Genetics and Developmental Biology; Minority Opportunities in Research; and Pharmacology, Physiology and Biological Chemistry. Supported research activities include: (1) basic behavioral research in model organisms; (2) computational modeling of human populations including behavioral and social factors; (3) studies of the efficacy of interventions in promoting research careers; (4) support of a range of behavioral and social sciences research at minority-serving institutions; and (5) predoctoral training at the interface between behavioral and biomedical sciences. Moreover, NIGMS continues to explore the potential for new directions in its funding of basic behavioral and social sciences research.

**Eunice Kennedy Shriver
National Institute of Child Health and Human Development
(NICHD)**

House Significant Items

Item

Demographic Research - The Committee encourages NICHD to continue its support of trans-NIH behavioral and social science research initiatives on disasters and health outcomes to develop more data on the consequences of disasters on the health of children and vulnerable groups. Further, the Committee encourages NICHD to continue its investment in large-scale data sets, such as the New Immigrant Study and National Longitudinal Study of Adolescent Health, because of their value and accessibility to researchers worldwide. Finally, the Committee encourages NICHD to continue research on how the structure and characteristics of the work environment affect child and family health and well-being and how health and well-being in the early years affect health and wellbeing later in life. (p. 120)

Action taken or to be taken

The NICHD currently funds eight research projects on the consequences of natural disasters, most focusing on the aftermath of Hurricane Katrina. Included are projects that track the New Orleans populations affected by Katrina both through on-the-ground surveys and through the analysis of longitudinal data collected for other purposes. NICHD projects also are examining the effects of Katrina by re-surveying two sets of participants in pre-Katrina studies in the New Orleans area, one on low-income families and one on Vietnamese-Americans. The NICHD international disaster portfolio includes research on the aftermath of the 2004 Indian Ocean earthquake and tsunami.

The NICHD also continues to support large data sets because of their value to researchers worldwide, including the New Immigrant Study (NIS) and the National Longitudinal Study of Adolescent Health (ADD Health). The NIS will provide the first representative longitudinal data on legal immigrants to the United States and their families. ADD Health is an ongoing longitudinal study of developmental and health trajectories of a large nationally representative sample of youths first interviewed in grades 7-12 during the 1994-95 school year and most recently interviewed at ages 24-32 in 2007-08. ADD Health data sets have been used in more than 300 independently funded research grants and 1,000 research articles. Innovations in 2007-08 (Wave 4) include collection of saliva DNA samples that will be genotyped using whole genome array technology.

Through research on how the structure and characteristics of the work environment affects child and family health, the NICHD continues to support the Work, Family, and Health Network, along with partners NIA, OBSSR, and NIOSH. The Network is currently implementing a workplace intervention in a single-site corporate headquarters with salaried workers and a geographically-dispersed setting with hourly workers; outcomes evaluated include health benefits for workers and workers' spouses and children, and overall benefits to the employers' business. The NICHD also funds several investigator-initiated grants on work-family issues, including research on work-family balance and women's physical activity and eating habits; and research on how child and family outcomes are affected by

paid family leave, maternal employment, non-standard work schedules, state and national work-family policies, and work-related travel.

The NICHD supports several grants investigating the early antecedents to child and adult health and well-being. Among these are projects examining how maternal stress affects birth outcomes, how genes and environmental factors such as socioeconomic status in early life interact to influence inflammation and the risk of cardiovascular disease and stroke in later life, and how genetic factors and social context interact to affect the trajectories of adolescent health risk behaviors and family outcomes.

Item

First Pregnancy Complications - Committee commends NICHD for identifying complications in first pregnancies as an important area requiring further research. This understudied group of women is at highest risk of developing preeclampsia, which puts them at risk for multiple devastating maternal complications, fetal death and preterm delivery. In the last decade, the rate of preterm births among first pregnancies increased 50 percent. The Committee encourages NICHD to move forward with initiatives to identify predictors and interventions to improve the outcome for first pregnancies and to lower the risks in subsequent pregnancies. (p. 121)

Action taken or to be taken

The health issues faced by women in their first pregnancy have long been understudied. Women for whom the current pregnancy will lead to their first delivery (nulliparas) comprise about 40% of pregnant women in the United States and account for 4 million births each year. Because there is no information from previous pregnancy outcomes to guide assignment of risk or mitigating interventions, adverse pregnancy outcomes in nulliparas are especially unpredictable. Complications during the first pregnancy impact subsequent pregnancies.

In order to identify predictors for adverse pregnancy outcomes with the goal of developing future interventions, the NICHD issued a Request for Applications in FY 2009, "Preterm Birth in Nulliparous Women: an unstudied population at great risk," and received over 35 responses. New grants will be awarded in FY 2010 to create a network of clinical sites with a central data collection site to study the mechanisms and prediction of adverse pregnancy outcomes in nulliparous women. The aim is to identify markers early in pregnancy that will identify women at the highest risk for preterm birth, preeclampsia, fetal growth restriction, and stillbirth. Detailed epidemiologic data, intensive clinical research assessments and biologic samples will be collected. Recent advances such as genomics, proteomics and epigenetics will be applied to elucidate the mechanisms of the interplay of genetic and environmental factors. As a result of this program, individualized interventions could be developed aimed at preventing adverse pregnancy outcomes. The grantees also will share the data with investigators outside the network to accelerate the pace of preterm birth research.

Item

Developmental Disabilities Research Centers - The Committee recognizes the important contributions of the Eunice Kennedy- Shriver Intellectual and Developmental

Disabilities Research Centers (IDDRC) toward understanding why child development goes awry, discovering ways to prevent developmental disabilities, and discovering treatments and interventions to improve the lives of people With developmental disabilities and their families. The Committee is particularly pleased with IDDRC contributions in the areas of autism, fragile X syndrome, Down syndrome and other genetic and environmentally induced disorders. The Committee urges NICHD to strengthen its support of the IDDRCs so that they can conduct basic and translational research to develop effective prevention, treatment and intervention strategies for children and adults with developmental disabilities. (p. 120, 121)

Action taken or to be taken

The NICHD supports 14 Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (IDDRCs) located at universities and children's hospitals throughout the country. The IDDRCs provide infrastructure via core facilities and support services for research in intellectual and developmental disabilities (IDD); although they differ from each other in many aspects, including their scientific focus, size, lifespan, and history, they share common features that include their ability to leverage resources from their host institutions, private donors, and other sources to facilitate growth. Each Center presently supports between 45 and 166 research projects, and at least 20 to more than 70 investigators, who receive funding from a variety of sources. This diversity allows the Centers to support substantially more projects and affiliates than would be possible using NICHD support alone. Between FY 2005 and FY 2008, the IDDRCs expanded the total number of projects supported by their cores from approximately 1,000 to 1,200, in spite of nearly flat funding during that time period. The breadth of research ranges from basic science studies of neural stem cells to clinical studies of chromosomal disorders such as Down syndrome and translational efforts to develop therapies for conditions such as Rett syndrome. A number of investigators affiliated with NIH-sponsored Rare Disease Cooperative Research Consortia, Fragile X Syndrome Research Centers (FXSRCs), and Muscular Dystrophy Clinical Research Consortia utilize core services provided by the IDDRCs.

Several Centers have generated successful new collaborative research projects in areas that include integrated patient registries across IDDRCs and multi-site studies of aberrant behavior in IDDs. Some of the IDDRCs are enhancing training efforts by developing a mentoring workshop for junior investigators, and several IDDRCs located in geographic proximity have held joint meetings to promote collaborative projects and training opportunities.

In FY 2009, the NICHD held a recompetition for funding the IDDRCs that attracted excellent applications. Competition for center support remains strong and vibrant based on the quality of the applications received and the number of new applications. The NICHD has provided new resources to the Centers in the form of administrative supplements via the American Recovery and Reinvestment Act of 2009 (ARRA). Thirteen supplements were awarded to the IDDRCs totaling approximately \$1.95 million over two years. This additional NICHD support to purchase state-of-the-art equipment and develop enhanced core services will position the IDDRCs to make significant advances over the next two years in basic and translational IDD research.

Item

Fetal Origins of Adult Disease - Research suggests that an inadequate prenatal environment may permanently alter and program the fetus for the onset of many diseases later in life, including hypertension, diabetes, cardiovascular disease, and obesity, as well as psychiatric and behavioral disorders. The Committee encourages NICHD to focus on efforts to improve pregnancy outcomes and ultimately improve the long-term health of the nation by predicting and preventing the onset of these chronic diseases. (p. 121)

Action taken or to be taken

In order to predict and prevent the metabolic and cardiovascular consequences of fetal growth impairment, NICHD is funding a large, prospective study of fetal growth in which serial ultrasound measurements are being taken at regular intervals on several thousand pregnant women throughout pregnancy. This study will establish standards against which aberrant fetal growth can be diagnosed and ameliorated. NICHD-supported scientists are also developing novel monitoring equipment such as three-dimensional ultrasound and fetal electrocardiography to assess the health and development of the fetus. Other scientists are using the technique of proteomics to develop new biomarkers of intra-amniotic infection and fetal hypoxia as early in pregnancy as possible in order to treat these conditions and increase the likelihood of a good birth outcome.

Maternal infection during pregnancy constitutes another detrimental environmental influence on the development of the brain during fetal life. For example, scientists have shown that maternal infections with strains of influenza virus type A and B during the first trimester of pregnancy may increase the risk of schizophrenia spectrum disorders later in life, and showed a similar effect of maternal infection with toxoplasmosis. NICHD-supported scientists are developing methods to rapidly diagnose such intrauterine infections by detecting minute quantities of microbial genomic material in maternal blood, urine or amniotic fluid. Early treatment of maternal infection should prevent or ameliorate the detrimental consequences of intrauterine infection and inflammation. Exposure to detrimental environmental agents during fetal life may also lead to the onset of disease later in life.

One adverse pregnancy outcome leading to an individual's increased likelihood for adult disease is preterm birth, a complex phenomenon involving the interaction of the environment with maternal and fetal genetic factors. These include the ways that maternal and fetal genes control the expression of proteins, infection-fighting agents and other active agents that may affect the pregnancy. To search the myriads of human genes and proteins for abnormalities that could help explain preterm birth, NICHD's Genomic and Proteomic Network for Preterm Research (GPN/PBR) was introduced as a five-year initiative in 2006. The main objective of this ongoing research network is to use wide-scale, high-output genomic and proteomic strategies to accelerate knowledge in the mechanisms responsible for prematurity. Together these research efforts will help lead to effective interventions to reduce or prevent the probability of a preterm birth.

The NICHD also has established the Obstetric Pharmacology Research Network to evaluate the pharmacokinetics and pharmacodynamics of medications in pregnancy to identify optimal dosing and therapeutics. This network is the only group focused on

commonly used medications in pregnancy for which there is little information on the appropriate dose, route or timing, and the longer term effects on both the pregnant woman and her fetus.

Item

Healthy Babies - The Committee encourages NICHD to continue its research to pinpoint the connections and causations between maternal obesity, diabetes, and heart disease and low birthweight babies, as well as other likely causes of poor infant health. (p. 121)

Action taken or to be taken

Maternal pre-pregnancy weight and weight gain during gestation are strong predictors of infant birth weight. Over the past two decades women have been getting heavier prior to conception and gaining more weight during gestation than in previous decades. A recent study of 63,000 U.S. women indicates that the situation has become a serious public health concern. These investigators reported that during the decade 1993-2003 the rate of pre-pregnancy obesity increased from 13 percent to 22 percent. Subgroup analysis revealed that women with the highest prevalence of obesity were those who were 20 to 29 years of age, who were African American, and who had three or more children. These analyses imply that their obesity may stem from post-partum weight gain after each pregnancy that is not lost between pregnancies. NICHD-funded scientists are currently performing studies of the effect of lactation on post-partum weight gain. Although the studies are not completed, they are expected to show that breast-feeding exerts an inhibitory effect on post-partum weight gain. Another effect shown of maternal obesity on the developing offspring is a doubling of the risk of congenital deformities, in particular neural tube and cardiac defects. The rise in the rate of congenital defects related to pregnancies affected by obesity is currently under study and appears to be a consequence of deranged glucose metabolism that attends obesity during pregnancy.

Women who are obese during pregnancy also are at a higher risk of developing gestational diabetes mellitus (GDM) than are non-obese pregnant women. Offspring born to women with GDM are likely to experience birth weights in the range of 10 to 14 pounds, a condition known as macrosomia. Such heavy babies have difficulty traversing the birth canal and are usually delivered by Caesarian section. These babies also have high levels of circulating insulin and are at risk of very low blood sugar and attendant seizures within the first four hours after birth. Women with GDM are at increased risk of a disorder known as pre-eclampsia, a serious condition characterized by high blood pressure and loss of serum protein in the urine.

Severe cases of pre-eclampsia may be accompanied by seizures. Offspring of pregnancies affected by GDM are at increased risk of obesity and type 2 diabetes later in life. To ascertain the effects on mother and fetus of moderately elevated levels of blood sugar that are not as high as in women with GDM, the NICHD and the NIDDK co-funded a large study of blood sugar levels in 23,000 pregnant women at 15 sites in nine countries. This comprehensive study revealed for the first time that even moderately elevated levels of blood sugar during pregnancy increase the rates of pre-eclampsia and premature delivery in the mother and the rates of macrosomia, elevated insulin levels, and neonatal hypoglycemia in the offspring. Other scientists funded by the NICHD have shown, in a

study of 1000 women with mild GDM, that monitoring of blood sugar four times daily coupled with careful control of blood sugar improved the outcome of their pregnancies compared to the outcome of pregnancies in the women with mild GDM who received usual care. Translation of the results of these two ambitious studies of glucose metabolism and glucose control during pregnancy should improve the care of pregnant women with GDM as well as pregnant women whose blood sugars are moderately elevated but who do not have GDM.

Item

Late Preterm Births - The Committee is aware that preterm birth rates continue to rise, reaching over 12 percent, and that the largest component of those births is in the late preterm birth category (deliveries between 34 and 37 weeks of gestation). The Committee understands that morbidity is significant for the babies, including respiratory complications, difficulty transitioning after delivery, and feeding issues. The Committee encourages NICHD to strengthen its research efforts to understand the causes of late preterm births and to facilitate research into better management and identification of interventions for their prevention. The Committee applauds NICHD for planning and conducting the Surgeon Generals' Conference on Preterm Birth. The Committee encourages NICHD to support research on preterm birth as outlined in the research agenda produced at the Conference. (p. 121)

Action taken or to be taken

The NICHD has taken steps to increase research into preterm birth and specifically into late preterm birth, including publicizing the report from the Surgeon General's conference and highlighting opportunities identified in the report to interested investigators.

The NICHD-supported Maternal Fetal Medicine Units Research Network (MFMU) is planning a new clinical trial targeting women at risk for late preterm birth. This is a multi-center randomized trial designed to investigate the role of antenatal (provided to pregnant women before birth) corticosteroids in reducing respiratory morbidity in newborns of women likely to deliver in the late preterm period: 34 to 36 completed weeks of gestation. This trial is focused on testing a potential treatment that can reduce respiratory morbidity in the newborn, which in turn can translate into a lasting effect on the health of children, and a reduction in burden on the health care system. Its primary aim is to determine whether administration of antenatal corticosteroids reduces the need for neonatal respiratory support in patients with a singleton gestation (one child) and an anticipated delivery in the late preterm period. Secondary aims include evaluating whether partial administration of antenatal corticosteroids confers the same potential benefit as a full course of corticosteroids; and to collect neonatal DNA samples for future analysis of the fetal in utero response to antenatal treatment. The trial design currently is going through intensive internal review, as required by the MFMU Network policy.

NICHD-funded intramural researchers are conducting a pivotal clinical trial to determine whether administration of progesterone, a natural hormone, in women with a short cervix will prevent preterm birth and neonatal mortality. In addition, Branch scientists have identified biomarkers that predict spontaneous preterm birth, and are developing a rapid

test to detect intra-amniotic inflammation at the bedside, which if treated with antibiotics, may greatly reduce a major risk factor for preterm labor and neurologic injury.

The research agenda produced at the Surgeon General's Conference also called for more rapid dissemination of new research findings on preterm birth to health care providers. In response, the NICHD has launched the National Child and Maternal Health Education Program, comprising the senior leadership of 32 professional organizations and federal agencies with significant involvement in maternal and child health. This group has already begun to take the newest scientific findings and turn them into educational products that will inform the practices of health care providers and increase awareness of their patients.

Item

Maternal Fetal Medicine Units Network (MFMU) - The MFMU has changed obstetrical practice by identifying new therapies and identifying practices that are not useful. The Committee encourages NICHD to vigorously support the MFMU so that therapies and preventive strategies that have significant impact on the health of mothers and their babies will not be delayed. (p. 121)

Action taken or to be taken

In accordance with the NICHD mission, "to ensure that every person is born healthy and wanted, that women suffer no harmful effects from reproductive processes, and that all children have the chance to achieve their full potential for healthy and productive lives, free from disease or disability," the NICHD supports the MFMU Network to provide evidence for obstetrical practice. Established in 1986, the MFMU responds to the need for well-designed clinical trials in maternal fetal medicine with the goal to improve pregnancy outcome and ultimately long-term health. Since its inception, the Network has conducted over 20 randomized trials and large scale observational studies and published over 150 peer-reviewed papers in major journals. Results from these trials have been translated into clinical practice through professional organizations such as the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Results from the Network's findings have stopped practices that were not beneficial (such as measuring fetal oxygen saturation during labor) and those that were harmful (screening and treating asymptomatic women for vaginal infections). In addition, research from the MFMU has identified interventions that improve outcomes (antibiotics in the setting of preterm premature rupture of the membranes which allows the pregnancy to last longer and improves the outcome of the baby; magnesium sulfate in the setting of preterm birth to reduce the risk of developing cerebral palsy). Only 63 women who are at risk for preterm delivery need to be given magnesium sulfate to prevent one case of cerebral palsy. Finally, the MFMU has identified preventative therapies such as progesterone for women with a prior preterm birth to reduce the risk of a subsequent preterm birth. The impact of this preventative therapy is enormous; only six women who have had a prior preterm birth need to be treated to prevent one preterm birth (delivery <37 weeks). The Network has also performed trials to identify which groups may and may not benefit from these therapies.

Other ongoing studies in the network include a trial of thyroid dysfunction, subclinical hypothyroidism or hypothyroxinemia, to evaluate, by IQ testing at age 5, if treatment during pregnancy can improve a child's health outcome. The Network is also working to develop a

set of valid quality measures for obstetric care through an observational study evaluating specific measures, the APEX (Assessment of Perinatal Excellence) study, where data from over 40,000 pregnancies have been reviewed.

The MFMU Network is funded as a cooperative agreement and is openly re-competed every 5 years. The NICHD is planning to issue the Request for Applications for the recompetition of the MFMU Network, for the 2011-2016 cycle, early in 2010.

Item

Pregnancy Effects on Pancreatic Beta Cells - During pregnancy, functional pancreatic beta cell mass increases in the mother to meet the increased metabolic demands associated with pregnancy. An inadequate expansion of functional beta cell mass may contribute to gestational diabetes. Insights into the mechanisms underlying the increased beta cell response may lead to new therapeutic directions for treatment of gestational diabetes, and also provide important insights into the biochemical signals and pathways promoting beta cell function. By understanding these mechanisms and pathways, insights will be gained that may help design therapies to expand, maintain or restore beta cell mass in gestational diabetes and potentially all major forms of diabetes. NIDDK and NICHD are encouraged to work together to promote research to explore the effects of pregnancy on beta-cell growth and function. (p. 121)

Action taken or to be taken

During the second trimester of pregnancy the beta cell mass expands to meet the increasing metabolic demands of the growing fetus and placenta. The beta cell mass expands by an increased rate of beta cell division, known as hyperplasia, and by an increase in the size of the beta cells, known as hypertrophy. The rate of programmed beta cell death, known as apoptosis, is diminished during pregnancy, a phenomenon that also contributes to increasing the beta cell mass. The result of this beta cell expansion is a doubling of the level of circulating insulin by the end of the third trimester compared to levels of insulin in the non-pregnant state.

Recent findings indicate that the growth hormone family of proteins plays a central role in the expansion of the beta cells mass. It is possible that one or a combination of these hormones could be used to stimulate beta cell hypertrophy (growth) and hyperplasia (cellular increases) in cases of Gestational Diabetes Mellitus (GDM) or Type 2 Diabetes Mellitus (T2DM). Transcription factors have also been shown to be necessary, but not sufficient, for beta cell expansion during pregnancy. Another protein has been implicated in beta cell expansion, which protects beta cells from apoptosis, and another controls gene expression. Menin, a protein found in beta cells, serves as a transcriptional regulator and an endocrine tumor suppressor. When found in high levels in beta cells, menin acts as a brake on beta cell division, and may be a potential target for novel hormonal, immunological, or small molecule therapy.

In order to take advantage of these findings, staff of the NICHD, the NIDDK and the Juvenile Diabetes Research Foundation (JDRF) have begun to develop a public/private partnership that would be designed to stimulate molecular biologists, obstetricians, experts in animal models of pregnancy, and beta cell biologists to work together in research

projects aimed at translating the molecular stimuli of beta cell expansion during pregnancy into novel therapies for GDM and T2DM.

Senate Significant Items

Item

Demographic Research - The Committee urges the NICHD to continue its support of trans-NIH behavioral and social research initiatives on disasters and health outcomes to develop more data on the consequences of natural and man-made disasters for the health of children and vulnerable groups. Further, the Committee encourages the NICHD to continue its investment in large-scale 100 data sets, such as the New Immigrant Study and National Longitudinal Study of Adolescent Health, because of their value and accessibility to researchers worldwide. Finally, the Committee urges the Institute to continue research on (1) how the structure and characteristics of the work environment affect child and family health and well-being and (2) how health and well-being in the early years (including before birth) affect health and well-being later in life. (p. 105)

Action taken or to be taken

Please refer to page 98 of this document for NICHD's response to this item.

Item

Fetal Origins of Adult Disease - The Committee urges the NIH to continue its research to pinpoint the connections and causations between maternal obesity, diabetes, and heart disease and low birthweight babies, as well as other likely causes of poor infant health. (p. 106)

Action taken or to be taken

Please refer to page 101 of this document for NICHD's response to this item.

Item

First Pregnancy Complications - The Committee commends NICHD for identifying complications in nulliparous (first pregnancy) women as an important area requiring further research, and it urges the Institute to move forward with initiatives to identify predictors, especially with interventions, to improve the outcome for first pregnancies and to lower the risk of subsequent pregnancies. (p. 100)

Action taken or to be taken

Please refer to page 99 of this document for NICHD's response to this item.

Item

Fragile X - The Committee commends the NIH for developing the NIH Research Plan on Fragile X Syndrome and Associated Disorders. The Director is encouraged to dedicate sufficient resources to implement this plan with the guidance of the recently established Fragile X Research Coordinating Group, and in collaboration with the NICHD Fragile X Research Centers, as well as the Fragile X Clinical and Research Consortium. Priorities should include clinical trials of therapies for treatment of Fragile X syndrome and translational research that shows significant promise of a safe and effective treatment for Fragile X syndrome and associated disorders. The Committee congratulates the NIH and

its private foundation partners for providing a Small Business Innovation Research grant to fund fragile X drug development, and it encourages more efforts of this kind. Finally, the Committee urges the NIH, working with the Fragile X Clinical and Research Consortium, to convene a consensus conference on translational research opportunities in fiscal year 2010. (p. 126)

Action taken or to be taken

Please refer to page 208 in the Office of the Director's section of this document for the response to this item.

Item

Hormonal Contraception in Obese Women - The Committee urges continued and increased funding for research into the efficacy and safety of hormonal contraceptives among overweight and obese women. (p. 100)

Action taken or to be taken

The NICHD is committed to developing safe and effective contraceptives for women with particular focus on obese women since they are more likely to experience pregnancy-related complications in the event of a contraceptive failure. However, clinical evidence to provide clear guidance on which existing hormonal contraceptive method is the most effective for obese women is not available in the existing literature. As the incidence of obesity continues to increase, millions of women in the United States are faced with a problem of trying to choose a safe and effective hormonal contraceptive, and yet their healthcare providers lack the clinical data to guide their choice. Pharmaceutical companies, whose products are already on the market, generally have been reluctant to conduct the additional, necessary comparative randomized controlled trials due to high costs and possible unfavorable outcomes for their products.

The NICHD is currently exploring the feasibility of supporting the necessary research to provide information about the safest and most effective contraceptive methods for overweight and obese women. Possible partnerships with other NIH Institutes and Centers include ORWH as well as NIDDK for this study because women with diabetes present a special challenge with respect to contraception. NHLBI's participation may be another possibility since obesity is an independent risk factor for thromboembolic disease and the combination of obesity and hormonal contraception increases that risk by several fold; however, pregnancy increases the risk of thromboembolic disease by a substantially greater amount.

Item

Intellectual and Developmental Disabilities Research Centers - The Committee recognizes the contributions of the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers [IDDDRCs] toward understanding why child development goes awry, discovering ways to prevent developmental disabilities, and discovering treatments and interventions to improve the lives of people with developmental disabilities and their families. However, the Committee continues to be concerned that the IDDDRC network does not have sufficient resources to sustain the progress made in these critical areas and is especially concerned with the cuts in support for recently funded centers. The

Committee urges NICHD to restore these reductions and, to the extent possible, provide additional resources to the IDDRCs. (p. 106)

Action taken or to be taken

Please refer to page 99 of this document for NICHD's response to this item.

Item

Late Preterm Births - The NICHD is encouraged to expand its research on the causes of late preterm births and to facilitate research into better management and identification of interventions for their prevention. (p. 106)

Action taken or to be taken

Please refer to page 103 of this document for NICHD's response to this item.

Item

Learning and School Readiness - The Committee recognizes the importance of NICHD research in establishing the basic scientific foundation of the development of children's reading, math and science skills, and it encourages continued work in this area. (p. 106)

Action taken or to be taken

The NICHD continues to support research on the experiences that children from diverse backgrounds need from birth through school age to prepare them to learn, read, and succeed in school. Such research focuses on the development of cognition, emergent literacy, language, numeracy and mathematics, social and emotional competence, metacognition and self-regulation, motor development, and physical health. Supported studies employ cross-sectional and/or longitudinal research designed to specify cause-effect relationships between children's early experiences and the development of specific abilities that lead to achievement, reading ability, social competence, and emotional well-being in kindergarten and early grades, as well as the mediating processes responsible for observed outcomes in learning and development.

NICHD research funded in this area is closely coordinated with the efforts of agencies that oversee the management of service delivery programs, including the Head Start and Child Care Bureaus in the Administration for Children and Families (ACF) within DHHS and the Institute of Education Sciences and the Office of Special Education and Rehabilitation Services in the Department of Education. With co-funding from these agencies, the NICHD currently supports studies of the effectiveness of integrative early childhood curricula that promote school readiness among children at risk for later school difficulties. This collaboration maximizes the potential for translation of this supported research into tangible changes in parent, preschool, child care, pediatric primary care, and other settings and practices. In 2009, the NICHD funded a new research network dedicated to conducting efficacy studies on school readiness interventions that target English Language Learner children, aged three years to five years, who are at risk for later school failure. ACF is funding the Data Coordinating Center that will support this research network.

In addition, the NICHD continues to provide support for foundational research to inform our understanding of the development of reading and mathematics abilities and disabilities.

The NICHD provides ongoing support for four Learning Disabilities Research Centers which include an emphasis on understanding the origins of learning disabilities that impact reading, writing and oral language development. In 2009, the NICHD funded five research studies on mathematics learning and learning disabilities that will examine developmental cognitive factors in math learning disabled and normal math learning children, including biological risk factors (e.g., genetics), brain development and specific interventions to prevent and/or reduce math disabilities.

Item

Maternal Fetal Medicine Units Network - The Committee notes that the NICHD Maternal Fetal Medicine Units [MFMU] Network has improved obstetrical practice by identifying new therapies and practices that are not useful. The Committee urges the NICHD to adequately fund the network so that therapies and preventive strategies that have significant impact on the health of mothers and their babies will not be delayed. (p. 106)

Action taken or to be taken

Please refer to page 104 of this document for NICHD's response to this item.

Item

Pediatric Research Acceleration - There is a significant need to enhance the level of NIH support for biomedical research focused on diseases and conditions that affect the pediatric population. The Committee is aware of a promising proposal to leverage limited additional resources through multiple research consortia that would enhance the infrastructure needed to accelerate basic and translational pediatric research. The Committee encourages the NIH to support this networked consortia model. (p. 106)

Action taken or to be taken

In fiscal year 2008, the NIH, through 22 Institutes and Centers, awarded nearly \$3 billion in support of pediatric research activities across the country. The funding was distributed to the research community through a full range of funding mechanisms, including investigator-initiated grants, contracts, research networks, and others. This flexibility allows for the extensive scientific expertise at the NIH and in the extramural research community to be specifically applied to children's health and development, diseases and conditions. Where the scientific challenge warrants, NIH Institutes and Centers (often in multi-institute collaboration) have created multidisciplinary centers of excellence and research networks to focus a range of expertise on a specific condition, such as autism, pediatric oncology, neonatology, and clinical trials network for adolescents with HIV/AIDS, to name a few. In addition, a number of the new Clinical and Translational Science Awards (CTSAs) sites include a strong emphasis on creating infrastructure to conduct pediatric clinical trials, which will allow pediatric researchers who focus on a wide variety of conditions to utilize this new resource and leverage the funding they would otherwise have needed to conduct a clinical trial. In 2009, the NICHD awarded more than \$8 million in supplements to the CTSA sites to expand research in pediatric pharmacology.

Item

Preterm Birth - The Committee encourages the NICHD to expand research on preterm birth as outlined in the research agenda produced at the 2008 Surgeon General's Conference on Preterm Birth. (p. 107)

Action taken or to be taken

The research agenda produced at the 2008 Surgeon General's conference on Preterm Birth, organized by the NICHD, as well as the 2006 Institute of Medicine report on preterm birth, provide guidance to the research community on this critical public health issue, and informed development of the NICHD's Pregnancy and Perinatology Branch's Strategic Plan. The NICHD continues to support research focused on many of these the topics raised by the conferees in their report to the Surgeon General, such as identifying the groups that may benefit from progesterone (through the NICHD-supported Maternal Fetal Medicine Units (MFMU) Network), including women with a prior preterm birth, women with twins, women with triplets and women with a short cervix, and supporting investigator-initiated research on the mechanism of progesterone action. The NICHD also funded a clinical trial showing that women taking folic acid preconception had a reduced risk of preterm birth.

Several NICHD-supported networks of researchers are conducting studies that will elucidate contributing aspects of preterm birth. The Genomics and Proteomics of Preterm Birth Network is collecting biological samples to create the biorepository called for by the conferees that will be easily accessible to researchers and further facilitate research into preterm birth. The MFMU Network has designed a clinical trial to test an intervention (corticosteroids) to improve outcome in late preterm births. The NICHD also recently issued and reviewed responses to a new Request for Applications addressing one of the long term goals of the conference, to identify predictors and develop interventions addressing preterm birth and other adverse outcomes in nulliparous (first pregnancy) women. The new grantees will create a network of eight clinical sites with a central data collection site to study the mechanism and prediction of adverse pregnancy outcomes in nulliparous women.

In addition, to address another of the long-term goals from the Surgeon General's workshop, the NICHD has plans for a March 2010 workshop to investigate the biologic basis of racial-ethnic and socioeconomic disparities and preterm birth entitled "Disparities in Perinatal Medicine: Focus on Infant Mortality, Stillbirth and Preterm Birth." The NICHD also has launched the National Child and Maternal Health Education Program, comprising the senior leadership of 32 professional organizations and federal agencies with significant involvement in maternal and child health. This group has already begun to take the newest scientific findings and turn them into educational products that will inform the practices of health care providers and increase awareness of their patients.

Item

Rehabilitation Research- The Committee encourages the Institute's National Center for Medical Rehabilitation Research [NCMRR] to work with the Office of the Director to engage in greater collaboration with other relevant NIH institutes and centers in order to

leverage the Federal investment in rehabilitation and disability research and enhance the translation of such research to clinical application. The Committee also commends the NCMRR for its focus on determining the most effective treatments for traumatic brain injury [TBI]. Given the comorbidity of TBI and behavioral problems, agitation, anger and memory loss, the NCMRR is encouraged to include behavioral interventions for TBI treatment in future trials as well (p 101)

Action taken or to be taken

The National Center for Medical Rehabilitation Research (NCMRR), a center within the NICHD, has been designated as the lead and continues to promote collaboration on disability and rehabilitation research through several trans-NIH and trans-agency activities. Several other NIH Institutes and Centers also support research to improve function and quality of life for people with disabilities, according to their specific missions, including NINDS, NIA, NIAMS, NIBIB and NIDCD. This research integrates neurological and musculoskeletal approaches, bioengineering, and behavioral and psychosocial support. Research on movement-based rehabilitation includes the use of therapeutic exercise, electrical stimulation, and/or pharmacological treatments to promote plasticity and adaptation in the nervous system, while other studies focus on musculoskeletal biomechanics and joint pathophysiology.

The NCMRR leads the trans-NIH Rehabilitation Coordinating Committee to highlight common programmatic interests, coordinate resources, and build cross-disciplinary research initiatives, such as a recent Program Announcement on “Networks for Research Partnerships to Improve Functional Outcomes.” Several NIH Institutes are collaborating to renew the multi-site Medical Research Infrastructure Network, which provides core support for a variety of research projects. In addition, multiple Institutes and Centers at NIH participate in the Trans-NIH Traumatic Brain Injury (TBI) Consortium. On a trans-agency level, NCMRR is the NIH representative to the Interagency Committee on Disability Research and is in the process of finalizing a CDC/NIH report on TBI research activities for Congress.

Cognitive impairments are a key sequela of TBI. Ongoing NIH research includes studies that evaluate the efficacy of treatment interventions to improve cognition and link pharmacological interventions with behavioral outcomes. The TBI Network has developed and received approval for protocols for clinical trials on drug treatments to improve functional and cognitive outcome for patients with TBI as well as for depression. NICHD’s Pediatric Critical Care and Rehabilitation Program has been continued and funds research on outcomes for children who are survivors of trauma, congenital anomalies, neonatal asphyxia and other devastating processes.

In addition, two projects supported with ARRA funds include the use of noninvasive, magnetic stimulation to promote brain plasticity and recovery of function in children and a clinical trial testing a drug to increase memory and attention in children who have suffered TBI.

Item

Spina Bifida - The Committee encourages the NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder in order to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with paralysis and developmental delay. (p 129)

Action taken or to be taken

Please refer to page 225 of this document for NICHD's response to this item.

Item

Vulvodynia - The Committee remains concerned with the lack of progress in expanding research efforts on vulvodynia in recent years, and it strongly urges that the NICHD employ a full range of award mechanisms to substantially increase the number of awards for vulvodynia studies in fiscal year 2010. In addition, new research indicates that chronic vulvovaginal pain is also highly prevalent in the adolescent population and has been documented in children as young as 4 years of age; therefore, the Committee urges that consideration be given to collecting data on vulvodynia and related pain conditions in the National Children's Study. The Committee notes the lack of vulvodynia experts on peer-review panels and again encourages the Director to work with the Center for Scientific Review and other institutes and centers to ensure their adequate representation. The Committee also calls upon the Institute to continue efforts with the ORWH on the vulvodynia educational campaign. Finally, the Committee notes that vulvodynia coexists with other persistent pain conditions, including interstitial cystitis, fibromyalgia, temporomandibular joint and muscles disorders, irritable bowel syndrome, endometriosis, and chronic fatigue syndrome. The Committee calls upon the NICHD to collaborate with the Office of the Director on a trans-NIH research initiative that will support studies aimed at identifying common etiological pathways among these disorders, with the goal of developing therapeutic targets.(p. 107)

Action taken or to be taken

The NICHD continues its efforts to determine the underlying causes and pathophysiology of vulvodynia and the multiple factors that are essential to diagnosing and treating this complex pain syndrome. The American Recovery and Reinvestment Act (ARRA) of 2009 provided the NICHD with an unexpected opportunity to solicit and potentially fund grant applications on vulvodynia. A funding opportunity provided by ARRA enabled the NICHD to fund an application for an epidemiologic study that plans to assess the role of immunological factors in the etiology of vulvodynia. Also, through ARRA, the NICHD and the NIH Office of Research on Women's Health (ORWH) solicited Challenge Grant applications in the area of Pelvic Pain, specifically including vulvodynia. While a number of applications were submitted in response to this solicitation, none received high enough scores from the review panel to warrant funding. However, it is likely that several of these will be resubmitted as new grant applications through the normal review process. As with the review of unsolicited applications dealing with vulvodynia, it is suspected that part of the reason for this disappointing outcome was the lack of specific expertise on the review

panels. To address this issue directly, the NICHD will issue a Program Announcement with special review (PAR) by the end of 2009 for funding in FY 2010 to ensure that responsive grant applications related to vulvodynia will be reviewed by scientists with the appropriate expertise.

NICHD also is expanding its interactions with the other NIH Institutes and Centers that are expanding their work related to pain research. For example, the NICHD is continuing its partnerships with the NIDDK, the NINDS and the ORWH on the Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network program. This program includes vulvodynia as a related pain condition with similarities to chronic systemic and urologic pelvic pain syndromes.

The NICHD will continue its efforts with the ORWH, the NINDS, other NIH ICs, and nonfederal partners such as the American College of Obstetricians and Gynecologists, the National Vulvodynia Association, and other organizations to implement a national educational outreach program for health care professionals, patients and the general public on vulvodynia symptoms, diagnosis and treatment options. During the last fiscal year, the NICHD Clearinghouse distributed hundreds of the Vulvodynia Information Kits and individual fact sheets to the general public upon request and at professional society meetings. The information kit contains vulvodynia brochures, fact sheets, and journal article reprints.

**National Eye Institute
(NEI)**

House Significant Items

Item

Age-Related Macular Degeneration (AMD)-The Committee commends NEI for its trans-institute research into the cause, prevention, and treatment of AMD, the nation's leading cause of blindness. The Committee is pleased that NEI plans initial safety trials of a protective version of the gene variant as a means to treat and even preempt the disease. The Committee also recognizes NEI research into a protein pathway as another means to prevent and reverse AMD. The Committee applauds NEI for the ongoing work in the second phase of its Age-related Eye Disease Study, in which additional dietary supplements are being studied to determine whether they demonstrate or enhance protective effects against the progression to advanced AMD. (p. 122)

Action taken or to be taken

NEI investigators are making significant progress in understanding and treating AMD, the leading cause of vision loss in older Americans. The major discovery of protective and harmful gene variants in the complement factor H (CFH) gene, which regulates inflammatory responses, affords the opportunity to develop rational therapies to prevent vision loss. One such potential therapy involves treating the disease with the protein product from a protective CFH gene variant to minimize damaging inflammatory responses in the retina. In cell culture studies, this approach has shown promise. Preclinical toxicity and efficacy studies are ongoing with the goal of gaining regulatory approval to begin clinical trial investigations.

Another promising finding is the recent discovery that a previously known protein, Robo4, also prevents neovascularization. Neovascularization is the term used to describe the growth of new blood vessels. In the advanced stage of AMD, blood vessel growth is mistakenly activated. The resulting vessels are highly permeable and leak fluid and serum, damaging the light-sensitive photoreceptor cells in the retina. Neovascularization can cause severe and irreversible vision loss. Previous studies have established that a protein called vascular endothelial growth factor (VEGF) spurs neovascularization and several therapies have been developed to prevent the abnormal activation of the VEGF protein. Robo4 was found to stabilize the existing vasculature and prevent neovascularization by inhibiting VEGF activity. This discovery creates the opportunity to develop more effective therapies to prevent advanced AMD.

The Age-related Eye Disease Study 2 (AREDS2) will build on the landmark finding that antioxidant supplementation can reduce the development of advanced AMD and severe vision loss by 25 percent. AREDS2 is investigating the effects of high supplemental doses of dietary xanthophylls (lutein and zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid, DHA, and eicosapentaenoic acid, EPA) on the development of advanced AMD. Previous epidemiologic work, including data from the original AREDS, suggests that these nutrients may ameliorate the course of the disease.

Senate Significant Items

Item

Age Related Macular Degeneration (AMD)-The Committee commends NEI for its research into the cause, prevention, and treatment of AMD, including the identification of gene variants associated with an increased risk for the condition, initial safety trials of a protective version of the gene variant as a means to treat and even preempt the disease, and ongoing work in the second phase of its Age-related Eye Disease Study [AREDS]. The Committee also recognizes NEI research into the Robo4 protein pathway as another means to prevent and reverse AMD. (p. 102)

Action taken or to be taken

Please refer to page 114 of this document for NEI's response to this item.

Item

Diabetic Eye Disease -The Committee applauds the NEI for the collaborative efforts of the Diabetic Retinopathy Clinical Research Network to test innovative treatments for diabetic eye disease. The Institute is encouraged to expand and extend the network by increasing the number of clinical trials with new drugs and therapeutics that can treat and prevent diabetic retinopathy. (p. 102)

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is dedicated to facilitating multicenter clinical research to improve the treatment of diabetic retinopathy, diabetic macular edema, and associated conditions. In the last year, DRCR.net has grown to include more than 199 participating sites with more than 670 clinicians throughout the country.

In FY 2010, DRCR.net will initiate three new clinical trials to evaluate treatment methods for diabetic retinopathy and its complications. One of these clinical trials will assess a drug treatment for proliferative diabetic retinopathy. In this advanced form of the disease, fragile, abnormal blood vessels grow into the vitreous, the clear jelly-like substance that fills the inside of the eye. These vessels are fragile and tend to leak blood into the vitreous, obstructing vision. Although the blood can resolve out of the vitreous over time, repeated episodes result in scarring of the retina and permanent vision loss. The current standard of care for proliferative diabetic retinopathy is laser surgery. While effective in preventing further bleeding, laser surgery itself causes some loss of vision. This clinical trial will evaluate Ranibizumab (Lucentis), a drug that prevents blood vessel growth. Ranibizumab is already FDA-approved for the treatment of one form of age-related macular degeneration, where abnormal blood vessel growth also leads to vision loss and eventually blindness.

A second clinical trial will evaluate Infliximab (Remicade) for diabetic macular edema. In this condition, the macula, the central portion of the retina, swells due to bleeding. About half of those with proliferative diabetic retinopathy also develop macular edema. Laser surgery is the standard of care, but only 60 percent of patients have a favorable response and macular edema tends to recur even in those who initially respond to laser surgery.

Infliximab is an anti-inflammatory drug approved for the treatment of Crohn's disease and other autoimmune disorders. In preliminary clinical studies Infliximab showed promise in reducing vision loss from macular edema.

A third clinical trial slated for early 2010 will evaluate topical treatment with non-steroidal anti-inflammatory drugs on the progression of non-center-involved (non-CI) diabetic macular edema. In non-CI macular edema, the center of the retina has less severe retinal thickening and is thought to be an early stage of the disease where treatment has the potential to prevent disease progression and vision loss. Taken together, these three DRCR.net clinical trials will answer pressing treatment questions for patients with diabetic eye disease.

Item

Genetic Basis of Eye Disease - The Committee congratulates the NEI on its leadership in elucidating the basis of devastating eye diseases such as AMD, retinitis pigmentosa, and glaucoma, and recognizes the progress that has been made in understanding the underlying disease mechanisms and developing appropriate treatments. The Committee commends NEI's leadership on the human gene therapy clinical trial for neurodegenerative eye disease Leber Congenital Amaurosis, in which the initial safety study demonstrated vision improvement in young adults. The Committee also applauds NEI's initiation of its Human Genetics Collaboration [NEIGHBOR] study into the genetic basis of glaucoma. (p.108)

Action taken or to be taken

Much of the progress NEI investigators have made in developing treatments for eye diseases is due to the considerable effort put forth to identify the gene variants associated with vision loss. Each gene discovery allows researchers to study the gene's function in health and disease to gain an understanding of the molecular mechanisms that lead to vision loss. These insights have enabled investigators to begin to develop rational therapies that address the root causes of eye disease. Recently published one-year follow-up results of gene transfer for Leber congenital amaurosis (LCA) in patients indicate that the treatment is safe with evidence of lasting visual improvement. Follow-up studies will evaluate gene transfer in younger patients with less severe disease, which may prove to be more efficacious. These encouraging findings are considered "proof-of-concept" that could help usher several other gene-based therapies for retinitis pigmentosa, macular degeneration, and related retinal diseases into clinical trials.

The genetics of common diseases like glaucoma and AMD are complicated by environmental and age-related risk factors, making it a challenge to identify gene variants. Although several important gene variants for AMD have been identified, less is known about the genetics of glaucoma. NEI established the NEI Human Genetics Collaboration (NEIGHBOR), a consortium of clinicians and geneticists at 12 institutions throughout the United States dedicated to identifying the genetics of glaucoma. The NEIGHBOR consortium will combine data from more than 4000 individuals (2000 cases and 2000 controls). In parallel with NEIGHBOR, the GLAUGEN consortium (Gene-Environment interactions in glaucoma) will collect data from 2400 individuals (1200 glaucoma cases and 1200 controls). The GLAUGEN consortium is a component of the NIH Gene-Environment

Initiative (GEI) established to identify the relationships of environmental exposures to gene-trait associations in common, complex diseases. NEIGHBOR and GLAUGEN are using standardized clinical definitions for glaucoma that will enable researchers to combine data across the consortia. Together, these two consortia will initiate large-scale, genome wide association studies (GWAS) for identifying genetic variants associated with glaucoma. These efforts will greatly aid the goal of developing more effective treatments for glaucoma.

Item

Neuro-Ophthalmic Network - The Committee recognizes NEI's initiation of its Neuro-Ophthalmology Research Disease Investigator Consortium [NORDIC] to initially study the impact of increased intracranial pressure on vision and the impact of thyroid eye disease. The Committee encourages the Institute to expand this network as appropriate. It also recognizes that the NEI has already begun coordinating with the Department of Defense's Vision Center of Excellence on the potential applicability of NORDIC findings for traumatic brain injury patients. (p.108)

Action taken or to be taken

The Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) is a clinical trial network of neuro-ophthalmologists established to address the spectrum of neuro-ophthalmologic disorders that collectively affect millions of people. Some of these visual disorders are associated with other systemic or neurological conditions such as multiple sclerosis, thyroid disease, and intracranial hypertension. Many more of these diseases are rare, requiring a national network of clinicians like NORDIC to identify and recruit patients for clinical trials. Because these disorders have not been thoroughly investigated, there is little consensus regarding standard of care for neuro-ophthalmic disorders. NORDIC will address this lack of clinical knowledge by conducting multicenter clinical trials that concern disease risk, diagnosis, and treatment.

The first NORDIC clinical trial, the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), will evaluate diet and diuretics, alone and in combination, and conduct a genetic association study to identify risk factors for the development of the disease. Idiopathic Intracranial Hypertension, also called pseudotumor cerebri, is a disorder of elevated intracranial pressure of unknown cause. It affects about 100,000 overweight women of childbearing age and its incidence is rising in parallel with the obesity epidemic. Most patients suffer debilitating headaches. Because of pressure on the optic nerve, the vast majority of patients also experience transitory visual disturbances that can lead to permanent vision loss if optic nerve pressure remains chronically elevated. Interventions to prevent loss of sight include diet, diuretics, and repeated spinal taps. None of these strategies have been evaluated in clinical trials. The long-term goals of the IIHTT are to establish convincing, IIH evidence-based treatment strategies to restore and protect vision and to determine its cause.

In February, 2009, the director of the Department of Defense (DOD) Vision Center of Excellence and the chairperson of NORDIC began working out details for collaboration with the newly formed NORDIC network. The goal was to develop one or more projects that could use the expertise of the neuro-ophthalmologists in NORDIC to further the care

of soldiers with traumatic brain injury (TBI) and visual disturbances. NORDIC investigators submitted a preliminary proposal to the DOD to develop and test methods that accurately measure double vision and the associated functional losses related to TBI. If funded, the study will be conducted across 8 sites. It will also utilize the NORDIC Web site for quality of life data collection with subjects entering their own replies. The outcomes will help inform clinical management for TBI and visual disturbances.

**National Institute of Environmental Health Sciences
(NIEHS)**

House Significant Items

Item

Endocrine Disruptors - Increasing evidence suggests that numerous chemicals, both natural and man-made, may interfere with the endocrine system at all stages of life and produce adverse effects in humans. The Committee is concerned about the lack of research relating to the dangers of endocrine-disrupting chemicals in the home, workplace, schools, and indoor and outdoor recreational environments. The Committee encourages NIEHS, in conjunction with the National Toxicology Program, to support, directly or by grant or cooperative agreement, state-of-the-art studies to increase efforts to understand the true nature and scope of the impact of endocrine disruptors. This research should address areas related to neurobiology, behavior and reproduction.

(p. 122)

Action taken or to be taken

NIEHS supports a wide variety of studies on the effects of endocrine disrupting compounds (EDCs). The National Toxicology Program (NTP) is studying the endocrine disrupting potential of genistein, ethinyl estradiol, and nonylphenol on reproduction and behavior. NTP's pubertal toxicity studies are evaluating the sensitivity of the Environmental Protection Agency's Pubertal Protocol in detecting endocrine disrupting chemicals. NIEHS' extramural program is also studying sources of exposure to EDCs and their effects. Studies show that ingestion of contaminated indoor dust is an important exposure route for toddlers and young children. An evaluation of indoor dust showed EDCs (polybrominated diphenyl ethers, polychlorinated biphenyls, phthalates, pyrethroids, dichlorodiphenyltrichloroethane (DDT) and its metabolites, and chlordanes) at levels high enough to be potential health threats. Results indicated that persistent substances, such as chlordane and polychlorinated biphenyls, can affect human health long after their uses are prohibited or restricted.

Another study concluded that one week of water consumption from a polycarbonate bottle increased urinary bisphenol A (BPA) concentration by two-thirds. Regular consumption of beverages from polycarbonate bottles is associated with a substantial increase in urinary BPA concentrations irrespective of exposure to BPA from other sources. Another study demonstrated that Ecstasy (3,4-Methylenedioxymethamphetamine or MDMA), a popular recreational substance, administered at dosages relevant to human intake causes a significant disruption of hypothalamic and gonadal function in healthy adult male rats and has potential relevance to humans who use Ecstasy even once. Rats exposed to Ecstasy had significantly lower gonadatropin-releasing hormone gene expression and lower serum testosterone concentrations. Other studies indicate that exposure to endocrine-disrupting chemicals during development may alter the epigenetic programming of the genome and result in adult-onset disease. A study showed that transient exposure to methoxychlor or its metabolites during fetal and neonatal development affects adult ovarian function. Another study focused on embryonic exposure to vinclozolin, a fungicide used in the fruit industry that promotes an epigenetic reprogramming of the male germ line correlating with

transgenerational alterations in the full complement of activated genes in the testes in subsequent generations. NIEHS' intramural scientists provided evidence that early-life exposure to the xenoestrogen diethylstilbestrol (DES) or the phytoestrogen genistein induces life reprogramming of the mouse uterine epigenome. Specific genes with no previously documented associations with the uterus were identified by an unbiased methylation-profiling methodology. These genes encode proteins involved in a wide-range of cellular functions.

Item

Translational Research - The Committee recognizes the importance of translational research programs and applauds NIEHS's investment in clinical research through the Disease Investigation Through Specialized Clinically-Oriented Ventures in Environmental Research program. (p. 123)

Action taken or to be taken

NIEHS has attained notable success with its Disease Investigation Through Specialized Clinically-Oriented Ventures in Environmental Research (DISCOVER) program. This initiative has three principal purposes: 1) it supports patient and clinically oriented projects, 2) it looks at mechanisms of how environmental factors influence disease and, 3) it supports the next generation of researchers developing their careers in translational research. Accomplishments during the first two years of the program include more than 20 studies published in peer-reviewed journals covering a wide range of subjects. Cutting-edge hypotheses are being tested by DISCOVER grantees. For example, an emerging hypothesis posits that exposure to environmental agents that are transmissible from mother to fetus will have profound influences later in life, resulting in increased susceptibility to chronic diseases such as asthma. This early-life exposure causes epigenetic or reprogramming of DNA that can affect later expression of genes important in health. A recent finding from a DISCOVER investigator identified a particular gene that was modified in umbilical cord blood (fetal exposure) that was found to be significantly associated with maternal airborne PAH (polycyclic aromatic hydrocarbon) exposure and with parental reports of asthma symptoms in children prior to the age of 5. In another study, results show a link between the disproportionately high burden of ambient metals and diesel emission sources in particles of 2.5 micrometer diameter (PM_{2.5}) and disproportionately high asthma morbidity among children as young as 2 years. Other studies are looking at the role of depression in caregivers of children with asthma; diesel exhaust's role in heart rate variability; and the effect of maternal diet on the risk of asthma in offspring.

NIEHS plans to enhance the translational research concept with its Virtual Consortium for Trans-disciplinary/Translational Environmental Research (ViCTER) program. The objectives of ViCTER are to develop a virtual consortia program and to foster trans-disciplinary collaboration and translational research. Research efforts will focus not only on the etiology of disease but also on prevention strategies, diagnosis, treatment, and intervention. It is envisioned that the new Virtual Consortia, under ViCTER, will create new research teams that embody basic mechanistic clinical, epidemiological, computational and engineering perspectives to focus on a disease-relevant central theme. These consortia are an opportunity for scientists from the same or multiple disciplines to work

interactively on a common problem that, in turn, stimulates interaction across the spectrum, from basic cellular and molecular laboratory studies, to animal models, to human epidemiological or clinical research. These joint, multi-disciplinary efforts will provide data and information for the prevention of, and intervention in, human disease.

Senate Significant Items

Item

Alternative Methods of Testing – The Committee remains concerned by the slow pace at which Federal agencies have moved to adopt regulations that would replace, reduce or refine the use of animals in testing. The Committee therefore urges the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods [NICEATM] and the Interagency Coordinating Committee on the Validation of Alternative Methods [ICCVAM] to hold workshops on the challenges of incorporating alternative methods and the difficulty of obtaining high-quality data for validating alternative methods. NICEATM/ICCVAM are also urged to establish timetables for completion of all validation reviews that are currently underway. (p. 103)

Action taken or to be taken

NIEHS is committed to the goals and vision of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), i.e., the advancement of research, development, translation, validation, and regulatory acceptance of alternative test methods that reduce, refine, and replace the use of animals in testing while maintaining scientific integrity and the protection of human health, animal health, and the environment.

NICEATM and the ICCVAM are planning two workshops in 2010 that will address the challenges of incorporating alternative testing methods and the difficulty of obtaining high-quality data for validating alternative methods. The target audience is scientists from regulatory agencies and industry toxicologists who are critical in the implementation of accepted and available alternative test methods that can replace, reduce, or refine the use of animals for safety testing. The workshops will provide information on appropriate alternative test method selection, conduct, and data interpretation in accordance with regulatory testing requirements and guidelines. Attendees will receive guidance on submitting and making available high quality testing data necessary to support the validation of alternative methods. In addition, the workshops will promote the appropriate use of alternative test methods for hazard and safety assessments.

NICEATM and ICCVAM have established milestones that describe available alternative testing methods and timetables for the completion of ongoing validation studies and test method evaluations. The online listing can be found at <http://iccvam.niehs.nih.gov/methods/milestones.htm> .

In April 2009, NICEATM signed a Memorandum of Cooperation between the United States, Canada, Japan, and the European Union that globally coordinates scientific recommendations on alternative toxicity testing methods. It is expected that this

international action should speed their adoption of these methods in each of the cooperating countries and thus, reduce the number of animals needed for product safety testing worldwide.

Item

Translational Research - The Committee recognizes the importance of translational research programs and applauds the NIEHS's investment in clinical research through the Disease Investigation Through Specialized Clinically Oriented Ventures in Environmental Research [DISCOVER]. (p. 103)

Action taken or to be taken

Please refer to page 120 of this document for NIEHS's response to this item.

**National Institute on Aging
(NIA)**

House Significant Items

Item

Alzheimer's Disease- An estimated 2.4 to 5.1 million Americans suffer from Alzheimer's disease. As the baby boom generation ages, the number of persons affected is projected to grow to 7.7 million by 2030 and as many as 13.2 million by 2050. The Committee encourages NIA to accelerate the translation of basic research findings into clinical studies and human trials, and to fully implement a study of individuals who are genetically predisposed to develop early-onset Alzheimer's disease. NIA is urged to work closely with NINDS and NIMH in these efforts. (p. 123)

Action taken or to be taken

NIA, in partnership with NINDS and NIMH, supports a Translational and Drug Discovery Initiative to expand and intensify the translation of basic research findings into clinical studies and human trials and expand the NIH investment in Alzheimer's disease (AD) research. This initiative includes four program announcements, "Alzheimer's Disease Drug Development Program" (PAR-05-148 and its successor, PAR-08-266) and "Grants for Alzheimer's Disease Drug Discovery" (PAS-05-022 and its successor, PAS-06-261) to build on NIH-supported discoveries related to molecular targets and facilitate the discovery, development, and preclinical testing of novel compounds for the prevention and treatment of the cognitive and behavioral symptoms associated with AD. There are currently over 40 projects funded under these Program Announcements, exploring a broad range of approaches, including agents that may potentially inhibit the development of AD's characteristic amyloid plaques and neurofibrillary tangles as well as immunotherapies, antioxidant drugs, and neuroprotective agents. It is anticipated that additional meritorious projects will be funded across the life of these PAs. NIA-supported investigators involved in drug discovery and drug development can also use the services of NIA's Toxicology Contract, "Investigational New Drug Toxicology for Drugs to Treat Alzheimer's Disease and Other Aging-Related Diseases."

In addition, NIA supports a robust program of pilot clinical trials to test interventions aimed at delaying the onset of or preventing AD, mild cognitive impairment (MCI), and age-associated cognitive decline; slowing, halting, or, if possible, reversing the progressive decline in cognitive function; and modifying the cognitive and behavioral symptoms in AD and MCI. The Pilot Trials Program originally focused on drug interventions, but has recently been expanded to include non-pharmacologic interventions such as exercise. Ten pilot clinical trials are currently ongoing, and it is anticipated that additional trials will be added in the future.

NIA has established the Dominantly Inherited Alzheimer's Network, a consortium of scientific investigators who will use imaging and biomarker analysis to identify the sequence of changes in pre-symptomatic gene carriers who are expected to develop early onset dominantly inherited AD. This information will provide critical information about the pathology of AD that may also be applicable to the more common late-onset form of the

disease. Investigators at the Washington University (St. Louis) Alzheimer's Disease Research Center coordinate the network, which includes five sites within the United States, as well as one site in England and three in Australia. Recruitment to this study began in 2009 and will end in 2014, with approximately 400 individuals expected to participate.

Item

Demographic and Economic Research- The Committee is aware that in 2010 NIA will be making five-year awards as part of its Demography of Aging Centers and Roybal Centers for Research on Applied Gerontology programs. If enough high quality applications are received, the Committee encourages the Institute, with support from its funding partners, to consider expanding the program. In addition, the Committee encourages NIA to increase the minority sample size of the Health and Retirement Study to understand the impact of the economic downturn on pre-retirees and retirees in those groups. (p. 123)

Action taken or to be taken

In FY 2010, NIA will continue to support the Centers on the Demography and Economics of Aging program. This program was renewed in FY 2009, and we received a large number of meritorious proposals. Grant awards were made for 14 Demography Centers, up from 13 Centers in the previous cycle. This includes one two-year program that was established using ARRA funds. The remainder are five years in duration, but can be renewed. The Centers will continue their groundbreaking work on research areas including Medicare, Social Security, the implications of health care reform on the elderly, and other policy-relevant topics.

The Roybal Centers for Translation Research on Aging are intended to improve the health, well being, and productivity of older people through the translation of basic behavioral and social sciences research into practical applications. The Roybal Centers currently focus on the following topics: health and mobility, disease and pain management, decision making and behavior change, and better data, measurement, and forecasting. NIA, in partnership with the NIH Office of Behavioral and Social Sciences Research, the Department of Education, and the Agency for Healthcare Research and Quality, will continue to support these Centers in FY 2010. The program was renewed in FY 2009. Twelve Roybal Centers were funded initially, and an additional two-year program was established using ARRA funds. Research at the Roybal Centers is wide ranging and encompasses behavioral economics, age-related behavior change, and the role of social networks in health-related behaviors.

Made possible by FY 2009 ARRA funds, the Health and Retirement Study (HRS) will enroll an additional 3,000 new participants, including more than 1,000 African-Americans and over 1,000 Hispanic individuals for a total of over 25,000 participants. More than doubling the current oversampling of minority adults in the study between the ages of 51 and 61 will improve the statistical power of HRS data to understand the impact of the economic downturn and the sources of disparities in health and economic status.

Item

Hematology- The Committee commends NIA for establishing a consortium of research centers focused on anemia of the elderly, with the goal of developing effective prevention and treatment strategies to reduce the burden of this disease. (p. 123)

Action taken or to be taken

Anemia is a common clinical condition among the elderly, and its prevalence increases with age. About 11 percent of men and 10 percent of women ages 65 years or older and about 20 percent of those older than 85 years in the National Health and Nutrition Examination Survey (NHANES)-III survey were found to have anemia. Causes of anemia in the elderly are divided into three broad groups: (i) nutritional deficiency/blood loss (34 percent of all cases), (ii) anemia of chronic disease (32 percent of all cases), and (iii) unexplained anemia (34 percent of all cases). Consequences of anemia/low normal hemoglobin levels in the elderly include adverse effects on the heart and other organs resulting from a decrease in the amount of oxygen in the blood, and anemia and “low normal” levels of hemoglobin in the elderly are associated with substantial increases in risk for a variety of adverse clinical outcomes in older people, including fall-related fractures, cognitive impairment, hospitalizations, and mortality.

A recent NIH Advisory Panel recommended that trials be conducted on safety and efficacy of interventions for unexplained anemia in the elderly. In response, the Partnership for Anemia: Clinical and Translational Trials in the Elderly (PACTTE) consortium, coordinated by the Duke University Clinical Research Center, was established in 2009. Other participants include the University of Chicago, Stanford, University of California-Los Angeles, Case Western Reserve University, Johns Hopkins University, Howard University, and the University of Utah. During the six-year support period, investigators will develop protocols and study procedures and implement several phase II clinical trials on effects of interventions against anemia or low normal hemoglobin levels on hematologic, clinical, and functional outcomes in older adults. Multiple studies may run concurrently at each site, and members can also develop and implement pilot translational and exploratory studies informing design of future trials. Approximately 400 individuals are expected to participate over the six years of the study.

Senate Significant Items

Item

Alzheimer's Disease- The Committee was disappointed to learn that the NIH is spending far less on Alzheimer's disease than was previously believed. Under the historical method of tracking NIH spending, the funding level was believed to be \$645,000,000 in fiscal year 2007; the revised categorization method put the total for that year at \$411,000,000. In light of the growing burden that Alzheimer's disease is placing on society, the Committee believes greater resources are clearly warranted. In particular, the Committee strongly urges the NIA to devote more funding to clinical studies, including studies of individuals who are genetically predisposed to develop early-onset Alzheimer's disease, and renewal of the Alzheimer Disease Neuroimaging Initiative, including biomarker development studies. The NIA is urged to work collaboratively with the NINDS and NIMH to speed the

translation of research findings into more effective treatments and prevention strategies.
(p. 103)

Action taken or to be taken

Recent changes in the way that expenditures for research supported by NIH are reported do not in any way change the nature or extent of the research supported by NIH. In the past, NIH reported funding for research categories such as Alzheimer's disease (AD) by combining reports provided by the Institutes and Centers. NIA, as the lead NIH Institute supporting AD-related research, reported its AD funding using a scientific reporting database system that was developed and evaluated in collaboration with the scientific community and the Alzheimer's Association. This report covered scientific studies that were either (1) directly relevant or (2) closely related to AD.

Through the new Research, Condition, and Disease Categorization (RCDC) system, the projects reported for AD include only those studies considered by scientific experts to be directly relevant to AD. This means that a large number of NIA projects previously counted at pro-rated funding amounts, including training projects, large center grants, and general epidemiologic and demographic studies that collect data on questions related to AD, such as the Health and Retirement Study, are no longer included. A large number of basic science projects that hold potential to increase understanding of a variety of diseases and conditions including AD are now reported in broad categories such as Neuroscience, Neurodegenerative Diseases, and Brain Disorders. Research projects listed in other disease categories such as Down syndrome, Parkinson's disease, frontotemporal dementia, and Huntington's disease also have relevance to AD but are not included in the AD category by the new RCDC system.

NIH remains strongly committed to its ongoing efforts against AD. For example, the Dominantly Inherited Alzheimer's Network, a consortium of scientific investigators who will identify, recruit, evaluate, and follow up individuals from families with early onset dominantly inherited Alzheimer's disease, was established in FY 2008. Renewal of the highly successful Alzheimer's Disease Neuroimaging Initiative (ADNI) is planned for FY 2011, and recently ADNI investigators were awarded funding under the American Recovery and Reinvestment Act for an ambitious project to determine the relationships among the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the early (pre-dementia) stages of AD. This project will build on existing work under ADNI and serve as a bridge to ADNI's renewal.

NIA, in partnership with NINDS and NIMH, supports a Translational and Drug Discovery Initiative to expand and intensify the translation of basic research findings into clinical studies and human trials and expand investment in Alzheimer's disease research. This initiative includes support for drug discovery and development, as well as for pilot clinical trials of drug and nondrug intervention to test interventions aimed at delaying the onset of or preventing AD, mild cognitive impairment (MCI), and age-associated cognitive decline; slowing, halting, or, if possible, reversing the progressive decline in cognitive function; and modifying the cognitive and behavioral symptoms in AD and MCI.

Finally, NIH currently supports over 40 active clinical trials of interventions to prevent or treat AD, and we anticipate that additional trials will be funded in the future. Of the currently active trials, 15 are anticipated to be completed by the end of FY 2011. Data analyses and trial results are generally available within 6 to 9 months following trial completion.

Item

Community Interventions- The NIA is encouraged to strengthen its portfolio of community studies to identify and/or evaluate promising interventions to reduce biological risk, chronic conditions, or improve outcomes relating to disability. (p. 103)

Action taken or to be taken

NIA supports a number of ongoing community-based studies. The following are some examples.

Several of NIA's Alzheimer's Disease Centers (ADCs) operate satellite facilities in underserved, rural, and minority communities. These facilities offer diagnostic and treatment services and opportunities to participate in community based research studies. ADC researchers are working to translate research advances into improved diagnosis and care for AD patients while, at the same time, focusing on the program's long-term goal of finding a way to possibly prevent or ultimately cure AD.

NIA is funding a major community intervention designed to improve social, cognitive and physical functioning among poor, inner-city elderly through the Experience Corps evaluation. Experience Corps recruits older people for cognitively challenging, meaningful roles as volunteers in inner-city elementary schools. The program is active in 19 cities nationwide. The evaluation is a double-randomized treatment-comparison group study of effects on both the older volunteers and on the school children in Baltimore.

NIA's Resource Centers for Minority Aging Research (RCMARs), which were established to improve the health and well being of older minority populations, include robust community health and outreach components.

NIA supports a number of comparative effectiveness research projects that have strong community health components. For example, one study is evaluating the Work and Health Initiative, a community-based program that provides mental health and vocational services to improve functioning and reduce productivity loss among individuals ages 50+ with depression; another is evaluating the effectiveness of cognitive assessment of older individuals in community-based primary care practices.

The Baltimore Longitudinal Study of Aging (BLSA), established in 1958, is the world's most comprehensive and longest running longitudinal examination of human aging. Ground-breaking research from this study has transformed the field of geriatrics. This study has provided a wealth of information on the physical consequences of aging and has helped distinguish age-related changes from those due to disease. For example, BLSA scientists have elucidated the relationship between age-related changes in the arteries and

cardiovascular disease and have distinguished normal age-related declines in cognitive ability from those associated with Alzheimer's disease and related conditions.

The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is a multidisciplinary, community-based, prospective longitudinal epidemiologic study examining the influences of race and socioeconomic status (SES) on the development of age-related health disparities among socioeconomically diverse African Americans and whites living in Baltimore. This study will investigate over a 20-year period whether health disparities develop or persist due to differences in SES, differences in race, or their interaction.

The Work, Family, Health Study is a multi-site intervention study in two industries, including long-term care and telecommunications, exploring how changes in the work environment can improve the health of workers and their families while benefiting organizations. NIA collaborates with NICHD in supporting this initiative.

Item

Demographic and Economic Research- The Committee is aware that in 2010 the NIA will be making 5-year awards as part of its Demography of Aging Centers and Roybal Centers for Research on Applied Gerontology programs. The Committee urges the NIA, with support from the NIH Office of Behavioral and Social Science Research and Office of AIDS Research, to fund at least the existing number of centers, and more if possible. In addition, the Committee encourages the NIA to substantially increase the minority sample size of the Health and Retirement Study to understand the impact of the economic downturn on pre-retirees and retirees. (p. 104)

Action taken or to be taken

Please refer to page 124 of this document for NIA's response to this item.

Item

Geroscience- The Committee recognizes the importance of the emerging interdisciplinary research approach known as geroscience. Given the size of the aging baby boomer population and the incidence of chronic disease in an aging society, it is critical to devote increased resources to understanding the connection between aging and disease. The Committee also believes that more resources should be dedicated to studies on prevention (such as exercise and diet) as well as other interdisciplinary approaches to understanding extended health span and healthy aging interventions that delay and prevent chronic disease. (p. 104)

Action taken or to be taken

The NIH Geroscience initiative, an interdisciplinary consortium, was established in late FY 2007 under the NIH Roadmap. It consists of 11 components, including seven R01-type interdisciplinary projects, one core (mass spectroscopy and imaging), and a training program that proposes to confer the first ever PhD in Geroscience. Currently, five NIH Institutes (NIA, NINDS, NIEHS, NIGMS, and NIDCR) participate in this initiative, which is coordinated through NIDCR. The project focuses on the basic biology of aging and age-

related diseases (particularly neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease).

A number of other NIH-supported initiatives and studies are exploring health span, as well as the development of interventions to prevent or delay chronic disease, including:

The Claude D. Pepper Older Americans Independence Centers- NIH supports 11 Pepper Centers with the goal to increase scientific knowledge that will lead to better ways to maintain or restore independence in older people. Each Center has a specific area of research focus.

The Long Life Family Study (LLFS)- LLFS is a unique international project that is studying families who have several members reaching a very old age (age 79 or older) in order to learn about factors that contribute to long and healthy life certain in families. Understanding these factors can help identify ways to improve the amount of time that others spend in good health during their lifetime.

The IDEAL Study- A new study of a subset of participants in the Baltimore Longitudinal Study of Aging, IDEAL (Insight into the Determinants of Exceptional Aging and Longevity), is being established. This project will study the genetic, environmental, social, and behavioral factors that preserve health and function for the healthiest of the oldest old.

Studies of Diet, Exercise, and Cognitive Health- NIH/NIA supports several studies to evaluate the ability of diet and exercise to influence cognitive health and prevent cognitive decline, including Alzheimer's disease.

The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) Study- A large body of research in animals indicates that substantially reducing caloric intake while maintaining optimal nutrition can significantly lengthen life span. The CALERIE study will help to determine if these effects extend to humans. This ongoing study began in January 2007, and has already produced several published findings related to the effects of caloric restriction interventions on weight loss and maintenance, metabolic rate, insulin sensitivity, and cardiovascular risk factors, among other parameters.

The Interventions Testing Program- Investigators at the three institutions involved in this long-running initiative are currently testing sixteen different compounds for their potential to extend the lifespan of a mouse model, providing preliminary data on potential interventions to promote healthy aging in people. Phase II testing has recently begun for the drug rapamycin, which produced highly promising results in the first round of testing.

Nathan Shock Centers of Excellence in Basic Biology of Aging- These Centers are currently being recompeted, and NIA expects to make 4-5 awards. In the context of geroscience, three of the Centers received supplementary funds last year to identify and characterize parameters of health span in mice. This field is critical for further molecular experimentation on longevity and health in animal models.

Item

Interdisciplinary Behavioral Research- The Committee encourages the NIA to promote joint efforts with other institutes to explore the interface of behavior, neuroscience, and epidemiology in studies of normal aging. One such area is affective neuroscience, with particular emphasis on the ways in which basic psychological processes such as emotional regulation, motivation, and executive function contribute to health and functioning over the life span. (p. 104)

Action taken or to be taken

A number of NIA and trans-NIH initiatives explore the interface of behavior, neuroscience, and epidemiology in the context of normal aging. Some examples follow.

Under an ongoing initiative dealing with the social neuroscience of aging, NIH supports research examining the neurobiological and genetic foundations and correlates of social behaviors and social relationships of relevance to aging, with particular emphasis on the mechanisms and pathways linking social behaviors and social relationships to the physical health, functionality, and psychological well-being of middle-aged and older adults. To date, seven projects have been funded as part of this initiative including one co-funded by the NIH Office of Behavioral and Social Sciences Research. Projects will continue for five years.

With the National Cancer Institute (NCI) and the National Institute of Mental Health (NIMH), NIA participates in a new initiative soliciting research proposals on the mechanisms and processes that link psychosocial stressors to health outcomes in older individuals. Projects will be funded under this initiative starting in FY 2010.

NIA, NCI, NIMH, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, are partnering on an initiative to solicit research proposals to expand basic and translational research on the processes and mechanisms involved in the experience, expression, and regulation of emotion. Innovative studies in social/affective neuroscience are particularly encouraged. To date, twenty-five applications have been received, and it is anticipated that grant awards will be made during FY 2010.

NIA supports six developmental grants in neuroeconomics of aging, examining how age influences decision making and risk taking in a variety of domains relevant to health and economic behavior. Several published findings have emerged from these studies, with more expected. For example, investigators found that stress may reduce older adults' risk-taking behaviors in a driving simulation. In another study, participants played a computer game designed to measure risk taking fifteen minutes after completing a stress challenge or control task; the investigators found that stress increased risk taking among men but decreased it among women.

NIA, NCI and NIMH are partnering on an initiative to solicit research proposals aimed at understanding the mechanisms underlying the links between psychosocial stress, aging, the brain and the body. This announcement was published in the summer of 2009, and

the first applications are expected in October 2009. This announcement will be active through 2012.

NIA also has an initiative to provide infrastructure support in specific emerging interdisciplinary areas of behavioral and social research in aging including affective neuroscience. Projects will be funded in FY 2010.

Item

Kidney Disease- The Committee encourages the NIA to support research that studies the basic biology of the aging processes in the kidney, the science of how aging impacts kidney injury and repair, and how chronic kidney disease [CKD] differs in the elderly compared to a younger population. Additional research should consider how age impacts CKD progression in comparison to the impact of other risk factors and how cognitive impairment and frailty are impacted by CKD treatment, including dialysis. (p. 104)

Action taken or to be taken

NIA's research programs explore the consequences of aging on all organs, including the kidney. Ongoing studies are exploring the consequences of decreased kidney function on aging, estrogen deficiency as a risk factor for CKD in older women, and the mechanisms of cognitive impairment in chronic kidney disease.

With NIDDK, NIA is currently soliciting basic, clinical, and translational research on chronic kidney disease (CKD) and its consequences in aging and in older persons. Projects will focus on the 1) biology and pathophysiology of CKD in animal models; 2) etiology and pathophysiology of CKD in the elderly; 3) epidemiology and risk factors for the development of CKD with advancing age; and/or 4) diagnosis, medical management, and clinical outcomes of CKD in this population. Research supported by this initiative will enhance knowledge of CKD and its consequences in the elderly and provide evidence-based guidance in the diagnosis, prevention, and treatment of CKD in older persons. Studies will run for up to five years, ending in approximately 2015.

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

House Significant Items

Item

Arthritis – The Committee encourages NIAMS to consider developing a national network of cooperating clinical centers for the care and study of children with arthritis. Federal funding of similar initiatives in childhood cancer have resulted in markedly improved outcomes, supporting the idea that participation in research protocols improves the standard for all children with cancer. (p. 123)

Action taken or to be taken

Juvenile idiopathic arthritis (JIA) is a type of arthritis with no definite cause and an onset prior to 16 years. There are multiple types of JIA that collectively are the most prevalent pediatric rheumatic illness and the most common cause of childhood disability in the United States. The NIAMS funds a broad range of research, from basic research studying the underlying mechanisms of arthritis, to clinical studies exploring new treatment options.

For example, the NIAMS supports investigators who utilize an existing network of clinical centers, known as the Childhood Arthritis and Rheumatology Research Alliance (CARRA). CARRA is a multi-center research network comprising the majority of pediatric rheumatologists in the United States. One NIAMS-supported project is a clinical trial examining the effect of early, aggressive therapy on remission of polyarticular juvenile idiopathic arthritis (poly-JIA), a condition in which five or more joints are affected. This research focuses on the identification and testing of new combinations of drugs not previously tested in pediatric patients. The study plans to establish best practices for achieving long-term beneficial effects for patients with poly-JIA, such as ceasing disease progression or inducing remission. Advances from this study will be made available as the research progresses. NIAMS encourages researchers examining the causes of, and potential treatments for, juvenile arthritis to utilize the CARRA network.

In addition, NIAMS recently used funds provided by the American Recovery and Reinvestment Act to support a Grand Opportunities (GO) grant to comprehensively expand the existing CARRA network to improve the outcomes and quality of life for all children with rheumatic diseases, and to transform the research culture of pediatric rheumatology toward universal participation. The "GO" grants program supports large-scale research projects aimed at accelerating critical breakthroughs, early and applied research on cutting-edge technologies, and new approaches to improve the synergy and interactions among multi- and inter-disciplinary research teams.

In other research supported by the NIAMS, investigators have examined the challenges associated with diagnosing the various subtypes of JIA. In a multi-center study, NIAMS-funded researchers looked closely at patients with the poly-JIA subtype of the disease. Using gene expression technology – a method by which scientists can determine the relative levels of expression of thousands of different genes at the same time – investigators discerned three subgroups of poly-JIA based on different patterns of gene

expression in their blood samples. In a related study, gene expression technology allowed investigators to further distinguish the major subtypes of JIA. Collectively, these findings take pediatric rheumatologists closer to more precisely classifying JIA, eventually allowing them to tailor personalized treatments, thus maximizing benefits, while minimizing risks.

Item

Bone Loss – The Committee urges NIAMS to support research into the pathophysiology of bone loss in diverse populations in order to develop targeted therapies to improve bone density, bone quality and bone strength. The Committee also encourages NIAMS to support research in the assessment of microarchitecture and bone remodeling rates to more accurately determine fracture risk, as well as anabolic approaches to increase bone mass, novel molecular and cell-based therapies for bone and cartilage regeneration. (p. 123)

Action taken or to be taken

Osteoporosis is one of the most prevalent bone diseases and is characterized by low bone mass and structural deterioration of bone tissue, affecting many people as they age. Osteoporosis and other bone diseases affect more than 10 million individuals today and cause approximately 1.5 million fractures annually, figures that will rise significantly with the country's aging population. NIAMS supports a wide variety of research activities that are investigating the many aspects of osteoporosis and its treatment.

NIAMS has partnered with NIA to support three long-term epidemiologic efforts focused on fracture risk in women and men—the Study of Osteoporotic Fractures (SOF), the Osteoporotic Fractures in Men study (Mr. OS), and the Framingham Osteoporosis Study. These projects have provided information that can now be used to examine gender differences. In May 2009, research analyzing data from the Mr. OS study concluded that bone strength in older men was inversely related to aging – a concept well-documented in women. Additionally, it was learned that men with the lowest bone mineral density at the beginning of the study were at greatest risk for subsequent bone loss, a factor that should ultimately help clinicians identify those men who may need treatment the most.

In another effort, researchers discovered that applying a sophisticated mathematical technique to men's quantitative computed tomography (qCT) scans – a technique for measuring bone mineral density – was a strong predictor of hip fracture, especially when combined with traditional bone mineral density measurements. A non-invasive strategy with an improved ability to predict fracture risk will enable physicians and patients to make informed decisions about the need for treatment, and to continue to evaluate whether the selected treatment regimen is beneficial.

Doctors have long known that factors such as advanced age, low body weight, and low calcium intake increase a woman's risk of hip fracture. Recently, NIAMS-supported research has revealed another potential risk factor - low blood levels of vitamin D, a vitamin that helps the body absorb calcium from food. In combination with a clinical trial supported by the NIH Women's Health Initiative (WHI) that showed calcium combined with vitamin D reduced the risk of fractures in women, these findings could significantly

enhance the understanding of hip fracture risk, and lead to ways to reduce it. However, additional studies are needed to confirm the role of vitamin D in clinical care.

Bone is constantly undergoing remodeling in response to damage caused by everyday life and requires two opposite actions. Resorption removes old bone cells while formation creates new bone tissue. Bone loss occurs when resorption outpaces formation. NIAMS-supported researchers have recently discovered that one molecule (TGF- β 1) is involved in the regulation of both of these processes. Not only does this enhance scientists' understanding of these highly coupled events, but it also provides a potential single target for new therapies when in the past only one process was targeted.

In addition to the work that seeks to understand and prevent bone loss, NIAMS has funded several studies that look to repair and regenerate cartilage and bone. One such study shows that a single injection of the same molecule that was responsible for bone resorption and formation also enhanced cartilage production in animal models. In other work, NIAMS-supported researchers have produced data that suggests that enhancing blood vessel formation at a fracture site in elderly patients may lead to faster bone repair. Both of these studies could lead to novel treatments that eventually repair or regenerate human tissue.

Item

Bone Diseases – The Committee encourages NIH to support genetic and other research on diseases such as osteogenesis imperfecta and Paget's disease and other rare bone diseases such as fibrous dysplasia, osteopetrosis, fibrous ossificans progressiva, melhoreostosis, and X-linked hypophosphatemic rickets. The Committee also encourages NIH to strengthen support across all institutes for new basic science and clinical investigators through the various K award mechanisms. (p. 123, 124)

Action taken or to be taken

The NIAMS, along with NIDDK and the NIH ORDR, co-sponsored the 1st Advances in Rare Bone Diseases scientific conference in October 2008. The conference examined the latest advances relating to a series of genetic bone diseases, while seeking to understand how they may be applied. It also encouraged collaboration between interested lay and expert participants in hopes of forging new areas of understanding and highlighting the need for research and therapeutics.

NIAMS-supported research continues to support research contributing to the understanding of hypophosphatemic rickets – a genetic metabolic condition that results in the malformation of bones and teeth – in which mineral metabolism is abnormal. For example, the Center for X-Linked Hypophosphatemic Rickets Research is a NIAMS-funded Center of Research Translation (CORT) aimed at determining the various molecular contributors to this genetic form of rickets and working toward developing new treatments. CORTs are designed to bring together basic and clinical research in a way that helps translate discoveries into new drugs, treatments, and diagnostics.

Paget's disease is a rare disease that causes bones to grow larger and weaker than normal, leading to fracture. It can also lead to other health problems, such as arthritis and

hearing loss. NIAMS-funded researchers are currently investigating particular genetic mutations that influence bone cell formation, which may trigger events that lead to the development of Paget's disease. Another research team supported by NIAMS is performing a clinical study to determine the rate of progression of the disease, so that the effects of future treatment strategies can be evaluated. Advances from these studies will be made available as the research progresses.

Fibrodysplasia ossificans progressive (FOP) is a rare, inherited genetic disease in which the body eventually forms a second skeleton from its own muscles, tendons, and ligaments. Although the genetic defect for FOP has been discovered, little is known about the cellular basis of this condition. Researchers supported by NIAMS have recently identified a cell that contributes to this debilitating condition. This discovery holds promise for therapeutic regulation of specific cell lines, and thus could lead to future treatment options for this painful condition.

The NIH remains committed to identifying and attracting new biomedical researchers, and will continue to explore novel ways to encourage early transition to independence. Investigators are encouraged to utilize existing training opportunities including the Research Career Awards (K awards) provide support for the development of independent scientists and clinicians. For example, one NIAMS-supported K award recipient is looking to characterize a particular molecular pathway central to X-linked hypophosphatemic rickets (XLH), while also trying to establish an expertise in metabolic bone research. This clinical research will attempt to unravel the pathophysiology of a key hormone involved in XLH, which could lead to safer and more effective therapeutic options.

Item

Lupus- The Committee urges NIAMS to strengthen support for research on the causes of and cures for lupus, a life-altering disease that affects women, men and children, but disproportionately women in the 15- to 44-year old age range and people of color. Further research is needed to expand knowledge on a possible genetic link and conditions that may trigger the disease, as well as on the disease's effect on specific organs. (p. 124)

Action taken or to be taken

Systemic lupus erythematosus (SLE, or lupus) is a serious and potentially fatal disease, and it can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Lupus is an autoimmune disease that affects many Americans, 90 percent of whom are women. It has been known for decades that females are more susceptible than males to most autoimmune diseases, including lupus. The role of sex hormones in the modulation of disease activity has been well-studied. However, the influence of sex hormones does not preclude additional effects mediated directly by sex chromosomes (X and Y chromosomes). For example, differences in gene expression between the sexes (XX females and XY males) may be associated with Y chromosome-specific genes in men, or higher doses of a gene expression from two X chromosomes in women. These could induce sex-specific patterns of immune system development or function that create gender differences in autoimmune disease prevalence.

Recent progress reported by NIAMS-supported researchers is helping to shed light on why certain autoimmune diseases, such as lupus, disproportionately affect women. Using genetically engineered mice that had XY chromosomes but were female instead of male, researchers found that the XX females had more severe autoimmune disease than the XY females. This finding indicates that some factor on the X chromosome plays a role in lupus, apart from sex hormones. Scientists will be able to use this information to explore novel treatment targets for various autoimmune diseases, including lupus.

A second study focused on a gene called IRAK1, which is encoded by another gene on the X chromosome, and is a critical mediator in the immune system's ability to recognize and respond to pathogens. Despite the extensive involvement of IRAK1 in the regulation of immune response, very little has been known about its contribution to autoimmune diseases, such as lupus. NIAMS-supported researchers have found compelling evidence that support IRAK1 as a disease gene in lupus, and its location on the human X chromosome as a possible explanation for female predominance of the disease. Identification and characterization of lupus-associated genetic markers should aid in the diagnosis of patients at risk, and provide important insights into the pathogenic pathways of the disease.

Lupus nephritis (lupus kidney disease) is a complication of the disease that can be quite severe. Previous studies have indicated that the drug hydroxychloroquine, an antimalarial medication also used in the treatment of lupus and other autoimmune diseases, was associated with a reduced risk of overall tissue damage. NIAMS-supported researchers determined that lupus patients treated with hydroxychloroquine were less likely to develop severe kidney disease, had lower disease activity, and used less steroid medication than those who had not been on the medication. These results add to a growing base of literature on the benefits of hydroxychloroquine use, and suggest that it may prevent renal damage and the impact such damage has on long-term morbidity and mortality.

Item

Marfan Syndrome – The Committee encourages NIAMS to strengthen its support for collaborative, multi-investigator research related to Marfan syndrome and to collaborate with NHLBI in support of the Pediatric Heart Network's clinical trial on Marfan syndrome. (p. 124)

Action taken or to be taken

Marfan syndrome is a heritable condition in which a mutation in the fibrillin gene leads to defective connective tissue. The small, weak muscles that often characterize Marfan syndrome patients are a result of limited muscle regeneration function. Scientists supported in part by the NIAMS and NINDS had previously discovered that the commonly prescribed blood pressure medication, Losartan, improves muscle regeneration and repair, which could lead to effective treatment options. These results have formed the basis for further research that is supported by NIAMS and other NIH Institutes, such as NHLBI and NINDS. For example, the NHLBI's Pediatric Heart Network has launched a clinical trial comparing beta-blocker therapy (Atenolol) to angiotensin II receptor blocker therapy (Losartan) in individuals with Marfan syndrome. The study, which began enrolling patients in February 2007, will include 604 individuals with ages that range from 6 months to 25

years, and will take approximately 6 years to complete. As of August 2009, the study had enrolled 452 patients (75 % of the total enrollment). The NHLBI network also provides an ideal structure to test new medical or surgical therapies in uncommon conditions, such as genetically-induced aortic aneurysms, which are associated with Marfan syndrome.

NIAMS participates in NHLBI's Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions (GENTAC): National Registry. The registry collects clinical data and samples from patients with aortic aneurysms that are caused by genetic alterations. The data generated from the registry could aid researchers in determining the best medical practices to advance the clinical management of cardiovascular complications associated with connective tissue diseases such as Marfan syndrome.

NIAMS continues to support a multi-site translational research project in Marfan syndrome. Researchers are studying genetically engineered mouse models of Marfan syndrome to uncover the abnormal cellular activities that contribute to this disorder, and they will translate this new knowledge into more effective therapies. The project utilizes a comprehensive and multidisciplinary approach that integrates the scientific interest and expertise of four leading laboratories in this and related research fields.

Finally, NIAMS recently used funds provided by the American Recovery and reinvestment Act to support two administrative supplements for grants currently studying Marfan syndrome. One focuses on the biology surrounding a family of molecules that regulate cell performance and survival and have been linked to the disease through their interactions with fibrillin. The other study concentrates on the bone physiology that is central to the skeletal manifestations that are characteristic of Marfan syndrome.

Senate Significant Items

Item

Bone Diseases. – The Committee urges the NIH to accelerate and expand research on osteoporosis and related bone diseases and related manifestations, such as cancer and bone loss leading to increased morbidity, mortality and disability. The Committee encourages more research on the pathophysiology of bone loss in diverse populations, with the goal of developing targeted therapies to improve bone density, quality and strength, assessment of microarchitecture and bone remodeling rates to more accurately determine fracture risk, as well as anabolic approaches to increase bone mass, novel molecular and cell-based therapies for bone and cartilage regeneration. Because the causes, symptoms and treatments of osteoporosis and related bone diseases cross scientific boundaries and impact various populations by age and gender, the Committee encourages continued collaboration among NIAMS, NCI, NIA, NICHD, NIDCR, NIDDK, NINDS and NIBIB. The Committee also urges NIH to expand genetics and other research on diseases such as osteogenesis imperfecta and Paget's disease and other rare bone diseases such as fibrous dysplasia, osteoporosis, fibrodysplasia ossificans progressive, melioreostosis, and X-linked hypophosphatemic rickets. Finally, the Committee encourages the NIA to conduct research aimed at translating basic and animal studies into novel therapeutic approaches to prevent age-related bone loss. (p. 116)

Action taken or to be taken

The NIH supports a wide range of research in bone biology and bone diseases across many of its Institutes and Centers. For example, in osteoporosis, which is one of the most prevalent bone diseases, NIAMS has partnered with NIA to support three long-term epidemiologic efforts focused on fracture risk in women and men—the Study of Osteoporotic Fractures (SOF), the Osteoporotic Fractures in Men study (Mr. OS), and the Framingham Osteoporosis Study. Initial findings from these studies are already available. For example, research results released in May 2009 indicated it was learned that men with the lowest bone mineral density at the beginning of the project were at greatest risk for subsequent bone loss, a factor that should ultimately help clinicians identify those men who may need treatment the most.

In another effort, researchers discovered that applying a sophisticated mathematical technique to men's quantitative computed tomography (qCT) scans – a technique for measuring bone mineral density – was a strong predictor of hip fracture, especially when combined with traditional bone mineral density measurements. A non-invasive strategy with an improved ability to predict fracture risk will enable physicians and patients to make informed decisions about the need for treatment, and to continue to evaluate whether the selected treatment regimen is beneficial.

Other NIH-supported research includes the Study of Women's Health Across the Nation (SWAN), a project supported by the NIA that is examining changes in bone mass, bone turnover, and strength in a multiethnic (Chinese, Japanese, African American and Caucasian) cohort as the participants age. NIDDK-supported research on hormonal regulation of bone cell development, turnover, and tissue interactions seeks to identify potential therapeutic targets to treat the thinning of bone that results in osteoporosis. Additionally, NIDCR-supported researchers are conducting a case-controlled study assessing the impact of bisphosphonate exposure on the risk of developing osteonecrosis of the jaw, a condition characterized by bone loss caused by reduced blood flow.

NICHD-funded investigators have begun a genome-wide association study (GWAS) that builds off of longitudinal bone mineral density study of 2,000 healthy children and adolescents, to reveal genetic variants associated with bone acquisition. Under the current study plan, data collection will be complete by 2012. Also, NICHD's intramural researchers, who in 2007 identified genetic mutations associated with a rare form of osteogenesis imperfecta (OI), discovered a mutation with a markedly higher incidence in African Americans. This finding has led to continued research efforts into the treatment of OI with limited doses of bisphosphonates that will optimize their benefit while limiting the detrimental side effects.

The NCI supports programs directed at clinically challenging bone cancers. In patients with bone metastasis or in osteosarcoma patients, bone loss due to the activation of bone degrading cells, or osteoclasts, is a major area of morbidity, including pain and bone fractures. NCI-funded investigators continue to delineate novel mechanisms involved in tumor-bone interactions that result in bone loss, and are trying to identify novel targets for therapy that may inhibit osteoclast-bone interactions.

Item

Fibromyalgia - The evaluation and treatment of patients affected by fibromyalgia represent a disproportionate financial burden on the national health care system in large part because of a persistent lack of knowledge regarding the fundamental pathophysiology underlying its complex symptoms. The Committee urges the NIH, particularly the NIAMS and NINDS, to expand their emphasis on fibromyalgia research, including animal models of the disorder, basic science of the pathophysiology of the disorder in humans, and the development of appropriate clinical models of patient assessment and care. The Committee also continues to urge the NIH to establish a center dedicated to fibromyalgia and related disorders and to support the convening of an international symposium on fibromyalgia. (p. 117)

Action taken or to be taken

NIH sponsors research that will improve scientists' understanding of the specific problems that cause or accompany fibromyalgia, in turn helping them develop better ways to diagnose, treat, and prevent this syndrome. For example, the Patient-Reported Outcomes Measurement Information System (PROMIS) is an NIH Common Fund initiative aimed at improving the way patient-reported outcome tools are selected and employed in clinical research and practice evaluation. Researchers supported by NIAMS are conducting an ancillary study to PROMIS focused on fibromyalgia. The goal of this work is to develop a disease-specific measurement instrument that will increase the efficacy of assessment and treatment methods for fibromyalgia. The current funding period for this project is scheduled to end in 2010.

The research on fibromyalgia supported by NIAMS covers a broad spectrum, ranging from basic laboratory science to studies of clinical interventions. For example, NIAMS-supported researchers are examining the development of symptoms in patients with juvenile primary fibromyalgia syndrome (JPFS) from adolescence through young adulthood. Information obtained will increase knowledge about the prognosis for patients with JPFS, and the complex relationship between physical and emotional symptoms in fibromyalgia syndrome. This effort will help to identify patients at greatest risk for severe outcomes which, in turn, will inform the design of targeted treatments. Other NIAMS-supported scientists are examining the influence of co-morbid conditions on the chronic pain associated with fibromyalgia. In a recent study, researchers determined that obesity reduced the amount and quality of sleep. This is significant, because abnormal sleep patterns are known to influence fibromyalgia symptoms, which may be exacerbated in patients with high body mass index. Further analysis and research is needed, examining the possibility of a co-morbid relationship between fibromyalgia and obesity. Finally, NIAMS will be supporting a conference in FY2010 that will investigate the basic science of pain and musculoskeletal disorders, which will include discussions on fibromyalgia.

The NINDS fibromyalgia portfolio focuses on elucidating the mechanism, and treating the chronic, unexplained pain in fibromyalgia. One project uses a specialized neuroimaging technique called functional MRI to investigate pain mechanisms involved in fibromyalgia, and to understand why patients show abnormal pain processing. A large project funded by NINDS is trying to understand how the pain experience (intensity, localization, persistence) in fibromyalgia and related co-morbid conditions, such as temporomandibular joint

disorders (TMJD), can exceed what would be expected based on the size of the tissue injury or extent of nervous system dysfunction. The larger NINDS pain portfolio includes a number of studies on characterizing pain pathways and defects, information which lays the groundwork for understanding and potentially treating fibromyalgia.

Item

Marfan Syndrome – The Committee encourages NIAMS to continue its support of collaborative, multi-investigator research related to Marfan syndrome and partner with the NHLBI in support of the Pediatric Heart Network's clinical trial on Marfan syndrome. (p. 104)

Action taken or to be taken

Please refer to page 136 of this document for NIAMS's response to this item.

Item

Mucopolysaccharidosis (MPS) - The Committee commends NIAMS for taking the lead role in supporting the 1st Advances in Rare Bone Diseases Scientific Conference. (p. 105)

Action taken or to be taken

The NIAMS, along with the NIDDK and the NIH Office of Rare Diseases Research (ORDR), was pleased to co-sponsor the 1st Advances in Rare Bone Diseases scientific conference in October 2008. The objectives of this conference were to (1) examine the latest advances in basic, translational, and clinical research relating to a series of genetic bone diseases; (2) understand how recent advances in science may be applied to the areas of bone biology and clinical study of bone; (3) encourage collaboration and spur innovation by allowing selected trainees and junior faculty to present their relevant work to an audience of experts in the field; (4) promote interaction between interested lay participants and medical and scientific experts, including representatives from pharmaceutical industry, involved in bone and orphan diseases; and (5) forge new areas of understanding and promote the need for research and therapeutics. Presentations provided the latest research and clinical information on rare diseases affecting the skeleton, as well as further developed partnerships between the research community and lay organizations dedicated to serving patients with rare bone diseases.

Item

Psoriasis - The Committee recognizes that scientists are identifying genes of immune cells involved in psoriasis, which gives promise to identifying and developing a permanent method of control for psoriasis and, eventually, a cure. The Committee recognizes that additional genetics, immunology and clinical research focused on understanding the mechanisms of psoriasis are needed and encourages NIAMS and NIAID to study the genetic susceptibility of psoriasis, develop animal models of psoriasis, identify and examine immune cells and inflammatory processes involved in psoriasis and elucidate psoriatic arthritis-specific genes and other biomarkers. The Committee also recognizes the mounting evidence of comorbidities associated with psoriasis and the potential higher risk of mortality and cardiovascular disease for people with severe psoriasis. The Committee urges NHLBI to consider these factors in its research, specifically that individuals with severe psoriasis have an increased risk of heart attack, independent of other major risk

factors, and that for people in their forties and fifties with severe psoriasis, the risk of heart attack is more pronounced. The Committee also encourages NIDDK to consider in its research that diabetes is more prevalent for patients with severe psoriasis than for those with mild disease. The Committee encourages NIMH to conduct research to better understand why it is estimated that as many as 52 percent of psoriasis patients report clinically significant psychiatric symptoms and that individuals with psoriasis are twice as likely to have thoughts of suicide. (p. 136)

Action taken or to be taken

NIH supports a wide range of research in psoriasis and psoriatic arthritis. For example, NIAMS is continuing to support genome-wide association studies (GWAS) aimed at identifying all the genetic factors behind psoriasis and psoriatic arthritis, how they interact with each other, and the environmental influences that may cause the disease. Additionally, animal models are being used to investigate the effect of immune cells, as well as other factors, involved in the development of psoriasis. Finally, the Center for Psoriasis Research Translation is a NIAMS-funded Center of Research Translation (CORT) centered around a mechanistic, safety, and preliminary efficacy study that is testing a novel photodynamic therapy for psoriasis. CORTs are designed to bring together basic and clinical research in a way that helps translate discoveries into new drugs, treatments, and diagnostics.

In an ongoing NHLBI-supported observational study since April 2009, investigators are comparing the levels of risk for myocardial infarction, ischemic stroke, and cardiovascular mortality in participants, with and without, psoriasis. Since psoriasis is associated with risk factors for cardiovascular disease, they are examining how comparative risk is influenced by traditional cardiovascular risk factors such as diabetes, hypertension, hyperlipidemia, smoking, and body mass index.

The inflammatory response associated with severe psoriasis is thought to contribute to an elevated rate of diabetes. A recent scientific workshop held by the NIDDK, "Inflammation, Immunity, and Metabolism at the Interface of Type 1 and Type 2 Diabetes," explored this relationship. Also, the NIDDK is testing an inexpensive generic anti-inflammatory medication in its Targeting Inflammation with Salsalate in Type 2 Diabetes (TINSAL-T2D) clinical trial. If successful, this research could offer a new therapy for diabetes associated with a number of inflammatory conditions, including psoriasis.

NIMH continues to co-sponsor the program announcement (PA) "Research on Co-Morbid Mental and Other Physical Disorders." This PA encourages research on mental disorders that are co-morbid with other physical disorders, like psoriasis, that are among the leading causes of morbidity and mortality in the United States.

The NIAID continues to support research into autoimmune diseases, including psoriasis. NIAID maintains its commitment to clinical trial networks including the Immune Tolerance Network, the Autoimmunity Centers of Excellence, and the Cooperative Study Group for Autoimmune Disease Prevention. Through a Small Business Innovation Research grant, NIAID supports a clinical trial of aminotrexate, an immunosuppressive agent, in patients with moderate-to-severe psoriasis.

Item

Psoriasis – The Committee is encouraged by NIAMS' support of a CORT grant and of a strong follow-up study to the GAIN grant. The Committee recognizes that researchers are identifying genes that control immune pathways involved in psoriasis and giving promise to identifying and developing a permanent method of control for psoriasis and, eventually, a cure. The Committee recognizes that additional genetics, immunology and clinical research focused on understanding the mechanisms of psoriasis are needed, and it encourages NIAMS and NIAID to study the genetic susceptibility of psoriasis, develop animal models of psoriasis, identify and examine immune cells and inflammatory processes involved in psoriasis, and elucidate psoriatic arthritis specific genes and other biomarkers. The Committee also recognizes the mounting evidence of comorbidities associated with psoriasis and the 50 percent higher risk of mortality for people with severe psoriasis. The Committee urges the NHLBI to consider these factors in its research, specifically that individuals with severe psoriasis have an increased risk of heart attack, independent of other major risk factors such as hypertension, diabetes and obesity, and that for people in their 40's and 50's with severe psoriasis, the risk of heart attack is more pronounced. The Committee also urges the NIDDK to consider in its research that diabetes is more prevalent for patients with severe psoriasis than for those with mild disease. The Committee encourages the NIMH to conduct research to better understand why it is estimated that as many as 52 percent of psoriasis patients report clinically significant psychiatric symptoms and that individuals with psoriasis are twice as likely to have thoughts of suicide. (p. 120)

Action taken or to be taken

Please refer to page 140 of this document for NIAMS's response to this item.

Item

Scleroderma - The Committee commends NIAMS for its support of research on scleroderma through the National Family Registry for Scleroderma and the Center of Research Translation. The Committee requests an update on these activities as part of the Institute's fiscal year 2011 congressional budget justification. (p. 105)

Action taken or to be taken

Though it is often referred to as if it were a single disease, scleroderma is really a group of diseases that involve the abnormal growth of connective tissue, which supports the skin and internal organs. In some forms of scleroderma, hard, tight skin is the extent of this abnormal process. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as the heart, lungs, and kidneys.

Scleroderma is a complex disease, presumably influenced by several risk factors. To address the genetic association of scleroderma, the NIAMS has supported the Scleroderma Family Registry and DNA Repository for several years. The aims of the registry are to identify the genetic changes that make an individual susceptible to scleroderma, and to build a repository of genetic material for researchers to use when studying scleroderma and other autoimmune diseases. The Family Registry has enrolled approximately 4000 participants. The information collected allows researchers to conduct

a genome wide association study (GWAS) of scleroderma, and confirm the existence of an autoimmune component. In this continuing effort, over 2000 participants have been recruited to this GWAS, which will seek to determine what genes are responsible for susceptibility to scleroderma, and which biological pathways are used to cause organ damage in the disease. Once available, the final dataset will be made available to the scientific community for additional analysis.

The NIAMS-supported Center for Research Translation in Scleroderma is examining the molecular basis of scleroderma in order to understand its underlying causes. Among the major aims of the center are to identify the cellular pathways causing disease, and explore the means to interrupt them. Investigators have already conducted detailed genetic analysis of blood samples from scleroderma patients, grouping them by ethnicity, gender, and the autoantibodies (proteins that attach to the body's healthy tissues by mistake) which are associated with specific subtypes. The most notable gene variants in these patients, relative to healthy controls, are within human leukocyte antigen (HLA) genes, which have significant roles in immune function. An important accomplishment of this research is the correlation of individual HLA gene variants and disease subtype-specific autoantibodies. Such findings could lead to new treatment options for patients.

**National Institute on Deafness and Other Communication Disorders
(NIDCD)**

House Significant Items

Item

Tinnitus - The Committee is aware that the incidence of tinnitus continues to increase and that tinnitus remains the number one service-connected disability for returning military personnel. Because tinnitus research will benefit all populations, the Committee remains interested in a multi-disciplinary approach to promote accurate diagnosis and treatment for tinnitus. The Committee encourages NIDCD to move ahead with a collaborative research initiative with the Department of Defense and the Department of Veterans Affairs and requests an update on the progress of such efforts in the FY 2011 budget justification report. (p. 124)

Action taken or to be taken

Tinnitus is a major health concern for many Americans. Approximately 25 million Americans have experienced tinnitus. The condition can range in severity from a mild condition which requires no intervention to a severe debilitating disease with significant emotional, social and economic impact. NIDCD continues to conduct research into the underlying causes of tinnitus, and to explore potential therapies for the treatment of affected individuals.

In August, 2009, NIDCD convened a workshop, *Brain Stimulation for Treatment of Tinnitus*, to identify neural prosthesis technologies that could successfully treat tinnitus in a way similar to how cochlear implants bring hearing to people who are profoundly deaf. Scientists from academic departments of neurophysiology, biomedical engineering, otology, and neurosurgery were invited, as well as representatives from the Department of Defense, the Department of Veterans Affairs, and the Food and Drug Administration. Experts reviewed the most recent devices developed by neural engineers, a number of which have the potential to modulate the perception of tinnitus, depending on their surgical placement in the cochlea, midbrain, deep brain, or cortex. A workshop summary was published in the Inside NIDCD Newsletter in December 2009, and future research applications on this topic are invited through two PARs.

A significant obstacle for advancement in this field is a lack of knowledge about the specific neural dysfunction(s) responsible for tinnitus. To address this problem, NIDCD supports an expanding portfolio of tinnitus research. A recent NIDCD funding opportunity announcement, *Understanding the Neural Mechanisms Responsible for Tinnitus*, invited applications to promote the development of novel intervention strategies. Currently supported research projects seek to (1) correlate tinnitus perception with patterns of neural activity in the brain, (2) couple neurophysiology studies with behavior in animal models, and (3) use brain imaging studies to delineate patterns of activity that are specific to human subjects with tinnitus. Understanding the basic biology underlying tinnitus will aid in more accurate diagnosis of affected individuals.

NIDCD continues to fund studies that encourage the development of novel treatments. Several strategies are under investigation, including drug therapy, non-invasive brain stimulation, brain stimulation through surgical implantation, as well as clinical trials on behavioral and environmental interventions. Findings from these studies are published in scientific journals and presented at scientific meetings. A similar process of research and development was used during the development of cochlear implants, which are now widely used in both civilian and veteran populations. NIDCD continues to solicit applications to translate advances from basic research into new technologies and therapeutic applications for tinnitus. These advances in knowledge are needed to develop treatments that provide relief for specific neural deficits giving rise to tinnitus after acoustic or closed head trauma.

Senate Significant Items

Item

Brain Plasticity - The Committee continues to support research on functional changes of synapses of the auditory pathways and cortex following hearing loss, and how these changes limit hearing capability, even with hearing aids or cochlear implants. Also recommended are investigations in animal models of neural mechanisms responsible for demonstrated auditory deficits following hearing loss. (p. 105)

Action taken or to be taken

NIDCD-supported scientists are conducting research to determine how the brain changes when an individual becomes hearing impaired. For example, scientists are studying the circuitry of the auditory nerve and the cochlear nucleus of the brain to elucidate the cascade of events that follows deafness. After inducing deafness in a cat model, scientists will determine the changes to the molecular composition of the synapses in the auditory pathways. In addition, the scientists will determine if a reduction in sound stimulation leads to a remodeling of the neural synapses in the cochlear nucleus. This study will inform developing strategies that attempt or replace hearing (via cochlear implants) in individuals who are deaf at birth. The results of this study are published in various journals and presented at scientific conferences.

In another project, NIDCD-supported scientists are studying the synaptic structure in the auditory nerve fibers of normal hearing, experimentally deafened, and congenitally deaf cats and mice. Structural and biochemical knowledge of the synapses of the nerves in the auditory pathway will determine if deafness leads to abnormal synapses, and if abnormalities occur across species, and if changes are dependent on the age at which deafness occurs. The scientists are also using multichannel cochlear implants in cats of different ages to test whether auditory nerve stimulation from the implant can prevent and/or reverse deafness-induced synaptic anomalies in the cochlear nucleus. This research will determine if stimulation from a cochlear implant can prevent synaptic abnormalities in the deafened auditory system. The results of this study are published in various scientific journals.

NIDCD intramural scientists are also conducting research on plasticity of the central auditory system. This research addresses the molecular, cellular, and systems level components of neuronal plasticity that lead to a better understanding of plasticity in the human nervous system. Scientists are trying to understand how synaptic transmission is

affected by hearing loss and whether there is a critical period in development which requires auditory experience. To accomplish this goal, intramural scientists are investigating plasticity using brain imaging technology. Other intramural scientists are studying how neural connections in the auditory system change as a result of congenital and early-onset deafness. These studies will guide treatment strategies, such as determining the optimal time for cochlear implantation in children who are deaf. The results of this study are published in various scientific journals.

Item

Cytomegalovirus – The Committee supports more research into the pathogenesis and treatment of cytomegalovirus, a leading cause of congenital sensorineural hearing loss. (p. 105)

Action taken or to be taken

The NIDCD continues to support research on cytomegalovirus (CMV) infection rate, the pathogenesis of CMV, and novel treatments for CMV infection. In 2005, NIDCD funded the University of Alabama School of Medicine in Birmingham to lead a long-term multicenter study called CHIMES (CMV and Hearing Multicenter Screening Study). The major focus of CHIMES is to determine if hearing loss develops in CMV-infected children who have no initial symptoms at birth. The CHIMES study is one of the largest studies of its kind and will be screening approximately 100,000 children at birth for CMV infection. Those who test positive for CMV will undergo follow-up diagnostic hearing testing to chart the onset, severity, and progression of hearing loss. Investigators will analyze the data to determine the extent to which CMV screening, combined with hearing testing, can improve the detection and prediction of permanent hearing loss in children. The results of this study are expected approximately one year after the contract end date of June 2012.

The NIDCD is also investigating how CMV infection damages the ability to detect sound. Why do children infected with CMV *in utero* have compromised hearing, while those infected after birth do not? NIDCD-supported scientists are testing the hypothesis that *in utero* CMV infection interferes with the growth and patterning of the developing cochlea – a snail-shaped structure in the human inner ear that translates sounds into electrical impulses that are sent to the brain. The investigators plan to use a cultured mouse cochlea to model the developing human cochlea to test the outcome of different timings of CMV infection during development. This study aims to generate a detailed description of the molecular events of CMV infection. A thorough understanding of these events is vital for determining how and when to treat an infected child in order to prevent, or halt progression of, hearing loss. The results of this study are expected approximately one year after the contract end date of June 2012.

The NIDCD is also funding a study to address the demand for safe and effective treatments for CMV-related hearing loss. Healthcare professionals know that antiviral drugs (such as gancyclovir) given to infants with symptomatic congenital CMV can stabilize or even improve hearing. However, these antiviral drugs have serious side effects when administered systemically; new treatment options are needed. One study attempts to avoid the side effects by delivering antiviral drugs directly to the affected area via an injection through the eardrum. The tests will be conducted in a well-developed guinea pig

model of CMV infection and hearing loss. The investigators hope to generate novel data to serve as the foundation for early clinical trials that will treat CMV-related inner ear disease by administering antiviral drugs to the middle ear. NIDCD is determined to maintain its substantial commitment to learning how to predict, effectively treat, and ultimately prevent CMV-induced hearing loss. The interim results of this study are published in the scientific literature.

Item

Hair Cell Regeneration and stem cell - The NIDCD should continue building on new approaches for regenerating lost hair cells, including developing technology for gene transfer and gene vector generation, and testing the viability of regenerated cells in animal models at the levels of nucleic acids and proteins. Comparative research on responses to hair cell damage in regenerating and non-regenerating species is also urged. The Committee encourages the NIDCD to expand and support stem cell research in the auditory system, with areas of focus to include the use of stem cells to replace lost hair cells and peripheral neurons via transplantation; integration of stem cells into sensory epithelium; and innervation/reinnervation of the partially deaf or deaf cochlea. The Committee continues to encourage further studies to correlate hair cell replenishment with improved hearing (p. 105)

Action taken or to be taken

Inner ear hair cell loss and lack of hair cell regeneration are the major causes of permanent hearing loss. NIDCD is supporting an active research portfolio to determine ways to regenerate auditory hair cells lost by disease, excessive noise, or exposure to ototoxic drugs. For example, NIDCD-supported scientists are continuing a landmark study that utilizes *Atoh1* gene transfer to successfully regenerate auditory hair cells in deafened guinea pigs. They are determining if these new hair cells are re-innervated to restore hearing. In another study, scientists are using mouse embryonic stem cells to generate hair cell-like cells and then transplanting the cells into a hereditary deaf mouse. The researchers will assess whether the cell-based therapy restores auditory hair cells in the deafened mouse's cochlea and reverses hearing loss. Further, it is known that hair cells continue to be produced in the inner ears of all cold-blooded and some warm-blooded vertebrates (birds) but not in mammals (mice). Scientists are currently identifying and comparing growth factors that regulate regenerative replacement of inner ear stem/progenitor cells after induced hair cell damage in the ears of chickens and mice. Other researchers are identifying mutations in zebrafish that alter hair cell regeneration in order to understand the molecular regulation of this process, identify hair cell precursors, and determine the self-renewing properties of hair cell stem cells. The results of these studies are published in various scientific journals.

NIDCD intramural scientists are conducting research related to the identification of genes and signaling pathways involved in the development of the mammalian cochlea. One aspect of this research focuses on the identification of factors that regulate the development of mechanosensory hair cells. In particular, previous results demonstrate that a transcription factor, *Atoh1*, plays a key role in directing cells towards a hair cell fate. Similarly, these scientists have demonstrated that two signaling pathways (notch and hedgehog) act to inhibit hair cell formation through direct modulation of *Atoh1* activity.

Since loss of hair cells is believed to be the underlying cause for hearing loss in many cases, identification of the genetic factors that promote or inhibit hair cell formation has the potential to lead to the identification of targets for regenerative therapies. Another NIDCD intramural laboratory is culturing neurospheres (a type of stem cell) from mammalian cochlea tissue. They will use an atomic force microscope to probe the spheres to see if mechanical factors may be important for the production of cells having hair bundles. The results of these studies are published in various scientific journals.

Item

Hereditary Hearing Loss – The Committee applauds the NIDCD’s efforts to identify and understand the structure, function, and regulation of genes whose mutation results in deafness and other communication disorders. It recommends continuation of such studies, with increased emphasis on the genetics of complex hearing loss and Meniere’s disease. (p. 105)

Action taken or to be taken

NIDCD’s Division of Intramural Research continues to support three productive laboratories in which research is directed at identifying hearing loss genes and describing their structure, function, and regulation. Recently, one of these labs, working in collaboration with an international group of researchers, identified heritable mutations in the gene, *HGF*, that lead to deafness. This gene is also implicated in tumorigenesis, neuronal survival and wound healing. The novel mutations identified further our knowledge of the regulation of HGF, and may lead to a better understanding of how it causes hearing loss, cancer progression, wound healing, and neuroprotection. The investigators will now use the tools of molecular and cell biology to determine how the genes are regulated, and how they function.

The NIDCD also continues to support numerous scientists at research institutions throughout the United States who are identifying genes in which mutation causes deafness and other communication disorders. Scientists hope to use information about the normal and mutated protein products of these genes to improve their ability to diagnose various forms of deafness and to improve the current treatments or assistive therapies for individuals who inherit deafness-causing mutations.

The understanding, treatment, and prevention of balance disorders such as Meniere’s disease are also important priorities for NIDCD. NIDCD-supported scientists approach balance problems from a wide range of perspectives. They are working to understand pathological changes associated with Meniere’s disease and comparing them to normal balance function. Other laboratories are investigating normal and disordered blood flow to the cochlea, which has been implicated in hearing loss and balance disorders. Another research project is investigating possible ways to prevent loss of hair cells after exposure to ototoxic drugs, which may lead to balance or hearing problems. Still another grantee is developing a prototype prosthetic device to compensate for balance problems that is currently being tested and optimized in animal models of balance disorders. NIDCD remains committed to investigating all causes of hearing loss and balance disorders, and is enthusiastic about continuing to support a strong research portfolio in this area. The results of these studies are being published regularly in peer-reviewed scientific journals.

Item

Noise and Environmentally Induced Hearing Loss - Of particular concern to the Committee is the epidemic proportion of noise-induced hearing loss in the military, a situation that will increase as veterans age. The Committee encourages the NIDCD to support critical research into prevention of hearing loss from noise trauma in military environments, as well as studies of post-exposure treatment. The Committee commends the NIDCD for its efforts to raise public awareness of the omnipresent threats to the auditory system posed by environmental noise. It advocates continued dissemination of information emphasizing dangers to hearing from workplace noise, recreational activities and loud consumer products, and describing ways to protect hearing during exposure, through such means as the "It's a Noisy Planet" and "Wise Ear" campaigns, and the NIDCD website and publications. The Committee also understands the potentially deleterious effects of environmental pollutants in water and air on the inner ear, and urges the NIDCD to support studies of the impact of such chemicals as lead and mercury, and carbon monoxide, on hearing, especially during prenatal and early postnatal development. Finally, the Committee encourages the NIDCD to continue and enhance support of behavioral research on ways to prevent or lessen the cumulative damage to hearing caused by environmental noise (p. 105, 106)

Action taken or to be taken

NIDCD-supported researchers are investigating ways to prevent noise-induced hearing loss (NIHL) after noise exposure. Prior work has shown that noise exposure triggers the formation of destructive molecules, called free radicals, which cause hair cell death. Researchers initially had thought that antioxidants—chemicals that protect against cell damage from free radicals—might prevent NIHL if the antioxidants were given before noise exposure. However, recent studies have discovered that there is a window of opportunity in which it is possible to rescue hearing after noise trauma. NIDCD-supported researchers are now conducting a clinical trial testing the ability of nutrients, such as anti-oxidant vitamins and minerals, to prevent temporary and permanent NIHL. While NIDCD's mission is not focused on military personnel, this study will examine military personnel in military environments with both acute and chronic damaging noise exposures, as well as civilians with occupational or leisure activity noise exposures. This clinical trial is scheduled for completion in June 2012 and findings from the study will inform NIHL prevention and treatment strategies for all Americans.

NIDCD is continuing its efforts to educate the public on the damaging effects of loud noise on hearing. In 1999, the NIDCD and the National Institute for Occupational Safety and Health launched "*WISE EARS!*" a national campaign to prevent NIHL in the general public and in people who work in noisy environments. The campaign's objectives are to educate the public about the risks of NIHL and to motivate individuals and organizations to increase awareness about preventing NIHL. Additionally, a new public education campaign, "*It's a Noisy Planet. Protect Their Hearing,*" reaches out to parents of tweens (children eight to twelve years old) to establish healthy hearing habits. Central to both efforts is the development and distribution of free educational materials that are available online and through a toll-free information clearinghouse.

Environmental exposure to ototoxic substances during prenatal and postnatal development of the hearing system is of great interest to NIDCD. The opportunity presented by ARRA has allowed NIDCD to expand its research efforts on this critical issue. NIDCD has committed ARRA funding to an ongoing cooperative agreement, currently supported by NICHD and NIAAA, which examines the effects of alcohol on infant brain function and maturation during pregnancy in Northern Plains Native Americans. Known as the Prenatal Alcohol and SIDS and Stillbirth (PASS) Network, NIDCD's investment will incorporate a pilot study of non-invasive quantitative measures of neurologic maturity and auditory function in the ongoing assessment of newborn and infant physiology. In this study, scientists will learn whether prenatal alcohol exposure causes damage to the auditory system. It will also give them the opportunity to gather critical epidemiological information on an understudied minority population.

NIDCD continues to support research that looks at the effectiveness of behavioral interventions to prevent NIHL. Currently, NIDCD-supported researchers are developing an interactive computer-based educational and motivational program to promote hearing conservation. Using a program that simulates hearing loss, participants will experience first-hand the functional consequences of reduced hearing. This is designed to make participants more aware of the risks posed by loud sounds, and motivate them to avoid loud sounds or use hearing protectors. This phase 1 SBIR project is scheduled for completion in January 2010.

Item

Presbycusis - The Committee urges the NIDCD to continue its support of physiological and neurological studies of the peripheral and central mechanisms of presbycusis. Studies of inner ear development pointing the way for regenerating cells lost in presbycusis are also urged (p. 106)

Action taken or to be taken

The NIDCD is supporting an active research portfolio in the area of presbycusis, or age-related hearing loss. NIDCD-supported scientists are working to identify genes and signaling pathways that are required for the development of the mammalian cochlea in the inner ear. Since loss of hair cells is believed to be the underlying cause for most hearing loss, including presbycusis, identification of the genetic factors that promote or inhibit hair cell formation may lead to the identification of targets for regenerative therapies. Another NIDCD intramural laboratory focuses on genetic variants causing complex hearing loss in mice. The researchers have identified a genetic variant, called *Ahl* (age-related hearing loss), and are currently making progress on the identification and characterization of two additional genetic variants for age-related hearing loss in mice – *Ahl5* and *Ahl9*. The investigators are reporting steady progress towards this goal via regular publications in scientific journals.

NIDCD-supported extramural researchers are also leading several projects related to presbycusis. One addresses basic questions related to how older adults understand speech and benefit from hearing aids in realistic listening environments. A second project uses neuroimaging to examine the structure and function of brain regions that are believed to contribute to age-related declines in speech recognition in older adults. A third project is

identifying specific versions of a gene associated with age-related hearing loss. Finally, a fourth project is examining the potential role of human blood-forming stem cells in the maintenance of non-sensory cells in the inner ear by characterizing the effects of aging and cochlear injury. These projects are ongoing but progress is being published regularly in scientific journals.

The NIDCD is also supporting two conferences related to presbycusis. The first, *The Ear-Brain System: Approaches to the Study and Treatment of Hearing Loss*, was held in 2009. The scientific literature shows that when listening to complex stimuli such as speech, the performance of hearing-impaired individuals is poorer than that of normal hearing individuals, even when stimuli are equally detectable. This demonstrates the importance of interactions between central and peripheral function in auditory rehabilitation. This conference addressed the interactions between the ear and the brain from neural, functional, and clinical perspectives, helping scientists develop ways to prevent age-related hearing loss.

The second NIDCD-supported conference, *Aging and Speech Communication: A Research Conference*, also held in 2009, took an international and interdisciplinary research approach to the problem of speech communication in older adults. Scientists approaching this problem have typically worked either in the area of sensory and perceptual processing (especially hearing) or in the area of cognitive science. Speech communication involves both sensory-perceptual processes and cognitive processes and aging can have a negative impact on either or both of these systems. By bringing together scholars actively involved in research in these areas, further progress was made in understanding and developing effective treatments for the speech-communication difficulties of older adults.

Item

Specific Language Impairment - The Committee recommends that the NIDCD expand research on the pathophysiology of specific language impairment. (p. 106)

Action taken or to be taken

Specific language impairment (SLI) is a delay in language development in the absence of other developmental delays or neurological symptoms. About eight percent of American children in kindergarten have SLI. These children have difficulty developing and using language. These difficulties may affect not only understanding and speaking, but also reading and writing abilities once these children enter school. A child with SLI typically scores within the normal range for nonverbal intelligence and has no hearing loss. Motor skills, social-emotional development, and the child's neurological profile are all normal. The only noticeable gap is in language development.

NIDCD-supported scientists are actively investigating the causes of SLI by examining multiple facets, including genetic, cognitive, physiological, and anatomical differences. Previous research has consistently demonstrated that SLI occurs in families, suggesting that genetic factors may play an important role in causing the disorder. Several studies are scanning the human genome for the location of genes that may cause SLI, using families in which multiple members have language/reading disorders. In addition, other NIDCD-

supported studies are investigating areas of the brain involved in cognition and language skills that may be altered by environmental input and learning style. These studies will help to provide valuable insights into the nature and intensity of interventions to help encourage language learning in children with SLI. The results of these studies are published in various scientific journals.

NIDCD-supported scientists are also studying SLI and its relation to Autism Spectrum Disorder (ASD). Research has shown that some children with autism show language deficits that are similar to those seen in children with SLI. Scientists propose using a non-invasive assessment of language impairment with a passive paradigm that is appropriate for autistic children. They hope that this test will provide insights into the neurobiological basis of language impairment in children with ASD. Extension of this work to younger populations will establish potential diagnostic tools to predict subsequent language impairments.

NIDCD-supported scientists studying language emergence have shown that up to 80 percent of children with language delays at age two will catch up by age seven. However, this also means that for one in five late-talking toddlers, language delays persist. Findings from the study suggest careful monitoring of language development, although it is still difficult to predict which late talkers will “catch up.”

Item

Tinnitus - The Committee recommends that the NIDCD expand its research into causal mechanisms underlying peripheral and central tinnitus and pursue research devoted to preventions, treatments, and cures of this prevalent disorder. (p. 106)

Action taken or to be taken

Tinnitus is a major health concern for many Americans. Approximately 25 million Americans have experienced tinnitus. The condition can range in severity from a mild condition that requires no intervention to a severe, debilitating disease with significant emotional, social, and economic impact. NIDCD continues to conduct research into the underlying causes of tinnitus and to explore potential treatment therapies.

Tinnitus is a symptom associated with many forms of hearing loss; however the pathological process that leads to its development is poorly understood. To address this problem, NIDCD supports an expanding portfolio of research on tinnitus. A recent NIDCD funding opportunity announcement, *Understanding the Neural Mechanisms Responsible for Tinnitus*, invited applications to address this issue and promote the development of novel intervention strategies. Many researchers hypothesize that tinnitus may be due to over-activity of certain brain regions after loss of input from sensory hair cells in the inner ear. They are exploring specific changes to brain cells that receive input from hair cells. Other scientists are exploring the influence of the emotional centers of the brain on the neural circuits that control hearing and they are looking at how changes in these connections may lead to the development of tinnitus. Finally, NIDCD-supported scientists are using brain imaging technologies (in both animals and people) to examine structural changes in the brain after hearing loss and identify how these changes lead to the development of tinnitus.

While research continues to elucidate the reasons why tinnitus occurs, efforts are also underway to prevent and treat the condition. NIDCD-supported researchers are currently identifying chemicals that could potentially disrupt the processes that lead to chronic tinnitus. Since tinnitus is often associated with hearing loss, scientists are examining how ototoxic drugs affect the hearing system and using that knowledge to develop better drug delivery methods for therapies that could prevent tinnitus. Several treatment strategies are also being explored. Drug treatments that suppress the hyperactivity of the hearing system are one option currently being explored. Brain stimulation techniques are another potentially effective treatment strategy.

These techniques may be non-invasive (not requiring surgery) or invasive (requiring the implantation of electrodes into the brain). Finally, various behavioral and environmental interventions are being explored. These may include the use of tinnitus maskers, white noise machines that distract attention from the tinnitus sensation, behavioral therapies, or a combination of the two to decrease the impact of tinnitus on daily life.

Item

Translational Research - The Committee urges the continuation of research activities and clinical trials relative to prevention and treatments of hearing loss from noise, drugs, aging, and genetic causes and translation of these studies to therapies. Efforts should include studies of agents to treat acoustic trauma and exposure to ototoxicants, including animal and clinical trials of antioxidants and studies of mechanisms to manipulate cellular pathways to protect against or prevent sensory cell and neuron loss. Clinical trials relevant to Meniere's disease, sudden deafness, and autoimmune inner ear disease, including trials of newer rheumatic drugs delivered directly to the ear, are also encouraged. (p. 106)

Action taken or to be taken

NIDCD is committed to building and expanding its clinical trials program to promote the development of interventions to treat or prevent communication disorders. The Institute encourages the translation of basic science discoveries into intervention and patient-oriented research. For example, NIDCD is supporting a five-year multi-site (15 centers in the U.S. and Canada) clinical trial that ends in 2010. This trial is comparing hearing improvement for sudden sensorineural hearing loss (SSHL) after the use of intratympanic or oral administration of corticosteroid therapy. SSHL is a disorder that affects thousands of Americans each year. Oral corticosteroids are the standard-of-care but have significant side effects and cannot be used by everyone. An alternative route of administration, intratympanic therapy, injects high-dose steroids directly behind the eardrum, which avoids systemic side effects. This method of administering steroids may have comparable benefit to systemic administration and make the therapy available to a much larger patient population.

In another NIDCD-supported clinical trial which will end in 2012, scientists are studying ways to reduce noise-induced hearing loss (NIHL), which affects an estimated 26 million Americans. Because noise-damaged sensory hair cells in the inner ear do not grow back, prevention of NIHL is critical. A micronutrient combination of antioxidants (beta-carotene,

and vitamins C and E) and the mineral magnesium (which acts in part as a vasodilator) is effective in preventing NIHL in animals.

Therefore, the NIDCD is supporting a Phase II clinical study to evaluate safety and efficacy of this intervention in humans. The trial will compare the micronutrient intervention with a placebo in four noise exposure settings (including “digital audio player,” “urban warfare,” “NATO airbase” and “stamping factory”). This study will determine if these micronutrients prevent temporary or permanent hearing changes in ears exposed to real-world noise.

NIDCD is also encouraging translational research by issuing several funding opportunity announcements. For example, one NIDCD program announcement encourages translation of basic research findings into clinical tools that can be used to treat communication disorders; another seeks the development of new or enhanced diagnostic, intervention, and treatment paradigms for communication disorders.

NIDCD intramural scientists are also collaborating with scientists in other NIH institutes to conduct clinical trials with individuals who may experience hearing loss as a result of medical disorders or exposure to pharmaceuticals. One protocol examines the effect of an interleukin 1-b inhibitor, called Anakinra, on individuals with neonatal-onset multisystem inflammatory disorder. It has been hypothesized that the sensorineural hearing loss in this disorder is a result of a systemic autoinflammatory process.

In another protocol, NIDCD intramural scientists determined that sensorineural hearing loss and/or vestibular dysfunction are side effects of the use of T cell immunotherapy to treat metastatic melanoma. Building on this knowledge, scientists instituted an auditory-vestibular surveillance program and a treatment algorithm (intra-tympanic steroid therapy) for individuals participating in this trial. Researchers will analyze the effects of this treatment, as well as the natural history of hearing and balance, in study participants.

Item

Vestibular Research - The Committee recommends developing better intervention strategies and clinical trials to improve the diagnosis and treatment of vertigo and balance disorders. Research on vestibular compensation is encouraged. (p. 106)

Action taken or to be taken

As people grow older, they may have problems with balance. Nearly 8 million American adults report having chronic balance problems, and an additional 2.4 million American adults report having chronic dizziness problems. In addition to serving as the organ of hearing, ears have a significant role in the control of balance. The inner ear houses the semicircular canals and otolithic organs – the sensory organs of the vestibular (or balance) system.

After injury to the inner ear, the brain adapts to altered sensory input to control balance and prevent the sensation of dizziness. This process is called “vestibular compensation.” In some people, this process is incomplete, causing dizziness and instability. NIDCD-supported scientists are studying the neurophysiology of how the brain achieves vestibular compensation.

A new direction for the management of vestibular disorders has recently emerged. Several research teams are developing an implantable neuroprosthesis, similar to a cochlear implant, which electrically stimulates the intact vestibular nerve. Such devices have recently been shown to provide a robust, controlled level of nerve stimulation. In the years ahead, the vestibular prosthesis may become a promising treatment modality for individuals who have lost vestibular sensation. The results of these studies are published in various scientific journals.

In addition to the vestibular sensory organs within the ear, vision and body position sensors provide the brain with information to maintain balance. However, under some stressful visual and motion conditions, and in some balance-disordered individuals, the balance control systems provide the brain with conflicting information, resulting in the distressing, even debilitating, symptoms of motion sickness. NIDCD is supporting a team of investigators to develop a behavioral training program that will habituate susceptible individuals to mismatched visual and vestibular signals to prevent motion sickness.

Although a number of genetic mutations that lead to hearing loss have been identified, molecular mechanisms underlying familial disorders affecting vestibular function appear to be rare and have not been well described. Ongoing research at NIDCD includes characterizing genes essential to normal development and function in the vestibular system, as well as the genetic basis of several inherited disorders of imbalance and uncoordination. The results of these studies are published in various scientific journals. Identifying these mutations may aid diagnosis of individuals at risk of developing balance disorders, and inform the development of potential treatments for affected individuals.

In addition, NIDCD and NEI intramural scientists are collaborating to study vestibular function in individuals with Usher syndrome, a recessive genetic disorder that causes sensorineural hearing loss, vestibular dysfunction, and progressive blindness. Since individuals with Usher syndrome have disordered vestibular function and vision, two of the three senses required for balance, this disorder provides an opportunity to study vestibular function and compensation. A major research emphasis is on how the brain learns to compensate for disease and trauma, and how this compensation can be promoted through better programs of physical therapy.

**National Institute of Mental Health
(NIMH)**

Senate Significant Items

Item

Children's Mental Health -- The Committee applauds the NIMH for its focus on identifying early risk factors and effective interventions for a variety of emotional and mental disorders among children. (p. 109)

Action taken or to be taken

In contrast to many other chronic medical conditions, the symptoms of mental disorders often begin to appear in childhood and adolescence, and these symptoms may wax and wane throughout a person's life. As described in the [NIMH Strategic Plan](#), the Institute will support research to compare trajectories of healthy development to those of mental disorders in order to better understand the initial occurrence when development is altered. This research will enable us to determine the best times and strategies to preempt the onset of symptoms or halt and reverse the progression and recurrence of illness. By predicting, detecting, and intervening early in the disease process, we can dramatically improve an individual's likelihood of a life free from the suffering of mental disorders.

In pursuit of these goals, NIMH has issued several requests for applications (RFAs) to encourage neurodevelopmental research. For example, the goal of one RFA is to accelerate and stimulate research on sensitive periods for the neurodevelopment of mental illness. Another RFA provides support for the development of novel efficacious interventions for autism spectrum disorders and other neurodevelopmental disorders, with the aim of improving various domains of functioning that are impaired across disorders and alter developmental trajectories.

NIMH has supported a number of recent projects focusing on early risk factors and effective interventions for children and adolescents. For example, the NIMH Child/Adolescent Anxiety Multimodal Study identified three effective treatments for childhood anxiety disorders, which are among the most common mental disorders in children and adolescents. The study found that combined treatment with cognitive behavioral therapy and antidepressant medication is the most likely to help children with anxiety disorders, but each of these treatments alone is also effective. This research provides strong evidence that a well-designed, two-armed treatment approach is optimal, while a single line of treatment is still effective.

In addition, NIMH supported the Treatment of Adolescent Suicide Attempters Study, which developed a novel treatment approach using medication plus a new type of psychotherapy to reduce suicide attempts among depressed teens. The psychotherapy, called cognitive behavioral therapy for suicide prevention, consisted of a 12-week acute treatment phase focusing on safety planning, understanding the circumstances and vulnerabilities that lead to suicidal behavior, and building life skills to prevent a reattempt. Although study findings on this treatment will need to be tested in randomized clinical trials, this research sheds

light on characteristics that identify who is most at risk for suicide reattempts and what circumstances may help protect teens from attempting suicide again.

Item

HIV/AIDS Behavioral Research -- The Committee supports additional research on how to change the behaviors that lead to HIV acquisition, transmission, and disease progression, and how to maintain protective behaviors once they are adopted, with a better understanding of the social and cultural factors that may impact different populations.
(p. 109)

Action taken or to be taken

NIH is committed to investing in research that will result in a decline in the incidence and progression of HIV infection. As the lead Institute pursuing behavioral strategies to ensure this end, the National Institute of Mental Health in collaboration with other NIH Institutes and Federal agencies supports a broad research program related to the primary and secondary prevention of AIDS and the neurological/psychological consequences of HIV infection. This collaboration allows an opportunity to build on current efforts, reduce redundancies, and maximize efficiency of ongoing research toward the ultimate goal of decreasing incidence of HIV infection and improving management of HIV disease long term. A number of strategies have been identified by all partners, and NIH is actively involved in defining and implementing these strategies.

Emerging priorities include:

- Research on the behavioral and social aspects of universal testing and treatment for HIV prevention, including acceptability, adherence, uptake, etc.;
- Development of innovative interventions for men who have sex with men;
- Improved and expanded integration of evidence-based behavioral prevention strategies into biomedical interventions (e.g., pre-exposure prophylaxis, microbicides, circumcision) to stop the spread of HIV as well as decrease the neurological consequences of HIV;
- Improved interventions for long term maintenance of behavior change for HIV prevention; and,
- Studies on factors affecting delivery/uptake of interventions designed to prevent mother to child transmission.

Ongoing efforts include:

- Developing and testing behavior-change and prevention interventions to reduce the further spread of HIV and other sexually transmitted diseases (STDs) directed toward individuals across the lifespan and targeting multiple levels of risk, including individual, interpersonal, and environmental factors;
- Preventing the negative consequences of living with HIV infection;
- Studying HIV infection of the central nervous system and the mechanisms underlying motor/cognitive dysfunctions in order to identify new approaches to slow HIV disease progression;
- Defining, preventing, and treating the clinical phenomena of HIV-related neuropsychological and neuropsychiatric disorders;

- Pursuing the development of therapeutic agents to prevent or reverse the negative effects of HIV on the CNS; and,
- Improving mental health comorbidities associated with HIV

Item

Immigrant health -- The Committee recognizes that immigrants experience unique stresses, prejudice and poverty, and can be considered at risk for health, emotional, and behavioral problems as well as, in the case of children, learning and academic difficulties. To address this, the Committee urges the NIMH to direct research on the adaptation, development, health, and mental health needs of diverse immigrant populations. (p.109)

Action taken or to be taken

NIMH continues to support research to understand the unique mental health needs of immigrant populations. Several epidemiological studies funded by NIMH examine the influence of immigration on mental illness and mental health care across various age groups, including children and adolescents. These studies explore the distribution and prevalence of mental disorders among immigrants, with an important focus on sub-ethnic analysis (countries of origin within Latino, Black, and Asian American groups) and nativity analysis (U.S. born/non U.S. born) of the distribution of mental illness and access to care. These studies also examine the mechanisms that might influence prevalence and access to care, such as language, immigration status, socioeconomic status, insurance coverage, time in the United States, and use of alternative therapies.

For example, one NIMH-supported project studies whether migration to the U.S. increases risk for mental disorders among Mexican-Americans and whether return migration or having transnational family networks increases risk among those in Mexico. This study will also explore how cultural orientation affects the perception of a mental health problem as a medical concern, using data on actual service use; perceived need for care; and willingness to seek treatment for mental health problems.

NIMH also continues to support research that examines the social, familial, and psychological processes that may increase risk for or protect against mental illness among immigrants. These studies will provide critical information for the development of culturally appropriate clinical practices, diagnostic tools, and interventions.

**National Institute on Drug Abuse
(NIDA)**

House Significant Items

Item

Pulmonary Hypertension - The Committee continues to note with concern a significant increase in the number of pulmonary hypertension diagnoses related to the abuse of methamphetamine. The Committee encourages NIDA, in partnership with the pulmonary hypertension community, to initiate appropriate research and awareness activities focused on this growing public health problem. (p. 125)

Action taken or to be taken

National surveys have shown a stabilization or decline in methamphetamine abuse, especially among young people. However, it remains a serious problem, particularly in western parts of the United States. NIDA recognizes the myriad problems this drug poses and has redoubled its research efforts since 2000 in response.

NIDA supports a comprehensive research portfolio that aims to understand how methamphetamine affects the brain and body and to develop effective prevention and treatment interventions. NIDA-supported research has shown that methamphetamine abuse can lead to cardiovascular problems, such as rapid and irregular heartbeat, increased blood pressure, and stroke. Chronic abusers can also exhibit violent behavior, anxiety, depression, confusion, insomnia, and psychosis. NIDA's research portfolio addresses the range of these abuse consequences—behavioral, cognitive, physiological and medical—while new research suggests additional adverse effects of stimulant abuse. For example, a study published in 2006 showed that patients with pulmonary arterial hypertension of unknown origin were 10 times more likely to have used stimulants (including methamphetamine) than patients with pulmonary hypertension and known risk factors.

NIDA research efforts have demonstrated that prevention interventions designed to target all drugs of abuse can significantly reduce methamphetamine abuse, even 6 years after the intervention. Moreover, recent studies have demonstrated the effectiveness of several behavioral therapies (e.g., motivational incentives and cognitive behavioral approaches) in treating methamphetamine addiction. NIDA is also pursuing research to develop a methamphetamine vaccine and other medications to enhance treatment and prevent relapse for those addicted. All of these efforts are critical to addressing the devastating consequences of methamphetamine abuse.

We will also further our dissemination efforts with the medical community as well as the general public, to ensure that our research is both useful and used.

Item

Reducing Health Disparities - The Committee notes that the consequences of drug abuse disproportionately impact minorities, especially African American populations, and is pleased to learn that NIDA continues to encourage researchers to conduct more studies in

this population, particularly in geographic areas where HIV/AIDS is high and/or growing among African Americans, including in criminal justice settings. (p 125)

Action taken or to be taken

As the Committee states, the pattern of addiction and the burden of disease are not shared equally among members of our population. For example, the disproportionate abuse of licit and illicit drugs including methamphetamine, among American Indians and Alaskan Natives—higher than any other subgroup—prompt a need for targeted interventions that can effectively reach these groups. However, overall rates of drug abuse are not higher among other ethnic minorities, particularly African Americans and Hispanics, who have rates similar to those in the general population. Nonetheless, these groups incur greater medical and social consequences of their drug use than Whites, including involvement with the criminal justice system and greater disease vulnerability.

African-Americans experience striking disparities in HIV infection rates compared with other populations, and they are at particularly high risk for developing AIDS. To illustrate, while African-Americans make up 12 percent of the U.S. population, they accounted for half of the new HIV/AIDS cases diagnosed in 2007. These stark disparities illustrate the need for research to elucidate the complex relationships between drug abuse, ethnicity, HIV/AIDS, and the criminal justice system. In response, NIDA has launched a \$10.6 million initiative titled Seek, Test, and Treat: Addressing HIV in the Criminal Justice System to encourage researchers to develop, implement, and test strategies to increase HIV testing and the provision of highly active, antiretroviral therapy (HAART) to HIV positive individuals involved with criminal justice system.

Another aspect critical to addressing these disparities involves providing equal access to drug abuse treatment, particularly in the criminal justice system, where substance abuse and other mental health problems are common. NIDA has invested heavily in its Criminal Justice-Drug Abuse Treatment Studies (CJ-DATS) multisite cooperative research program to explore the issues related to the complex system of offender treatment services and to tackle the implementation of effective treatment approaches in criminal justice settings, including for populations with co-occurring disorders.

Finally, NIDA has developed a separate Strategic Plan on Reducing Health Disparities that includes research on risk and protective factors (e.g., genetic variation), as well as efforts aimed at community outreach and infrastructure and capacity building. Several institute-wide initiatives and policies have led to progress in addressing health disparities and the under-representation of certain groups in drug abuse research. Some of these efforts include recruitment and training programs to increase diversity, development of targeted program announcements and requests for applications, research development and technical assistance workshops, and enhancement of the underrepresented populations supplement program.

Senate Significant Items

Item

Adolescent Brain Development - The Committee encourages NIDA to continue its emphasis on adolescent brain development to better understand how developmental processes and outcomes are affected by drug exposure, the environment, and genetics. (p. 114)

Action taken or to be taken

Adolescence, a time when the brain is still actively maturing and when drug experimentation is most likely to occur, represents a period of heightened vulnerability to drug addiction. Research investigating factors contributing to adolescent vulnerability to drug abuse holds great promise for the development of more effective prevention and treatment approaches for youth.

NIDA's wide-ranging research portfolio includes both animal and human studies aimed at increasing our understanding of factors that underlie age-dependent vulnerability to the effects of drug exposure, which put adolescents at great risk for acquiring a substance use disorder. For example, compared to adults, adolescent animals show differences in sensitivity to the rewarding and aversive effects of various drugs of abuse, including nicotine, cocaine, and alcohol; they self-administer greater amounts of these drugs and exhibit more persistent changes in cognition and global brain functioning following drug exposure. Human studies of adolescent vulnerability are applying genetic techniques to study developmental effects of early drug exposure, recent studies having uncovered specific genetic variants linked to heightened risk of future drug problems in those who started using during adolescence.

NIDA is also targeting the influence of social factors on teen decision-making, a critical focus for understanding drug abuse. For example, several NIDA-funded research programs are investigating how parental monitoring, parental drug use, deviant peer affiliation, and popular culture influence initiation and maintenance of teen drug use across different stages of development. NIDA is taking steps to translate resulting knowledge into innovative, developmentally-sensitive drug abuse treatments for adolescents. To elicit responsive studies, NIDA released a FY 2010 RFA entitled "Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment".

Further, recent NIDA workshops titled, "Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities" and "Not Just a Matter of Gray and White: Exploring the Importance of Evolution, Genes, and Experience on Brain Development," explored how developmental neuroimaging and genetic data could be added to longitudinal studies of psychosocial outcomes to definitively examine how genes and/or brain development in early life may relate to drug abuse outcomes in young adulthood. NIDA, along with SAMHSA's Center for Substance Abuse Prevention (CSAP), sponsored the "CSAP-NIDA Innovations in Prevention Symposium" in October 2009 to help develop sustainable partnerships among schools, communities, and universities and to facilitate the delivery of scientifically- tested interventions to reduce adolescent substance use and abuse.

Item

Anti-Drug Campaign Research– The Committee urges NIDA to support behavioral research on message framing to help tailor the most effective anti-drug use media campaigns. (p. 114)

Action taken or to be taken

Three decades of research have informed large public health education campaigns, which have inspired continuing declines in teen drug use and dramatic reductions in cigarette smoking and related disease and death over the last 30 years. The most effective substance abuse prevention campaigns are informed by scientific research findings that reveal what works best with real-world audiences.

Although an important part of anti-drug policy, drug prevention media campaigns have been controversial in the degree to which they deter drug use. For instance, a 2006 report by the Government Accountability Office titled *ONDCP MEDIA CAMPAIGN: Contractor's National Evaluation Did Not Find That the Youth Anti-Drug Media Campaign Was Effective in Reducing Youth Drug Use* concluded that the \$1.4 billion National Youth Anti-Drug Media Campaign has not been effective.

NIDA supports the exploration of new strategies, such as interactive web-based technologies and use of brain imaging to better target media messages. Future efforts informed by innovative use of imaging technologies will help to predict which prevention messages resonate with which target audiences and whether that translates into more healthful behaviors. A recent study showed that low-key and attention-grabbing anti-smoking public service announcements (PSAs) stimulated different activity patterns in smokers' brains, with smokers more likely to remember seeing the low-key PSAs than the attention-grabbing ones (Langelben et al., 2009 - *Neuroimage* 46:219).

This research and several other NIDA-funded studies, solicited under a 2007 RFA entitled, "Brain Imaging Drug Use Prevention Messages," will set the stage for development of evidence-based methodology to evaluate and design anti-addiction PSAs and achieve more effective public health campaigns generally. New tools have the potential to ensure that prevention messages are effective and that taxpayers' dollars are efficiently used.

Item

Behavioral Research and Long-Term Cognitive Improvement – The Committee commends NIDA's continued support of behavioral research on the relationship between cognitive development and childhood experience, especially in children gestationally exposed to drugs, and encourages further research to better understand the complex relations among socioeconomic status, cognitive development and life experience (p. 114)

Action taken or to be taken

NIDA will continue to pursue knowledge on how the brain develops throughout the lifespan, especially in utero and during the protracted transition from adolescence to young adulthood. These two stages present critical windows of vulnerability to the negative effects of drug exposure. Several NIDA-funded research programs are examining

associations between exposure to drugs of abuse in utero, genetic makeup, neurobehavioral outcomes, and increased vulnerability to drug use and risky behaviors in early childhood and adolescence.

The brains of adolescents are not fully developed, with the connections between areas governing emotion, judgment, and decision-making being among the last to mature. As a result, adolescents are more likely to engage in risky behaviors, such as drug experimentation. To better understand and address these behaviors, NIDA supports research investigating the mechanisms underlying adolescents' increased sensitivity to social influences (i.e., peer pressure) and decreased sensitivity to the possibility of negative consequences. Study areas include the effect of parental monitoring, parental drug use, deviant peer affiliation, and popular culture on the initiation and maintenance of teen drug use. On the other hand, a brain that is still in flux offers unique opportunities for interventions that could lead to greater resilience. NIDA therefore also supports resiliency research, focusing on both animal and human studies, which holds great promise for the development of more effective prevention and treatment approaches for youth.

Through such RFAs as “Integrating Translational Neuroscience and Adolescent Drug Abuse Treatment,” NIDA continues to stimulate research on cognitive development, childhood experience, and drug abuse and seeks to understand how this knowledge can be used to strengthen behavioral treatments for adolescents who abuse drugs.

NIDA also convenes meetings to identify new research opportunities. For example, a 2009 workshop titled “Drug Abuse Vulnerability and Neurodevelopmental Effects of Early Exposure to Secondhand Tobacco Smoke: Methodological Issues and Research Priorities” addressed the issue of environmental tobacco exposure, cognitive development, and implications for drug use during adolescence. Participants recommended an array of future research priorities, including developing animal models of smoke (as opposed to nicotine) exposure, identifying “best practices” measures of exposure and outcomes, and expanding upon current research to include differential effects based on sex and age.

Item

Blending Research and Practice The Committee applauds NIDA for its collaborative Blending Initiative with SAMHSA, an effort to translate research into practice and incorporate bidirectional feedback from multiple stakeholders to make the best drug abuse and addiction treatments available to those who need them. (p. 108)

Actions taken or to be taken

Efforts to systematically move science-based interventions and practices into community settings are occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN), composed of practitioners from community treatment programs who formulate, adapt, and test promising interventions. This research is being translated more quickly into mainstream drug abuse and addiction practice through the NIDA-SAMHSA Blending Initiative, which uses blending teams of NIDA researchers and representatives from SAMHSA's Addiction Technology Transfer Centers to develop research-based “products” and to train treatment providers in their use. The Blending Initiative has produced five Blending products to date, including those on implementing a buprenorphine detoxification

regimen, motivational interviewing, and use of motivational incentives to encourage and maintain drug abstinence.

NIDA's translation efforts are garnering growing support from state agencies and treatment practitioners. One successful component of this effort is the NIDA Blending Conference designed to narrow the "translational gap" by affording attendees the opportunity to engage in dynamic dialogue with one another and to disseminate science-based findings directly into the hands of practitioners. This annual event showcases latest findings on a range of topics, including screening and brief intervention, co-occurring disorders, drug courts, prescription opioid abuse, and Blending Team products. A post-conference evaluation from the last Blending Conference, convened in June 2008, documented that more than 95% of attendees found the conference either "completely" or "considerably" useful, and nearly three-fourths of them said they intended to change their clinical practice as a result of attending. Follow-up efforts six months later indicated that two-thirds (66%) of conference participants had already utilized the information gained at the Blending Conference in their clinical practice and/or in their direct supervision of staff. Clinical practice changes included adding motivational interventions, establishing closer ties with the medical community, and conducting more staff education. These data, coupled with the dissemination activities of state and local policy-makers, underscore the crucial impact of the Blending Initiative across multiple levels of the substance abuse field.

Future plans include NIDA's hosting of the 8th Blending Conference on April 22–23, 2010, in Albuquerque, New Mexico, in partnership with the University of New Mexico, the University of Arizona, and the University of California, San Francisco. *The "Blending Addiction Science and Practice: Evidence-Based Treatment and Prevention in Diverse Populations and Settings Conference"* will unveil the newest and sixth Blending product titled: "Buprenorphine Treatment for Young Adults." This product provides an overview of buprenorphine and highlights NIDA-funded research that demonstrated successful treatment effects of buprenorphine for opioid addicted young adults.

Item

Effectiveness Research – The Committee encourages NIDA to continue its investment in effectiveness research so that proven models of addiction treatment and prevention can be further refined. (p. 108)

Action to be taken

NIDA supports research to assess the effectiveness of proven treatments, crucial in bringing research to practice, through a variety of mechanisms. Foremost among these is the Drug Abuse Treatment Clinical Trials Network (CTN). The CTN was initiated in 1999 and charged to improve nationwide the quality of drug abuse treatment using science as the vehicle. It created a unique partnership between treatment providers and academic researchers to test behavioral, pharmacological and integrated treatment approaches in a broad range of community settings with diverse patient populations. Similarly, research supported through our Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) also facilitates a mutually beneficial exchange of knowledge and experience between research and practice domains, in this case to better integrate drug abuse treatment with public health and public safety systems. NIDA is also partnering with communities to diffuse

promising drug abuse prevention strategies, testing the effectiveness of universal prevention programs.

NIDA's latest CTN initiatives include determining the relative merits of treatments for smoking cessation in the presence of comorbid conditions—in this case depression; evaluating the potential value of exercise as an add-on to inpatient treatment for substance abusers; and, testing the usefulness of buprenorphine as a treatment for patients who are addicted to pain medications.

Leveraging the CTN infrastructure, NIDA can address the current lack of scientific evidence comparing the effectiveness of offering HIV screening with and without counseling—a priority research area identified by The Institute of Medicine as needing comparative effectiveness research. Using funds from the American Recovery and Reinvestment Act (ARRA), NIDA will adapt a current CTN protocol to include clinics treating sexually transmitted diseases (STDs) to determine the effect of counseling at screening on the incidence of sexually transmitted infections, sexual risk behaviors, substance use during sex, and cost and cost-effectiveness of counseling and testing.

Interventions to reduce risk factors for drug abuse and related problem behaviors can have tremendous impact, particularly when implemented early. NIDA supports the testing of multiple prevention programs targeting behaviors appropriate to a child's developmental stage and integrating family, school, and community efforts. Programs begun as early as first grade can significantly reduce the likelihood of substance abuse and addiction, delinquency, and incarceration when these children become adolescents or young adults. However, more work is needed to implement effective programs. NIDA is funding an implementation study of an innovative community–university partnership model known as PROSPER—Promoting School–community–university Partnerships to Enhance Resilience—to promote the adoption of evidence–based prevention programs by middle schools across multiple public school districts. This initial study was supported by ARRA funds and is expected to be completed in 2011.

Item

Prescription Drug Abuse – The Committee continues to urge NIDA to support research aimed at reducing prescription drug abuse, especially among our Nation's youth, and at developing pain medications with reduced abuse liability (p. 115).

Action to be taken

While most illicit drugs have shown considerable declines in use over the past decade or so, most prescription drugs have not, with the notable exception of amphetamines. According to the 2008 Monitoring the Future Survey (MTF) nearly 1 out of 10 12th graders reported past-year nonmedical use of the prescription opioid Vicodin, making it among the most commonly abused drugs by high school seniors. The 2008 figures for OxyContin (another opioid painkiller) for grades 8, 10, and 12 have held fairly steady since 2002, standing at 2.1, 3.6, and 4.7 percent, respectively. Use of sedatives and tranquilizers also remained near their recent peaks. New questions in the survey show that relatives and friends play a key role in the diversion of prescription drugs to youth.

NIDA continues to sponsor research to elucidate these worrying trends and develop effective counter strategies. Through PA-08-127, NIDA and NIMH have called for research to reduce prescription drug abuse while supporting the appropriate medical use of abusable medications. Projects include studies on the effect of prescription opioids in drug and non-drug abusers, new screens for prescription opiate misuse, the long-term effects of methylphenidate (e.g. concerta, Ritalin, MPH) abuse, and the identification of risk/protective factors for prescription opioid use and abuse in pain patients.

A recent grand opportunity (GO) grant has been awarded (with ARRA funds) that will develop and implement a prescription drug diversion surveillance program using available epidemiological data to estimate the diversion from retail pharmacies of 25 different controlled, mostly abusable prescription drugs. This 2-year effort should lead to improvements in resource allocation, public health, and health care delivery.

The National Drug Abuse Treatment Clinical Trials Network (CTN) has completed the recruitment, treatment, and follow-up phases for the Prescription Opioid Addiction Treatment Study (POATS), a large-scale, multi-site study to test the effectiveness of Suboxone (buprenorphine), with either standard or enhanced medical management, for addiction to opiate medications. NIDA continues to support research at the intersection between prescription opiate abuse and pain management, including the development of new pain medications with less addiction liability, educational tools for nurses, doctors, and chronic pain patients. NIDAMED (a NIDA initiative targeting the medical community) includes a new resource that will assist medical professionals in screening their patients for use and abuse of addictive substances, including prescription drugs.

In February 2009, NIDA and the NIDCR jointly organized a roundtable of experts to discuss a range of topics, including prescription practices, dentists' perceptions of risk and safety of opioid analgesics, and opioid abuse among teens. The meeting highlighted the need for developing a research agenda on these issues involving dentists, oral surgeons, and drug abuse researchers. As a follow-up, NIDA issued an amendment to its Prescription Drug Abuse Program Announcement to foster research into opioid prescribing practices in dental settings and the potential relationship to abuse of opioid medications.

Item

Pulmonary Hypertension – The Committee encourages NIDA to support research aimed at assessing the growing frequency of pulmonary hypertension in patients who abuse methamphetamines. (p. 115)

Action taken or to be taken

Please refer to page 159 of this document for NIDA's response to this item.

Item

Raising Awareness for the Medical Community – The Committee commends NIDA for raising the awareness of physicians of the potential impact of substance abuse on their patients' illnesses and outcomes. Specifically, NIDA has created the Centers of Excellence for Physician Information and developed a Screening, Brief Intervention, and Referral to

Treatment initiative. The Committee understands that these projects will serve as national models to support the advancement of addiction awareness in primary care practices (p. 115).

Action taken or to be taken

In April 2009, NIDA launched its first comprehensive Physician's Outreach Initiative, NIDAMED. The NIDAMED suite of products is designed to assist medical professionals as the first line of defense against substance abuse and addiction. Health professionals are in a unique position to intervene early and potentially enhance medical care by, (1) increasing awareness of the likely impact of substance use on a patient's overall health, (2) identifying those at low or moderate risk and preventing escalation to abuse and addiction, and (3) identifying patients at high risk and referring them for specialty assessment and treatment, if necessary. Moreover, because drug abuse can be a factor in the course and progression of a variety of other medical diseases (including adherence to treatment regimens), assessing a patient's level of drug abuse can assist healthcare providers in treating a number of other conditions.

At the heart of NIDAMED is the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test (NMASSIST). This web-based interactive tool (adapted from the ASSIST Version 3.0 developed by the World Health Organization) guides clinicians through a series of screening questions for tobacco, alcohol, and illicit and prescription drug abuse; based on the patient's responses, this tool generates a substance involvement score that suggests the level of intervention needed. The NMASSIST site has been accessed more than 1,500 times since data collection began on September 17, 2009. The weekly access rate is approximately 120 times per week. A number of resources accompany NMASSIST, including a Clinician's Resource Guide, a Quick Reference Guide, and a Patient Postcard designed to encourage patients to discuss all drug use with their doctors to help ensure proper medical care.

The broad availability of these tools is an important step toward the goal of integrating substance abuse screening, brief intervention, and referral to treatment (SBIRT) into medical care. However, more research is needed on the effectiveness of systems-level models of care that would integrate SBIRT into primary care medical settings. In 2008, NIDA awarded eight grants to address this issue, including studies of SBIRT for opioid dependence in emergency department settings, for emerging adults in primary care, and in comparing computer vs. therapist-delivered brief interventions in primary care.

Finally, to help integrate substance abuse and addiction diagnosis, referral, and treatment into standard medical practice, NIDA has launched a project specifically targeting physicians in training. In 2006, NIDA established four Centers of Excellence for Physician Information (CoEs) at several medical institutions across the country to develop educational materials that advance medical students' and resident physicians' understanding of drug abuse and addiction, with a particular focus on methamphetamine and prescription drug abuse. NIDA launched these curriculum resources on November 6, 2009 at the Association of American Medical Colleges Annual Meeting.

Item

State Substance Abuse Agencies – The Committee continues to support NIDA's State Substance Abuse Agency infrastructure grants, which help States conduct research to create, implement, expand, and/or sustain science-based improvement in the publicly funded prevention and treatment system. (p. 115)

Action taken or to be taken

NIDA continues to build and enhance the productive partnership with state directors of substance abuse agencies, also known as “Single State Authorities” (SSAs), charged with managing the nation’s publicly funded substance abuse system. SSAs look to NIDA to obtain credible information on selecting, implementing, and sustaining science-based and cost-effective treatment and prevention interventions.

NIDA’s successful history of collaboration with SSAs has been facilitated by the productive partnership with the National Association of State Alcohol and Drug Abuse Directors (NASADAD), which strengthens our communications with Substance Abuse and Mental Health Services Administration (SAMHSA) and treatment practitioners in the field.

The Strategic Prevention Framework collaborative initiative between NIDA and SAMHSA, provides support for the cross-site evaluation of the State Incentive Grant project. In addition, NIDA continues to help fund grants under the RFA, “Enhancing Practice Improvement in Community–Based Care for Prevention and Treatment of Drug Abuse or Co–occurring Drug Abuse and Mental Disorders.” Among five ongoing grants are those examining an electronic information system to improve practice at an opioid treatment program, approaches to enhance substance abuse treatment services for women offenders, and the technology transfer implementation of Motivational Interviewing to promote change and improve patient retention and engagement in treatment as part of a large therapeutic community.

Item

Teens and Drug Abuse – The Committee commends NIDA for its educational efforts to raise awareness among teens regarding the harmful health effects associated with drugs of abuse. Examples include the "After the Party" public service campaign and Chat Day, which enabled youth from across the country to ask questions of leading addiction science professionals. The Committee encourages NIDA to continue the expansion of these efforts. (p. 115)

Action taken or to be taken

NIDA is committed to expanding its efforts to communicate with teens about the negative health effects of abusing drugs. Teens are particularly vulnerable to these effects, including addiction; therefore, preventing early drug use is the best way of preventing future problems with addiction.

NIDA uses an array of communications vehicles and formats to reach teens with messages about drug abuse, including an interactive teen website, targeted public service announcements (PSAs), “Chat” Days, a teen blog, colorful publications and posters, and more. Our evolving communications approach strives to be “two–way,” giving teens a

chance to ask questions and get answers about everything from how drugs of abuse affect the brain to how to avoid peer pressure. The recently revamped teen website provides multiple opportunities for teens to engage with information they can use, presented in a format that is both educational and entertaining. For example, the website includes a feature called “cool downloads,” which allows teens to download and print out iron-ons, stickers, buddy icons for instant messaging, computer wallpaper, etc.

The teen website also features videos as well as a new teen blog known as the Sara Bellum Blog (SBB), an innovative effort to meet teens where they are and to share with them science-based messages about health. The blog—the first Federal Government blog aimed strictly at teens and the first to allow comments—emphasizes personal responsibility and encourages readers to share what they have learned with their peer networks. Thousands of teens are visiting the blog and metrics are being kept to help evaluate its impact. For example, latest data show that in November, the blog had 14,000 unique visits and 150,000 page views—and it continues to grow each month.

Other efforts to stimulate interest among teens in science include NIDA’s presentation of a special Addiction Science Award at the Intel International Science and Engineering Fair—an unprecedented acknowledgement of projects that advance addiction science. A resourceful study into the effect of third-hand smoke on genetic mutation risk in fruit flies won the top prize, followed by a retrospective analysis of medical examiner data demonstrating carnivorous scavengers’ dislike of the remains of humans who had abused methamphetamine. The third place prize went to a computer science project that generated highly detailed maps integrating correlated indicators of danger and tranquility in the urban region of the entrant’s hometown. NIDA also continues its enduring partnership with Scholastic magazine, sent out quarterly to thousands of youth across the country to communicate to them the consequences of drug abuse.

Finally, NIDA’s “After the Party” PSAs, which grew out of a previous campaign designed to inform teens about the link between drug abuse and HIV, have aired more than 25,000 times between September 2007 and May 2009, which translates into nearly \$4.4 million in free media time garnering almost 2.4 million media impressions (estimated viewers for the time slots in which the PSAs aired). Another extraordinary event designed for teens is NIDA’s annual Drug Facts Chat Day, in which NIDA scientists answer questions about drugs and their impact on the teen brain and body. This year at the the third annual Chat Day, experts answered more than 1,300 questions from students across the Nation.

Item

Tobacco Addiction – The Committee recognizes that while significant declines in smoking have been achieved in recent decades, too many Americans, particularly youth, remain addicted to tobacco products. The Committee applauds the recent progress of NIDA-supported researchers toward identifying genetic factors that contribute to nicotine dependence and affect the efficacy of smoking cessation treatments, and it urges NIDA to continue developing much-needed evidence-based treatments, medications, and prevention strategies to combat nicotine addiction. (p. 115)

Action taken or to be taken

Tobacco use remains the leading cause of preventable morbidity and mortality in the United States, resulting in over 400,000 deaths per year – 12 million since 1964 – mainly due to lung cancer, coronary heart disease, respiratory disease and chronic obstructive pulmonary disease. Public health interventions and biomedical advances have led to dramatic reductions in the prevalence of tobacco use. However, despite the availability of medications and behavioral treatments to aid smoking cessation, ~71 million Americans report being current users of tobacco. This significant number highlights the urgent need for additional research into the development of more effective therapeutic and preventative interventions.

In recognition of this urgency, NIDA designated the eradication of tobacco addiction as one of its signature areas for the American Recovery and Reinvestment Act (ARRA) funds. The ARRA dollars will be used to accelerate the research and development of novel medications and vaccines to treat tobacco addiction.

NIDA has been supporting an aggressive and comprehensive program using a range of strategies including genetic analyses to determine vulnerability to addiction and treatment responsiveness, imaging to ascertain how tobacco exposure effects the body and the brain, medications development, including immunotherapies and novel compounds, and behavioral approaches to both prevent and treat tobacco addiction. These approaches have already yielded substantial knowledge on specific genetic and environmental variables (including prenatal tobacco exposure, social environment, and developmental stage) that contribute to nicotine addiction as well as prompting new avenues for medications development.

One approach that has garnered recent excitement is the use of immunotherapy to promote tobacco cessation and prevent relapse. Using ARRA funds, NIDA joined forces with Nabi Biopharmaceuticals to support a clinical trial to test the safety and efficacy of NicVax, which works by stimulating the immune system to produce antibodies against nicotine, sequestering it in the bloodstream, and preventing it from entering the brain and exerting its rewarding effects. Thus far, NicVax results have been promising, with subjects that exhibited high antibody responses to NicVax showing significant reductions in the number of cigarettes smoked per day compared to their own baseline values before treatment.

Behavioral interventions continue to play an integral role in smoking prevention and cessation. NIDA actively supports research to improve the accessibility and decrease the cost of behavioral interventions, including tobacco quit-lines and the use of web-based technologies. Programs range from self-help materials to individual cognitive-behavioral therapy, which teaches smokers how to recognize high-risk smoking situations, develop alternative coping strategies, manage stress, improve problem-solving skills, and increase social support. NIDA is also targeting vulnerable populations, supporting longitudinal studies on the developmental effects of tobacco exposure or second-hand smoke during pregnancy, childhood and adolescence, and supporting research in individuals with co-morbid health and mental health conditions, such as HIV, schizophrenia and depression.

**National Institute on Alcohol Abuse and Alcoholism
(NIAAA)**

Senate Significant Items

Item

Behavior Change Research - The Committee encourages NIAAA to support interdisciplinary research that integrates biomedical, psychological, and social science perspectives on mechanisms of behavior change. (p. 107)

Action taken or to be taken

The goal of the NIAAA Mechanisms of Behavior Change (MOBC) research initiative is to stimulate research on mechanisms inducing and affecting positive behavior change among heavy drinkers, both those receiving professional treatment and those who change their drinking without it. The MOBC initiative is capitalizing on advances in a number of scientific disciplines such as genomics, neuroscience, neuroeconomics, psychology, and social science and working to exploit recent advances in mathematical modeling techniques to integrate information from these disparate fields of study. This interdisciplinary approach will enable researchers to model behavior as a complex dynamical system, a significant advance over previously applied techniques.

To date, NIAAA has funded 13 exploratory/developmental projects to investigate the underlying psychological, social, and neurophysiological processes that drive behavior change within the context of evidence-based behavioral treatments for alcohol use disorders. These studies are expected to lay the groundwork for understanding the causal relationship between potential mechanisms of behavior change and treatment outcomes. Recently NIAAA issued a Broad Area Announcement for trans-disciplinary research to support efforts to develop a common taxonomy, identify the research areas most likely to lead to breakthrough findings within the next 5 to 10 years, and support the development and maturation of inter-field research. NIAAA has been a leader in stimulating trans-NIH research efforts in the area of behavior change. NIAAA, National Institute on Drug Abuse (NIDA) and National Institute of Mental Health (NIMH) have worked closely with the Office of Behavioral and Social Science Research to stimulate trans-NIH research on approaches to patients with multiple adverse health behaviors, such as smoking, excessive drinking, poor diet and lack of exercise. NIAAA also worked with the National Institute on Aging (NIA), NIDA, NIMH and other Institutes and Centers on a pilot NIH Roadmap project on the Science of Behavior Change. Based solidly in basic and applied science, the Science of Behavior Change initiative represents the establishment of a new direction in behavior change research that integrates basic science research on the mechanisms underlying behavior change and applied research on behavioral interventions to improve health outcomes.

Item

Dissemination of Research Findings - The Committee encourages NIAAA to continue its leadership role by disseminating science-based, user-friendly information on the health effects of alcohol. (p. 107)

Action taken or to be taken

NIAAA disseminates research information on the health effects of alcohol to a range of target audiences in a number of ways. Capitalizing on the important role of primary health care providers in advising their patients on health related behaviors, NIAAA is actively engaging the medical community to increase the number of primary care and mental health clinicians who advise, counsel, and treat their patients regarding harmful patterns of alcohol use, including alcohol dependence. In partnership with the American Medical Association, NIAAA promoted and disseminated The NIAAA Clinician's Guide: Helping Patients Who Drink Too Much. To date, over 330,000 copies of The Clinician's Guide have been distributed. NIAAA has produced online training for physicians and nurses that includes video case studies demonstrating how to effectively use The Clinician's Guide. More than 24,000 clinicians (physicians, nurses, physician assistants, and other health professionals) have viewed the interactive video cases since their release in 2007 and almost 10,000 have completed the programs for continuing education credit.

With input from the extramural research community, NIAAA is also working on a practitioner's guide for screening children and adolescents for alcohol involvement. The goal of this document is to provide simple, easy to use guidance that is acceptable to practitioners on how to screen children and adolescents for alcohol consumption, binge drinking, and alcohol use disorders, as well as to identify those who have not initiated drinking but are at high risk for alcohol use. This will enable pediatricians to provide information to their patients and their parents about the health effects of alcohol on the developing body and brain. Information about the health effects of alcohol on children and adolescents can be found in The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking for which NIAAA provided the scientific foundation and continues to promote in collaboration with the Office of the Surgeon General.

NIAAA recently launched an interactive website and supporting booklet, Rethinking Drinking (<http://rethinkingdrinking.niaaa.nih.gov>), to help individuals recognize and reduce their risk for alcohol problems. These new resources offer evidence-based information about risky drinking patterns, the alcohol content of drinks, and the signs of an alcohol problem, along with information about medications and other resources to help people who choose to cut back or stop drinking. The website also provides interactive on-line tools, such as a calculator to estimate the alcohol content in common cocktails. Nearly 200,000 copies of the Rethinking Booklet have been distributed since its release in March 2009, and almost 250,000 visitors have accessed the website.

Recently, the Institute launched the NIAAA Spectrum, NIAAA's first-ever webzine. NIAAA Spectrum offers accessible and relevant information on NIAAA and the alcohol research field for a wide range of audiences. Each issue includes feature length stories, news updates from the field, charticles and photo essays, and an interview with an NIAAA staff member or alcohol researcher. NIAAA Spectrum is published three times a year.

For more in depth information about specific topics such as alcoholic liver disease the NIAAA publishes Alcohol Research and Health and the more streamlined Alcohol Alert, available on the web at <http://www.niaaa.nih.gov/Publications>.

**National Institute of Nursing Research
(NINR)**

Senate Significant Items

Item

Preparing Nurse Faculty – The Committee recognizes that the NINR is integral to the future of the Nation’s healthcare system and plays a vital role in educating the next generation of nurse researchers who will serve as nurse faculty in nursing schools.
(p. 107)

Action taken or to be taken

Through its portfolio of research training programs, NINR seeks to develop and empower the innovative, multidisciplinary research community of the future. These programs are designed to provide the next generation of scientists with the necessary research skills and education that will enable them to further expand the evidence-base for clinical practice, improve quality of life for those with chronic illness, and support preventative health. This research will provide the needed scientific evidence to support many of the reforms that will take place in the health care system in the coming years. Finally, many of these scientists will also serve as faculty in schools of nursing, responsible for educating future nurses that are vital to improving patient health and the effectiveness of the Nation’s health care. NINR’s commitment to supporting training programs to enhance the research workforce and pipeline of faculty in schools of nursing will continue in FY 2011.

NINR supports training programs and opportunities that encourage participants not only to develop expertise in clinical areas, but also to employ interdisciplinary collaborations as part of their standard research practice. For example, the NINR Summer Genetics Institute (SGI), sponsored by the NINR Intramural Research Program, is an intensive summer training program that provides graduate students and faculty with a foundation in molecular genetics to enhance their research and clinical practice. SGI graduates, of which there are over 180, are successfully building programs of research in genetics related to nursing; disseminating findings through publications; and integrating genetics content in nursing school curricula across the country. In addition, the BNC Fellowship, supported by the Bravewell Collaborative in collaboration with NINR and the NIH Clinical Center, trains individuals to address key issues in integrative health research and encourages multi-disciplinary collaborations designed to optimize health and healing for individuals and society.

NINR also funds training opportunities that seek to facilitate earlier entry into research careers. For example, NINR supports investigators under the NIH Pathway to Independence Program (K99/R00). This program provides an opportunity for new scientists to receive both mentored and independent research support from the same award. Another program, the K22 Career Transition Award, funds postdoctoral research in two phases: an intramural phase at NIH, and an extramural phase to aid the transition to tenure-track research and faculty positions at university schools of nursing.

Finally, in addition to supporting pre-doctoral and post-doctoral students under the NIH-wide Ruth L. Kirschstein National Research Service Award (NRSA) program for individuals and institutions, NINR participates in the NIH Graduate Partnerships Program (GPP). The GPP is a doctoral fellowship training program that coordinates training and funding for doctoral students attending a school of nursing currently supported by a NINR-funded NRSA Institutional Research Training (T32) grant. The program combines the academic environment of a university and the breadth and depth of research at NIH.

**National Human Genome Research Institute
(NHGRI)**

Senate Significant Items

Item

Genes and Environment — The Committee encourages the NHGRI to continue its emphasis on the development of real-time environmental monitoring technologies, and the advancement of tools to measure psychosocial stress and its influence on gene expression (p. 109).

Action taken or to be taken

NHGRI is continuing work on identifying the genetic and environmental determinants of common, complex diseases through the Genes, Environment and Health Initiative (GEI). The GEI program supports research that will lead to better understanding of genes, environmental factors, and their interactions in common disease. In FY 2009, NHGRI continued to work with the National Institute of Environmental Health Sciences to emphasize development of real-time environmental monitoring technologies, and the advancement of tools to measure psychosocial stress and its influence on gene expression, for use in studying the interactions of genes and environment.

NHGRI also coordinated efforts to solicit and award programs in replication, systems biology, functional studies, and pilot translational studies. Through GEI programs, research studies will explore important questions regarding the genetic and environmental contributions to health disparities. Research will be conducted to collect and analyze genotype, phenotype, and exposure data, while simultaneously measuring other factors within disease subgroups (e.g., race, ethnicity, behaviors, geography, genetic backgrounds, exposures and social environments) that may lead to differential health outcomes.

Another component of GEI, the GENEVA (Gene Environment Association Studies) consortium, is using rapidly evolving technologies in genome-wide association studies to find genetic risk factors in common conditions, and assess their interplay with non-genetic risk factors. In FY2009, GENEVA finalized and released genome-wide association data for three large studies of alcohol addiction, lung cancer, and diabetes, and is in the process of finalizing datasets in prematurity and maternal metabolism. As these conditions can be caused or worsened by psychosocial and other environmental stresses, the National Institute of Environmental Health has concurrently developed the GEI Exposure Biology Program. This program will work in tandem with NHGRI's GEI Genetics Program to develop tools for assessing individual exposure to environmental stresses including airborne chemicals, psychosocial stress, use of addictive substances, diet and physical activity as well as measures of the biological response to those stressors.

GEI will be completed in 2011. Findings are expected in late 2011 and early 2012, though the data resources produced by GEI are anticipated to continue to produce valuable findings well beyond that.

**National Institute for Biomedical Imaging and Bioengineering
(NBIB)**

No Significant Items Requested

**National Center for Research Resources
(NCRR)**

House Significant Items

Item

Clinical and Translational Science Awards (CTSAs) -For the CTSA program, the Committee assumes the same funding level and budget allocation between NCRR and the Common Fund as in the budget request. The Committee is pleased with the progress of the CTSA program and urges NCRR to continue to support the implementation of this initiative consistent with the plan outlined in the budget justification. The Committee is pleased that the K-30 Clinical Research Curriculum Awards mechanism has been continued for those institutions that have not yet received a CTSA Award. (p. 126,127)

Action taken or to be taken

Working together as a national consortium, CTSA institutions share a common vision to improve human health by transforming the research and training environment to enhance the efficiency and quality of clinical and translational research. Eight new CTSAs were awarded in 2009, bringing the total to 46. The budget request for FY 2010 was \$441,748,000 for NCRR and \$25,245,000 from the Common Fund, for a total of \$466,993,000. The Consolidated Appropriations Act, 2010 provides sufficient funding for NCRR to meet its budget request. The goal of the program is to support a total of 60 CTSAs by 2011.

The K30 Clinical Research Curriculum Award (CRCA) is designed to attract talented individuals to the challenges of clinical research and to provide them with the critical skills that are needed to translate basic discoveries into clinical treatments. The awards stimulate the inclusion of high-quality, multidisciplinary, didactic training as part of the career development of clinical investigators. The awards support the development and/or improvement of core courses designed as in-depth instruction in the fundamental skills, methodologies, and theories necessary for the well-trained, independent, clinical researcher.

Institutions receiving a CTSA award have their K30 grants incorporated into their CTSA award, while those institutions that have not received a CTSA award continue to receive a separate K30 grant. There are currently 13 institutions that have a K30 award but do not have a CTSA. Since those K30 awards will end in July 2010, NCRR issued a funding opportunity announcement and anticipates funding approximately 16 new K30 awards for three years duration. This will give institutions without a CTSA an opportunity to have a K30 to strengthen their CTSA applications.

Senate Significant Items

Item

Clinical and Translational Science Awards-The NCRR receives a larger percentage increase under the Committee's recommendation than other institutes and centers because some of the costs of the Clinical and Translational Science Awards [CTSAs]

program will shift to the NCRR from the Common Fund. The Committee recommendation includes a total of \$473,600,000 for the CTAs in fiscal year 2010, divided as follows: \$448,355,000 from the NCRR, compared with \$430,642,000 in fiscal year 2009; and \$25,245,000 from the Common Fund, down from \$53,224,000 in fiscal year 2009. The fiscal year 2009 total for CTAs was \$483,866,000. (p. 110)

Action taken or to be taken

The amount for NCRR indicated by the Senate for the CTAs, \$448,355,000, is \$6,607,000 more than NCRR requested. Due to the fact that the Consolidated Appropriations Act, 2010 provided sufficient resources to meet the funding level identified in the Senate report language, no additional reductions were required from other NCRR programs.

Item

Human Tissue Supply -The Committee remains interested in matching the increased needs of NIH grantees and intramural and university-based researchers who rely upon human tissues and organs to study human diseases and search for cures. The Committee encourages the NCRR to increase support for nonprofit organizations that supply human tissue. (p. 110)

Action taken or to be taken

The National Disease Research Interchange (NDRI) is the parent nonprofit organization in the United States funded by NCRR to provide human tissue and organ specimens to biomedical researchers for basic and clinical research. NCRR is the lead Institute/Center for the NIH cooperative agreement that funds the Human Tissue and Organ Resource (HTOR), a division of NDRI. Since 1995 to 2009, over 68,600 normal and diseased tissues and organ specimens have been shipped by HTOR to biomedical researchers to study diseases such as Alzheimer's, Crohn's Disease, cystic fibrosis, diabetes, glaucoma, heart disease, HIV-AIDS, malaria, multiple sclerosis, and Parkinson's. Over 480 active biomedical researchers used this program in FY 2009, including 279 that are NIH-funded.

NCRR maintains the core funding (\$739,000 in FY 2009) for the HTOR cooperative agreement, now in its nineteenth year, with co-funding (\$585,000 in FY 2009) from NEI, NHLBI, NIAID, NIAMS, NIDDK and the Office of Rare Diseases Research (ORDR). NDRI and other sources of tissues (e.g., tissue banks, eye banks, pathology departments, and NIH funded repositories) are instrumental in providing tissue and organ resources to researchers; NIH is continuously identifying ways to improve the collection, storage, and distribution of tissues. In addition, NIH Institutes, which are better poised to gauge the specific tissue and organ needs of their researchers, provide funds for mission-specific tissue resources. The ORDR provided additional one-time funding to be used in FY 2009 for the NDRI Rare Disease Initiative to support tissue distribution, tissue source and database development, and outreach to advocacy groups for patients with rare diseases and other members.

Item

Infrastructure Projects -The Committee is concerned that schools of dentistry may not be receiving adequate infrastructure funding from the NCRR. The Committee encourages the

NCRN to explore ways of ensuring an equitable distribution of infrastructure funding among various scientific programs. (p. 110)

Action taken or to be taken

In FY 2009, NCRN provided \$16.6 million to schools of dentistry, including \$11.2 million in support through the Institutional Development Award (IDeA) Program to five Centers of Biomedical Research Excellence located at dental schools.

In FY 2009, NCRN also provided funding through a supplement to the CTSA at the University of North Carolina at Chapel Hill to develop a web-accessible clinical research “toolkit” that can standardize methodological practices among dental schools. Of the current 46 institutions with CTSA, 27 have dental schools/programs, providing a platform for the development of best practices and enabling dental researchers to work together within the national CTSA consortium.

Using ARRA funding, NCRN also awarded a \$5.1 million construction grant to the Dental Research Institute at the University of California, Los Angeles and a \$335,000 shared instrumentation grant to the University of Connecticut School of Medicine and Dentistry in FY 2009. NCRN will award many more construction and shared instrumentation grants with ARRA support in FY 2010. Dental schools were among the applicants for these grants and, therefore, may receive an award if they are determined to be meritorious by the NIH peer review process. There were a significant number of grant applications received by NCRN for construction and instrumentation grants, which provides an indication of the need for this type of support.

NCRN recognizes the importance of supporting the infrastructure of dental schools that are conducting biomedical research and will, through its various programs, continue to provide support to meritorious applications in FY 2010 and beyond.

Item

Primate Research -The Committee believes that nonhuman primates are extremely important models for conducting research to help understand and treat conditions such as heart disease, hypertension, cancer, diabetes, hepatitis, kidney disease, Alzheimer’s disease, and Parkinson’s disease. In addition, nonhuman primate research is necessary for pursuing an HIV/AIDS vaccine and enhancing the Nation’s emerging infectious disease and biodefense response capabilities. Therefore, the Committee appreciates the efforts of the National Primate Research Center [NPRC] directors to outline a 5-year initiative to address the upgrades and program expansions required to meet the demanding nonhuman primate research needs of the Nation, and encourages the NCRN to work with the NPRCs to ensure that they are provided with the resources necessary to contribute to the overall effectiveness of the Federal investment in biomedical research. (p.110, 111)

Action taken or to be taken

The National Primate Research Centers (NPRCs) provide the infrastructure and expertise for investigators using non-human primates (NHPs) in biomedical research. Support for the NPRCs comes from the base grants funded by the NCRN and the income leveraged by these base grant funds. Income is derived from per diem fees for use of animals on

site, fees for assay services and the occasional sale of animals. The base grants contribute, on average, about one-third of the operational costs of an NPRC, with income contributing to the balance of the total expense. In FY 2008, base grant funding to the NPRCs was \$86.1 million (\$80.3 million from NCRR and \$5.8 million from other NIH Institutes and Centers, ICs). In FY 2009, the non-ARRA base grant funding to the NPRCs increased to \$94.7 million (\$93 million from NCRR and \$1.7 million from other NIH ICs). This included supplemental non-ARRA funding specifically aimed at enhancing the informatics infrastructure and capacity to support infectious disease research at the NPRCs. In FY 2009, the NPRCs supported approximately 1,000 projects, involving more than 2,000 investigators, and housed approximately 25,000 NHPs.

In FY 2009, ARRA funding, totaling approximately \$13 million, enabled the NPRCs to support new scientific and animal husbandry staff, develop new scientific programs in areas such as stroke and diabetes, and enhance the information technologies necessary for efficient management of facilities and animal colonies.

NCRR and the NPRCs have worked together for several years to develop consortium-based activities, aimed at promoting cost savings across the NPRC system by eliminating redundancies and increasing efficiency. Working groups have been organized jointly by NCRR and the NPRCs in several functional areas, including colony and behavioral management, pathology, genetics and biobanking.

In FY 2010, the NCRR will continue to support the NPRCs in their mission to facilitate the biomedical enterprise in research areas such as infectious disease, neurobiology, diabetes and metabolic syndrome. Through this support, the NPRCs will be able to increase the supply of specific pathogen free rhesus monkeys for AIDS research, enabling analysis of mechanisms of pathogenesis of AIDS viruses and testing of new vaccines and microbicides. Other potential areas of focus may include: a) systems biology-based approaches to better understand the mechanisms of infectious diseases such as influenza and AIDS; b) studies of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases in monkey models using state of the art imaging technologies; and c) enhancement of the informatics infrastructure and consortium-based activities of the NPRCs to realize cost savings and increase efficiencies of operation.

Item

Research Centers in Minority Institutions - The Committee continues to recognize the critical role played by minority institutions at both the graduate and undergraduate level in addressing the health research and training needs of minority populations. The Research Centers in Minority Institutions [RCMI] program impacts significantly on these issues. The Committee encourages the NIH to strengthen the research environment at minority institutions so that they may fully engage in and build upon NIH initiatives. Specifically, the Committee recommends NCRR supplemental funds be directed to high-impact, high-risk research activities within the RCMI program such as creating an integrated translational research network to help reduce health disparities. (p. 111)

Action taken or to be taken

The Research Centers in Minority Institutions (RCMI) Program develops research infrastructure in predominantly underrepresented minority institutions that award doctorates in the health professions or health-related sciences. The 18 institutions currently funded via the RCMI program have an outstanding track record of producing minority scholars in science, medicine, and technology. According to the most recent available data, 23 percent of the Ph.D.s earned by minorities in the biomedical sciences were awarded by these institutions in FY 2006¹. The eight medical schools included in this group produced 17.5 percent of the minority M.D.s in the United States in FY 2008².

In FY 2008, funding for the RCMI Program was \$53.2 million. Funding for the program was increased to \$57.9 million in FY 2009. Supplemental funding was utilized to support institutional infrastructure and research on health disparities through the RCMI Infrastructure for Clinical and Translational Research (RCTR) awards and the RCMI Translational Research Network (RTRN). Supplemental funding to the RCTR awards is aimed at developing institutional infrastructure, enhancing training and career development activities, and accelerating the process of translating research advances to improved health outcomes, especially in minority communities. The RTRN is a cooperative research network that consists of researchers from various RCMI programs, other academic health centers, community providers, community organizations, and a Data and Technology Coordinating Center. The RTRN received supplemental funds to facilitate expansion of the data center capabilities to support the consortium activities and to initiate multi-site collaborative pilot research projects focused on cardiovascular disease, HIV/AIDS, cancer and other diseases that disproportionately impact minority populations. In FY 2010, NCRP will use additional funding to strengthen institutional capability for research on health disparities, and provide the resources necessary to support the integrated translational research network's high risk, high impact activities to help reduce health disparities.

Item

NIH-DOE Collaborations -The Committee applauds the successes that have been achieved when the NIH has collaborated with the Department of Energy's National Laboratories, including the Human Genome Project, advances in bioinformatics, and breakthroughs in atomic resolution structural biology. The Committee strongly encourages the NIH Director and directors of the institutes and centers to pursue additional opportunities for sustained collaboration in research and development. (p. 119)

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). While the two agencies have distinct missions, there are areas of science that are relevant to both. Both agencies benefit from cooperative discussion, planning, and funding activities. These productive collaborations take place at the highest levels of both agencies as well as among the staff at several NIH

¹ *Science and Engineering Doctorate Awards: 2006*. Division of Research Statistics, NSF, 2009

² *Enrollment and Graduates Data: Total Graduates by U.S. Medical School and Race and Ethnicity, 2008*. AAMC 2008.

Institutes and Centers with DOE Offices. A few examples of the numerous, ongoing, and synergistic collaborations are given below.

NIH and DOE have formed an NIH/DOE Nuclear Medicine Working Group to help address the issues of planning for the availability of research isotopes and the training of radiochemists. The group is drafting a document to identify radioisotopes needed for biomedical research, as well as working to define the process for NIH/DOE interactions to facilitate production of biomedical isotopes to meet research needs. The group has also developed the concept underpinning the new DOE funding opportunity announcement that focuses on a radiochemistry program of excellence and training and NIH will provide funding to supplement the training component. The impact of this integrated research and training program will fulfill the need for trained investigators to produce radiotracers that are used by biological, biomedical and environmental sciences communities.

Breakthroughs in atomic resolution structural biology have been made possible in part through the cooperative stewardship of synchrotron management by NIH and DOE. NIH is currently planning to build and operate beamlines for the most advanced structural biomedical research at the National Synchrotron Light Source-II (NSLS-II). NSLS-II is a new DOE synchrotron facility that will replace the existing NSLS at Brookhaven National Laboratory (BNL). Experimental facilities at NSLS-II will provide an X-ray beam with properties that will provide greater efficiency and will allow interrogation of more challenging specimens than currently exists at other synchrotrons. NSLS-II is scheduled to become fully operational in 2015. Access to these beamlines will be available to all investigators with meritorious peer-reviewed biomedical research projects. NIH has set aside \$45 million over the next five years for these activities.

The NIH and DOE have a rich history of cooperation and collaborative support for the most advanced research and development activities which will continue, to the benefit of both agencies and their stakeholders. This productive alliance is attributed to collegial relationships among the agencies' program staff in addition to the positive official liaisons the agencies have established.

**National Center for Complementary and Alternative Medicine
(NCCAM)**

No Significant Items Requested

National Center on Minority Health and Health Disparities (NCMHD)

House Significant Items

Item

Project EXPORT - The Committee commends NCMHD for its successful Project EXPORT initiative and urges continued support for this important program. (p. 127)

Action taken or to be taken

The NCMHD Centers of Excellence program formerly referred to as “Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT)” remains one of the NCMHD’s leading research programs to understand the etiology and progression of diseases that disproportionately affect underserved populations, and the many factors that contribute to health disparities.

The Centers of Excellence (COE) were established to develop novel programs that would make significant advances and contributions to easing the health burden in underserved populations and in reducing and ultimately eliminating health disparities. With 49 active Centers throughout the United States, Puerto Rico, and the U.S. Virgin Islands, the Centers of Excellence are making progress and providing new insights into combating disparities. For example, researchers at the Center of Excellence at Mt. Sinai School of Medicine in New York City recently created a tracking and feedback registry that increased the likelihood of consultations between breast cancer surgeons and oncologists. Use of this intervention reduced underuse of adjuvant treatment –cases in which physicians recommend therapy and patients do not refuse care but care still does not ensue. Among black women, the underuse rate changed from 34 percent before to 14 percent after the use of the intervention, and from 23 percent to 13 percent among Hispanic women. The tracking and feedback registry was most effective at municipal hospitals that had greater frequencies of underuse due to system failure.

A study conducted by the Penn-Cheyney EXPORT Center for Inner City Health determined that, in minority neighborhoods in two of three cities analyzed, unhealthy outdoor advertising (ads for fast-food, alcohol and tobacco) tended to be clustered near child-serving institutions, like day care centers, and schools. Such findings could suggest possible unrecognized influences underlying obesity in minority children.

NCMHD will continue to support its Center of Excellence program and other programs such as its investigator-initiated research project grants program, its Community-Based Participatory Research Program, its Loan Repayment Program, Endowment program, and other programs that support innovative, interdisciplinary, translational and clinical research, research capacity-building and training aimed at reducing and eventually eliminating health disparities.

Item

Research Endowment - The Committee commends NCMHD for its leadership in addressing the longstanding problem of health status disparities in minority and medically

underserved populations, and encourages NCMHD to continue its successful research endowment program as an ongoing initiative. (p. 127)

Action taken or to be taken

NCMHD's Research Endowment program has been instrumental in enhancing the training and research capacity of academic institutions as part of the continuing nationwide effort to address health disparities. The NCMHD is committed to continuing support for the Research Endowment program. The research endowment grants provide multi-year awards to support activities such as basic and clinical research, faculty and student training, research infrastructure, and endowed faculty chairs. For example, Morehouse School of Medicine has utilized its research endowment funds to support 36 seminars with such topics as Relationship between Family History of Cardiovascular Disease and Left Ventricular Mass in African Americans: Is there a gender difference? and Transcription Factors and Prostate Cancer. Another example is the University of Montana, which has utilized its research endowment grant to support several studies, including: a major effort to assess the role of pharmacogenomics in American Indian populations; mechanistic studies of brain injury, or neurodegeneration; and studies of a unique agent showing promise as a neuroprotective agent when used up to six hours after stroke injury. Eligibility for NCMHD Research Endowment grants is limited to health professions schools funded under section 736 of the PHS Act, through the Health Professions Centers of Excellence Program administered by the Health Resources and Services Administration (HRSA). The NCMHD will continue to explore ways to expand the eligibility of the Research Endowment Program to continue its support for enhancing training and research capacity.

Item

Translating NIH Research to Address Racial and Ethnic Health Disparities – The Committee is encouraged by the efforts of the Director to translate the benefits of NIH research into clinical practice. The Committee notes, however, that while the benefits of NIH research have led to an overall decline in mortality across a range of diseases, racial and ethnic health disparities have continued to increase. Therefore, the Committee requests the Director, working closely with the Director of NCMHD, report to the Committees on Appropriations of the House of Representatives and the Senate on the steps NIH has taken to ensure that racial and ethnic minorities are able to access the clinical benefits of NIH research. The report should include a brief summary of the NIH's outreach efforts to include racial and ethnic minorities. (p. 139)

Action taken or to be taken

Translational Research is a priority for the NIH Director, NCMHD, and the other Institutes and Centers (ICs). Scientific discoveries must be translated into practical applications if they are to improve health, and eliminate health disparities. The NCMHD's Centers of Excellence, its Community Based Participatory Research Programs, and the National Heart, Lung and Blood Institute's (NHLBI) Comprehensive Sickle Cell Centers, are three examples of NIH's efforts to ensure racial and ethnic minorities gain from the clinical benefits of NIH research.

For example, the NCMHD's Community Based Participatory Research program supports intervention research that is done in collaboration with communities to foster sustainable efforts at the community level that will accelerate the translation of research advances to health disparity populations. The program has three separate phases that support: a) three-years of planning activities; b) five years to conduct the research intervention; and c) three-years for community outreach and information dissemination based on the research results.

One of the most important critical first steps that the NIH undertook to ensure that racial and ethnic minorities gain from the clinical benefits of research was the enactment of a policy to include women and members of minority groups and sub-populations in all NIH supported clinical research projects. There are numerous outreach efforts to support the translation of NIH research to address racial and ethnic health disparities including: efforts of the National Library of Medicine (NLM), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and NCMHD programs to target low health literacy.

The [National Diabetes Education Program](#) (NDEP) and the [National Kidney Disease Education Program](#) (NKDEP) both tailor materials for minority groups at high risk. NCMHD is also working with the Substance Abuse and Mental Health Services Administration (SAMHSA) on the National Network to Eliminate Disparities (NNED) which is an on-line network and learning community where academic institutions and community-based organizations can collaborate and share translational best practices in learning clusters on a broad range of health disparities topics.

The NNED works closely with the National Alliance of Multi-Ethnic Behavioral Health Associations (NAMBHA) which is comprised of four affiliate organizations, namely the National Asian American Pacific Islander Mental Health Association (NAAPIMHA), the National Latino Behavioral Health Association (NLBHA), the National Leadership Council on African American Behavioral Health (NLC); and the First Nations Behavioral Health Association (FNBHA). The National Cancer Institute's Patient Navigator Research and the Community Networks programs are also designed to translate NIH research into clinical practice. [InfoSIDA](#) is a Spanish-language version of the comprehensive AIDSinfo Web site administered by NIH.

Senate Significant Items

Item

Glomerular Disease Research - The Committee notes the recently discovered link between the MYH9 gene and the high prevalence of focal segmental glomerulosclerosis among African Americans. The Committee urges the NCMHD to collaborate with the NIDDK to support expanded research on this condition's effect on minorities and the specific implications of this genealogical linkage. (p. 111,112)

Action taken or to be taken

Developing an integrated, cross-disciplinary research agenda on health disparities is a specific priority for NCMHD. The NCMHD continues to include glomerular disease research as an area of emphasis in its Requests for Applications. The NCMHD launched

its intramural research program in FY2009. This is another opportunity for the NCMHD to expand its research efforts and build on its collaborations with the NIDDK to advance the study of diseases and conditions affecting health disparity populations and the NIDDK's body of research to better understand and address the high prevalence of focal segmental glomerulosclerosis in African Americans. The NIH Health Disparities Strategic Plan, coordinated by NCMHD, pursuant to P.L. 106-525, is an important tool which promotes collaboration among the NIH Institutes and Centers, and is another venue for the NCMHD and the NIDDK to employ in planning their priorities for health disparities.

Item

Minority Institutions - The Committee continues to be pleased with the NIH Director's implementation of various programs focused on developing the research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions and the programs sponsored by NCMHD. The Committee encourages the Director of NIH to work closely with the Director of NCMHD to establish a program of coordination among these various mechanisms and partner with minority health professions schools to address their infrastructure needs. (p. 135)

Action taken or to be taken

The NIH is committed to strengthening the research infrastructure and capacity at minority health professions institutions as evidenced by the NIH Health Disparities Strategic Plan and Budget, which identifies three goals. The goals are: 1) Research; 2) Research Infrastructure and 3) Community Outreach i.e. information dissemination and public health education. Goal #2 focuses on research infrastructure which includes expanding research training opportunities and career development for research investigators from racial and ethnic minority populations and enhancing the ability of institutions to conduct health disparities research. Accordingly, the strategic plan will continue to be used as a mechanism to foster coordination and collaboration among the Institutes and Centers to develop and expand programs aimed at strengthening the research infrastructure of minority health professions schools.

Research Infrastructure programs at the NCMHD and the NCRH are among the NIH programs making strides to strengthen the capacity at minority health professions schools. For example, the NCMHD RIMI program is aimed at establishing, strengthening and/or improving the scientific infrastructure and environment of academic institutions such as Tougaloo College which has recently added state-of-the art equipment to the existing biomedical research infrastructure; new faculty; a "Distinguished Faculty Seminar Series," and two new undergraduate research/science courses with RIMI funding. The NCMHD Research Endowment Program provides grants to build research and training capacity at institutions to facilitate health disparities research. Meharry Medical College for example, has developed a cancer biology endowed chair program to support and offer cancer research opportunities for several researchers focusing on areas such as breast and lung cancer. This program will help to strengthen the institution's cancer disparities research portfolio, and through its research, add to the scientific knowledge base to better understand and address cancer health disparities.

The NCRR and NCMHD partnership through the NCRR Research Centers in Minority Institutions program, supports the RCMI Translational Research Network (RTRN), and a Data and Technology Coordinating Center (DTCC) which provides physical infrastructure, personnel, and processes that facilitate multi-site clinical and translational research in areas with the highest level of disparities related to health access and outcomes. The University of Hawaii coordinates the six disease-based research clusters which focus on cancer and immunological disease, cardiovascular diseases, obesity and metabolic disorders, community-based participatory research, neurology and mental health disorders, and HIV/AIDS and infectious diseases. The DTCC of the RTRN was established at Jackson State University in Jackson, Mississippi. One example of RTRN research is a pilot project that will study the effect of vitamin D3 on cardiovascular risk factors and function. Enrollment of the randomized control trial began in July 2009. This project is establishing a template for implementing processes and tools that can be used in future studies to decrease the time between protocol approval and study start-up. The RTRN has also established a small grants program which provides funding for projects that promote interinstitutional, interdisciplinary translational research and a total of six awards of \$50,000 each were made in 2009.

Item

Primary Care Practice Research - The Committee recognizes the role of NIH in researching primary care and prevention interventions in order to improve health outcomes, reduce health care-associated infections, and reduce the overall costs of healthcare. The Committee requests that the Director work with the Agency for Healthcare Research and Quality, CDC, and the Office of the Secretary to develop a coordinated approach to research in primary care practice, with a specific focus on improving health among populations with disparate health outcomes. (p. 137)

Action Taken or to be Taken

Research has established that primary care and prevention interventions can have a positive effect on population health. NCMHD has supported several recent studies that explored primary care and improving health among health disparity populations. For example a study co-authored by a researcher at an NCMHD Center of Excellence at Morgan State University addressed the under-diagnosis of depression in elderly Mexicans, especially in primary care. It showed that the benefits of treatment in primary care units may offset the associated costs, and that treatment may lower utilization rates and free up resources for further improving the functional status of older adults. The study has implications for improving the treatment of depression in the elderly. Researchers recommend increasing the training of primary-care physicians on the detection and management of depression in elderly patients, and utilizing primary-care teams to improve treatment results not the primary-care physician alone.

In another investigation, research supported by the Center of Excellence at Virginia Commonwealth University found that an academic health center reduced emergency department overcrowding when it contracted with community primary care physicians to care for uninsured patients. Additional research will be needed to assess whether the findings are sustainable or transferable to other settings. One of the sustainable outcomes

of the study has been the Primary-Care Physicians Network which continues to function five years after the data collection for the study ended.

NCMHD will continue to support research involving primary care and prevention interventions as a means of improving health outcomes in health disparity populations, reducing healthcare-associated infections and reducing the overall costs of healthcare. The Federal Collaboration on Health Disparities Research (FCHDR), is an initiative developed by the Department of Health and Human Services (HHS) to lead the coordination of research activities on health disparities. The NCMHD co-chairs the Executive Committee with the HHS Office of Minority Health and plays a lead role in coordinating the efforts of key Federal agencies to develop an integrated cross-disciplinary national health disparities research agenda. NCMHD's next steps will involve setting an overall national target for action to reduce health disparities along with a coherent strategic vision and plan. As part of this process, the NCMHD/NIH will be positioned to foster greater collaborations with other HHS agencies such as the Agency for Healthcare Research and Quality, CDC, and the Office of the Secretary to continue development of a coordinated approach to research in primary care practice.

Item

Project EXPORT - The Committee commends the National Center on Minority Health and Health Disparities for its leadership in addressing the longstanding problem of health status disparities in minority and medically underserved populations. The Committee also commends NCMHD for its successful Project EXPORT initiative, which sponsors multidisciplinary and interdisciplinary research into some of the most prevalent and debilitating diseases affecting health disparity populations. (p.111)

Action taken or to be taken

Please refer to page 185 of this document for NCMHD's response to this item.

Item

Severe Asthma - The Committee encourages the NCMHD to work with the NHLBI to expand and strengthen research on severe asthma in minority populations. (p. 112)

Action taken or to be taken

Asthma is of particular concern to NCMHD because African Americans and Hispanics generally experience a higher prevalence, and the condition is more frequently under-diagnosed or undertreated in these populations.

In addition, a small percentage of these patients (10 percent or less) have severe asthma that is refractory to conventional treatment modalities, including treatment with systemic corticosteroids. Although severe asthmatics represent only a small percentage of the asthmatic population, their disease has a major impact on the health care system, consuming resources disproportionately, in terms of time and health care dollars. In addition, this patient subgroup bears the most significant burden in relation to poor quality of life, high risk for mortality, and a high investment of health care costs for marginal management. Yet, we have very little knowledge of the pathophysiology of severe asthma in the general population and especially among minority subgroups, and how it differs from

mild-to-moderate asthma within all groups. This information is critical for the development of effective treatment modalities for severe asthma patients.

The NCMHD will continue to build on the research currently being undertaken through its programs, and its longstanding collaborations with the National Heart, Lung and Blood Institute (NHLBI) to explore and expand research on severe asthma to accelerate research on the pathophysiology of severe asthma in minority populations and how it differs from mild-to-moderate asthma. Findings from current efforts are expected to generate evidence on new therapies and management protocols for patients with severe asthma who are suboptimally controlled by standard measures.

The intramural research program is another avenue for NCMHD and NHLBI to foster this collaborative research on severe asthma. The NIH Health Disparities Strategic Plan provides a mechanism for the NCMHD and NHLBI to strengthen their health disparities research collaborations to build on the work that they are already doing on severe asthma in minority populations.

Severe asthma in minority populations will be considered as the NCMHD continues to develop and expand its health disparities research priorities. Examples of the current research on asthma being supported by the NCMHD include: the NCMHD Center of Excellence at the University of Puerto Rico Pediatric Asthma Community-Based Program (PACBP): Eliminating Asthma Disparities which is testing the effectiveness of a comprehensive multi-level asthma management program that involves the family and providers in the decision-making and care management.

The Xavier University Pharmacy Endowment for Minority Health focuses on asthma education and prevention. Through the Center of Minority Health and Health Disparities Research and Education within the College of Pharmacy, the institution will continue to build the capacity for research with particular emphasis on supporting faculty research on asthma.

The NCMHD also partners with the National Institute of Environmental Health Sciences (NIEHS), the NHLBI and other academic and research institutions, to support the HEAL (Head-off Environmental Asthma in Louisiana) Project. One of the objectives of this study includes research that will help identify the underlying functional changes and environmental mechanisms that contribute to the initiation and progression of asthma in children with moderate to severe asthma.

Item

Urban Indians - The Committee is aware of the need for greater focus on the health of urban Indians, a group known to experience severe health disparities in such areas as diabetes, alcohol-related deaths and sudden infant death syndrome. The Committee encourages the NCMHD to put a priority on addressing the needs of this population. (p. 112)

Action taken or to be taken

NIH has several ongoing studies focusing on the health of American Indians in the areas of diabetes, alcohol abuse, and sudden infant death syndrome. Results from some of these ongoing investigations are expected to be published throughout the remaining three years of the project periods and may provide greater insight on the health of American Indians in urban areas and further inform the NIH health disparities research agenda, particularly as the NIH Health Disparities Strategic Plan and Budget is updated.

For example, in all of its programs, including collaborations with its Centers of Excellence, NCMHD continues to place a high priority on addressing the health disparity needs of rural and urban American Indians. Well documented health disparities for American Indian adults and youth related to the abuses of alcohol, tobacco, and illicit drugs extends to the growing urban American Indian population which constitutes more than 60% of the total American Indian population. The NCMHD Center of Excellence at Arizona State University has created a culturally grounded substance abuse prevention intervention targeting urban American Indian youth of middle school age. To date, the program has condensed and analyzed feedback from three American Indian adult focus groups on the goals and methods of the study, and curriculum issues; extracted multiple themes with high cultural relevance for the curriculum adaptation; and worked with a local Indian Center and two Washington District Elementary Schools to conduct the pilot tests of the new curriculum. Another NCMHD-supported research project conducted at the University of Kansas Medical Center is utilizing community based participatory research to pilot test several smoking cessation initiatives in order to implement a culturally appropriate smoking cessation program in an urban American Indian/Alaska Native community. This is an ongoing project that will be in effect until 2013. The outcomes of this intervention could potentially impact recreational smoking rates among American Indian/Alaska Native communities.

NCMHD also co-funds the Tribal Epidemiology Centers (TECs) at the Indian Health Service. One example is the TEC at the Urban Indian Health Institute in Seattle, WA, which focuses on urban American Indian/Alaskan native populations. The Urban Indian Health Institute has developed and released the 2009 Community Health Profiles of 34 distinct AI/NA communities served by the network of Title V funded urban Indian health organizations (UIHO) across the country. The NCMHD-funded Center for American Indian Diabetes Health Disparities at the University of has established a formal partnership with the Oklahoma City Area Inter-tribal Health Board and its Southern Plains Inter-Tribal Epidemiology Center. The Inter-tribal Health Board represents all federally recognized tribes in Oklahoma, Kansas, and Texas. The Southern Plains TEC, is one of the two Tribal epidemiology centers in the United States authorized by Congress to improve the health of American Indian/Alaska natives in Kansas, Oklahoma and Texas by providing public health services in epidemiology, data management, and analysis, training, health promotion/disease prevention and research through outreach and creative partnerships.

John E. Fogarty International Center (FIC)

House Significant Items

Item

Global Health Research Training and Workforce Capacity -- The Committee commends FIC for its continuing work to strengthen biomedical research capacity in the developing world, and by doing so advancing the global efforts against malaria, neglected tropical diseases, and other health issues that disproportionately impact the developing world. The Committee is aware that having a trained and expert local workforce as well as a research infrastructure for them to use has significant benefits for efforts to research and combat diseases of global priority. The Committee recognizes that expanding in-country research capacity will complement associated United States efforts to improve global health, and strongly supports FIC's efforts to achieve these objectives. (p. 127)

Action taken or to be taken

Fogarty is committed to continuing and further strengthening its efforts to build research capacity in the developing world for both communicable and non-communicable diseases. This commitment is described in the FY 2008-FY 2012 FIC Strategic Plan located at http://www.fic.nih.gov/about/plan/strategicplan_08-12.htm.

The five goals highlighted in the plan are:

- Mobilize the scientific community to address the shifting global burden of disease and disability;
- Bridge the training gap in implementation research;
- Develop human capital to meet global health challenges;
- Foster a sustainable research environment in low- and middle-income countries;
- Build strategic alliances and partnerships in global health research and training.

The third goal focuses on training and workforce capacity and supports the continuation of long-standing FIC research training endeavors such as: the AIDS International Training and Research; the Global Infectious Disease Research Training; the International Training and Research in Environmental and Occupational Health; the Global Research Training in Population Health; and the International Research Ethics Education and Curriculum Development Award Programs. These and other FIC research training programs support research training at U.S. and/or developing country partner research institutions. Foreign scientists trained at U.S. institutions are encouraged to return to their home countries to conduct their own research and to train the next generation of scientists. Collectively, Fogarty research training programs work in over 100 foreign institutions, including institutions in Latin America, Africa, Asia, the Middle East, Russia and Eastern Europe. From this long-standing effort, FIC has supported the training of over 4,000 researchers. Through continuous monitoring and evaluation of these programs, we have determined that 90% of these trainees have returned to their home countries to train over 800 second generation scientists. This has strengthened the ability of individuals and institutions in

low- and middle-income countries to conduct locally relevant research and implement evidence-based findings.

For example, researchers implemented a comprehensive task-shifting program in Lusaka, Zambia, among existing health providers and community-based workers, where a large public-sector antiretroviral treatment (ART) program had enrolled over 71,000 HIV-infected adults and children across 19 program sites. They found that a three-pronged approach, including training, mentorship, and continuous quality assessment, allowed the rapid roll-out of services despite notable resource constraints. This task-shifting strategy demonstrated that it is possible to expand ART services with extreme health worker shortages without compromising clinical care quality.

A team of Fogarty-supported researchers and trainees recently informed national TB control efforts in India. Up to 50% of India's population is estimated to have latent TB. Targeted isoniazid preventative therapy (IPT) has been shown to reduce the risk of active TB by up to 60 percent, but was not recommended in clinical care guidelines for HIV-infected persons with latent TB in India. Fogarty-supported researchers and trainees assessed the impact of maternal HIV and TB coinfection on maternal and infant health outcomes in the absence of IPT, and concluded that administration of IPT to antepartum HIV-infected women would likely prevent a significant number of postpartum maternal TB cases.

Efforts also include newer programs designed to strengthen research capacity in the area of implementation science, such as in the International Clinical Operational and Health Services Research Training Programs in Non-Communicable Diseases and HIV/AIDS and TB. Many current and former FIC grantees and trainees are also engaged in U.S.-supported global health programs, including the President's Emergency Program for AIDS Relief (PEPFAR) and the President's Malaria Initiative (PMI).

For example, Fogarty is supporting advanced degree training for the Deputy Director for Research of the Joint Clinical Research Center (JCRC) in Uganda. JCRC is engaged in an extensive ARV treatment program, with support from the Global Fund and PEPFAR, for over 3,000 Ugandans who are currently on ARV and are being followed in one of Africa's largest treatment cohorts. The trainee is a co-investigator on this large cohort, which has the potential to answer critical questions regarding ARV use, adherence, resistance, and response in an urban East African treatment population.

Fogarty also supports training in clinical, implementation, operational and health services research at GHESKIO - the Haitian's government's central training center for the scale-up of HIV services in Haiti, supported through PEPFAR and Global Fund. In support of Haiti's national scale-up of HIV prevention and care services, Fogarty supports: 1) Short term training in HIV care and prevention and research methods; 2) A Masters in Public Health Program offered in collaboration with Quisqueya University; and 3) long-term practical training through the conduct of mentored implementation, operational and health services research projects.

Fogarty's International Malaria Clinical, Operational and Health Services Research Training Program (MICOHRTA) supports related research training only in PMI countries, and requires that grantees coordinate with PMI partners. For example, Uganda's MICOHRTA program at Makerere University is working with several partners, including the CDC and Ministry of Health. Under this award, PMI malaria program managers can receive training in program management, vector control, cost-effectiveness analysis and clinical research. In Malawi, MICOHRTA grantees are partnering with PMI, the Ministry of Health and the National Malaria Control Program to train District Health Management Team members in areas such as program management, monitoring and evaluation, and data for decision making.

Given the steep rise in chronic, non-communicable disease (diabetes, cardiovascular disease, cancer, etc.) in low- and middle-income countries, recent efforts include building research capacity in non-communicable diseases through the Millennium Promise Awards: Non-Communicable Chronic Diseases Research Training Program, as well as the expansion of the Fogarty International Clinical Research Scholars and Fellows Program into the area of non-communicable diseases. These efforts are intended to train a cadre of experts who can: assess the magnitude of diseases such as cancer, stroke, lung disease, and obesity as well as genetics, environmental factors, and lifestyle factors related to these conditions in low- and middle-income countries; perform research in chronic non-communicable diseases; and translate research into public health policy and into programs of care.

Senate Significant Items

Item

Depression -- The Committee urges the FIC to work with other institutes, particularly the NIMH, to combat the enormous worldwide incidence of depression. (p. 112)

Action taken or to be taken

Fogarty has a number of programs that invite projects addressing global mental health and depression through research and research training. We envision over the next several years building a strong alliance and partnership with the NIMH on global health and mental disorders.

NIMH was a strong partner at the inception of some of the programs. These include the original International Clinical, Operational, and Health Services Research Training Award Program focusing on non-communicable diseases and disorders; the Trauma and Injury Research Training Program; the Fogarty International Research Collaboration Awards Program (in both Basic Biomedical, and the Behavioral and Social Sciences); and the Brain Disorders in the Developing World Research Program.

Fogarty provided input to the NIMH Strategic Plan on Global Health. In addition, NIMH Director Dr. Thomas Insel described his vision for global mental health to the FIC Advisory Board in September 2009. NIMH has recently hired Dr. Pamela Collins as Director, Office for Special Populations & Office of Global Mental Health. She recently joined FIC Program Director Dr. Kathleen Michels in visiting research sites in Uganda after both participated in

a meeting convened by the Ugandan National Academy of Sciences and the U.S. Institute of Medicine on the quality of care for mental illness and neurological diseases and disorders in Sub-Saharan Africa.

Item

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Action taken or to be taken

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**National Library of Medicine
(NLM)**

Senate Significant Items

Item

Native Hawaiian Healthcare Resources- The Committee urges the NLM to work with Native Hawaiian organizations to provide support in the areas of biomedicine and healthcare. (p. 113)

Action taken or to be taken

NLM continues to work with the Native Hawaiian community to ensure access to high quality health information. In addition to work started previously, NLM is working with Papa Ola Lokahi (POL), a federally-funded non-profit, community-based organization, authorized by the Native Hawaiian Health Care Act of 1988 (PL 100-579), as amended, to develop a website on Native Hawaiian Health. This is being done at the request of POL. Previously NLM had supported POL to develop their own website and sites for the Native Hawaiian health systems on a number of the islands. Currently, this new site is under development and will become available to the public in late 2009. This is a collaborative activity and ongoing maintenance will be done jointly. NLM continues to work with the Native Hawaiians from POL who participated in NLM's Information Fellowship for Native Americans in 2004-2006.

One of the ongoing efforts involves the use of Geographic Information Systems (GIS) technology to map traditional Hawaiian factors with current health data. NLM has also refined and expanded its collection development policy to include materials related to traditional Hawaiian (and other Native American) health and healing practices. The Library also encourages the digitization and preservation of these materials by local institutions. In 2010, NLM is supporting implementation of an exciting new project developed by the Waianae Comprehensive Community Health Center that promises to fulfill a longstanding ambition to preserve the cultural heritage and teaching of Native Hawaiian healers, beginning with those elder Kupuna whose numbers are rapidly diminishing due to advanced age. Twenty to twenty-five elders and their students from throughout Hawaii will be interviewed and videographed. This unique digital record will be preserved, archived, and made accessible at the newly dedicated Native Hawaiian Healing Center in Waianae.

NLM has funded POL to work with the Miloli'i Native Hawaiian community (on the Big Island) to implement a satellite-based Internet connection to the Miloli'i community computer lab that will enable the community to increase knowledge about available health information. To highlight traditional Native health and healing practices, NLM is planning to mount a major exhibition on this topic in 2010. The Library has actively sought input and participation from Native tribes and communities in order to include personal statements in this exhibition. In 2009, the Library interviewed and video graphed for the exhibition 21 Hawaiian traditional healers and other health professionals.

Item

MedlinePlus Magazine- The Committee is pleased that NLM has expanded the distribution of NIH MedlinePlus magazine and recently began testing a new bilingual version of the magazine, NIH MedlinePlus Salud, with good results. The Committee calls on NLM to increase the distribution of these important sources of consumer health information to reach all physician offices, federally qualified health centers, hospitals, libraries and free-standing health clinics. (p. 113)

Action taken or to be taken

Health professionals and consumers alike benefit from access to free, timely, authoritative, and comprehensive sources of health information such as NIH MedlinePlus magazine. With assistance from other NIH components and outside partners, NLM continues to increase the distribution of the NIH MedlinePlus magazine. NLM will continue to expand the distribution of both the English and bilingual versions of the NIH MedlinePlus magazine in 2010. Distribution has increased from 50,000 copies of each issue in 2006 to a distribution of over 600,000 English and Spanish copies of the spring 2009 issues.

To broaden our audience, the NIH joined the NLM, the Friends of the NLM, and the National Alliance for Hispanic Health, in launching a Spanish version of the NIH MedlinePlus magazine in January 2009. The pilot issue of NIH MedlinePlus Salud, which was produced half in English and half in Spanish, featured Cuban American journalist Cristina Saralegui who is well known for her Univision talk show, the Cristina Show, as well as her work on behalf of health and wellness causes. NIH MedlinePlus Salud is the NIH's first general interest consumer magazine in Spanish. The 30-page compendium of the latest research from NIH and useful health tips for the public is distributed nationwide through doctors' offices, federally qualified health and community centers, clinics and hospitals, and medical libraries.

In addition to reaching Spanish-speaking populations, the NLM is partnering with other NIH Institutes and interested consumer organizations to increase the free distribution of both the English and Spanish magazine to the widest possible audiences. For example, in 2009, the NLM partnered with the American Diabetes Association and the PAD (Peripheral Artery Disease) Coalition, among others, to double the distribution of the magazine. To test new distribution outlets, beginning in November 2009, the NLM will partner with the Prince George's Hospital Center and its affiliate hospitals in Maryland to distribute the magazine to their patients at time of discharge via its hospital discharge planners.

**Office of the Director
(OD)**

House Significant Items

Item

Office of AIDS Research (OAR) - The Committee believes that NIH continues to be the world's leader in research to respond to the critical needs of the AIDS pandemic, both in the U.S. and around the world. The Committee commends NIH for supporting the NIH AIDS and non-AIDS funding allocation at the current relative rate and endorses the continuation of this policy. The Committee continues to endorse the importance of OAR, including its critical trans-NIH budget authority and its status as a unique "institute without walls" The Committee commends the Office for its leadership in setting trans-NIH AIDS research priorities, including important new basic science initiatives in the area of genomics, and its ongoing support for innovative research and community outreach to address the complex issues of AIDS in racial and ethnic minority populations in the U.S. (p. 131)

Action taken or to be taken

OAR operates as an "institute without walls" vested with responsibility to oversee and track all NIH AIDS-related research carried out in every NIH Institute and Center (IC), including extramural, intramural, domestic and international research and training, and RMS. OAR, unlike other OD offices, has construction authority as well as authority to transfer funds across ICs. OAR's unique authorities also include the development of an annual trans-NIH AIDS research strategic plan and trans-NIH AIDS research budget (in the Overview of this request) explicitly tied to the objectives of the strategic plan. These authorities allow the OAR to manage the trans-NIH AIDS research effort. The authorizing law provides that the OAR "shall receive directly...all funds available for AIDS activities of the NIH" for allocation to the ICs in accordance with the Plan. Subsequently, an agreement with Congress provided that rather than receiving a separate single appropriation, OAR would apportion each IC's AIDS research budget to be included within the IC total appropriation. It also was agreed that funding for AIDS and non-AIDS would grow at approximately the same rate; that is, as an "Institute without walls," AIDS research, as determined by the OAR, would receive the same increase as the other Institutes. Thus, AIDS research has historically represented approximately 10% of the total NIH budget. OAR develops each IC's allocation based on the scientific priorities of the Plan, scientific opportunities, and the IC's capacity to absorb and expend resources for the most meritorious science – not on a formula. This process reduces redundancy, promotes harmonization, and assures cross-Institute collaboration.

OAR's trans-NIH planning process, involving both government and non-government experts, results in the identification of clear, overarching AIDS-research priorities and specific research objectives and strategies. These priorities are aligned with and provide the scientific foundation for achieving the goals of the President's National AIDS Strategy. OAR identifies emerging scientific opportunities and public health challenges that require focused attention; manages and facilitates multi-Institute and trans-Institute activities to address those needs; fosters research by designating funds and supplements to jump-start

or pilot program areas; sponsors reviews or evaluations of research program areas; and facilitates domestic and international AIDS research, training, information dissemination, and community outreach, particularly to address the disproportionate impact of the epidemic on racial and ethnic populations in the United States.

Item

Amyloidosis - The Committee encourages NIH to continue to intensify its research efforts into amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. These diseases are often fatal and there is no known cure. Treatment involving large-dose intravenous chemotherapy followed by stem cell replacement or rescue is effective for many patients, but this procedure is risky, unsuitable for some patients, and not a cure. The Committee urges NIH to keep the Committee informed on the steps that need to be taken to increase the understanding prevention and treatment of this devastating group of diseases. (p. 132)

Actions taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) drafted a Program Announcement based on research priorities identified through prior workshops. Issuance of the announcement was delayed because of the ORDR “Rare Diseases Clinical Research Network” Request for Applications and the American Recovery and Reinvestment Act (ARRA) challenge grant opportunities.

This year, a randomized clinical trial of a small molecule inhibitor of amyloid fibril formation, identified in NIDDK-funded research, has shown promise in preventing clinical progression of transthyretin (TTR) amyloidosis. TTR amyloidosis is the most common hereditary form of amyloidosis, resulting in autonomic or sensory motor impairment including orthostatic hypotension, gastrointestinal abnormalities, carpal tunnel syndrome, inability to sweat, nephropathy, and urinary retention or incontinence and possibly hydrocephalus, dementia, psychosis, seizures, visual impairment, and ataxia. This study validates a promising new approach for the treatment of systemic amyloid diseases in general and TTR amyloidosis in particular.

In addition, the new NIH Undiagnosed Diseases Program at the NIH Clinical Center hospital supported by ORDR, the National Human Genome Research Institute, and the Clinical Center works to provide diagnoses to patients with previously undiagnosed conditions and advance medical knowledge about novel rare and common diseases. Recently, a patient was accepted into the program seeking an evaluation after receiving a tentative diagnosis of amyloid light-chain amyloidosis that causes protein build-up in tissues. The program referred the patient to the Mayo Clinic for a successful, life-saving stem cell transplant.

Item

Basic Behavioral Research – The Committee is pleased that the NIH leadership has launched an initiative to develop a basic behavioral research blueprint modeled after the Neuroscience Blueprint to help ensure funding of the basic behavioral research necessary to advancing and improving health outcomes. The Committee notes that an April 2008 report from NIH indicated that basic behavioral research is funded in 13 of the 27 NIH

institutes and centers. The Committee continues to be concerned, however, that the NIH, after many years of encouragement from this Committee, has not assigned scientific leadership for this research portfolio to an appropriate institute or center, such as the NIGMS. (p. 132)

Action taken or to be taken

Basic behavioral research is encompassed in the missions of all NIH Institutes and Centers (ICs). NIH fosters collaborations that span all of the traditional and emerging disciplines of the life, physical, engineering, computer behavioral and social sciences. Under the existing scientific leadership structure for basic behavioral and social science research at NIH, 21 ICs, the Office of the Director and the Common Fund provided support for this research in fiscal year (FY) 2008. This information was included in the April 2008 NIH report, not the number 13 erroneously reported above. NIH believes that this leadership structure, coordinated through the Office of Behavioral and Social Sciences Research (OBSSR) in the Division of Program Coordination, Planning, and Strategic Initiatives, remains the optimal structure for supporting basic behavioral research at the NIH.

The National Institute of General Medical Sciences (NIGMS) supports bBSSR and training related to its mission areas. This investigator-initiated research is supported through the following centers/divisions: Bioinformatics and Computational Biology; Genetics and Developmental Biology; Minority Opportunities in Research; and Pharmacology, Physiology and Biological Chemistry. Supported research activities include: (1) basic behavioral research in model organisms; (2) computational modeling of human populations including behavioral and social factors; (3) studies of the efficacy of interventions in promoting research careers; (4) support of a range of behavioral and social sciences research at minority-serving institutions; and, (5) predoctoral training at the interface between behavioral and biomedical sciences.

Moreover, NIGMS continues to explore the potential for new directions in its funding of basic behavioral and social sciences research. NIGMS's Director, Dr. Jeremy Berg, has met with scientific organizations in the behavioral and social sciences to discuss perspectives on needed advances in basic research. NIGMS, in collaboration with OBSSR, also held a conference on "Modeling Social Behavior" that reviewed basic behavioral and social science research on interpersonal and collective behaviors and identified opportunities, challenges, and gaps in knowledge needed to develop useful models of social behavior.

In October 2009, the NIH established a new initiative to accelerate and expand basic behavioral and social sciences research. The NIH Basic Behavioral and Social Science Opportunity Network (OppNet) will identify common IC interests in the basic behavioral and social sciences and support new research through targeted initiatives. Under the leadership of Drs. Jeremy Berg of NIGMS and Richard Hodes of the National Institute on Aging and facilitated by OBSSR, OppNet will target those basic research challenges that are best met collectively. Funding for OppNet activities in its first year will be provided under the American Recovery and Reinvestment Act (ARRA) at an estimated \$10 million in FY 2010.

Item

Bioethics Research and Training Initiative - The Committee provides \$5.0 million for the new bioethics research and training initiative proposed in the budget request, but funds it throughout the institutes and centers rather than in the Office of the Director. The Committee believes it is important to have each NIH entity engaged in the bioethics effort. However, the Committee expects the Office of the Director to maintain central oversight of this initiative. (p.130)

Action taken or to be taken

Funding for bioethics research and training supports the identification and exploration of ethical questions raised by scientific advances and technological developments. Bioethics research and training inform the conduct of biomedical and behavioral research; the development and use of new technologies; and the introduction of research findings into clinical practice and public health. It helps inform the development of rational science and public health policies and sustains public trust and confidence in science.

NIH's interest and commitment to bioethics research and training are longstanding. In recent years, NIH has been exploring ways of enhancing its engagement in bioethics. In 2007, an extramural policy working group carried out an analysis of bioethics training needs and articulated specific goals and an expanded role for NIH in supporting bioethics training. In 2009, the Acting Director of NIH formed a task force to develop a short-term agenda for bioethics research and training and, with input from the public, a strategic plan for the future that assures the integration of bioethics across the research spectrum, from basic research to the translation of clinical findings into practice. The task force is composed of representatives from the NIH Institutes and Centers (ICs) and components of the Office of the Director (OD). The task force is also formulating a plan for spending FY 2010 bioethics research and training funds. The plan, which will be submitted to the NIH Director and IC Directors for consideration, will focus on both bioethics research and bioethics training. Funds will be awarded through the ICs, and the OD will maintain central oversight.

Item

Celiac Disease — The Committee recognizes that celiac patients are at dramatically increased risk of developing many other serious and fatal conditions including neurological problems, cancer, and autoimmune disorders including type 1 diabetes, thyroid and liver disease. The committee encourages the Director to develop an agenda for basic and clinical research for the treatment of celiac disease and to consult with patient stakeholder organizations when considering the development of the research agenda. (p. 136)

Action taken or to be taken

NIH is aware of the serious risks that exist for patients with celiac disease. These risks were vividly demonstrated in a recent research study of undiagnosed celiac disease and its consequences, supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The study revealed that Air Force personnel with undiagnosed celiac disease had higher death rates over the past 50 years than healthy individuals. The study also demonstrated that undiagnosed celiac disease has increased more than four-

fold over the past 50 years, echoing the acute need for greater awareness of celiac disease, as established by the panel of experts from the Celiac Disease Consensus Development Conference sponsored by the NIDDK and the NIH Office of Medical Applications of Research. In response to recommendations made by the panel, NIDDK launched the Celiac Disease Awareness Campaign in 2006. The Campaign is successfully meeting its goals of providing current, comprehensive, science-based information about the symptoms, diagnosis and treatment of celiac disease to health professionals and the public. Celiac disease and type 1 diabetes are autoimmune diseases that share susceptibility genes. An ancillary study to “The Environmental Determinants of Diabetes in the Young” (TEDDY) project, which is monitoring newborns with genetic risks for diabetes for a period of 15 years, is being supported by NIDDK. This study is expected to provide significant information regarding the long-term effects on children who are also at risk for celiac disease.

NIH’s support of celiac disease research is in concert with the recommendations of the National Commission on Digestive Diseases (<http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/FinalResearchPlanPosting.htm>). For example, special one-time funding from the NIH Office of the Director has been awarded to conduct a genome-wide association study in celiac disease. This study is expected to identify important genes and genomic regions that increase susceptibility to celiac disease, providing scientists with greater knowledge of this complex disease that could lead to therapeutics to reduce the diet restrictions and morbidity for patients with celiac disease. An Intestinal Stem Cell Consortium is being established by NIDDK and the National Institute of Allergy and Infectious Diseases. The Consortium will increase research on stem cells that are responsible for forming the lining of the intestine. Greater understanding of these cells and how they function is expected to aid in the development of therapies for intestinal diseases, such as celiac disease, where regeneration of damaged cells that compose the intestinal lining is an important component of the healing process.

Item

Chromosome Abnormalities –The Committee urges the NIH to convene a state-of-the-science meeting on chromosome abnormalities involving multiple contiguous genes, for the purpose of creating a plan to collect data regarding dosage-sensitive and dosage-insensitive genes, and to establish phenotyping and genotyping standards for data collection. The Committee also encourages the NIH to create funding mechanisms to support independent investigators whose work could provide pilot data or insight into future directions for the study of chromosome abnormalities, particularly those involving chromosome 18. (p. 104)

Action taken or to be taken

Since its inception, research on chromosomal abnormalities and the resulting developmental and health conditions of affected individuals has been a core part of the NICHD’s mission. These abnormalities, which can include trisomy (an abnormality characterized by an additional chromosome), mosaicism (a condition in which an organism or part of an organism is composed of two or more genetically distinct tissues), or chromosome rearrangements, cause approximately 20 percent of intellectual disabilities.

The Institute continues to support research efforts targeted toward understanding the causes and treating or ameliorating these conditions, which include Down syndrome, Prader-Willi syndrome, Angelman syndrome, Fragile X syndrome and disorders of chromosome 18.

The NICHD supports a wide range of grants in these areas through a number of different funding mechanisms, from small business research grants to investigator-initiated grants to program projects. Current grants include biomedical and biobehavioral grants, as well as longitudinal natural history studies (Prader-Willi and Angelman syndromes). Several investigators have been funded to look at single genes within the phenotype that contribute to the condition. The NICHD also is supporting a large grant with ARRA funds to obtain high quality, standardized data on “copy number variations” (small regions of genomic difference) that will be linked to clinical information from large populations, with the goal of providing clinicians with information on whether these small chromosomal differences have functional significance. The data from this study will be used to produce standard vocabularies and data dictionaries, and create a data repository that will become available to clinicians and investigators nationwide.

The NICHD also sponsors numerous scientific conferences and workshops, such as the World Congress on Chromosome 18, held three years ago to bring researchers in a given field together to share their findings and explore possible collaborations. In addition, the Institute recently led two trans-NIH planning efforts to develop research plans for Down syndrome and Fragile X syndrome. After extensive public input, each will serve to guide the NICHD’s and other interested Institutes’ research activities for the next several years.

Item

Conflict of Interest-Extramural--The Committee is encouraged that NIH has issued an advance notice of proposed rulemaking as a first step in responding to the Committee's directive in fiscal year 2009 to develop a conflict of interest policy for extramural grantees, both institution administrators and scientists. The Committee understands that the comment period- on the advance notice has just ended. It urges NIH to rapidly review the comments received and take the next steps to develop a robust extramural- conflict of interest policy. It is clear from reports of continued abuses that NIH policy must be strengthened to deal with the increasing complexity of public-private interactions in biomedical research. (p. 113)

Action taken or to be taken

The NIH believes that it is vital to maintain objectivity in research and that all research must be conducted with the highest scientific and ethical standards and in a manner that assures the integrity of the scientific record. The NIH takes its responsibilities in this area very seriously and is committed to preserving the public trust in objective scientific research. On May 8 2009, NIH published an Advance Notice of Proposed Rulemaking (ANPRM) seeking public comment on whether the HHS should amend its regulations on the responsibility of applicants for promoting objectivity in research for which PHS funding is sought (42 CFR Part 50 Subpart F and 45 CFR Part 94). The public comment period closed on July 7, 2009. The ANPRM asked for public comment on whether the regulations

should be amended to strengthen NIH oversight and Institution's management in six broad areas:

- Expanding the scope of the regulation and disclosure of interests
- Definition of "significant financial interest" (SFI)
- Identification and management of conflicts by Institutions
- Assuring Institutional compliance
- Requiring Institutions to provide additional information
- Defining Institutional conflict of interest

Since the NIH is revising the regulation on behalf of the Department of Health and Human Services (HHS) and the Public Health Service (PHS), the new regulation must include input from all relevant HHS offices and agencies. This process extends the time it takes to clear the new regulation and may result in a short delay in the anticipated schedule.

Proposed Schedule:

Sep-Nov 2009: Trans-NIH committee considers the responses to the Advance Notice of Proposed Rulemaking (ANPRM) and drafts proposed revisions to the regulations.

Dec 2009-Jan 2010: A Notice of Proposed Rulemaking reviewed and cleared by all relevant HHS offices and agencies, and by OMB.

Feb 2010: Notice of Proposed Rulemaking published in the Federal Register for 60 day public comment period.

April-May 2010: Comments analyzed and final regulations drafted.

June 2010: Final regulations reviewed and cleared by all relevant HHS offices and agencies, and by OMB.

July 2010: Final regulations published.

Item

Fragile X - The Committee commends the NIH for developing the NIH Research Plan on Fragile X Syndrome and Associated Disorders. The Director is encouraged to dedicate sufficient resources to implement this plan with the guidance of the recently established Fragile X Research Coordinating Group, and in collaboration with the NICHD Fragile X Research Centers, as well as the Fragile X Clinical and Research Consortium. Priorities should include clinical trials of therapies for treatment of Fragile X syndrome and translational research that shows significant promise of a safe and effective treatment for Fragile X syndrome and associated disorders. The Committee congratulates the NIH and its private foundation partners for providing a Small Business Innovation Research grant to fund fragile X drug development, and it encourages more efforts of this kind. Finally, the Committee urges the NIH, working with the Fragile X Clinical and Research Consortium, to convene a consensus conference on translational research opportunities in fiscal year 2010. (p. 117)

Action Taken or to be Taken

The NIH Fragile X Research Coordinating Group (FXRCG), led by NICHD, and including nine NIH Institutes and Centers, has continued to work collaboratively to facilitate research in the area of Fragile X syndrome and the associated disorders of Fragile X-associated

Tremor/Ataxia Syndrome (FXTAS) and Fragile X-associated Premature Ovarian Insufficiency (FXPOI) across the NIH. The group meets on an ongoing basis to discuss implementation of the *Research Plan on Fragile X Syndrome and Associated Disorders*. Currently, each goal area of the report is being addressed by grants funded across the member Institutes that address one or more specific research objectives: (1) advancing the understanding of the pathophysiology of Fragile X; (2) improving appropriate and timely diagnosis of individuals with Fragile X; (3) validating and using functional measures of the manifestation of Fragile X across the life span; (4) initiating a broad-based program of research on the efficacy of treatments for Fragile X; (5) advancing understanding of the ramifications of Fragile X for families; and (6) creating a Fragile X research infrastructure and resources. The Coordinating Group also is exploring methods to further stimulate research in the associated disorders of FXTAS and FXPOI.

In early 2010, the NICHD, in collaboration with NINDS, NIMH, the Office of Rare Diseases (ORD), and other NIH offices, will hold a multidisciplinary scientific meeting to evaluate cognitive, behavioral and physical outcome measures for use in clinical trials in individuals with Fragile X. Participants will include clinicians who treat children with Fragile X, researchers with experience in clinical trials of pharmaceuticals with children with Fragile X, representatives from the Food and Drug Administration, and other outside experts. The meeting will focus on identifying core measures and instruments in existence that can be effectively used to assess Fragile X treatments, and what further development is required. As progress continues in translational research to develop treatments for Fragile X, this meeting is an important forum to bring knowledge from a variety of disciplines together and applying the knowledge to facilitate clinical trials

Item

Gender Differences – For many disorders, the gender of the patient influences disease etiology, natural history, diagnosis and treatment alternatives and outcomes. The Committee encourages each of the institutes involved in the NIH Neuroscience Blueprint to carefully analyze their Neuroscience Blueprint research portfolio to ensure that gender is included as a variable, when appropriate, and to require that all reported results include gender-specific analysis. (p. 121)

Action taken or to be taken

The NIH Blueprint aims to catalyze research progress by funding the development of tools and resources that enable neuroscience research. Recently, Blueprint has started funding scientific “grand challenge” projects that may provide new insight into sex-based differences. The 15 Institutes and Centers (ICs) of the NIH Blueprint for Neuroscience Research recognize the importance of sex and gender in studies of the nervous system. As required by law (PL103-43), NIH mandates that women and minorities be included in all of its clinical research studies and that sufficient numbers are included for valid analyses in all Phase III clinical trials. Research from all Blueprint ICs analyzes results by sex or gender when appropriate.

In July 2009, Blueprint launched the five-year Human Connectome Project (HCP), an initiative designed to develop and share knowledge on how the cells and structures of the human brain communicate with each other. This project aims to combine cutting-edge,

non-invasive imaging technologies to acquire data about neural connections from brains of hundreds of healthy adults. Demographic data (including sex) and data regarding sensory, motor, cognitive, emotional, and social function will be collected, as will DNA samples and blood. Through this project, communities of scientists will be able to better understand how sex/gender influences structure, function, and connectivity of the human brain.

Transgenic mice generated and distributed with Blueprint funds may also contribute to molecular and behavioral studies of sex differences. The Blueprint has made existing mouse models easily accessible through a central repository. The Blueprint also helps fund the Gene Expression Nervous System Atlas (GENSAT) project, which includes the generation of mice that produce visible fluorescent signals wherever and whenever a particular gene is expressed. One study that has taken advantage of a marker mouse line from the GENSAT project mapped brain pathways involved in sex-specific reproductive and defensive behaviors in mice.

Several Blueprint clinical research tools may facilitate analysis according to sex/gender. The NIH Pediatric MRI Study of Normal Brain Development is collecting images of the brain throughout development in order to provide reliable control data for studies of childhood disorders and diseases that affect the brain, and it may aid in the development of new diagnostic tools. The project includes both girls and boys and could be a powerful tool for exploring sex/gender differences in brain structures during development.

In addition to Blueprint-supported tools and resources, subsets of Blueprint ICs have participated in announcements to stimulate research that addresses sex differences. For example, Blueprint ICs have joined the Office of Research on Women's Health in supporting research that will provide scientific knowledge related to sex/gender differences on several chronic pain conditions that are more prevalent in women than in men, such as migraine, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and interstitial cystitis.

Item

Glomerular Disease — The Committee is aware of opportunities to increase collaborative research efforts regarding the glomerular disease Focal Segmental Glomerulosclerosis (FSGS) and encourages ORD to consider FSGS for inclusion in its Rare Disease Clinical Research Consortia Program. (p. 114)

Action taken or to be taken

NIH has established a Nephrotic Syndrome Rare Disease Clinical Research Network. It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy. The researchers will investigate the underlying disease mechanisms and assess the responsiveness of these diseases to various treatment approaches. This Consortium will provide a readily accessible research and education resource that will significantly advance the study, classification, characterization, diagnosis, and treatment of these diseases. It will also bring clinical and translational scientists together with lay research and patient foundations to educate patients with these diseases.

The Rare Diseases Clinical Research Network, sponsored by the NIH Office of Rare Diseases Research in conjunction with multiple NIH Institutes and Centers, facilitates the identification of biomarkers for disease risk, disease severity and/or activity, and the identification of measures of clinical outcomes appropriate for applicability to clinical trials. It encourages the development of new approaches to diagnose, prevent, and treat rare diseases.

Item

Hereditary Hemorrhagic Telangiectasia (HHT) - The Committee encourages NIH to establish a trans-institute research group to coordinate implementation of research recommendations identified at the 2006 NIH HHT conference, with a particular focus on understanding the cause, diagnosis, prevention, and treatment of HHT.

Action taken or to be taken

The NIH has already made strides toward implementing recommendations of the 2006 HHT meeting, which was a trans-NIH workshop sponsored by the NHLBI in concert with NHGRI, the Office of Rare Diseases Research (ORDR), and the HHT and Grace Nolan Foundations. One of the most promising opportunities for HHT research that was identified during the workshop is investigation of the molecular mechanisms and signaling pathways involved in the vascular abnormalities observed in HHT. Two gene defects have been identified in patients with HHT, one in the gene associated with the protein endoglin and the other in a gene related to activin receptor-like kinase 1. A number of interesting mouse models and genetic tools relevant to this research have also been generated. This research holds much promise for generating a better understanding of the cause of the disease and improving diagnosis and treatment in the future. The NHLBI is pleased to be advancing this area via support of two investigator-initiated grants that employ the models and tools to elucidate the role of these genes in the onset of HHT. Investigator-initiated grants related to HHT are also being supported by other NIH components. The ORDR and NINDS recently co-funded the Brain Vascular Malformation Consortium as part of the NIH Rare Diseases Clinical Research Network. This group will study several types of brain diseases affecting the development of brain blood vessels, including HHT. Possible future initiatives that address vascular diseases are also expected to provide opportunities for trans-institute coordination.

Item

Irritable Bowel Syndrome (IBS) - The Committee is pleased with the increased focus on IBS at ORWH and encourages the Office to continue strengthening research on this prevalent functional gastrointestinal disorder. (p. 130)

Action taken or to be taken

NIH and ORWH thank the Committee for recognizing its efforts on interdisciplinary research on IBS. The Committee can be assured that additional research is being conducted to stimulate research with a focus on the basic and clinical studies to improve causes and treatment of IBS.

The ORWH led the development and implementation of the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) program at the Center for Neurovisceral Sciences and Women's Health (CNS/WH) at the University of California, Los Angeles. The objectives of this research are to understand the interplay of gut and brain pathways; design effective treatments and examine sex and gender differences. Basic and clinical studies done at this SCOR Center have resulted in collaboration with several pharmaceutical companies to develop and evaluate novel pharmacological treatments for several conditions including IBS, depression, anxiety, and stress disorders.

On behalf of NIH, NIDDK led the National Commission on Digestive Diseases, in partnership with ORWH, which offered several recommendations in the area of functional gastrointestinal diseases and motility disorders including IBS. NIDDK is positioned to implement these recommendations by encouraging investigator-initiated research applications (RO1s) that explore the basic mechanism of IBS, which include brain – gut interactions, alterations in the enteric system, and neurohormonal influences on gut function. <http://www2.nidDK.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/>

NIDDK, in collaboration with the ORWH and other NIH ICs, has promoted research discussions via scientific conferences and symposia that offer the opportunity to foster team science. These activities have led to cross talk among scientists in addressing the pathophysiology of IBS as well as therapeutic approaches in the management of patients with IBS.

The NIH Pain Consortium, a Trans-NIH interdisciplinary program, was established to enhance pain research across a range of diseases and conditions and promote coordinated collaboration among NIH ICs with research programs and activities addressing pain. IBS is among the chronic pain syndromes included in the Pain Consortium, and several neuroscience research initiatives have been undertaken

Item

Lyme Diseases - The Committee encourages NIH to intensify research on tick-borne diseases, including research that will increase understanding of the full range of Lyme disease processes and the physiology of *Borrelia burgdorferi*, including the mechanisms of persistent infection. Recognizing NIH's collaborative role with CDC and other agencies in the development of diagnostics, the Committee encourages NIH to support research that may lead to the development of more sensitive and accurate diagnostic tests for Lyme disease capable of distinguishing between active and past infections. The Committee encourages the Director, in collaboration with the Director of NIAID, to sponsor a scientific conference on Lyme and other tick-borne diseases. The Committee believes that the conference should represent the broad spectrum of scientific views on Lyme disease and should provide a forum for public participation and input from individuals with Lyme disease. (p. 134,135)

Action taken or to be taken

Research on Lyme disease and other tick-borne diseases remains a priority for NIAID. The Institute supports a broad range of investigator-initiated research as well as intramural research aimed at understanding the basic biology of *Borrelia burgdorferi*, the mechanisms by which this bacterium causes Lyme disease, and the interactions between *B. burgdorferi* and its tick vectors. Using mouse models, NIAID-supported researchers are also examining the mechanisms of persistent *Borrelia* infection, including studies of antibiotic efficacy in persistent infections, and of how the *Borrelia* bacteria evade the immune system. In addition, NIAID physicians at the NIH Clinical Center are conducting clinical studies to increase our understanding of Lyme diagnosis, clinical manifestations, and immune responses. These studies include patients with the full spectrum of Lyme-associated illness, including classical Lyme disease and post-Lyme disease syndrome.

There is a great need to develop additional simple, sensitive, and rapid procedures to distinguish those who are actively infected with *B. burgdorferi* from those who have either recovered from a previous infection or have been immunized previously. To address this need, NIAID supports a diverse applied research portfolio aimed toward the development of new, more sensitive and accurate diagnostic tests. For example, through Small Business Innovation Research grants, NIAID is supporting the development of improved peptide antigen assays to detect *Borrelia* infection and other diagnostics technologies using *in vivo* expression of *Borrelia* antigens. NIAID scientists are also working to develop better serological tests to detect infection with *Borrelia* and related bacteria. More recently, with ARRA support, NIAID funded multiple new projects including one designed to study the persistence of *Borrelia* infection after antibiotic treatment in humans.

The Institute is planning to host a scientific workshop in the spring of 2010 to review current challenges in the diagnosis of Lyme disease. Experts from the private sector, academia, and government will identify potential research opportunities to develop more sensitive and accurate Lyme disease testing.

NIAID appreciates the Committee's support for a scientific conference on Lyme disease and other tick-borne diseases and is working with other Institutes and Centers at the NIH to coordinate such a scientific conference that comprehensively addresses Lyme disease and associated syndromes.

Item

Lymphatic Research and Lymphatic Disease - The Committee urges NIH to begin to implement the recommendations of the trans-NIH working group on lymphatic research. The Committee encourages NIH to work toward the creation of centralized core facilities for: (a) experimental molecular and diagnostic lymphatic imaging; (b) the development and standardization of research reagents; and (c) the generation of virtual networks to facilitate basic, translational, and clinical research. (p.135)

Action taken or to be taken

Considerable progress has been made toward implementing the recommendations of the 2007 Trans-NIH Working Group Meeting on Lymphatic Research. In March 2009, Dr. Raynard Kington submitted the report "Research on Lymphatic Diseases," in response to

Senate Report 110-140 requesting a comprehensive update on NIH short and long-term plans to advance research on the lymphatic system and lymphatic diseases. Many of the recommendations of the Working Group currently form the basis of ongoing extramural research supported by NIH grants and research conducted in the NIH intramural program, including quantitative and molecular imaging of lymphatic function, generation of new animal models, and identification of biomarkers for lymphatic research. Three examples that are either active or completed and may lead to an initiative or even in additional research directions: [1] Currently active Program Announcement: PAR-07-420 “Lymphatic Biology in Health and Disease”; [2] NIDDK working group “Lymphatics in the Digestive Systems, Physiology, Health and Disease” November 3-4, 2009; [3] NIH Research Festival 2009, Symposium “Lymphatic Biology and Disease: The Cinderella of the Vascular System finally gets Invited to the Ball”.

Nearly all of the studies supported by NIH grants derive from the four initiatives released during the last eight years at the behest of the Trans-NIH Coordinating Committee for Lymphatic Research. This year the Committee has been actively engaged in developing ideas for novel approaches to interest and train established and new vascular biologists in lymphatic research. In addition, NHLBI has established patient registries and lymphatic tissue banking. The NHLBI’s expert consultant in lymphatic diseases, hired through the Intergovernmental Personnel Act, contributes to these discussions and provides critical insight on areas of need in lymphatic biology and treatment of lymphatic diseases.

Item

Minority Institutions - The Committee continues to be pleased with the NIH Director’s implementation of various programs focused on developing the research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions and the programs sponsored by NCMHD. The Committee encourages the Director of NIH to work closely with the Director of NCMHD to establish a program of coordination among these various mechanisms and partner with minority health professions schools to address their infrastructure needs. (p. 135)

Action taken or to be taken

The NIH is committed to strengthening the research infrastructure and capacity at minority health professions institutions as evidenced by the NIH Health Disparities Strategic Plan and Budget, which identifies three goals. The goals are: 1) Research; 2) Research Infrastructure and 3) Community Outreach i.e. information dissemination and public health education. Goal #2 focuses on research infrastructure which includes expanding research training opportunities and career development for research investigators from racial and ethnic minority populations and enhancing the ability of institutions to conduct health disparities research. Accordingly, the strategic plan will continue to be used as a mechanism to foster coordination and collaboration among the Institutes and Centers to develop and expand programs aimed at strengthening the research infrastructure of minority health professions schools.

Research Infrastructure programs at the NCMHD and the NCCR are among the NIH programs making strides to strengthen the capacity at minority health professions schools. For example, the NCMHD RIMI program is aimed at establishing, strengthening and/or

improving the scientific infrastructure and environment of academic institutions such as Tougaloo College which has recently added state-of-the art equipment to the existing biomedical research infrastructure; new faculty; a “Distinguished Faculty Seminar Series,” and two new undergraduate research/science courses with RIMI funding. The NCMHD Research Endowment Program provides grants to build research and training capacity at institutions to facilitate health disparities research. Meharry Medical College for example, has developed a cancer biology endowed chair program to support and offer cancer research opportunities for several researchers focusing on areas such as breast and lung cancer. This program will help to strengthen the institution’s cancer disparities research portfolio, and through its research, add to the scientific knowledge base to better understand and address cancer health disparities.

The NCRR and NCMHD partnership through the NCRR Research Centers in Minority Institutions program supports the RCMI Translational Research Network (RTRN), and a Data and Technology Coordinating Center (DTCC) which provides physical infrastructure, personnel, and processes that facilitate multi-site clinical and translational research in areas with the highest level of disparities related to health access and outcomes. The University of Hawaii coordinates the six disease-based research clusters which focus on cancer and immunological disease, cardiovascular diseases, obesity and metabolic disorders, community-based participatory research, neurology and mental health disorders, and HIV/AIDS and infectious diseases. The DTCC of the RTRN was established at Jackson State University in Jackson, Mississippi. One example of RTRN research is a pilot project that will study the effect of vitamin D3 on cardiovascular risk factors and function. Enrollment of the randomized control trial began in July 2009. This project is establishing a template for implementing processes and tools that can be used in future studies to decrease the time between protocol approval and study start-up. The RTRN has also established a small grants program which provides funding for projects that promote interinstitutional, interdisciplinary translational research and a total of six awards of \$50,000 each were made in 2009.

Item

Mitochondrial Disease — The Committee is aware that the study of mitochondrial disease and dysfunction presents a number of unique research challenges and opportunities. The Committee expects that the Director will continue to treat mitochondrial disease research as a high priority area within the resources provided in the Common Fund, including through expanded efforts to advance fundamental understanding of mitochondrial function and variation, improved detection and analysis of mitochondrial proteins, and the accelerated application of systems biology and computational modeling approaches. The Committee also requests the Director to work to coordinate and promote mitochondrial disease research across the numerous appropriate institutes and centers and, in particular, that the Director review and consider implementing recommendations developed by the NHLBI’s Working Group on Modeling Mitochondrial Dysfunction. (p. 135)

Action taken or to be taken

The NIH has taken a leadership role in research and education for mitochondrial disease and dysfunction and sponsored a number of activities in recent years to advance this science.

The NIH Common Fund supports programs that have broad overarching goals and do not specifically focus on particular diseases, although the individual projects that make up the large programs may have specific disease relevance. Consequently, the Common Fund supports a wide range of research topics related to mitochondrial function and disease — basic mechanistic studies; translational research to identify new targets for drug development; and development of new tools, technologies, and approaches to study mitochondrial function in living systems. In FY2009, basic mechanisms underlying mitochondrial contribution to aging, neurodegenerative disease, diabetes, and cancer were addressed through the Transformative R01 and Epigenomics Programs to support exceptionally innovative, high-risk, original and/or unconventional research projects. Several projects funded through the Molecular Libraries and Imaging Program focused on the development and application of high-throughput screening approaches to identify chemical compounds that can correct for defects in mitochondrial metabolism and biogenesis, potentially leading to new therapies for mitochondrial diseases. Although the specific portfolio of grants funded through the Common Fund revolves, this type of support for mitochondrial biology is expected to continue. The Director will continue to work to coordinate and promote mitochondrial disease research across the NIH Institutes and Centers, as appropriate.

Item

Mitochondrial Disease - The Committee applauds NHLBI for its work to support improved understanding of the role of mitochondrial dysfunction in cardiovascular illness, including through a recent request for applications. The Committee is aware that NHLBI has held working group and other meetings related to mitochondrial dysfunction and cardiovascular disease that have identified opportunities to strengthen mitochondrial research through steps such as adopting a systems biology approach, promoting cross-disciplinary research collaboration, and developing improved tools and models. The Committee requests that NHLBI move forward to implement these identified opportunities (p. 135)

Action taken or to be taken

The NHLBI convened several working groups to discuss current advances in the understanding of mitochondrial biology in cardiovascular health and disease in order to explore the application of new therapeutics targeting mitochondrial function to modulate cardiac risk factors and treat cardiovascular disease. To implement opportunities identified in working groups, the NHLBI recently solicited applications for multidisciplinary teams utilizing a systems approach to study cardiomyocyte mitochondria and their metabolic, genetic, and molecular contributions to myocardial adaptations and heart disease progression.

Item

Mitochondrial Disease — The Committee is aware that more than one in 4,000 children born in the U.S. each year will develop a mitochondrial disease by ten years of age. The Committee therefore encourages NICHD to increase its research commitment in the area of mitochondrial disease and to utilize the National Children's Study as a vehicle for research into the epigenomics, incidence and pathology of mitochondrial disease. (p.135, 136)

Action taken or to be taken

As currently planned, the National Children's Study is a large, longitudinal study to examine the environmental and genetic influences on human growth, development, and health outcomes. Its vanguard (in seven sites around the country) is conducting preliminary work to assess the feasibility, acceptability, and cost of the various procedures and data collections being considered for the main study. When this work has been completed, a determination will be made about the hypotheses to be addressed and the range of study assessments to be included. Collectively, these projects provide a multi-faceted approach to mitochondrial disease and exemplify the manner through which the NIH Common Fund and Institute monies support board/specific topics.

Item

Nontuberculous Mycobacteria-NTM - The Committee commends the NIAID for its planning meetings regarding NTM, outreach to the NTM patient community, and leading NTM treatment center. The Committee recommends further collaboration with the NHLBI, CDC, the advocacy community and other Federal agencies to provide leadership that will enhance diagnostic and treatment options as well as medical and surgical outcomes through the stimulation of multi-center clinical trials and promotion of health care provider education. (p. 98)

Action taken or to be taken

In 2009, an NIAID-led research team analyzed hospital discharge data to estimate the prevalence of pulmonary nontuberculous mycobacteria (NTM) hospitalizations and concluded that NTM is an increasing cause of illness in the United States, particularly among women in certain geographic areas. NIAID researchers and collaborators had previously conducted a multi-year study of risk factors associated with NTM which found that pulmonary NTM patients were primarily Caucasian women over 60 years old and that susceptibility to pulmonary NTM infection is likely inherited.

NIAID remains committed to basic and clinical research on NTM to improve the understanding, diagnosis and treatment of NTM infections. As a part of this commitment, NIAID continues to advance diagnostic and treatment protocols for NTM and to promote collaborative efforts to increase the understanding of NTM. For example, NIAID currently supports a clinical trial planning grant to establish an NTM Research Consortium (NTMRC) and to design a Phase II trial to re-assess the safety, tolerability, and efficacy of the standard three-drug treatment regimen for previously untreated patients with pulmonary *Mycobacterium avium* complex (MAC) infection. MAC accounts for over 75 percent of pulmonary infections caused by NTM. The NTMRC will include clinical sites that care for many NTM patients as well as highly experienced microbiological reference laboratories experienced in NTM culture and identification. The planning grant should allow researchers to finalize the protocol and complete the regulatory and administrative requirements for the Phase II trial.

NIAID intramural researchers remain central collaborators in the NTM consortium and continue in their efforts to understand NTM prevalence and disease. For example, researchers are studying airway epithelial cell dysfunction and its role in predisposition to

bronchiectasis, the critical underlying factor in pulmonary NTM infection. They are also studying the role that innate immunity plays in determining susceptibility to mycobacterial infections. Working closely with NHLBI, other NIH colleagues, and collaborators from other federal agencies and the extramural community, NIAID researchers continue to elucidate the underlying causes of NTM infection in order to guide the development of new therapeutic strategies.

NIAID continues to support research that may lead to more effective and accepted prophylactic and therapeutic approaches for preventing and controlling respiratory infections and strongly encourages researchers to submit grant applications on NTM. In addition, NIAID is assisting the research community by including NTMs in its reagent support contracts and is planning to expand all TB-specific research resources to include NTM and other non-TB organisms. NIAID continues to be actively engaged with the NTM advocacy community and is planning a workshop on natural history of NTM pulmonary infections in FY 2010- 2011. NIAID is collaborating with the research community on providing services for whole genome sequencing of major NTM pathogens.

Item

Neurofibromatosis (NF) - NF is an important research area for multiple NIH Institutes. Recognizing NF's connection to many of the most common forms of cancer, the Committee encourages NCI to strengthen its NF research portfolio in pre-clinical and clinical trials by applying newly developed and existing drugs. The Committee also encourages NCI to support NF centers, virtual centers, SPORE programs, pre-clinical mouse consortia, patient databases, and tissue banks, and to coordinate with other NIH institutes and government agencies in doing so. The Committee also urges additional focus from NHLBI, given NF's involvement with hypertension and congenital heart disease. The Committee encourages NINDS to continue to aggressively explore NF's implications for conditions such as spinal cord injury, learning disabilities and memory loss. In addition, the Committee continues to encourage NICHD to expand funding of clinical trials for NF patients in the area of learning disabilities, including the creation of NF centers involved with treating and curing these disabilities. NF can result in deafness; the Committee therefore encourages NIDCD to expand its NF research portfolio. (p. 136)

Action taken or to be taken

The NCI supports comprehensive basic, translational, and clinical research programs directed at neurofibromatosis-related cancers. NCI's basic research program includes a number of grants that investigate the function of the NF1 and NF2 tumor suppressor genes, their protein products, and the consequences of their inactivation that underlie NF. As examples, one project is examining a dynamic process used by the NF1 protein to regulate and fine tune an important cell communication protein termed Ras, which is deregulated in NF. Another project is investigating how leukemia-associated genetic defects, including NF1, lead to the deregulation of the Ras network to identify targets for effective therapy. NCI also supports a significant number of grants examining the role of Ras and the protein m-TOR in cancers, which could provide key knowledge to affect the understanding and treatment of NF and lead to the identification of novel compounds that target these pathways in Malignant Peripheral Nerve Sheath Tumor (MPNST) and astrocytoma—a type of brain cancer.

NCI-funded researchers are studying the role of the NF1 gene in malignant astrocytoma using genetically modified mice to understand the early molecular events of tumor initiation and the cell of origin. In one project, a novel genetic mosaic system was developed in the mouse to inactivate NF1 and other tumor suppressor genes in a very small number of cells within an otherwise normal mouse, mimicking the clonal origin of human cancers, and providing a model in which to study the in vivo function of these genes during tumor initiation. Another project is focused on proteins integral to mast cell function and tumor progression that have a role in the genesis of a common type of congenital tumor called plexiform neurofibromas. These studies suggest that developing small molecules that inhibit the function of specific mast cell proteins could be useful as a molecularly-based therapeutic. Another area of investigation focuses on the role of the microenvironment in the development of optic gliomas in NF. Evidence suggests that genetic changes and signaling cues in neighboring microglial cells, are critical for optic glioma development and growth.

Clinical trials on NF are underway in the NCI's extramural Children's Oncology Group and within the NCI intramural Pediatric Oncology Branch (POB). The Children's Oncology Group is specifically treating children with NF1-associated tumors, particularly the low-grade gliomas. Most low-grade gliomas in children are curable by surgery, but some cannot completely be removed and could progress unless treated. The Children's Oncology Group Phase 1/Pilot Consortium recently completed a clinical trial of a new treatment regimen for children with unremovable low-grade gliomas to determine the maximum tolerated dose of two drugs, carboplatin and weekly vinblastine in patients with both newly diagnosed progressive and/or symptomatic low-grade gliomas and patients with recurrent tumors. The treatment routine will now be considered for further evaluation within the Children's Oncology Group. The NCI's POB is coordinating a number of Phase I, II, and natural history trials, many with multiple participating sites, specifically related to NF1 and inoperable, progressive plexiform neurofibromas, and to MPNST. Phase II trials of the farnesyltransferase inhibitor tipifarnib and the antifibrotic agent pirfenidone were recently completed. If the results are promising, the agents will move into larger Phase III studies. One of the ongoing trials is a phase I study of sorafenib, a drug that targets several pathways thought to be critical to the pathogenesis and progression of plexiform neurofibromas, for children and young adults with inoperable disease and with NF1. The POB also developed an ongoing multi-institutional phase II clinical trial of chemotherapy for naïve, sporadic, and NF1-related MPNST. A phase II trial of the mTOR inhibitor RAD001 alone and in combination with the angiogenesis inhibitor bevacizumab for patients with chemotherapy refractory sporadic and NF1 associated MPNST is currently in development.

The National Heart, Lung and Blood Institute (NHLBI) will pursue discussions with fellow institutes to identify opportunities to incorporate hypertension and congenital heart disease in existing and future NF programs, with the goal of increasing the visibility of these understudied areas within the NF research community.

The National Institute of Neurological Disorders and Stroke (NINDS) has a broad-based portfolio related to NF and related complications of the disorder. NINDS funds research to

study deficits in spatial learning in a mouse model of NF and to understand the underlying cellular mechanisms of how the NF1 mutation results in learning disabilities in the human condition. Another NINDS-funded project is specifically looking at reading disabilities in patients with NF. Using behavioral and functional magnetic resonance imaging methods, the researchers are hoping to determine the best interventions to help improve reading ability for these individuals. NINDS-funded researchers are also pursuing studies to understand how disruptions in the cellular mechanisms involved in memory consolidation lead to cognitive problems in NF patients. While spinal cord injury does not occur at an increased incidence in NF, patients do have a higher incidence of bone abnormalities, such as scoliosis. NINDS, as well as other NIH institutes, are funding studies to better characterize and understand skeletal abnormalities associated with NF, including scoliosis and other spinal abnormalities.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supports 14 Intellectual and Developmental Disabilities Research Centers (IDDRCs) around the country, which provide infrastructure (core facilities and services) for over 1,000 research projects supported by many of the NIH institutes and centers and other government agencies. Funding from the NICHD and their structure allows these centers to maximize support from their home academic institutions. One of the IDDRCs supports the Department of Defense's Neurofibromatosis Consortium based at the University of Alabama- Birmingham, which is conducting clinical trials for NF-related complications, particularly tumor burden of this disorder. In addition, NICHD intramural researchers are participating with NCI on clinical studies of patients with NF.

The National Institute on Deafness and Other Communication Disorders (NIDCD) is supporting research on Neurofibromatosis type 2 (NF2), an autosomal dominant genetic disorder that is strongly associated with bilateral nerve tumors called vestibular schwannomas (or acoustic neuromas). These tumors grow specifically on the auditory-vestibular nerve that runs from the ear to the brain and can cause hearing and balance disorders as well as life-threatening compression of the brainstem. NIDCD-supported extramural scientists are studying the cellular signals that lead to these schwannomas with hope that potential drug treatments could be developed to prevent these tumors. Other scientists are developing an auditory brainstem implant which can better convey the features of sound to individuals who have lost auditory nerve function during the surgical removal of the NF2 tumors. NIDCD intramural scientists are collaborating with scientists from NCI and NINDS on clinical trials that are studying the natural history of tumor formation and growth in individuals with NF2.

Item

Porphyria - The Committee encourages the ORD to develop an agenda for basic and clinical research for the treatment of porphyria, to devote dedicated resources for this purpose, and to consult with patient stakeholder organizations when considering the development of the research agenda. (p. 114)

Action taken or to be taken

The Rare Diseases Clinical Research Network (RDCRN) includes the new Porphyria Rare Diseases Clinical Research Consortium for the next five years. The consortium is co-

funded by ORDR and the NIDDK. The research will focus on the inborn errors of heme biosynthesis which underlie these diseases. Participating institutions will focus on all seven porphyrias – Acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), aminolevulinic acid dehydratase deficiency porphyria (ADP), porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), and congenital porphyria (CP). This interdisciplinary team of translational and clinical investigators will advance clinical research in the porphyrias through clinical studies and trials at the following five institutions: Mount Sinai School of Medicine; University of Texas Medical Branch; University of California at San Francisco; University of Alabama at Birmingham; and University of Utah School of Medicine. They will partner with the American Porphyria Foundation (APF). The collaboration of these five major centers with recognized experts throughout the US and the APF will lead to increased basic and clinical research and culminate in opportunities for a clear perspective of future research. NIH, in the Biennial Report of the Director to Congress will report regularly on the progress of the Rare Diseases Clinical Research Network including the Porphyria Rare Disease Clinical Research Consortium and in a section on future directions of research.

Item

Pregnant Women in Clinical Studies - While over the last two decades, women have increasingly been included in clinical studies, pregnant women continue to be largely excluded from medical research, leading to a troubling lack of knowledge about how to treat pregnant women's illnesses and limited understanding of how illness in pregnancy affects women's health over time. Many pregnant women suffer from serious medical conditions including diabetes, hypertension, depression, autoimmune disorders, and cancer. Pregnancy significantly changes women's physiology, including blood flow, digestion, kidney function and hormonal and enzymatic activity, in ways that can dramatically change the nature and progression of disease and the way that medications work. Despite these important differences, pregnant women are rarely involved in health research and, as a result, in many cases little is known about how to safely and effectively manage illness in pregnancy. The Committee encourages NIH to expand research on pregnant women with the goals of better understanding the long-term health effects on women of disease states in pregnancy, the proper therapeutics for pharmacologic treatments for pregnant women who face illness, and the safety and efficacy of medications administered to pregnant women and fetuses. (p. 136)

Action Taken or to be Taken

NICHD is addressing many of the challenges associated with the inclusion of pregnant women in research to augment knowledge on a range of conditions affecting pregnancy as well as how treatment may improve outcomes for mothers and children.

NICHD has a leading role in expanding research on pregnant women, e.g., investigator-initiated supported trials, the Maternal Fetal Medicine Units Network (MFMU), the Stillbirth Collaborative Research Network, the Community Child Health Research Network, a major treatment trial for spina bifida (MOMS), and the Nulliparous Network, which will involve women in their first pregnancies. When possible, these studies and trials have incorporated long-term maternal health effects. For example, the MOMs trial includes outcomes of maternal reproductive health after fetal surgery. The MFMU is conducting

ongoing trials to evaluate the safety and efficacy of medications administered in pregnancy, such as evaluating whether thyroxine treatment for subclinical hypothyroidism or hypothyroxinemia diagnosed during the first half of pregnancy is associated with intellectual improvement in children. Previously, the MFMU identified that progesterone was beneficial in preventing recurrent preterm birth in women with a prior preterm birth, which also results in improved long-term health of the mother. An ongoing study is evaluating the impact of H1N1 on hospitalized pregnant women and their fetuses at 29 hospitals across the U.S.; pregnant women are the highest risk group for mortality from H1N1 (the rate thought to be double that of the general U.S. population).

NICHD's Obstetric Pharmacology Research Network (in partnership with ORWH) is the only group evaluating the pharmacokinetics and pharmacodynamics of commonly used medications in pregnancy to identify optimal dosing, delivery, timing and therapeutics.

Item

Primary Care Practice Research - The Committee recognizes the role of NIH in researching primary care and prevention interventions in order to improve health outcomes, reduce health care-associated infections, and reduce the overall costs of healthcare. The Committee requests that the Director work with the Agency for Healthcare Research and Quality, CDC, and the Office of the Secretary to develop a coordinated approach to research in primary care practice, with a specific focus on improving health among populations with disparate health outcomes. (p. 137)

Action taken or to be taken

Please refer to page 189 of this document for NCMHD's response to this item.

Item

Rehabilitation Research - The Committee recognizes the importance of supporting research efforts to improve an individual's function and quality of life. The Committee encourages NIH to evaluate the efficacy of movement-based rehabilitation interventions, such as therapeutic exercise, to improve physical function in individuals with musculoskeletal conditions including arthritis, back pain, hip fracture, and major joint replacements. The Committee recognizes the advances that NIH-funded research has achieved in the area of stroke rehabilitation; The Committee encourages continued focus on rehabilitation interventions, especially physical therapy, to maximize an individual's function and quality of life after a stroke. The Committee encourages the Director to work with the National Center for Medical Rehabilitation Research (NCMRR) and relevant NIH institutes and centers to enhance and increase collaboration and support for medical rehabilitation and disability research across NIH. The Committee believes that rehabilitation and disability research is well-suited for the type of cross-disciplinary, translational research that the Director's office has made a priority in recent years. (p.137)

Action taken or to be taken

The National Center for Medical Rehabilitation Research (NCMRR)/NICHD, and other programs across the NIH continue to promote institute-sponsored and investigator-initiated research to improve function and quality of life for people with disabilities. This research integrates neurological and musculoskeletal approaches, bioengineering, and behavioral

and psychosocial support. Research on movement-based rehabilitation includes the use of therapeutic exercise, electrical stimulation, and/or pharmacological treatments to promote plasticity and adaptation in the nervous system, while other studies focus on musculoskeletal biomechanics and joint pathophysiology.

NIH-supported rehabilitation research also focuses on reducing disabilities and improving quality of life. The recently re-competed, Pediatric Critical Care and Rehabilitation Program, funds research on outcomes for children who are survivors of trauma, congenital anomalies, neonatal asphyxia and other devastating processes. NCMRR staff has worked with the Patient-Reported Outcomes Measurement Information System initiative, an NIH Roadmap activity to improve assessment of outcomes and quality of life, to increase emphasis on disability, especially with respect to children. The NCMRR also recently participated in two workshops on how technology can facilitate healthy aging and independent living. Because rehabilitation research tends to focus on reducing disability rather than on the underlying pathophysiology itself, these research approaches may be relevant to a wide range of disabling musculoskeletal and neurological conditions.

Stroke research remains a high priority, especially with new strategies for supporting damaged brain tissue and promoting activity-driven brain plasticity. NIH-supported stroke research includes major clinical trials on constraint-induced therapies to improve arm function and gait training to improve mobility. The NINDS, in collaboration with the NICHD and other agencies, recently held a workshop entitled, “Promoting Generalization in Stroke Rehabilitation,” and further research in this area is being encouraged through a NIH Program Announcement on the “Mechanisms of Functional Recovery after Stroke.”

The NCMRR continues to promote collaboration on disability and rehabilitation research through several trans-NIH activities. Representatives from other NIH Institutes take an active role in the biannual National Medical Rehabilitation Research Advisory Board meetings, which provide advice to the NIH on research priorities and collaborative opportunities. In addition, the NCMRR leads the trans-NIH Rehabilitation Coordinating Committee to highlight common programmatic interests, coordinate resources, and build cross-disciplinary research initiatives, such as a recent Program Announcement for “Networks for Research Partnerships to Improve Functional Outcomes.” Several NIH institutes also are collaborating to renew the multi-site Medical Research Infrastructure Network, which provides core support for a variety of research projects.

Item

Research Centers in Minority Institutions - The Committee continues to recognize the critical role played by minority institutions at both the graduate and undergraduate level in addressing the health research and training needs of minority populations. The Research Centers in Minority Institutions [RCMI] program impacts significantly on these issues. The Committee encourages the NIH to strengthen the research environment at minority institutions so that they may fully engage in and build upon NIH initiatives. Specifically, the Committee recommends NCRR supplemental funds be directed to high-impact, high-risk research activities within the RCMI program such as creating an integrated translational research network to help reduce health disparities. (p. 111)

Action taken or to be taken

The Research Centers in Minority Institutions (RCMI) Program develops research infrastructure in predominantly underrepresented minority institutions that award doctorates in the health professions or health-related sciences. The 18 institutions currently funded via the RCMI program have an outstanding track record of producing minority scholars in science, medicine, and technology. According to the most recent available data, 23 percent of the Ph.D.s earned by minorities in the biomedical sciences were awarded by these institutions in FY 2006³. The eight medical schools included in this group produced 17.5 percent of the minority M.D.s in the United States in FY 2008⁴.

In FY 2008, funding for the RCMI Program was \$53.2 million. Funding for the program was increased to \$57.9 million in FY 2009. Supplemental funding was utilized to support institutional infrastructure and research on health disparities through the RCMI Infrastructure for Clinical and Translational Research (RCTR) awards and the RCMI Translational Research Network (RTRN). Supplemental funding to the RCTR awards is aimed at developing institutional infrastructure, enhancing training and career development activities, and accelerating the process of translating research advances to improved health outcomes, especially in minority communities. The RTRN is a cooperative research network that consists of researchers from various RCMI programs, other academic health centers, community providers, community organizations, and a Data and Technology Coordinating Center. The RTRN received supplemental funds to facilitate expansion of the data center capabilities to support the consortium activities and to initiate multi-site collaborative pilot research projects focused on cardiovascular disease, HIV/AIDS, cancer and other diseases that disproportionately impact minority populations. In FY 2010, NCCR will use additional funding to strengthen institutional capability for research on health disparities, and provide the resources necessary to support the integrated translational research network's high risk, high impact activities to help reduce health disparities.

Item

SMA Carrier Screening – The Committee encourages NHGRI, NICHD, and NINDS to work collaboratively to develop specific recommendations and guidelines for providers and patients on pan-ethnic carrier screening for SMA. The Committee urges the institutes to partner with the relevant professional societies and the advocacy community in this effort. The Committee expects an update on these activities in the fiscal year 2011 congressional budget justifications. The Committee also encourages the Director to establish a trans-NIH working group on SMA composed of the relevant institutes to ensure ongoing support of SMA research and drug development.

Action taken or to be taken

Carrier Screening for SMA. NICHD, along with NHGRI and NINDS, co-sponsored and collaboratively planned a scientific meeting entitled, "Examining the Scientific Basis for Spinal Muscular Atrophy Carrier Screening," on September 30 and October 1, 2009.

³ *Science and Engineering Doctorate Awards: 2006*. Division of Research Statistics, NSF, 2009

⁴ *Enrollment and Graduates Data: Total Graduates by U.S. Medical School and Race and Ethnicity, 2008*. AAMC 2008.

Participants included: (1) representatives from the research community; (2) the advocacy community, including the Genetic Alliance, the March of Dimes, the Muscular Dystrophy Association, the Claire Altman Heine Foundation, Inc., Families of SMA, Spinal Muscular Atrophy Foundation; (3) professional organizations including the National Society of Genetic Counselors, the American College of Medical Genetics, and the American College of Obstetricians and Gynecologists; (4) private partners including Genzyme Genetics and Athena Diagnostics and; (5) other Federal partners including HRSA. Discussions at the meeting encompassed the current status of research involving population screening for SMA, lessons learned from other conditions such as Cystic Fibrosis, and public health considerations regarding SMA Carrier screening. Each of the professional and advocacy organizations presented its perspectives and concerns on carrier screening. The group as a whole discussed the priorities for moving the field forward and the next steps that need to be taken to facilitate these actions.

SMA Research and Drug Development - NICHD continues its commitment to research in the field of SMA, e.g. facilitating the development of treatments for the disorder. NICHD currently has a broad portfolio of research projects that focus on the pathophysiology and molecular mechanism underlying SMA. This research helps guide the science towards effective targets for therapeutics. One of the many currently funded research projects is a study to identify lead drug-like compounds that increase intracellular SMN protein levels. Identifying appropriate lead compounds is the first step toward the development of effective drug treatments. A second project involves identifying the optimal window in the developmental process for effective treatment. The investigator proposes that motor neuron denervation, a hallmark of SMA, is progressive over time and that treatment must be initiated early to effectively moderate disease severity. In the coming year, NICHD will continue funding research that may lead to effective treatments for SMA. It will also continue working collaboratively with NHGRI and NINDS to explore ways to provide effective carrier screening for SMA.

Item

Spina Bifida - The Committee encourages NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder in order to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with both paralysis and developmental delay. (p. 138)

Action taken or to be taken

Neural tube defects (NTDs) are the most frequent and severe developmental anomalies of the central nervous system. Spina bifida, a developmental malformation resulting from abnormal or incomplete closure of the end of the neural tube, is still not well understood. Animal models such as mice are assisting researchers in deciphering the mechanisms underlying neural tube closure, while studies on human populations are helping to clarify the genetic, epidemiological and environmental causes. Both will increase our ability to understand, treat and ultimately prevent this structural birth defect.

The NICHD supports a number of projects studying the hereditary basis of NTDs, by identifying genes that predispose humans to spina bifida and other NTDs. Preliminary work has been assessing the genetic makeup of affected individuals using detailed phenotypic descriptions, newly developed statistical techniques, and rapid genetic marker genotyping. Studies on individuals are complemented by examinations of the effects of environmental conditions in order to tease out the complex relationships between genetic susceptibility and environment. To facilitate these endeavors, a data resource has been created to examine the potential genetic determinants of spina bifida in a well-characterized sample of approximately 500 affected individuals, along with the biological parents and unaffected siblings. Also, a range of NINDS-funded studies on the developmental mechanisms of neural tube closure in animal models may point to targets of intervention and a recently completed NINDS study, with data from more than 180,000 pregnant women found that low levels of dietary choline increased the risk for neural tube defects and that higher levels were protective.

It is well established that folic acid, when taken before and during pregnancy, is an effective agent in reducing the occurrence and recurrence of NTDs, as well as other common congenital malformations. While, the metabolic and molecular basis for the preventative effects is unknown, recent studies are exploring both the nutritional and genetic aspects of folate-related factors that may interact to cause NTDs. Neural tube defects are also commonly found as a result of gestational diabetes mellitus. Abnormal maternal metabolism in diabetic pregnancy appears to deregulate gene expression during early nervous system development in the embryo, resulting in an increased incidence of NTDs. In one NICHD-supported study, which used a maternal diabetes mouse model, the expression of 143 genes was significantly changed in mouse embryos exposed to maternal diabetes during development. Other studies focusing on the NTD-specific group of genes are in progress to determine which can serve as predictive markers for failure of the neural tube to close properly.

Item

Stem Cell Research Supported with Recovery Act Funds - The Committee is pleased that stem cell research was included as a special emphasis area in the NIH Challenge Grant program, a special initiative supported by ARRA funds to focus on health and science problems amenable to significant progress within a 2-year time frame. The Committee also welcomes the recent release of guidelines for the use of human embryonic stem cells [hESC] with NIH funds, but is concerned that implementing the guidelines will delay the funding of ARRA awards to support hESC and thus frustrate congressional intent to expedite this important area of research. Therefore, the Committee encourages the NIH to allow full 2-year funding of stem cell research awards with ARRA funds in fiscal year 2010. (p. 121)

Action taken or to be taken

The NIH Guidelines for Human Stem Cell Research, released on July 7, 2009, provide opportunities for significant expansion of this important area of research. As indicated on the NIH stem cell web site, <http://stemcells.nih.gov/index.asp>, NIH began accepting requests for human embryonic stem cells (hESCs) to be considered for use in NIH-funded research on September 21, 2009. NIH also announced the members of the Working

Group of the Advisory Committee to the Director. Approved lines will be posted on the new NIH Stem Cell Registry.

In addition, NIH published a GUIDE notice on July 15, 2009,) that describes how applications will be peer reviewed and awarded in conformance with the new NIH Guidelines for Human Stem Cell Research (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-123.html>). Specifically, this GUIDE notice indicates:

- For applications submitted in response to ARRA funding opportunities: Grantees will be asked to identify eligible hESC lines from the Stem Cell Registry once they are posted. Review of all ARRA Grand Opportunity (GO/RC2) and competitive revision applications that propose the use of hESC will be reviewed and eligible for award by September 30, 2009, thereby allowing for two years of funding. These awards will be restricted from using funds to conduct hESC research until the grantee identifies eligible hESC lines that have been approved through the new NIH process and appear on the new NIH Registry. All ARRA Challenge Grant (RC1) applications involving hESC research were peer reviewed in September 2009 and will be eligible for award in February 2010. Since these applications are for ARRA funding but awards will be delayed until FY2010, they will be funded for 24 months.
- Other meritorious hESC applications that were peer reviewed before April 17, 2009, but held pending issuance of the final NIH Guidelines as well as administrative supplements are now eligible for award. Similar to the ARRA GO/RC2 and competitive revisions, these awards will be restricted from using funds to conduct hESC research until the grantee identifies eligible hESC lines that have been approved through the new NIH process and appear on the new NIH Registry.

Thus, NIH has developed and is implementing procedures to ensure that funded applications involving hESC research supported by the Recovery Act will be able to receive two years of support. In addition, every effort is being made to ensure that all applications to NIH for hESC research are proceeding expeditiously through the grant making process and in observance of the new NIH Guidelines for Human Stem Cell Research.

Item

Sturge-Weber Syndrome (SWS) – The Committee encourages the Director to support collaborative research on SWS conducted by appropriate NIH institutes and centers, other government agencies and voluntary organizations. The Committee commends NINDS for its leadership role and collaboration with ORD in SWS research. The Committee encourages NIH to support multidisciplinary research studies into seizures, stroke, the blood-brain barrier, blood flow, angiogenesis, immune suppression, hormone abnormalities and co-morbidities such as attention deficit hyperactivity disorder. The Committee also encourages NIH to support research on SWS and inflammatory response, growth factors, and the identification of markers in vasculature. (p. 138)

Action taken or to be taken

The NIH Office of Rare Disease Research (ORDR) helps stimulate, coordinate, and support research on rare diseases including Sturge-Weber Syndrome (SWS). ORDR has organized scientific conferences on SWS, developmental brain injuries, and angiogenesis to help catalyze research in these areas. With guidance from ORDR, several NIH Institutes support varied avenues of research that are increasing scientific understanding of the causes of SWS and that will provide better care options for patients suffering from SWS.

NINDS continues to support a large study collecting brain images of children with SWS to identify the relation between specific changes in brain structure and activity and the range of neurological and cognitive outcomes seen in patients. Researchers have already found several imaging markers that can be used not only in the prediction of disease progression and the development of cognitive deficits but also may assist in guiding treatment choices. ORDR and NINDS recently co-funded a five-year award for a Brain Vascular Malformation Consortium as part of the NIH Rare Diseases Clinical Research Network. This group will study several types of brain vascular malformation diseases, including SWS.

For children with SWS, early and effective management of seizures, migraines, glaucoma, and stroke-like episodes is important. NINDS and other NIH Institutes support a strong research portfolio on the causes and effects of pediatric seizures, headaches, and stroke, and on therapeutic strategies in children. For example, one

NINDS-funded study will use a mouse model of pediatric stroke and seizures to test whether some anticonvulsants promote better cognitive outcomes while others may have harmful effects on cognition. Other NINDS-supported studies focus on neuroprotection and neuroregeneration strategies after a seizure or stroke.

NIH, in particular the Institutes of the NIH Blueprint, supports a broad research program on the biological processes of brain development. Specifically, several projects funded by NINDS study the development of brain blood vessel malformations, such as the ones that cause SWS. NHLBI also supports different research approaches to understand normal blood vessel development and regulation, which may lead to therapeutic targets for SWS patients.

Surgical brain procedures are often best guided by imaging techniques. NIBIB supports the development of technologies to help neurosurgeons identify areas of the brain that need to be removed to improve seizures and which may also allow more detailed studies of the development of blood vessel abnormalities in animals. Researchers funded by NIBIB, NIAMS, and NCRR are also developing better options for the removal of the facial vascular birthmarks characteristic of SWS, caused by blood vessel lesions in the skin, which can be life-threatening in some cases.

Item

Temporomandibular Joint Disorders (TMJDs) - Similarly, the Committee looks forward to the results of the current prospective study exploring risk factors for the onset of TMJD. However, minimal progress has been made in understanding the causes of TMJD and

mechanisms that might explain the presence of many co-morbid conditions with TMJD that are also associated with pain, such as chronic headache, vulvodynia, irritable bowel syndrome, interstitial cystitis, chronic fatigue and immune dysfunction syndrome, fibromyalgia and generalized pain syndromes. Resolution of TMJD problems is further hampered by inadequate diagnostics, ineffective and even harmful treatments, and the failure to develop effective medications to treat this and other chronic pain conditions. Therefore, the Committee requests the NIDCR to take the lead in developing a comprehensive 5-year TMJD research plan that articulates the strategies and goals necessary to resolve the issues that have plagued TMJD studies over the decades. The plan should include research to develop definitive diagnostic criteria; support an updated epidemiology, including a count of co-morbid conditions; examine genetic and other factors that increase risk for TMJD; and support endocrine, immune and nervous system research on pain mechanisms and treatments. The plan's research goals should incorporate the appropriate mix of basic, clinical and translational science, recruitment of scientists from the pertinent disciplines, and meaningful training programs to enlarge the pool of investigators and indicate what funding mechanisms should be employed. (p. 93)

Action taken or to be taken

TMJDs are a complex set of diseases involving tissues of the face and the temporomandibular joint. TMJDs may occur together with other chronic painful disorders such as fibromyalgia, trigeminal neuralgia, chronic fatigue syndrome, irritable bowel syndrome, vulvodynia, interstitial cystitis, and migraine headache. The NIDCR continues to support research leading to the discovery of common etiological and pathophysiological mechanisms underlying this set of chronic disorders that overlap with TMJDs. The NIDCR recently published its five-year Strategic Plan for 2009-2013. The plan highlights research priorities for basic, clinical, and translational research and training, and provides the framework for the future of TMJD research, including new discoveries through genetic and genomic approaches; TMJD as a model system for understanding complex interactions between sensation, mechanical forces, tissue, and the immune system; reconstruction and regeneration of damaged craniofacial tissues through biological, bioengineering, and biomaterials research approaches; collaboration with schools of dentistry to maintain a critical mass of investigators as well as welcoming new disciplines poised to expand oral, dental and craniofacial research; accelerating the rigor of clinical studies by encouraging NIDCR investigators to interface with the NIH-funded Clinical and Translational Science Awards (CTSA) program; and augmenting research capacity through enhanced training to create a cadre of scientists skilled at conducting clinical trials and community-based research.

The NIDCR moved quickly to implement our Strategic Plan related to TMJD research, and recently approved two five-year funding Initiatives. The first one encourages multidisciplinary research on understanding how acute orofacial pain conditions such as TMJD progress to chronic painful disorders. Results from these studies will provide novel biologic, behavioral, and genetic phenotypes that will lead to improved diagnoses for TMJD and other comorbid conditions, and new therapeutic targets for treating these disorders. The second initiative encourages research to characterize genomic regions and genetic variants that affect human disease risk with the goal of driving development of effective diagnostic, therapeutic, and preventive approaches. The NIDCR also

sponsored a workshop on *Genetics of Temporomandibular Joint Disorder and Comorbid Chronic Pain Conditions: Current Status and Next Steps*. The recommendations from this workshop will entail the development of forward thinking research programs to identify pain phenotypes and associated genotypes that are both common among these conditions comorbid with TMJD and specific for each disease.

NIDCR also participates in the NIH Blueprint for Neuroscience Research. This group has just approved a six-year initiative to fund chronic neuropathic pain research *Harnessing Our Understanding of Neural Plasticity to Elucidate the Transition from Acute to Chronic Pain*. This funding opportunity will include the development of pilot research projects, training of new investigators in the methodologies and measurement of chronic neuropathic pain, and support for large multidisciplinary research projects focused on studies of the transition from acute to chronic pain. A guiding principle of this funding opportunity is the inclusion of new scientific expertise and research tools that will provide novel approaches to resolving chronic pain conditions.

Item

Transfer of Funds - The Committee continues a provision granting authority to the Office of the Director of Director of the National Institutes of Health (NIH) to enter directly into transactions in order to implement the NIH Roadmap for medical research and permitting the Director to utilize peer review procedures, as appropriate, to obtain assessments of scientific and technical merit. (p. 198)

Action taken or to be taken

The NIH Director currently uses the authority to enter directly into transactions (referred to as the Flexible Research Authority, or FRA) to fund awards through the Common Fund Nanomedicine Program. This unique program has established the very high risk goal of developing new therapeutic strategies through engineered nano-scale cellular machines by FY2014. This program will undergo rigorous peer review in FY2010 to refine and enhance the specific goals for each of the awardees. The FRA in future years will allow the NIH to amplify those awards that prove fruitful while eliminating awards for which the therapeutic goals prove impossible to reach.

The NIH Director is also interested in making use of the FRA for new programs that require rapid response. The flexibility afforded by the FRA allows new types of application and review processes to be developed so that the Common Fund can be nimble in responding to emerging needs and opportunities. As the NIH Director undertakes a strategic planning process in FY2010, specific scientific areas that would benefit from the FRA will be articulated.

Item

Tuberous Sclerosis Complex (TSC) – The Committee is encouraged by the potential of NIH-funded TSC research to reveal a better understanding not only of TSC, but more prevalent disorders such as autism, epilepsy and cancer. Because of the "gateway" potential of TSC research into these disorders, the Committee encourages a significant expansion of TSC research at all relevant institutes, and stronger coordination of this effort through the TransNIH TSC Coordinating Committee. In particular, the Committee

encourages expanded research at the NICHD, NINDS, NIMH, and ORD targeted on the role of the TSC1/2 genes and the mTOR pathway in the mechanisms of epilepsy, autism and mental health issues. Furthermore, the NINDS, NIAMS, NICHD, NHLBI, NIDDK, NCI, ORD, and NHGRI are urged to collaborate on the mechanisms of tumor growth and drug target testing in preclinical models of TSC, TSC/polycystic kidney disease and lymphangi leiomyomatosis [LAM]. Finally, the Committee encourages all relevant NIH institutes to support clinical trials for the manifestations of TSC and LAM: epilepsy, autism, developmental delay, neurocognitive and mental health issues, and tumor growth in the kidneys, brain, skin, heart, liver and eyes. (p. 122)

Action taken or to be taken

The trans-NIH TSC Working Group continues to effectively coordinate TSC activities among NIH Institutes, the TS Alliance, and Department of Defense. NIH Institutes also co-fund workshops and jointly sponsor conferences with patient voluntary organizations. Recent workshops include: the NINDS workshop “mTOR Signaling: From Cancer to CNS Function” and the subsequent NCI/NINDS workshop “Cancer Cell Metabolism”; the TS Alliance’s “International TSC Conference: From DNA to Therapeutics,” with support from NINDS, NCI, NIDDK, NICHD, and NIAMS; and NHLBI’s continued co-funding of the LAM Foundation’s Annual International LAM (*lymphangi leiomyomatosis* – a lung disorder seen in many TSC patients) Research Conference. The Working Group will continue to actively coordinate research in FY2010 and will facilitate joint workshops and other activities, as appropriate.

NIH-funded research has shown the “gateway” potential of TSC and the mTOR pathway in understanding a variety of biological conditions and diseases. mTOR is a protein that promotes cell growth, and abnormal mTOR activity in TSC leads to tumor formation. NINDS-funded researchers showed that the drug rapamycin (also known as sirolimus), which inhibits mTOR signaling, eliminated seizures and improved learning and memory in TSC mouse models. NINDS-funded research has also implicated mTOR in a related condition, neurofibromatosis type 2. Current NINDS research aims to further understand regulation of mTOR and its role in neurological symptoms of TSC including epileptogenesis and memory formation. NHLBI-funded scientists determined that TSC gene dysfunction underlies LAM and that rapamycin mimics the function of missing or abnormal proteins needed to control LAM cell growth. Research is ongoing to: find additional treatment targets; identify molecular markers; and determine the role of estrogen and mechanisms of lung destruction. NHLBI also supports the collection, processing, and distribution of LAM tissue through the NIH-supported National Disease Research Interchange

Other NIH Institutes support research on the cellular pathways in TSC as related to each Institute’s mission. NIMH’s portfolio focuses on TSC behavioral and cognitive deficits related to autism and autism spectrum disorders. NIDDK’s portfolio on polycystic kidney disease (PKD) is important in understanding the commonalities between PKD and TSC. NCI supports studies on tumor growth in TSC, including regulation of signaling pathways that feed into or diverge from the TSC-mTOR pathway to help understand why malignancy is rare in TSC. NIAMS funds studies on mTOR signaling in normal cellular processes and abnormal conditions. NHGRI supports tools that enable preclinical research of TSC, PKD,

and LAM. Projects recently funded by NINDS, NIDDK, NCI, and NHLBI through ARRA build on the work described above.

While industry is leading clinical efforts with a number of trials in TSC, NIH supports clinical trials of sirolimus in manifestations of TSC. NHLBI's Multicenter International LAM Efficacy of Sirolimus (MILES) trial has found that patients with LAM appear to differ in their sensitivity to sirolimus, suggesting that multiple drug therapy is likely to be important. NCI is supporting a study using sirolimus for treating kidney angio-myolipomas, i.e., benign kidney growths seen in many TSC patients. To date, over 50 percent of the patients enrolled have responded to treatment (30 percent reduction in tumor size).

Item

Vulvodynia - The Committee encourages NIH to support the educational outreach campaign on vulvodynia, launched in 2007, to ensure that developed materials are more widely disseminated to the public, patient and medical communities. In addition, because five years have passed since the last NIH vulvodynia conference, the Committee requests that ORWH convene, with the support of relevant ICs, a research conference on vulvodynia during fiscal year 2010. (p. 134)

Action taken or to be taken

The Office of Research on Women's Health (ORWH) at NIH continues to collaborate with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke, the NIH Pain Consortium, and the National Library of Medicine. Other partners within the U.S. Department of Health and Human Services include the Health Resources Services Administration, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the non-governmental community to develop research and communication strategies to both address the difficult research questions posed by pain syndromes such as vulvodynia, and to educate women and their health care providers about the existence and impact of vulvodynia. ORWH was a co-sponsor with National Institute on Diabetes and Digestive and Kidney Disease in a 2007 meeting of NIH staff and advocacy groups that focused on multidisciplinary approaches to the study of the chronic pelvic pain syndromes, including vulvodynia. ORWH will explore with other relevant NIH Institutes and Centers a scientific meeting to be held in early FY 2011. This meeting will evaluate the current state of knowledge, especially in terms of the new NIH Strategic Plan for Women's Health Research that will be announced in September 2010. For the interim, the materials from the Vulvodynia Awareness Campaign (VAC) launched by ORWH and its partners continue to be a valuable resource for health professionals and the public. These materials can be accessed through <http://orwh.od.nih.gov/health/vulvodynia2.html>, Medline Plus (<http://www.nlm.nih.gov/medlineplus/aboutmedlineplus.html>), and from the partner sites.

Vulvodynia was the subject of an ORWH podcast "Pinn Point on Women's Health." These podcasts are conversations between the ORWH Director, Dr. Vivian Pinn, and NIH experts concerning important topics in women's health. The transcript of this podcast and the VAC are available on the ORWH website and the NIH National Library of Medicine's web site on Women's Health Research at the NIH

(<http://www.nlm.nih.gov/medlineplus/vulvardisorders.html>). ORWH also distributed information on vulvodynia at several national, regional and local scientific meetings.

For FYs 2009 -2010, NIH issued the NIH Challenge Grants in Health and Science Research, resulting from the American Recovery & Reinvestment Act of 2009. Several new grants were funded as part of the Translational Science Challenge Grant on Pelvic Pain.

Senate Significant items

Item

Amyotrophic Lateral Sclerosis (ALS) - The Committee encourages NIH to continue to pursue collaborations and partnerships with voluntary health associations to advance basic, translational, and clinical research into ALS. Support for NIH translational research, the Office of Rare Diseases, SBIR grants and investment in cross-cutting, trans-NIH programs, including those that support high-risk, high-reward initiatives, are among the priorities through which NIH can create significant opportunities to advance ALS and other rare disease research. The success in advancing spinal muscular atrophy [SMA] research through NIH's translational programs, specifically the SMA Project, provides a model for what can be accomplished via these initiatives. The Committee encourages NIH to undertake similar efforts for ALS that can accelerate the development of therapeutic candidates for the treatment of the disease. (p. 124)

Action taken or to be taken

NINDS funds a wide range of research on ALS, with a number of projects funded through the NINDS Cooperative Program in Translational Research, a milestone-driven program supporting preclinical therapeutic development. These include studies to: identify compounds that regulate the function of proteins responsible for the neurodegeneration seen in ALS; develop a mouse model to test a technique to silence genes involved in some cases of ALS; test different delivery methods for growth factors that are showing promise in the treatment of ALS; and optimize the therapeutic potential of a specific anti-inflammatory compound to address neuroinflammation in ALS. A large-scale drug discovery project to conduct high-throughput screens for small molecules, targeting four different mechanisms involved in ALS, is also funded through this NINDS Program. A number of SBIR grants funded by NINDS focus on advancing therapies for ALS. These include projects to determine if a formulation of human growth factor is a potential therapy for ALS. Two projects focus on identifying and maximizing the effectiveness of neuroprotective compounds as a strategy to combat ALS. To encourage high-risk, high-reward research, NINDS participates in the funding opportunity announcement (FOA), "Exceptional, Unconventional Research Enabling Knowledge Acceleration (EUREKA)." This announcement solicits exceptionally innovative research on novel hypotheses or difficult problems, solutions to which would have an extremely high impact on biomedical or biobehavioral research. Applications on ALS research are strongly encouraged.

NINDS regularly partners with voluntary health associations in sponsoring workshops and meetings that bring together experts and stakeholders to discuss ways to advance a field. In January 2008, NINDS and the ALS Association sponsored a meeting to identify barriers

and to address ways that findings in basic research can be translated into clinical research on ALS. Participants from academia, industry and government discussed future directions and opportunities for drug development in ALS.

The SMA Project, in which NINDS adopted the methods used in the pharmaceutical industry to carry out drug discovery and development activities for SMA, is showing progress toward developing potential therapies for SMA. While this is one approach for developing therapies, there are other activities that NINDS is pursuing to advance therapeutic development for other neurological diseases, including ALS. In August 2008, NIH issued two FOAs to promote translational research in neuromuscular disease, including diseases of the motoneuron such as ALS. These announcements have already been very effective in encouraging translational research in neuromuscular disease, and ALS researchers are encouraged to apply for funding through the program. In addition, NINDS is part of an exciting new FY 2011 initiative of the NIH Blueprint – a cooperative effort among the 16 NIH Institutes, Centers and Offices that support neuroscience research - for drug development for nervous system disease. The FOA, “Drug Discovery for Nervous System Disorders,” was issued by five of the Blueprint institutes, including NINDS, in early October 2009. This initiative builds on lessons learned from the SMA Project and includes many of the successful components of the SMA Project including access to industry expertise and services.

Item

Chronic Fatigue Syndrome (CFS) - The Committee urges the ORWH to strengthen the network of investigators funded under the fiscal year 2007 CFS neuroimmune research initiative by stimulating new research initiatives and building multicenter collaborations. The Committee again urges the NIH to establish an intramural CFS research program with relevant areas of scientific expertise to study disease pathophysiology, identify biomarkers, objective diagnostic tools and better therapeutic approaches. The Committee urges the NIH to ensure that study sections responsible for reviewing grants on CFS include experts who are qualified in the appropriate disciplines. (p.114)

Action taken or to be taken

The NIH expanded the network of principal investigators funded under the CFS neuroimmune initiative by including CFS researchers funded by other mechanisms. The ORWH, in collaboration with the Trans-NIH Working Group on Chronic Fatigue Syndrome, plans to expedite this expanded network by establishing and maintaining a *Wikipedia* site. This site will permit discussion and establishment of working groups for developing and disseminating best practices. We plan to reissue RFA-OD-06-02, Neuroimmune mechanisms and CFS to help build on these new collaborations. Negotiations to establish an intramural fellowship program for CFS continue with the Foundation for the NIH, the Intramural Psycho-immunology Program (IMPP), in which the expertise to address the relevant scientific issues resides, and the Chronic Fatigue and Immune Dysfunction Association of America (CFSAA).

The study section responsible for reviewing CFS grants has been relocated in the Integrative, Functional and Cognitive Neuroscience Internal Review Group as the

Chronic Fatigue Syndrome/Fibromyalgia Syndrome Special Emphasis Panel (IFCNG/CFSSEP) and is supported by a wide array of scientists who are frequently multidisciplinary. Experts are selected from disciplines appropriate and tailored to the science represented by the grant applications reviewed in each cycle.

Item

Dystonia - Intramural - The intramural program at NIH continues to advance research activity in dystonia, and the Committee encourages continued support in this area of study. (p. 117)

Action taken or to be taken

Dystonia is a disorder of the brain circuits that control movement. In dystonia, brain signals cause strong and abnormal co-contraction of muscles that produce opposite movements. This can be widespread or localized to certain parts of the body and leads to abnormal postures, impaired movement control, and pain. The NINDS Intramural Research Program's Human Motor Control section has a strong research program to understand how abnormal movement control in the brain results in dystonia and to translate those insights into therapies. Recent research from the intramural program has shown abnormal function of certain types of nerve cells in the cerebral cortex that normally inhibit the activity of other nerve cells, which may represent the fundamental problem that underlies dystonia. The intramural program is continuing its clinical research efforts to understand how abnormal movement control circuits in the brain lead to dystonia using imaging of brain activity, measurements of brain electrical activity, clinical assessments of movement, and genetic analyses.

Intramural investigators are also working to translate new findings into novel therapeutic strategies for dystonia. Studies have included drugs, including botulinum toxin, devices, including transcranial magnetic stimulation and deep brain stimulation, and behavioral interventions that alter abnormal brain circuits. The Intramural group frequently publishes findings from their multiple dystonia studies, and we expect that will continue in the coming year.

Item

Fragile X- The Committee commends the NIH for developing the NIH Research Plan on Fragile X Syndrome and Associated Disorders. The Director is encouraged to dedicate sufficient resources to implement this plan with the guidance of the recently established Fragile X Research Coordinating Group, and in collaboration with the NICHD Fragile X Research Centers, as well as the Fragile X Clinical and Research Consortium. Priorities should include clinical trials of therapies for treatment of Fragile X syndrome and translational research that shows significant promise of a safe and effective treatment for Fragile X syndrome and associated disorders. The Committee congratulates the NIH and its private foundation partners for providing a Small Business Innovation Research grant to fund fragile X drug development, and it encourages more efforts of this kind. Finally, the Committee urges the NIH, working with the Fragile X Clinical and Research Consortium, to convene a consensus conference on translational research opportunities in fiscal year 2010. (p. 117)

Action taken or to be taken

Please refer to page 208 of this document for OD's response to this item.

Item

Headache Disorders - The Committee notes that NIH-funded research efforts on headache disorders have not been commensurate with their enormous disease burden. The Committee strongly urges the NINDS to solicit grant applications for fundamental and translational research on headache disorders and to recruit new investigators to the field. The Committee also urges the establishment of a screening program for therapies for headache disorders comparable in scope to the Anticonvulsant Screening Program [ASP]. The Center for Scientific Review is encouraged to provide fair peer review by ensuring that applications submitted in the area of headache research will be considered by study sections that include members who are principally headache research scientists. The Committee commends the NINDS for recently initiating a process towards defining headache disorders research benchmarks and requests an update on the progress of this program in the fiscal year 2011 congressional budget justification. The Committee also requests an update on the status of NIH intramural research programs related to headache disorders. (p. 126)

Action taken or to be taken

In the past few years, NIH has issued Funding Opportunity Announcements (FOAs) relevant to headache disorders, including a 2007 FOA on the "Neurobiology of Migraine." Recent NINDS studies funded through this FOA include a project to study migraine triggers, specifically the role of ovarian hormones, and a whole genome association study in women to identify genes and genetic variants involved in migraine. A new initiative of the NIH Blueprint - a collaborative framework through which 16 NIH institutes, centers, and offices support neuroscience-related research - is focused on facilitating partnerships between pain scientists and non-pain neuroscientists to understand the underlying neural changes responsible for the transition from acute to chronic pain. NINDS has developed several new initiatives to enable investigators pursuing drug discovery and therapy development to find new treatments for a disease, including the NINDS Cooperative Program in Translational Research and an FY 2011 Blueprint initiative for drug development for nervous system disease. We believe that these will be more effective and less limiting for headache disorders than the epilepsy ASP, which is limited to initial screening of compounds. Headache researchers are encouraged to apply for funding through any of these initiatives.

Grant applications submitted to the NIH are evaluated through a peer review process that is fair, timely, and conducted in a manner free of bias. Study sections are required to have appropriate expert representation depending on the scientific areas reviewed. The Director of the Center for Scientific Review, Dr. Toni Scarpa, is interested in receiving nominations for reviewers from professional groups and would welcome nominations from the headache community.

NINDS has been moving ahead with efforts to identify priorities and opportunities for headache research and to engage all stakeholders in the process. To this end, NINDS has organized small meetings and discussions in preparation for a larger meeting to be held in

Spring 2010. NINDS led informal discussions during the NIH co-sponsored 6th Headache Research Summit (October 2008) and also held discussions with physicians and researchers from the NINDS Clinical Research Consortium Chronic Migraine Treatment Trial on how best to approach a large-scale planning effort in headache research. In addition, NINDS organized a meeting prior to the American Academy of Neurology meeting in April 2009 to discuss the status of the field and to plan for the 2010 meeting. Topics addressed included both the development of therapeutic targets and the training of the next generation of researchers and physician-scientists in headache. These are expected to be some of the themes for the 2010 meeting. The April 2009 meeting included – and the 2010 meeting will include - headache researchers as well as researchers from other areas whose expertise might help to inform the field.

Dr. Kathleen Merikangas, an intramural researcher in the National Institute of Mental Health (NIMH), is studying mechanisms for comorbidity between mood and anxiety disorders with other medical disorders including migraine. Her work, showing that individuals with headache are more likely to have a variety of physical and mental disorders, has important implications for the clinical evaluation and treatment of headache disorders. The NIH Intramural Program also has an active pain research program to study basic mechanisms of pain and novel approaches to treat pain.

Item

HIV Pre-Exposure Prophylaxis (PrEP) - The Committee is aware that there are currently seven clinical trials testing the safety and effectiveness of Pre-Exposure Prophylaxis (PrEP), and that PrEP is considered among the most promising of potential HIV prevention interventions now being studied. The Committee encourages the agencies sponsoring these trials—NIH, CDC, and the U.S. Agency for International Development—to jointly develop a five year coordinated PrEP research plan. (p. 102)

Action taken or to be taken

Please refer to page 86 of this document for NIAID's response to this item.

Item

Irritable Bowel Syndrome - The Committee is pleased with the ORWH's increased focus on IBS. (p. 115)

Actions taken or to be taken

Please refer to page 211 of this document for OD's response to this item.

Item

Neurodegeneration with Brain Iron Accumulation (NBIA) - The Committee urges the ORD to put a higher priority on research involving NBIA, a disease for which there is no treatment or cure. (p. 114)

Actions taken or to be taken

ORDR will continue to work with patient support organizations to encourage research on all rare diseases including this devastating illness of children. Several years ago, scientists from around the world gathered for the Second Scientific Workshop on

Neurodegeneration with Brain Iron Accumulation (NBIA), which ORDR co-funded. A major goal of the workshop was to foster collaboration among scientists working on related diseases. One of the goals was to define NBIA research priorities and determine resources that are needed in order to foster and advance research in this area.

In September 2009, ORDR staff met with representatives of the NBIA Disorders Association including one of the five researchers in this area to explore means by which research could be moved forward. ORDR staff and association representatives discussed a number of approaches that could stimulate research in this area, some of which are in the purview of the ORDR and others that reside elsewhere. To respond to the need to place a high priority on NBIA, ORDR will work with the association to support a planned scientific workshop that includes other similar and related illnesses or, alternatively, will co-fund with other Institutes, such as the Eunice Kennedy Shriver National Institute of Child Health and Human Development and/or the National Institute of Neurological Disorders and Stroke (NINDS), a scientific conference that would work toward developing a collaborative research effort on NBIA.

ORDR will put current researchers and the NBIA Disorders Association in touch with rare diseases' researchers in Italy and Germany to increase the possible pool of researchers and to facilitate researchers in reaching more patients. Similarly, Korea and Japan are countries of interest where ORDR expects to approach rare diseases organizations and departments together with US researchers and representatives of the NBIA Disorders Association.

In the past, NINDS supported and co-sponsored the second scientific conference on NBIA. In addition, through an R13 conference grant, NINDS is expecting to support another scientific conference on NBIA and neuroacanthocytosis: *Brain, Blood, and Iron: Advances in the cell biology of neurodegeneration*. NINDS is also supporting an R01 grant, The Mucolipin TRP Ion Channels from an investigator at the University of Michigan whose recent findings have opened a new avenue for studying lysosomal Ca²⁺ signaling and Fe²⁺ release and its effect on iron metabolism. The results [published in *Nature*, Dong et al. (2008) 455:992-996] have provided clinical insights into potential therapeutic approaches for iron-related disorders (anemia and iron overload as in NBIA), degenerative diseases (retinal and neural degeneration), and aging.

Item

Neurofibromatosis (NF) — NF is an important research area for multiple NIH institutes. Recognizing NF's connection to many of the most common forms of cancer, the Committee encourages the NCI to substantially increase its NF research portfolio in pre-clinical and clinical trials by applying newly developed and existing drugs. The Committee also encourages the NCI to support NF centers, virtual centers, SPORE programs, pre-clinical mouse consortiums, patient databases, and tissue banks, and to work together with other NIH institutes and Government agencies in doing so. The Committee also urges additional focus from the NHLBI, given NF's involvement with hypertension and congenital heart disease. The Committee encourages the NINDS to continue to aggressively explore NF's implications for conditions such as spinal cord injury, learning disabilities and memory loss. In addition, the Committee continues to encourage the NICHD to expand funding of

clinical trials for NF patients in the area of learning disabilities, including the creation of NF centers involved with treating and curing these disabilities. NF2 accounts for approximately 5 percent of genetic forms of deafness; the Committee therefore encourages the NIDCD to expand its NF2 research portfolio. (p.118, 119)

Action taken or not to be taken:

Please refer to page 218 of this document for OD's response to this item.

Item

NIH-DOE Collaborations.—The Committee applauds the successes that have been achieved when the NIH has collaborated with the Department of Energy's National Laboratories, including the Human Genome Project, advances in bioinformatics, and breakthroughs in atomic resolution structural biology. The Committee strongly encourages the NIH Director and directors of the institutes and centers to pursue additional opportunities for sustained collaboration in research and development. (p.119)

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). While the two agencies have distinct missions, there are areas of science that are relevant to both. Both agencies benefit from cooperative discussion, planning, and funding activities. These productive collaborations take place at the highest levels of both agencies as well as among the staff at several NIH Institutes and Centers with DOE Offices. Below are a few examples of the numerous, ongoing, and synergistic collaborations.

NIH and DOE have formed an NIH/DOE Nuclear Medicine Working Group to help address the issues of planning for the availability of research isotopes and the training of radiochemists. The group is drafting a document to identify radioisotopes needed for biomedical research,, as well as working to define the process for NIH/DOE interactions to facilitate production of biomedical isotopes to meet research needs. The group has also developed the concept underpinning the new DOE funding opportunity announcement that focuses on a radiochemistry program of excellence and training. NIH will provide funding to supplement the training component. The impact of this integrated research and training program will fulfill the need for trained investigators to produce radiotracers that are used by biological, biomedical and environmental sciences communities.

Breakthroughs in atomic resolution structural biology have been made possible in part through the cooperative stewardship of synchrotron management by NIH and DOE. NIH is currently planning to build and operate beamlines for the most advanced structural biomedical research at the National Synchrotron Light Source-II (NSLS-II). NSLS-II is a new DOE synchrotron facility that will replace the existing NSLS at Brookhaven National Laboratory (BNL). Experimental facilities at NSLS-II will provide an X-ray beam with properties that will provide greater efficiency and will allow interrogation of more challenging specimens than currently exists at other synchrotrons. NSLS-II is scheduled to become fully operational in 2015. Access to these beamlines will be available to all investigators with meritorious peer-reviewed biomedical research projects. NIH has set aside \$45 million over the next five years for these activities

Item

Overlapping Chronic Disorders – The Committee notes that millions of Americans suffer with one or more of the following chronic disorders: chronic fatigue syndrome, endometriosis, fibromyalgia, headache, interstitial cystitis, irritable bowel syndrome, temporomandibular joint and muscle disorders and vulvodynia. A growing body of evidence demonstrates that these conditions frequently co-exist or overlap, yet all are poorly understood. Progress in treating these prevalent, life-altering disorders has been hindered by their complex genetics and heterogeneous etiologies; however, studying related or clinically overlapping chronic conditions can yield unique biological insight into the mechanisms underlying common disease. The Committee calls upon the Director to coordinate, with all relevant institutes and centers, a trans-NIH research initiative in fiscal year 2010 that will support studies aimed at identifying common etiological pathways, with the goal of identifying potential therapeutic targets. The Committee also requests that the Director hold a conference in fiscal year 2010 that will bring together a wide range of basic and clinical researchers from multiple specialties, as well as professional and patient advocacy organizations, to present and discuss the latest scientific discoveries and develop future research recommendations. The Committee requests an update on progress made in this area in the fiscal year 2011 congressional budget justification. (p. 119)

Action taken or to be taken

NIH is in a good position to act on this recommendation in FY2010. Because the multi-systemic nature of Chronic Fatigue Syndrome (CFS) requires multidisciplinary and interdisciplinary research efforts that cut across the missions of all NIH Institutes and Centers (ICs), NIH has coordinated CFS research through a Trans-NIH Working Group for Research of Chronic Fatigue Syndrome (CFSWG) chaired by the Office of Research on Women's Health for the past nine years. The CFSWG is guided by an action plan centered on enhancing CFS research at NIH and among the external and intramural scientific communities. Membership includes 18 ICs that conduct independent research programs relevant to each of the multiple overlapping disorders such as fibromyalgia, temporomandibular joint disorders, and interstitial cystitis as well as those that provide the tools and mechanisms necessary to build research collaborations. Although many of these disorders are already dealt with as comorbidities, the CFSWG will incorporate a broader focus to include these overlapping disorders in its planned 2010 activities that will expedite meeting the Committee's objectives for 2011. This will include planning and sponsoring a scientific meeting that will inform a new funding opportunity to encourage researchers to study and think more inclusively about the common underlying neuro-immune mechanisms in these chronic overlapping disorders.

Item

Pain Research - The Committee is disappointed with the pace at which NIH is expanding and improving pain research in general and in particular with the slow startup of the Pain Progress Review Group. The Committee urges the NIH to invigorate the NIH Pain Consortium and focus its efforts on identifying and filling important gaps in the pain research agenda, not simply showcasing the relatively small amount of work currently being done in this area. The Committee also urges the NIH to work with the Departments

of Defense and Veterans Affairs to coordinate their respective research efforts on pain conditions afflicting troops returning from the current conflicts in Iraq and Afghanistan. (p. 120)

Action taken or to be taken

The NIH shares the Committee's concern for the millions of Americans who are suffering from pain. The lack of adequate pain management for many patients is a major public health problem, and one the NIH takes seriously. Indeed, the NIH continues to augment the pain research portfolio -- overall projected funding for chronic pain research is expected to increase in 2010 by about 5% over 2007 levels. Furthermore, many Institutes and Centers at NIH are utilizing resources they received through the American Recovery and Reinvestment Act of 2009 (ARRA) to expand their pain research portfolios. Through ARRA-related programs, the NIH challenged its researchers to tackle a variety of pain-related topics. The funding of these grants will jump start projects that are likely to lead to long-term, cutting edge science. The NIH Roadmap for Medical Research Transformative R01 Program provided another opportunity to expand pain research across NIH Institutes.

Through this exciting new program, NIH encouraged applications for studies on the transition from acute to chronic pain conditions. This topic opens up a new area in pain research and one likely to lead to better understanding of risk factors for developing chronic pain and providing new approaches for therapeutic interventions. The NIH Blueprint for Neuroscience Research initiated a six-year project to provide new funding for chronic neuropathic pain research, *Harnessing Our Understanding of Neural Plasticity to Elucidate the Transition from Acute to Chronic Pain*. This program focuses on understanding what goes wrong with the neuronal wiring when individuals with acute infection, nerve damage, or trauma develop chronic neuropathic pain even after the infection or injury has disappeared. The NINR, together with the other Pain Consortium Institutes, will re-issue the NIH-wide Program Announcement for *Mechanisms, Models, Measures, and Management in Pain Research*. The purpose of this announcement is to inform the scientific community of the pain research interests of the various Institutes and Centers at the NIH and to stimulate and foster a wide range of basic, clinical, and translational studies on pain. The NIDCR has recently approved a new funding initiative for FY 2011 on *Collaborative Research on the Transition from Acute to Chronic Pain: New Models and Measures in Clinical and Preclinical Pain Research*. This program will focus on TMJD and other orofacial pain conditions and will encourage basic, clinical, and translational research projects. The NIDCR recently sponsored a workshop on the *Genetics of Temporomandibular Joint Disorder and Comorbid Chronic Pain Conditions: Current Status and Next Steps*. A likely outcome of this workshop will be recommendations for funding of new collaborative genetic and genomic studies of TMJDs and comorbid chronic pain conditions. Taken together, these new activities will address knowledge gaps and capitalize on discoveries to enhance the pain research.

The Pain Consortium has discussed the development of a Pain Progress Review Group to assist with a long-term strategy for pain research support. This effort is envisioned as a collaborative effort among NIH Institutes, academic researchers, industry representatives, health care providers, and patient advocates interested in research, prevention, and treatment of pain. The Pain Consortium is continuing to refine this process and develop the

most appropriate approach to accomplish the goals of the project. Currently, the NIH has ongoing collaborative efforts with the Department of Veterans Affairs (VA) and Department of Defense (DoD). NIH is exploring the possibility of joint efforts with both the Rehabilitation R&D Program at the VA and the Congressionally Directed Medical Research Programs (CDMRP) at DoD and is in contact with staff to determine how best to coordinate potential collaborations. The NIH, together with the VA, DoD, and Centers for Disease Control are sponsoring the Second Trauma Spectrum Disorders Conference. It will examine the best existing science to assess and treat trauma injury as it relates to service members and veterans.

Item

Porphyria - The Committee encourages the ORD to develop an agenda for basic and clinical research for the treatment of porphyria, to devote dedicated resources for this purpose, and to consult with patient stakeholder organizations when considering the development of the research agenda. (p. 114)

Action taken or to be taken

Please refer to page 221 of this document for OD's response to this item.

Item

Rehabilitation Research - The Committee urges the Director to take administrative steps to work with the National Center for Medical Rehabilitation Research [NCMRR] and other relevant NIH institutes and centers to enhance and increase collaboration and support for medical rehabilitation and disability research across the NIH. The Committee believes that rehabilitation and disability research is well-suited for the type of cross-disciplinary, translational research that the OD has made a priority in recent years. Medical rehabilitation research on traumatic brain injury, spinal cord injury, stroke and amputation could all benefit from this approach (Pg 129)

Action taken or to be taken

Please refer to page 222 of this document for OD's response to this item.

Item

Spina Bifida - The Committee encourages the NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder in order to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with paralysis and developmental delay. (p.121)

Action taken or to be taken

Please refer to page 241 of this document for OD's response to this item.

Item

Spinal Muscular Atrophy (SMA) - Given the near-term scientific opportunity for an effective treatment, the Committee encourages the Director to establish a trans-NIH

working group on SMA composed of NINDS, NICHD, and NIAMS, as well as other relevant institutes, to ensure ongoing support of SMA research and drug development, including vitally needed support for clinical research efforts in the field. In particular, the Committee encourages the NINDS to plan for each of the successive stages of SMA research, including preclinical testing of multiple compounds and the necessary clinical trials infrastructure that is needed on a national and coordinated level to ensure effective treatment studies; it encourages the NICHD to support large-scale pilot studies that support the development of a national newborn screening program for SMA; and it encourages NIAMS to take an active role in research that would provide a better understanding of the effects of SMA-linked mutations on muscle as well as research that could provide therapeutic benefit through actions on muscle. On a related matter, the Committee is concerned by the lack of progress made towards the development of a pan-ethnic carrier screening program for SMA. The Committee strongly encourages the NHGRI, NICHD, and NINDS to work collaboratively to develop specific recommendations and guidelines for providers and patients on such a screening program, and it urges the institutes to partner with the relevant professional societies and the advocacy community in this effort. The Committee expects an update on these activities in the fiscal year 2011 congressional budget justification. (p. 121)

Action taken or to be taken

As the Committee noted, research to develop therapies for SMA is a high priority because of the near-term opportunity and the public health burden. NINDS and NICHD fund investigator-initiated research on the mechanisms that underlie SMA and on the development of drugs based on that understanding. NINDS also funds research on gene therapy for SMA, including a major Grand Opportunity (GO) grant via ARRA. The Institute has funded stem cell research relevant to SMA as well, including important recent findings on iPS cells (induced pluripotent stem cells) derived from SMA patients. In addition to investigator-initiated research, the NINDS SMA Project is an innovative, contract-based, “virtual pharma” approach to drug development. To complement these SMA therapy development projects, NINDS and NIAMS issued a solicitation in August 2008, which will be active through September 2011, to encourage new investigator-initiated preclinical therapy development strategies for SMA and other neuromuscular diseases. Through this solicitation, NINDS recently funded a milestone-drive project in the institute’s Cooperative Program on Translational Research. This collaboration between academic and industry researchers will develop small molecule drugs for SMA, following preliminary work that non-governmental SMA organizations supported.

NIH recognizes that clinical research must prepare for testing SMA therapies emerging from preclinical therapy development. In 2004, NINDS convened an international scientific workshop on clinical trials for SMA, which published recommendations on the challenges and opportunities. NINDS-funded clinical studies and pilot clinical trials in SMA have provided lessons for future trials. NICHD also supports clinical research, including current studies to define when SMA interventions must be given to be effective. The recently hired NINDS Associate Director for Clinical Research, who leads the Institute’s Office of Clinical Research, has extensive expertise in SMA clinical research, including clinical trials.

NHGRI recently led a collaborative meeting with NINDS and NICHD on pan-ethnic carrier screening for SMA. At this meeting, in September 2009, SMA advocates, professional organizations, clinicians, researchers, industry experts, and federal agency representatives examined the state of the science and the ethical and social ramifications of carrier screening for SMA. The productive discussions provided a basis for determining next steps regarding the potential for SMA pan-ethnic carrier screening. Because of the success of the meeting, the participants proposed that the NIH Institutes involved collaborate and convene a similar workshop on SMA therapeutics development, with a major focus on the transition from preclinical to early clinical development. NINDS will take the lead on organizing the meeting working closely with other NIH Institutes.

Item

Stem Cell Research Supported with Recovery Act Funds - The Committee is pleased to note that stem cell research was included as a special emphasis area in the NIH Challenge Grant programs special initiative supported by funds from the Recovery Act to focus on health and science problems amenable to significant progress within a two-year time frame. The Committee is also pleased to note that NIH has recently published guidelines for the use of human embryonic stem cells (hESC) with NIH funds. In recognition that the implementation of these new guidelines will delay the funding of Recovery Act awards to support hESC and thus frustrate Congressional intent to expedite this important area of research, the Committee encourages NIH to utilize full two-year funding of stem cell research awards with Recovery Act funds in fiscal year 2010. (p. 138)

Action taken or to be taken

Please refer to page 226 of this document for OD's response to this item.

Item

Stroke in Women – The Committee urges increased research into new therapies for stroke in women as well as ways to enhance vascular health of all Americans, including observational research on differences in the way men and women present with stroke symptoms; research addressing how stroke influences the likelihood and severity of cognitive impairment in women; a clinical trial of carotid endarterectomy and angioplasty/stenting in women; studies of differences in how men and women respond to antiplatelet agents for recurrent stroke prevention; basic science research to address unique brain cell death and repair mechanisms in females; and clinical and basic research on hormone physiology and its impact on women's vascular health. (p. 115)

Action taken or to be taken

NIH recognizes the substantial burden of stroke on women and is committed to supporting research aimed at understanding, preventing, and treating stroke in women and in all Americans, including major clinical studies continuing in 2011.

NIH supports studies on stroke risk factors in women and in the broader population. For example, the NINDS REasons for Geographic and Racial Differences in Stroke (REGARDS) study, an observational study of over 30,000 participants (55 percent women), will examine how gender affects the relationship between risk factors and incident stroke. NINDS also supports a study investigating sex differences in vascular markers of

stroke risk, focusing on hormones and menopausal status. NHLBI will use the Nurses' Health Study cohort to examine the relationship between the risk for stroke and biomarkers related to sex hormones and other factors.

Several NIH-funded clinical studies support the investigation of stroke-related cognitive impairment. Under separate funding, the REGARDS cohort will be used to examine whether physical activity influences stroke outcome and cognitive impairment in population subgroups, including gender. In addition, NHLBI is funding the Women's Health Initiative Memory Study, which is examining the influence of menopausal hormone therapy on cognitive impairment and the role of stroke and cerebral ischemia in dementia.

Intervention studies for the prevention of both first and recurrent stroke are a priority for NIH. The NINDS-funded Carotid Revascularization Endarterectomy versus Stenting Trial will determine whether carotid endarterectomy, "cleaning" a clogged blood vessel, or carotid artery stenting, which widens the vessel by inserting a device, is more efficacious for reducing the risk of subsequent stroke. NIH-funded investigators are also researching the use of antiplatelet agents for stroke prevention in people at risk for first or recurrent stroke. The NINDS Secondary Prevention of Small Subcortical Strokes (SPS3) trial is studying the benefit of clopidogrel added to aspirin for preventing recurrent stroke and cognitive decline. All of these trials will analyze data based on gender.

NIH also prioritizes research on acute treatment of stroke. NINDS funds the Specialized Programs of Translational Research in Acute Stroke Network, which are centers that perform clinical projects and promote new approaches to stroke therapy. NINDS has also created a Neurological Emergencies Treatment Trials (NETT) Network to study acute injuries affecting the nervous system.

Basic research on brain cell death and repair mechanisms, as well as on hormone physiology and vascular health, is also an area of emphasis for NIH. For example, NINDS-funded researchers are studying how cell death pathways of males and females are differentially regulated by chemicals and genes. NINDS is also funding a study on the role of estrogen on the growth of new blood vessels.

Item

Systems Science Initiative - The Committee acknowledges the collaborative work of OBSSR with other institutes and centers to encourage methodological advances in systems science and help cutting-edge areas of behavioral and social sciences research evolve and advance. (p. 113)

Action taken or to be taken

The NIH Office of Behavioral and Social Sciences Research (OBSSR) serves as the focal point for activities related to strengthening research in the behavioral and social sciences at NIH. OBSSR is continuing its efforts to work collaboratively across NIH Institutes and Centers (ICs) on the development and application of systems science approaches to address public health challenges and to advance cutting-edge behavioral and social sciences research.

Systems science methodologies provide tools for understanding the contributions of multiple social, economic, behavioral, and biological factors in both producing and ameliorating complex problems such as obesity and other chronic diseases. The OBSSR-led program in systems science research seeks to: raise awareness of the value of these methodologies as means of scientific inquiry; provide training in their use; and support research on the development and application of systems science methodologies for improving health. The first sets of awards under the OBSSR-led funding opportunity announcement (FOA), *Using Systems Science Methodologies to Protect and Improve Population Health*, were made in 2009. Activities to build this relatively new scientific field include: the first *Institute on Systems Science and Health*, sponsored by OBSSR and CDC (May, 2009); the *First Annual Workshop on Dynamic Modeling for Health Policy*, co-chaired by OBSSR and the University of Saskatchewan (July, 2009); the 2010 conference, *Social Computing, Behavioral Modeling and Prediction*, to be chaired by OBSSR; and, presentations/workshops at the 2010 meetings of the *Society for Prevention Research* and the *World Congress on Computational Modeling*.

OBSSR works with its IC partners to support other cutting-edge, scientific areas through the following activities: organization of the annual *Conference on the Science of Dissemination and Implementation*; participation in the NIH Roadmap Science of Behavior Change workgroup to stimulate transformative research on this topic; facilitation of the basic BSSR Opportunity Network (OppNet), a new initiative that will pursue shared opportunities to strengthen basic behavioral and social science research across the NIH; organization with the National Research Council of *Social Factors, Stress, Physiology and Health*, a planning workshop to explore research on how the broader social environment (e.g., poverty, education, culture, and discrimination) influences physiological stress pathways and health; leadership of FOAs entitled *Behavioral and Social Science Research on Understanding and Reducing Health Disparities*; and support of *Application of System Approaches to Health Disparities and Population Health*, a contract awarded to the University of Michigan to explore new research approaches that will improve the understanding of and help eliminate health disparities.

Item

Vulvodynia - The Committee calls upon the ORWH to allocate sufficient additional resources to the educational outreach campaign on vulvodynia, launched in 2007, to ensure that materials are more widely disseminated to the public, patient, and medical communities, as well as federally funded health centers and college health clinics. The Committee also notes that 5 years have passed since the last NIH vulvodynia conference, and requests that the ORWH convene, with the support of relevant institutes and centers, a research conference on vulvodynia in fiscal year 2010. (p. 115)

Action taken or to be taken

Please refer to page 231 of this document for OD's response to this item.

Conference Significant Item

Item

National Children's Study (NCS) — Unlike the past 2 years, the Committee bill does not include a specific amount of funding for the NCS. The NIH informed the Committee for several years that the total cost of the NCS would be approximately \$3,100,000,000. Later estimates conducted internally at the NIH put the total figure significantly higher, but the NIH did not provide the revised estimate to the Committee until recently, despite the Committee's strong interest in and support of the initiative. The Committee considers this withholding of information to be a serious breach of trust. The NIH now plans to extend the pilot phase of the NCS and postpone a final decision about whether to proceed with the full study until more is known about whether it is possible to achieve the original objectives of the NCS without drastically exceeding the budget that was initially presented to the Congress. The Committee welcomes that decision. However, given the lack of transparency involved with the study so far, the Committee believes it should have the most up-to-date information possible before settling on a specific funding level, if any, for the NCS, and thus will delay that decision until conference. (p. 113, 114)

Action taken or to be taken

The FY 2011 budget request of \$194,400,000, in the National Institutes of Health (NIH) Office of the Director, will support continuation of the National Children's Study (NCS) pilot, or feasibility phase, termed the Vanguard Study. The Vanguard Study began in January 2009 with two centers and expanded in April 2009 with five additional centers. The Vanguard Study will run in parallel to, but ahead of, the Main Study to allow the NCS to develop and refine operational approaches and assessments for the Main Study.

This budget request will allow the NCS to continue data acquisition, evaluate the methods used in the Vanguard Study, and make data-driven recommendations for the methodology of the Main Study. The Main Study protocol will thus be designed with assurance that its approaches are feasible and effective and can be accommodated within the budget. Before field implementation of the Main Study, the protocol will be further refined based upon peer review by an expert panel convened by the Director, NIH.

Analysis of early data from the current Vanguard Study locations suggested that initial assumptions regarding the rate of recruitment were overly optimistic. For this reason, the NCS intends to use FY 2011 funds to enhance community outreach and communications and to assess alternative recruitment strategies in additional locations. This will allow recruitment strategies based on Vanguard Study experience to inform the design of the Main Study with more accurate performance and cost estimates. In addition, having data on several alternatives will allow greater flexibility to select the most effective recruitment strategies for each city, town, or local area.

The administrative components of the NCS include a data coordinating center, an information management system, and logistics and communication support for the Vanguard Study Centers.

The NCS budget request will continue to support, through the NCS repository, bio-specimen and environmental collections. Several federal agencies and non-federal partners are collaborating with the NCS to evaluate the collection, transport, storage, and analytic techniques for environmental chemicals and biological samples and to optimize the logistical components of the study, to achieve greater efficiency and cost effectiveness.

Item

Office of AIDS Research (OAR) - HIV/AIDS - The conferees expect that NIH will work to strengthen its policy of supporting AIDS and non-AIDS research funding allocations at the current relative rate when allocating the second year of Recovery Act funding. House Report 111–220 had similar language. The Senate did not include comparable language. (p. 1031)

Action taken or to be taken

NIH will encourage the Institutes and Centers to give due consideration to any AIDS research projects that might benefit from this additional one-year funding.

Item

Research Project Grants - The conference agreement provides that, as proposed in Senate Report 111–66, with regard to section 516 of the bill, “program, project, or activity” applies to all sub-mechanisms and stand-alone activities in institute and center mechanism tables, except for the research project grants mechanism, in which case the restriction applies at the subtotal level. The House did not include comparable language. The conferees understand that NIH is upgrading its financial business system and is implementing hard funds controls. The conferees expect NIH to ensure that these funds controls will be established at the levels identified above to proactively enforce the reprogramming thresholds. The conferees request a detailed explanation and timeline in the 2011 congressional budget justification describing how the NIH enterprise system will proactively ensure full compliance with the reprogramming thresholds. (p. 1029, 1030)

Action taken or to be taken

The NIH is committed to implement hard funds control to proactively enforce reprogramming thresholds. As noted by the Conferees, the NIH is upgrading its enterprise financial and business system to implement hard funds control in FY 2011 to proactively prevent violations of the Anti Deficiency Act. A preliminary assessment of how best to implement hard funds control at the more granular sub-mechanism level specified by the Conferees has been undertaken. Additional systems modifications will be required, and it appears that the most efficient course of action is to implement those controls as part of a planned software upgrade to Oracle version 12.FSIO, currently planned for implementation in FY 2013.

In addition to these systems changes, NIH will be taking immediate actions both to ensure compliance and to minimize any potential program impact. An assessment is being undertaken to determine the extent to which changes to the current submission and review cycles for extramural awards may be necessary, and can be reasonably phased-in, to best align award decisions with the timeline for reprogramming notifications. Also, additional reporting capabilities will be developed for grants and budget personnel in FY 2010 so that

they can monitor obligations against budget allocations at the sub-mechanism level, and so that they can take action as necessary to avoid incurring obligations that would exceed reprogramming thresholds until proactive system controls are in place.