SIGNIFICANT ITEMS (SIs)

FY 2009 House Appropriations Subcommittee Print
and
FY 2009 Senate Appropriations Committee Report 110-410

Table of Contents

National Institutes of Health –Institutes and Centers

A

B

C

D

E

F

G

H

I

L

M

N

O

P

R

S

T

U

V

W

National Cancer Institute (NCI)

House Significant Items

Item

***Bone Cancer* -** The Committee encourages NCI to enhance its research program in osteosarcoma biology through grant mechanisms that emphasize development of suitable genetic and cell transplantation models, studies on the role the tumor microenvironment plays in tumor progression, the identification of tumor progenitor cells, and the biology of tumor invasion. The Committee also urges NCI to support research on the development of clinically-relevant experimental models of tumor dormancy, studies on dormant tumor cells and their interaction with the microenvironment, and identification of factors that trigger dormancy of invasive tumor cells or activation of dormant cells. (p.139)

Action taken or to be taken

The NCI supports basic, translational and clinical research programs directed at bone cancers and recognizes the need to encourage more research on these clinically challenging cancers.

In September 2008, NCI, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, as well as the American Academy of Orthopaedic Surgeons supported a Symposium entitled the "Molecular Biology and Therapeutics in Musculoskeletal Oncology." An executive summary of the meeting will be published and provide a significant resource for investigators interested in pursuing career focused on sarcoma research.

A paper presented at the Symposium reported on activation or dysregulation of the mTOR pathway and its impact on sarcomas. The mTOR pathway is a key regulator of cell growth and proliferation. Evidence suggests its activation or dysregulation can be linked to several features of the cancer phenotype including cellular proliferation, resistance of apoptosis (cancer cell death), autophagy, angiogenesis and metastasis. As a result, mTOR is a target for new cancer drug development. Recent results have shown a combination therapy of Insulin-Like Growth Factor 1 Receptor and rapamycin are highly effective in preclinical models of some childhood sarcoma, including Ewing's sarcoma and rhabdomyosarcoma.

In 2008, NCI supported a special workshop on hormone refractory cancers (e.g., breast and prostate) which dominantly metastasize to the bone. The focus was on current knowledge on the role of steroid hormone receptors in promoting growth of breast and prostate cancer metastases including bone metastasis**.**

Since 2006, NCI, through Tumor Microenvironment Network (TMEN) grant program, has devoted targeted resources towards understanding the role of the

tumor microenvironment in tumor progression, the identification of progenitor cells, and the biology of tumor invasion at institutions across the country in which the primary research objective is to delineate mechanisms of tumor-host interactions. The focus of one of the TMEN working groups is on bone marrow derived cells involved in bone cancers, and studies on bone metastasis.

The NCI-supported Pediatric Preclinical Testing Program (PPTP) is a comprehensive program to systematically evaluate novel agents against a molecularly characterized set of childhood cancer models, including models for the bone cancers osteosarcoma and Ewing sarcoma. For more information about PPTP access the following link: http://pptp.stjude.org/.

Item

Cancer Centers **-** The Committee commends NCI on the success of its cancer centers program. Given that minority populations suffer disproportionately from virtually every form of cancer, the Committee encourages NCI to consider supporting the establishment of a comprehensive center at a minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 139)

Action taken or to be taken

NCI continues to strengthen the nation's research, treatment, prevention and education network to ensure African American and other minority communities have access to the comprehensive cancer programs available throughout the National Cancer Program. NCI's Cancer Centers Director's Report to the National Cancer Advisory Board in 2007 provided a blueprint for how the Cancer Centers could partner with the NCI to accelerate the process required to reduce the cancer burden and underscored the need for new strategies to address health disparities. NCI continues involvement of the Minority-Based Community Clinical Oncology Program and the Minority Institution/Cancer Center Partnership (MI/CCP) Program in efforts to improve primary and secondary prevention, expand current outreach programs to increase the recruitment of minority populations to cancer clinical trials, and to support other collaborative efforts with the Cancer Centers Program to help alleviate the disproportionate burden of cancer borne by members of racial and ethnic minority groups

Through the MI/CCP Program, established in 2001, NCI is focused on facilitating research, education, training, and outreach to the minority community and to minority researchers, with the goal of improving the participation of minorities in all aspects of cancer research. This brings together Minority-Serving Institutions and Cancer Centers to take advantage of their expertise in educating ethnic minorities and engaging in research, training, career development and community outreach activities respectively. This partnership is a critical step toward building comprehensive cancer center programs at minority institutions that include a strong interactive research base as well as state-of-the-art care

and a wide spectrum of prevention, care, education, information, and dissemination activities that broadly serve their communities.

Item

Endometrial Cancer and Obesity - With the current obesity trend that is occurring in the U.S., it is becoming apparent that this rate of rise is parallel to that seen in endometrial cancer. This is due to the fact that the unopposed estrogen that drives endometrial cancer formation in the majority of women occurs in the peripheral fat. Additionally, there is a strong link between endometrial cancer and insulin resistance, implying endometrial cancer may be in the continuum of the metabolic syndrome. The Committee is concerned about this disturbing increase in mortality in a cancer that is the leading gynecologic cancer in the U.S. The Committee urges NCI to prioritize resources for prevention and therapeutic strategies against endometrial cancer in addition to funding that is already allocated to obesity research. (p. 139/140)

Action taken or to be taken

The NCI is collaborating on the molecular biology and prevention of endometrial cancer with the Walter Reed Army Medical Center, the Centers for Disease Control and Prevention, Duke University, Northwestern University, and the Bowman Gray School of Medicine. One of the current projects focuses on identifying underlying biological causes for associations between obesity and endometrial cancer. Obese patients are not only at risk for developing endometrial cancer but also more likely to die from cancer when compared to lean women with endometrial cancer. Preliminary data has revealed that global gene expression in endometrial cancers from obese and lean women is different. Further studies are underway with more definitive analysis tools to identify expression differences between obese and lean women with endometrial cancer that might provide opportunities for development of chemopreventive agents and/or therapeutics in the future.

Differences in estrogen metabolism among obese women may be associated with endometrial cancer. Studies are planned to analyze the estrogen levels in urine/serum/blood samples from the Gynecologic Oncology Group (GOG) 210 Endometrial Cancer Repository. Tissue samples would be analyzed to correlate with the metabolic data.

NCI researchers are determining the molecular changes in endometrial cancer fibroblasts by analyzing differential expression in mRNA, microRNA, and proteins. This may uncover new therapeutic strategies based on RNA silencing.

Working with the international Gynecologic Cancer Intergroup, NCI co-sponsored a workshop on endometrial cancer treatment trials in 2007. At this workshop, representatives from 15 clinical trials cooperative groups and centers of excellence in endometrial cancer research from around the world identified the

key clinical questions in the treatment of endometrial cancer and forged consensus for the design of the next generation of clinical trials.

The NCI supports the operations of the groups most active in endometrial cancer clinical trials in the United States, namely the Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG), as well as provides partial support to the data centers of two other groups active in endometrial cancer research, the NCI-Canada Clinical Trials Cooperative Group and the European Organization for Research and Treatment of Cancer. The University of Texas MD Anderson Cancer Center Uterine Specialized Programs of Research Excellence (SPORE) is also working to identify new targets for prevention and treatment of endometrial cancer. These SPORE investigators are also closely integrated into the scientific research programs of the GOG and RTOG, ensuring a collaborative environment. The GOG is one of NCI's funded cooperative cancer research groups. It's the only group which focuses its research on women with pelvic malignancies, such as cancer of the ovary, uterus, and cervix.

Item

Gynecologic Oncology Clinical Trials - The Committee recognizes NCI's longstanding commitment to improving the health of women through gynecologic oncology clinical trials. These clinical trials have led to the identification of new therapeutic agents and techniques for treating gynecologic cancers. The Committee encourages NCI to continue its support of gynecologic oncology clinical trials through public-private partnerships. Priority should be given to translational research involving biologic prognosticators and targeted therapies to speed the development and delivery of new cancer treatments to women with gynecologic cancers (p. 140).

Action taken or to be taken

NCI, in collaboration with the Gynecologic Oncology Group (GOG) and the Cancer Genetics Network (CGN), a national network of centers specializing in the study of inherited predisposition to cancer, is conducting a 5-year prospective study to identify ways to lower the risk of developing ovarian cancer and to improve the ability to detect this cancer at an earlier, more readily curable, stage. The *"National Ovarian Cancer Prevention and Early Detection Study"* targets women at elevated risk, either because they have a strong family history of breast or ovarian cancer or because they have tested positive for changes in genes which increase the risk of developing ovarian cancer. For more information about this study access the following link: http://www.cancer.gov/clinicaltrials/ft-GOG-0199.

NCI-sponsored studies are pursuing molecular profiling of DNA, RNA, and protein markers to shed light on the successes and failures of treatment in patients with gynecological cancers and also to provide a basis for individualization of therapy. Toward this end:

- Investigators are developing a custom microarray chip from an independent set of 80 tumors as a prognostic tool of ovarian cancer outcome
- An international scientific team led by NCI researchers found elevated levels of certain proteins typically associated with keeping cancer cells alive may actually correspond with improved patient survival in ovarian cancer.

NCI sponsors four Specialized Programs of Research Excellence (SPOREs) in ovarian and gynecologic cancer. These work closely with the NCI and the Clinical Trials Cooperative Groups to facilitate translational research in gynecologic cancer. The SPOREs and Cooperative Groups are also represented on the Gynecologic Cancer Steering Committee, which establishes priorities for phase III treatment trials sponsored by the NCI.

The GOG is working with the NCI Intramural researchers in the Center for Cancer Research, to study serum proteomic profiles among women with adnexal masses who are to undergo surgery to rule out ovarian cancer. This study may help separate those women who do not have ovarian cancer, and, therefore, may avoid surgery altogether, from those women who do have ovarian cancer and should undergo surgery immediately by a gynecologic oncologist. A second study, again conducted in a partnership between GOG and NCI, focuses on women with ovarian cancer who have just completed primary treatment. Serum proteomic profiles may help identify those women at low risk for recurrence, who may avoid chemotherapy, and those at high risk for recurrence, who may benefit from more aggressive and prolonged chemotherapy.

Item

***HPV Vaccine and Cervical Cancer* -** The Committee encourages NCI to study if there are clinical and cost benefits of prospectively tracking pap test results and outcomes in women who have been vaccinated for human papillomavirus (HPV). The Committee encourages NCI to support research that will identify the most cost-effective management strategy for cervical cancer screening in the era of HPV vaccines and to identify the circumstances where pap test/HPV screening fails in vaccinated women. (p. 140)

Action taken or to be taken

To date, prevention for cervical cancer is achieved primarily through cytologic testing (e.g., Pap smears and cervical cytology), and more recently with of HPV testing. This strategy is successful, as evidenced by the 70 percent reduction in cervical cancer mortality since screening was implemented, but it is expensive, costing billions of dollars per year. The HPV vaccine has shown near complete protection against new infections and lesions caused by HPV types contained in the vaccine. By implementing complementary vaccination and screening protocols, overall costs may be reduced by providing optimal protection and reducing the consequences for unnecessary treatment of women. Studies are

underway to determine the most cost-effective, evidence-based cervical cancer prevention strategies.

Continued cervical cancer screening in vaccinated populations remains a priority because vaccination does not treat established infections and does not protect against all types of HPV that can cause cancer and precancer. Since duration of protection and long-term vaccine effects are not fully understood, research opportunities exist to define the long-term effects of vaccination and determine what the optimal post-vaccination follow-up strategy should be for cervical cancer prevention. In turn, this work should inform a modification of current screening practices and change the standard of care.

Recently published modeling data suggest it would be ideal to target vaccination among women at younger ages before initial HPV infection. 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. Further modeling efforts by health economists will help to estimate how screening could be modified, but model calibration targets require data that are currently not available and could only be provided by large-scale population-based studies including extensive registry programs with record-linkage systems.

Studies to prospectively evaluate longer-term vaccination effects and to track Pap cytology and HPV typing results linked to vaccination status will help to understand the long-term impact of HPV vaccination and determine the most cost-effective, evidence-based screening strategies for vaccinated populations,. NCI is extending follow-up of women enrolled in a 7,500-woman community-based trial of an HPV-16/18 vaccine in Costa Rica, which 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 to inform changes in cervical cancer screening protocols and policies. See the following link for more information: http://clinicaltrials.gov/ct2/show/NCT00128661?term=hpv+costa+rica&rank=1.

Item

Liver Cancer **-** The Committee encourages NCI to develop a comprehensive research program to slow the incidence of primary liver cancer and to develop viable treatment options that will improve survivability. The Committee supports additional research aimed at discovery of new interventions for the early detection, management and treatment of cancer associated with hepatitis. The Early Detection Research Network continues to be an impressive and Productive programmatic model (p. 140).

Action taken or to be taken

Liver cancer, the majority are known as hepatocellular cancer (HCC), is the most rapidly increasing type of cancer in the United States. It accounts for at least 14,000 deaths in the U.S. annually and it ranks eighth as cause of cancer mortality in men.

NCI continues to actively sponsor the clinical development of new, investigational agents in liver cancer. Over the past year, NCI has sponsored development of approximately 12 new agents in 15 phase I and phase II clinical trials for patients with liver cancer and has additional studies with new investigational agents under review. The NCI Gastrointestinal Steering Committee, formed as part of the NCI's efforts in restructuring the national clinical trials enterprise to ensure it is founded on the best science, in conjunction with the NCI-sponsored Cooperative Group Clinical Trials program has developed two phase III trials that are expected to open in 2009 involving the drugs sorafenib and doxorubicin. NCI sponsored a State of the Clinical Science meeting concerning HCC on December 12-13, 2008, to explore new avenues of both clinical and translational research in this disease.

NCI is supporting three new initiatives aimed at increasing our understanding of the fundamental etiologic mechanisms involved in HCC. These Trans-NIH funding announcements seek applications on the etiology of HCC, including the identification of viral and host factors in the initiation of HCC; the development of animal models for HCC that imitate the full spectrum of the disease from initial infection through malignancy; examination of the development of HCC in the sequelae of HIV, hepatitis B and hepatitis C infections; the development of prevention and control strategies, including chemoprevention; and preclinical and clinical trials of new agents.

Currently, less than 15 percent of newly diagnosed HCC patients survive beyond the first year, because of the disease's propensity to invade surrounding tissues and the lack of early detection tools. Alpha-fetoprotein (AFP) is currently the only diagnostic biomarker for HCC. Unfortunately, elevated AFP levels are detectable in only about 60 percent of HCC patients and when it is detected, most of these patients have advanced disease. In addition to AFP often missing many early-stage HCC cases, this biomarker often gives false-positive results.

Advances in molecular profiling in HCC have given insight into signatures of disease and have implications in early detection, prevention, treatment and prognosis. More translational and clinical research is needed to fully harness this knowledge into molecularly targeted approaches. Meanwhile, NCI-sponsored scientists are making headway in identifying new biomarkers for HCC.

The Early Detection Research Network (EDRN) is continuing to play an important role in finding biomarkers for HCC. For a recent report on EDRN activities involving biomarkers, access the following link:
http://prevention.cancer.gov/files/edrn4th.pdf.

Item
Lung Cancer **-** The Committee is concerned about the continued high level of mortality among lung cancer patients. The Committee encourages NCI to strengthen its research to improve lung cancer diagnosis and treatment and to undertake additional research to better understand the role gender plays in this disease. (p. 140)

Action taken or to be taken

Lung cancer is difficult to detect in its early stages; in most cases, tumors are detected at advanced stages and the overall five-year survival rate for all stages combined is approximately 15 percent. Thus it is particularly important to understand the early events that precipitate development of lung carcinogenesis.

Current research suggests that pro-inflammatory conditions, particularly those related to pulmonary irritation, contribute to lung cancer development. An NCI initiative focused on the relationship between alterations in the lung microenvironment caused by inflammation and carcinogenesis has resulted in nine new basic research investigations that will explore the role of inflammation and sequential changes that occur in lung cells as they progress from normal to malignant. Some of the studies in the initiative focus on lung cancer stem cells that may be important to improving therapy.

Greater understanding of the genetic alterations that occur with smoking should provide greater insight into the development of cellular targets for treating, and possibly preventing, lung cancer.

For example: NCI researchers examining gene expression profiles found over 100 genes that were differently expressed in tumors of smokers versus never-smokers, and found similar expression of many genes among current smokers and former smokers. Thus, smoking seems to cause long-lasting gene expression changes that can contribute to lung cancer development long after cessation; if confirmed, these genes could become important targets for prevention and treatment. For more information about prevention, genetics and causes of lung cancer access the following link: http://www.cancer.gov/cancertopics/prevention-genetics-causes/lung.

The identification of molecular biomarkers will also serve to improve lung cancer diagnosis and prediction of prognosis. Ongoing work at NCI in this area includes:

- Determining whether levels of signaling protein cytokine and a gene expression signature called Cytokine Lung Adenocarcinoma Survival Signature (CLASS-11) can be used as clinical markers of lung cancer diagnosis, prognosis, and therapeutic outcome.
- A large, ongoing, national NSCLC clinical trial called MARVEL (Marker Validation for Erlotinib in Lung Cancer) to validate whether a biomarker can predict clinical benefit in the treatment of this disease. The biomarker would identify a target, known as epidermal growth factor receptor (EGFR), which is increased in some lung cancers due to extra copies of its coding gene and can activate tumor growth. Drugs that block this activation could have a significant impact on lung cancer treatment. For more information about the

search for biomarkers to help guide treatment for lung cancer access the following link: http://www.nih.gov/news/health/oct2008/nci-02.htm.

NCI's Surveillance Epidemiology and End Results Program provides statistics by gender on the incidence, prevalence, and life-time risk for lung cancer. Similarly, models created through the Cancer Intervention and Surveillance Modeling Network help examine how tobacco control interventions, treatments, and public policies may affect lung cancer incidence and mortality. The Tobacco Research Network on Disparities is examining the effects of tobacco control policies on diverse populations of low socioeconomic status women and girls. Through the Cancer Care Outcomes Research and Surveillance Consortium, NCI supports cohort studies on approximately 5,000 lung cancer patients. The initiative examines how patient characteristics influence treatment and outcomes.

Item

Neuroblastoma **-** The Committee encourages 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 research, both intramural and extramural. (p. 140)

Action taken or to be taken

The NCI research activities for neuroblastoma described are organized around specific research programs that have a substantial neuroblastoma component and that contribute to NCI's overall goal of improving diagnosis and identifying treatments that improve survival.

The Children's Oncology Group (COG) develops and coordinates cancer clinical trials at over 200 member institutions throughout the United States and in Canada, Europe, and Australia. A high priority trial for COG is evaluating the role of the chimeric antibody 14.18 in high-risk neuroblastoma patients following myeloablative therapy and stem cell transplant. The NCI manufactured the antibody so that COG could definitively evaluate this neuroblastoma-targeted agent. In 2008, COG researchers reported genes on chromosome 6p22 are important in the development of neuroblastoma and identified activating mutations in the ALK oncogene as the primary cause of familial neuroblastoma, present in about 10 percent of sporadic neuroblastoma cases. This discovery has immediate clinical implications, as small molecule ALK inhibitors are already under clinical evaluation. NCI supports the COG Phase I/Pilot Consortium that includes a subset of COG institutions and is responsible for expeditiously developing and implementing pediatric phase I and pilot studies.

An important component of NCI's research effort for neuroblastoma is the Childhood Cancer TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Initiative. The goal is to identify and validate therapeutic targets for childhood cancers. The Neuroblastoma TARGET Project, will perform

specialized genetic analysis and sequencing of 100 genes from 300 neuroblastoma tumors. (See http://target.cancer.gov/ for more information about the TARGET project.)

The objective of the NCI-supported Pediatric Preclinical Testing Program (PPTP), a comprehensive program to evaluate new agents against childhood solid tumor (including neuroblastoma) and leukemia models, is to identify novel agents with the potential for significant activity when clinically evaluated against selected childhood cancers.

The NCI-supported New Approaches to Neuroblastoma Treatment (NANT) Consortium is a group of 13 university and children's hospitals with strong neuroblastoma research and treatment programs. The NANT Consortium focuses on new therapies for neuroblastoma patients who no longer respond to standard treatments.

Use of genetic markers could improve diagnostic accuracy and open the way for genetic-based therapies. NCI scientists identified a gene expression signature that can diagnose neuroblastoma. Investigators also found 19 genes that can be used to predict survival for individual neuroblastoma patients.

Several clinical trials for neuroblastoma patients are underway involving the use of ABT-751, an orally bioavailable tubulin inhibitor. NCI is enrolling patients in a clinical trial of treatment that incorporates a tumor vaccine and autologous cell therapy for patients with newly diagnosed or late recurrent neuroblastoma.

Item

Reproductive Scientists Development Program **-** 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. (p. 141)

Action taken or to be taken

The NCI, together with NICHD, met its initial commitment and funded the Reproductive Scientists Development Program (RSDP) for gynecologic oncologist training during fiscal year 2007. The training of the RSDP Scholars is unique and has a two phase design with the first two years (Phase I) at $100,000 per year. The scientists are placed in laboratories of prominent scientists, usually emphasizing a basic science training, (i.e. not in predominantly medical departments such as obstetrics and gynecology). This allows the clinician to be exposed to molecular and cellular research in oncology for the initial two years (Phase I). Phase II is their first three years on faculty during which a minimum of 75% effort is protected for research under a mentor's direction. Phase II is funded by partnerships with philanthropic organizations, leading obstetric/gynecologic organizations, pharmaceutical companies, scholar-initiated

grants, and departmental resources. A department must agree to accept the Scholar on faculty and to provide the required support before the Scholar can apply for an RSDP Scholarship. The NCI will investigate the possibility of reinvigorating this program by again partnering with NICHD in the future.

Item

Symptom Research **-** The Committee encourages NIH to strengthen its research on the treatment and management of symptoms and side effects associated with cancer and cancer treatment and to evaluate the role of nursing interventions in the amelioration of such symptoms and side effects. (p.141)

Action taken or to be taken

The goal is to achieve a future when cancer is uncommon and easily treated. Once almost uniformly fatal, cancer has become a chronic illness for many and, for growing numbers of people, curable. Today, there are nearly 12 million cancer survivors in the U.S. As we focus on the needs of people after cancer diagnosis and treatment, we have many questions about their health status and quality of life. Unfortunately, it is clear that most of our current treatments will produce some measure of adversity. NCI is committed to increasing its investment in symptom research, one that both acknowledges and strives to learn from the growing numbers of cancer survivors.

In the fall of 2007, NCI created the Trans-NCI Pharmacoepidemiology and Pharmacogenomics Working Group (PPWG). Specifically, NCI will support research to identify epidemiologic (i.e., lifestyle, occupation, behavior, demographics, dietary and environmental exposures), clinical, and genomic profiles associated with:

1) Increased cancer risks or protective effects from newly developed and commonly used pharmaceuticals.
2) Acute and longer-term adverse events associated with therapies used to treat cancer, and palliative agents used to ameliorate cancer treatment side effects.
3) Enhanced responses (or lack of response) to therapies used to treat cancer, and supportive and palliative agents used to ameliorate cancer treatment side effects.

The NCI Community Cancer Centers Program (NCCCP) is a three-year pilot program to test the concept of a national network of community cancer centers to expand cancer research and deliver the latest, most advanced cancer care to a greater number of Americans in the communities in which they live. Building on the new ASCO treatment summary forms, the pilot sites created a survivorship care planning tool for women completing breast cancer treatment. The template includes detailed information on treatments received, guidelines for surveillance, as well as a list of risk factors for potential long-term and late effects of therapy and approaches to monitor and address these possible problems. Use of the breast cancer treatment summaries by physicians and patients will be evaluated over the next year.

NCI partners across NIH to fund research on the treatment and management of symptoms and side effects associated with cancer and cancer treatment. With the National Institute of Nursing Research (NINR), NCI participates on a program

announcement on Symptom Clusters in Cancer and Immune Disorders.. With the National Institute of Child Health and Human Development (NICHD), NCI co-sponsors a program announcement on Optimizing Technologies for the Preservation of Fertility.

Senate Significant Items

Item

Bone Cancer **-** The NCI is encouraged to enhance its research program in osteosarcoma biology through exploratory and other grant mechanisms emphasizing the following priorities: development of suitable genetic and orthotopic models, studies on the role the tumor microenvironment plays in tumor progression, the identification of tumor progenitor cells and the biology of tumor invasion. The NCI is also urged to support research on the development of clinically relevant experimental models of tumor dormancy, studies on dormant tumor cells and their interaction with the microenvironment, and identification of factors that trigger dormancy of invasive tumor cells or activation of dormant cells. (p. 92)

Action taken or to be taken

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

Item

Health Communication **-** The Committee encourages the NCI to continue its investment in the Health Information National Trends Survey [HINTS], and to consider expanding the survey to track how public information campaigns may influence attitudes about cancer screening and vaccines. (p. 92)

Action taken or to be taken

The first and only survey of its kind, HINTS collects data on the American public's need for, access to, and use of cancer information. HINTS data is collected biennially via telephone interviews using a representative national sample of American adults, with over-sampling of the largest ethnic minority populations. The survey began in 2001 and provides a unique set of data that enable investigators to examine the relationship between health communication and cancer-related knowledge, attitudes, and behaviors. The data identify communication trends and practices; provide updates on changing information patterns, needs, and opportunities; assess cancer information access and usage; and provide insight about how cancer risks are perceived.

For example researchers found that in 2005, prior to approval of the human papillomavirus (HPV) vaccine, awareness among American women about HPV and its link to cervical cancer was low. In fact, 60 percent of respondents had never heard of HPV and 43 percent of those surveyed were unaware of the virus' connection to cervical cancer. Awareness was lowest among women who were

older, less educated, or less exposed to health information. The majority of respondents who heard of HPV knew it was a common infection that does not go away without treatment.

NCI continues to conduct studies to track changes in this awareness most likely related to the influx of recent media coverage and pharmaceutical marketing surrounding HPV. For example, the 2007 HINTS survey added new questions such as, "…before today, have you ever heard of the cervical cancer vaccine or HPV shot," and "A vaccine to prevent the human papillomavirus or HPV infection is recommended for girls aged 11-12 and is called the cervical cancer vaccine, HPV shot, or GARDASIL®. If you had a daughter that age, would you have her get it?" Data from this HINTS survey will help researchers further examine the relationship between public information campaigns and attitudes about vaccines.

Using HINTS data, researchers also found that most Americans know that mammograms, pap smears, and colonoscopies are screening exams for cancer, but are unaware of the appropriate age to initiate these tests. Another trend uncovered by HINTS data are the significant "knowledge gaps" among factions of the population with regard to what is known about preventing cancer and where information on cancer can be obtained. NCI looks forward to helping communication practitioners use HINTS data to understand health communication and cancer-related knowledge, attitudes, and behaviors.

Item

Liver Cancer- The Committee continues to urge the NCI to develop a comprehensive research program to slow the incidence of primary liver cancer and to develop viable treatment options that will improve survivability. The Committee urges more programs aimed at the discovery of new interventions for the early detection, management and treatment of cancer associated with hepatitis. The Early Detection Research Network continues to be an impressive and productive programmatic model. (p. 92)

Action taken or to be taken

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

Item

Lung Cancer - The Committee encourages the NCI to expand its research to improve lung cancer diagnosis and treatment and undertake additional research to better understand the role gender plays in this disease. (p. 92)

Action taken or to be taken

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

Item

Melanoma - The Committee is aware of the ongoing dialogue between the NCI and the advocacy and extramural research community on prioritizing NIH-funded melanoma research, most recently with the 2007 ''Community-Oriented Strategic

Action Plan for Melanoma Research.'' The Committee encourages the NCI to better target its funds in three categories: targeted therapies in melanoma; host response in melanoma; and prevention, including exploring the feasibility of a randomized trial of screening for melanoma. (p. 92)

Action taken or to be taken

The 2007 Community-Oriented Strategic Action Plan for Melanoma identifies opportunities in melanoma research and provides a set of recommendations for the Director. It is a five-year strategic plan proposed to address new directions and targets for future melanoma research. In July 2008, NCI submitted to Congress an implementation plan to follow the strategic plan. The NCI continues to initiate projects to advance the following three major research goals: reduce melanoma mortality through prevention and early detection; streamline the development of personalized melanoma diagnosis and treatment to improve diagnostic accuracy, disease classification, and prediction of treatment response; and improve survival from advanced melanoma.

The NCI Cancer Therapy Evaluation Program (CTEP) is supporting large, phase III clinical trials that are testing targeted therapies, including immunotherapy, immunostimulating agents, and melanoma vaccines. Additionally, CTEP has more than 10 phase I and II trials using drugs such as sorafenib and imatinib to target genetic mutations commonly found in melanoma cells. Novel approaches, such as the use of histone deacetylase inhibitors to control cell growth, are being investigated as new ways to fight the disease in a targeted fashion. For more information about CTEP, access the following link: http://ctep.info.nih.gov/.

The NCI-sponsored Specialized Program of Research Excellence (SPORE) on skin cancer supports innovative research in the prevention, detection, and treatment of melanoma by funding multidisciplinary translational projects at various institutions in the country. The Wistar Institute is conducting a phase III trial using sorafenib, an inhibitor of the enzyme produced by the BRAF gene, in conjunction with chemotherapy, in more than 800 patients. If effective, this combination therapy may become a first line treatment for patients with metastatic melanoma. For more information about the SPORE on skin cancer, access the following link: http://spores.nci.nih.gov/current/skin/skin.html.

New approaches to understanding host response in melanoma development and treatment are being explored. Intramural investigators are developing strategies that use drugs to block formation of melanosomes (cell structures containing melanin), or that inhibit the function of drug transporters in order to make melanomas more drug-sensitive. Clinical samples of melanoma tumors are being used to study the expression of approximately 380 genes thought to contribute to drug resistance in cancer.

In addition, the new melanoma risk assessment tool (MRAT) developed by NCI researchers will be validated and refined in an upcoming trial to identify participants at high risk. The MRAT uses a short series of questions to estimate the five-year absolute risk of disease. In the trial, the tool could be used to screen potential participants and identify those at high risk who would receive the greatest benefit from a targeted screening intervention.

Item

NCI Community Cancer Centers Program - The Committee commends the NCI for launching the NCI Community Cancer Centers Program [NCCCP] early in 2007. The NCCCP, now in a 3-year pilot phase, seeks to bring more Americans into a system of high quality cancer care, increase participation in clinical trials, reduce cancer healthcare disparities, and improve information sharing among community cancer centers. The program encourages collaboration of private-practice medical, surgical, and radiation oncologists as well as providing links to NCI research and the NCI designated Cancer Centers. The Committee supports these goals and encourages the NCI to continue supporting this program. (p. 92)

Action taken or to be taken

As the pilot phase of the NCI Community Cancer Centers Program (NCCCP) concludes its first of three years, each participating community hospital has taken steps to accelerate cancer research and raise the quality of care—and to do both with a special emphasis on minority and underserved patients.

The 16 participating hospitals have made considerable progress toward achieving the major goals of the pilot. The hospitals are accruing more patients into clinical trials and are at the forefront of putting into place national standards for handling biospecimens bound for research laboratories. Some sites have begun moving their decentralized, paper-based records systems into computerized data that will improve both cancer research and patient care, while enabling minorities and underserved patients to more effectively benefit from the most up-to-date, evidence-based care.

The pilot is beginning to define for the NCI what it will take to build a network of community cancer centers that are fully engaged with the research community and that provide the latest evidence-based, multidisciplinary care and treatment to patients of all racial and ethnic backgrounds and socioeconomic standings in their home communities. NCCCP hospitals have entered into new collaborations with NCI-designated Cancer Centers located at major research institutions around the country and expanded their relationships with local private medical practice oncology physicians. Through these connections, NCI is extending the reach of its research programs into rural, inner-city, and underserved communities.

In the remaining two years of the NCCCP pilot, the sites are working on their individual plans to meet the long term goals of the initiative. In addition, they will continue collaborating to further strengthen this network of community cancer centers and keep looking ahead to continue learning from this public-private partnership for the best ways to advance state-of-the-art cancer care and research in the community setting.

Item

Neuroblastoma

The Committee urges the NCI to significantly expand its research portfolio on neuroblastoma, with a focus on clinical trials for high-risk patients. Given the poor survival rates for children with advanced disease, the Committee encourages the NCI to prioritize support for all promising neuroblastoma research in this population, both inside and outside of the Children's Oncology Group. (p. 93)

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 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. 93)

Action taken or to be taken

The National Cancer Institute (NCI) supports a comprehensive, collaborative preclinical and clinical research program for children. This research program extends from preclinical research aimed at identifying and validating new therapeutic targets for specific childhood cancers to clinical trials that evaluate whether the preclinical discoveries can be translated into clinical benefit. In 2008, over 20 pediatric phase I, II, and III cancer clinical trials were initiated and 90 clinical trials were open to enrollment. The NCI also supports multi-institutional studies, such as the Childhood Cancer Survivor Study, designed to assess the long-term effects of childhood cancer treatment and help develop therapies that minimize harmful effects.

The Children's Oncology Group (COG) coordinates clinical trials at over 200 institutions that are advancing the field of pediatric oncology. In 2008, results from a treatment study for Ewing sarcoma, the second most common bone tumor in children and young adults, showed that patients receiving chemotherapy every 2 weeks versus every 3 weeks were more likely to be cured. COG researchers also reported in 2008 that adding the molecularly targeted agent imatinib to standard chemotherapy for Philadelphia chromosome positive acute

lymphoblastic leukemia (ALL) appears to improve outcome for this aggressive form of leukemia. A subset of COG institutions, the COG Phase I/Pilot Consortium, allows new agents to be introduced in the pediatric setting with close monitoring of unanticipated toxicities and with state-of-the-art pharmacokinetic evaluations to determine how children metabolize the agent.

The NCI-supported New Approaches to Neuroblastoma Treatment Consortium is a group of 13 university and children's hospitals focusing on new therapies for neuroblastoma patients who no longer respond to standard treatment. The Pediatric Brain Tumor Consortium is a clinical trials group that includes 8 children's cancer centers that is supported by NCI to evaluate new, innovative treatment strategies for children with brain cancers.

NCI's Childhood Cancer TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Initiative is focusing on ALL (a fast-growing type of leukemia) and neuroblastoma and identifying genes consistently mutated or altered in specific cancers that may provide critical leads for identifying therapeutic targets. The ALL project has identified an ALL subtype with very poor outcome and made progress in identifying the ALL subtype's molecular characteristics that may lead to more effective treatment. Another project found that the ALK gene is activated through mutation in approximately 10 percent of high-risk neuroblastoma cases, and small molecule ALK inhibitors are already under clinical evaluation.

Item

***Prostate Cancer Imaging* -** The Committee is aware of the potential of prostate imaging to improve early diagnosis and minimally invasive treatment of prostate cancer, and it encourages the NCI to provide additional funding for research and the development of technologies for prostate cancer detection and treatment, comparable to state-of-the-art mammograms. (p. 93)

Action taken or to be taken

NCI-supported development of new imaging technology continues to provide promising methods for the early diagnosis and treatment of minimally invasive prostate cancer.

In addition to magnetic resonance (MR) and MR spectroscopy imaging, newer techniques are developing. Clinical trial results have shown MR spectroscopic imaging can help evaluate local recurrence after external beam radiotherapy. This condition was not previously considered amenable to standard radiological assessment.

Other ongoing studies evaluate how imaging results correlate with biopsies and how functional imaging can evaluate response to radiotherapy. Imaging science is playing an increasing role in the minimally invasive treatment of prostate cancer leading to improved quality of life in treated patients. Studies combining

focused ultrasound and MR imaging or MR-guided ultrasound allow for accurate detection of the disease, measurement of tissue temperature changes, and confirmation of thermally induced tissue changes, thus resulting in improved treatments with less morbidity.

Brachytherapy for prostate cancer has been increasing in use as long-term survival data in treated prostate cancer patients has shown it to be comparable to more invasive surgical prostatectomy, but without the long-term side effects of urinary incontinence and sexual impotence. The success of brachytherapy chiefly depends on the ability to intraoperatively tailor the radiation dose to the patient's individual anatomy. NCI-sponsored clinical trials are in progress to design, develop, and test methods for intra-operative localization of the implanted seeds in relation to the prostate.

In June 2008, the NCI convened a comprehensive prostate cancer meeting to focus on the promise of imaging science to improve the early diagnosis and treatment of all stages of prostate cancer. A meeting summary will be published in an imaging science or cancer research journal.

Overtreatment of prostate cancer is a significant health care issue. Many men are diagnosed with low grade disease, yet have had to choose between "watchful waiting" or whole gland therapies (surgery and radiation), which render a high percentage of patients impotent or incontinent. Organ-sparing focal therapy has not been possible because of limitations on our ability to use imaging techniques to direct therapy precisely into the lesion. Recently, scientists at NCI, in collaboration with the Philips Company, have developed a technique which fuses magnetic resonance (MR) and Positron Emission Tomography (PET) data with real-time ultrasound, making it possible to guide and monitor biopsy and therapy procedures to the target lesions with high fidelity. Current research is focused on developing focal ablative therapies using this technology.

Item

Vaccine Research - The Committee recognizes that aspects of science surrounding an HIV vaccine and cancer vaccines contain many similarities and synergies. Therefore, the Committee urges the NCI to incorporate the development of an HIV vaccine into cancer vaccine research efforts. The Committee also supports new partnerships between the NCI and Institutes that are capable of supporting a joint HIV/cancer vaccine program. In addition, the Committee urges the OAR to increase HIV/AIDS funding at NCI. (p. 93)

Action taken or to be taken

NCI has a substantial ongoing research effort in developing therapeutic approaches to combat cancer through the development of cancer vaccines and other strategies to arm the immune system. This effort is built on a substantial and longstanding foundation of basic immunology research within the NCI. One challenge in this effort is that most cancers are immunologically almost identical

to normal cells and fail to elicit a strong protective immune response. Also, patients with cancer often have defects in their immune system. Certain cancers, such as primary effusion lymphoma, are caused by viruses that can provide immunologic targets, but these tumors often arise in the face of substantial immunodeficiency. NCI has a robust research effort to investigate these phenomena and to develop strategies to overcome them.

NCI also a history of making breakthrough advances in AIDS, including the development of the first blood test and the first drugs, and continues to have an active research program in HIV and AIDS malignancies. An active research effort focused on the development of a vaccine to HIV is ongoing. The scientific community's efforts to develop an effective vaccine against HIV has to date been stymied by the difficulty in inducing a robust protective immune response, the multiplicity of circulating subtypes, and the ability of HIV to mutate in response to immune responses. These barriers are similar to those existing in the development of vaccines to cancers, and there are substantial areas of synergy and potential cross-fertilization between research in cancer vaccines and HIV vaccines.

Work by NCI researchers led to the development of an effective vaccine against human papillomavirus (HPV). It is anticipated that this vaccine, which was approved by the Food and Drug Administration in 2006 and has been administered to approximately 25% of U.S. teenage girls, will dramatically reduce the incidence of cervical cancer, anal cancer, and other cancers induced by HPV over the next several years.

NCI has taken a number of administrative steps to find synergies between the vaccine efforts against HIV and cancers. In the past year, NCI launched a collaborative effort with a local virology research institute to bring together scientists working on vaccines against HIV and against various cancers. One focus of this collaboration is the development of a vaccine directed against a common epitope that is expressed by many subtypes of HIV and thus has the potential to induce broad protective immunity. The goal of all these efforts is to find complementary strategies and new perspectives in order to overcome the barriers to vaccine development against both cancer and HIV.

National Heart, Lung, and Blood Institute (NHLBI)

House Significant Items

Item

Alpha-1 Antitrypsin Deficiency - The Committee encourages NHLBI to work with the Office of Rare Diseases (ORD) to finalize a universal treatment algorithm for the treatment of Alpha-1. At present, there is not a universally utilized treatment algorithm in the United States for this condition. The Committee believes a recognized treatment algorithm will assist in treating Alpha-1 since it is an under-recognized condition frequently misdiagnosed as simple Chronic Obstructive Pulmonary Disease (COPD) or asthma. It is common to have long delays, averaging in excess of seven years, between the onset of symptoms and the initial diagnosis. (p. 141)

Action taken or to be taken

The NHLBI and the ORD recognize the need for an updated version of an universal treatment algorithm to help physicians correctly diagnose alpha-1 antitrypsin deficiency in a timely fashion and to guide treatment of the disease. The NHLBI and the ORD are actively promoting both research and education on alpha-1. New molecular and cellular mechanisms have been identified whereby alpha-1 antitrypsin is involved in the mucous production, inflammation, and cell death that occur in the lungs of patients with COPD. State-of-the-art approaches have led to the discovery of multiple biological roles of alpha-1 antitrypsin in the organism, including its ability to enter cells and protect them from injury.

The NHLBI in FY 2008 funded a large study of the genetics of COPD that will identify other genetic factors contributing to the development of COPD in persons with and without alpha-1 deficiency. The NHLBI COPD awareness program, *Learn More / Breathe Better*, continues to raise public awareness that alpha-1 is a genetic risk factor for COPD and that it can cause COPD even in people who have never smoked. To complement this progress, the NHLBI and the ORD will work with representatives of professional organizations, as appropriate, to update the current algorithm for the diagnosis and treatment of this disease.

Item

Cardiovascular Diseases - The Committee applauds NHLBI for the development and launch of its institute-wide strategic plan. The Committee believes that NHLBI should focus on the support of current studies to enhance the prevention, diagnosis, and treatment of cardiovascular diseases and research to explore new and promising scientific opportunities. (p. 142)

Action taken or to be taken

Major areas of current research emphasis include coronary artery disease (CAD), heart failure (HF), and heart rhythm disturbances including sudden

cardiac death (SCD). Additionally, the incidence, prevalence, and distribution of cardiovascular disease and its risk factors in the community are the subjects of several large ongoing epidemiological studies.

Fundamental mechanisms of CAD initiation and progression are being studied to inform the development of new treatments, and clinical trials of several therapeutic approaches are under way. For instance, the Future Revascularization Evaluation in Patients with Diabetes Mellitus Optimal Management of Multivessel Disease trial is evaluating angioplasty or coronary artery bypass for CAD patients who have diabetes. The Surgical Treatment for Ischemic Heart Failure (STITCH) trial is determining the role of revascularization in CAD patients who have HF.

An important theme is the prevention of CAD. The new Systolic Blood Pressure Intervention trial will determine whether treating elevated blood pressure to a lower level than is currently recommended reduces the risk of heart attack, stroke, and kidney dysfunction. AIM High examines the usefulness of raising HDL cholesterol. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study of patients with diabetes examines whether the use of fibrates will reduce cardiovascular disease compared with standard treatment. Other projects that will report results soon include a clinical trial to determine whether aerobic exercise training reduces deaths and hospitalizations in persons with HF, studies of interventions to improve control of hypertension in African Americans, and research on approaches to reduce obesity at worksites. Studies are planned to prevent and treat childhood obesity.

The Treatment of Preserved Cardiac Function in Heart failure with an Aldosterone Antagonist (TOPCAT) trial examines the role of aldosterone antagonist (which blocks the action of the steroid hormone aldosterone) in the treatment of HF patients with preserved systolic function. The Heart Failure Clinical Research Network, a consortium of nine clinical research sites, conducts trials of heart failure management interventions such as controlling volume overload and treating valve dysfunction. Other studies are assessing the role of ventricular assist devices in HF treatment. In the basic science arena, the Institute plans to support a new initiative titled The Role of Cardiomyocyte Mitochondria in Heart Disease: An Integrated Approach." Additional basic, translational, and applied interdisciplinary research is being solicited and supported through a program announcement, Nutrition and Diet in Causation, Prevention, and Management of Heart Failure.

NHLBI supports research to elucidate the causes and means to prevent heart rhythm disorders, including both atrial (AF) and ventricular (VF) fibrillation. A clinical trial is testing whether fish oils are effective in controlling the occurrence of AF. Other studies are devising better diagnostic tools to identify high-risk patients who would benefit from an implanted cardiac defibrillator. The Resuscitation Outcome Consortium, a network of 10 regional centers and more than 200 emergency medical agencies across North America, is testing early

prehospital interventions for out-of-hospital cardiac arrest. An extensive portfolio of investigator-initiated grants supports basic research describing mechanisms of arrhythmia and the development of new antiarrhythmic therapies.

Item
Chronic Obstruction Pulmonary Disease (COPD) - The Committee is pleased with the NHLBI's success in launching the COPD Learn More Breathe Better national campaign to improve awareness among those at greatest risk for the disease. The Committee encourages NHLBI to amplify the success of this campaign through active collaboration with CDC's National Center for Chronic Disease Prevention in an effort to help ensure that all 50 States develop COPD Action Plans. (p. 142)

Action taken or to be taken
Supporting state-based initiatives on COPD awareness and education is a major component of the NHLBI *COPD Learn More/ Breathe Better* campaign. Since the NHLBI launched the campaign in January 2007, organizations representing more than 15 states have pledged support and become regular participants in conference calls convening state partners. Three states have developed COPD Action Plans that incorporate the *COPD Learn More/ Breathe Better*, awareness plan and many others have taken steps toward writing plans. On its Web site, www.learnaboutcopd.org, the NHLBI campaign offers resources for states that are implementing awareness and education activities. In November 2007, the campaign began providing information about COPD to state health departments through the CDC Coordinating Center for Environmental Health and Injury Prevention's communications to its state asthma directors. Greater collaboration through the National Center for Chronic Disease Prevention is desired and planned.

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 are women aged fifty and younger more likely to die following a heart attack than men of the same age. (p. 142)

Action taken or to be taken
NHLBI-supported research has led to improved diagnostic tools and methods for prevention and assessment of heart disease in women and, in some cases, sex-specific recommendations in treatment guidelines. This progress has been reflected in steadily declining cardiovascular disease death rates for women.

The Women's Ischemia Syndrome Evaluation provided new and practical insights into clinical presentation, diagnostic evaluation, new and conventional risk factors, and comorbidities. New or improved approaches for risk assessment and diagnosis (e.g., evaluation of microvascular dysfunction) and interventions to prevent ischemic heart disease in women have resulted. Despite notable progress, however, the higher death rate for women under age 50 who have had a heart attack remains a challenge that must be the subject of further research.

Diastolic heart failure is most common in elderly women. Other than treatment of comorbid conditions such as hypertension, coronary artery disease, and diabetes, effective therapy for diastolic heart failure is not available. However there are indications that the drug spironolactone may be useful in this disease, and its effectiveness is under evaluation in the NHLBI-supported clinical trial TOPCAT. Results are expected in July 2012.

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 to continue to prioritize support for this promising research in 2009 and to work with the Marfan syndrome community on strategies for establishing specialized treatment centers for Marfan syndrome. (p. 142)

Action taken or to be taken

The NHLBI works with patient associations representing a broad range of diseases and conditions that fall within its mandate. The NHLBI's partnership with the National Marfan Foundation (NMF) has proven to be an extremely productive collaboration for a clinical trial on a rare disease. The losartan drug trial – through the NHLBI Pediatric Heart Network – will enable rapid evaluation of emerging new therapeutic strategies without the need for new disease-specific specialized treatment centers. This approach has saved considerable time and money and ensures top-notch scientific assessment. It has received the support of the Marfan syndrome community.

The NMF provides funds for several ancillary studies and encourages recruitment of their patient and physician communities. It is instrumental in getting out the message to its membership that participation in the losartan clinical trial is necessary for a scientific basis to guide therapy. Moreover, the NMF has contributed travel and training funds for extra study sites and is sponsoring a travel fund to help patients who live a long distance from study sites. This trial is also supported by the FDA's Office of Orphan Drugs with funds for pharmacologic aspects.

In 2008, NHLBI, in partnership with the NMF and other NIH Institutes, created a comprehensive award-winning website to provide parents and healthcare

providers information needed to understand clinical research in children and make informed decisions about participating in a study. The site is formatted to many educational levels by combining text, graphics and documentary film footage of experts, parents and children themselves sharing their experiences in clinical research. It can assist healthcare providers as they answer questions and research teams to augment the consent process and can be visited at: www.ChildrenAndClinicalStudies.nhlbi.nih.gov.

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. 142)

Action taken or to be taken

The NHLBI is aware of the interest and had discussions with the PH community about establishing a PH clinical network. The daunting problem of achieving recruitment of substantial numbers of participants required for network protocols is an important consideration. In fact, two ongoing, relatively small clinical trials of PH supported by the NHLBI are struggling now to reach recruitment targets. How network protocols could compete with pharmaceutical-sponsored trials for the relatively small numbers of patients available is a significant issue. In light of these concerns, establishing a PH clinical network may not be the best strategy for promoting PH clinical research at this time.

The NHLBI will release two new translational research initiatives in early 2009 that present important opportunities for the community to advance clinical research on PH. Unlike a network, which typically entails studies that recruit substantial numbers of patients, the initiatives will support smaller-scale phase 2 trials combined with mechanistic studies and collaborative basic and clinical projects. The work will focus on identifying novel therapies for respiratory diseases and moving new therapies from bench to bedside. Applications from the PH community for these opportunities would be encouraged. The NHLBI is open to exploring other opportunities with the community to advance clinical research in PH.

Item

Sleep Disorders - The Committee continues to support the National Sleep Awareness Roundtable and encourages the National Center on Sleep Disorders Research to continue to work with other partners such as CDC to implement a sleep education and public awareness project dealing with the impact sleep and the circadian cycle have on the development of pulmonary and cardiovascular disease. (p. 142)

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR) interacts regularly with the National Sleep Foundation, the parent non-governmental organizer of the National Sleep Awareness Roundtable (NSART) and its partner organizations, to discuss areas for potential coordination and to share information on NIH activities related to sleep disorders education and research. NSART is in the process of developing an education agenda and strategy, and the NCSDR will continue to partner in this process as a federal liaison member. In 2008, the NCSDR director made a presentation to the NSART partners on the status of NIH sleep disorders research, NCSDR contributions to the Healthy People 2010 agenda, and interim progress on the sleep-related Healthy People objectives.

The NHLBI continues to collaborate with Centers for Disease Control and Prevention (CDC) components to develop the fundamental evidence needed to guide national education and public awareness efforts. The Institute co-funds the National Health and Nutrition Examination Survey of the National Center on Health Statistics to collect surveillance data on the prevalence of sleep disorder signs and symptoms and of physician-diagnosed sleep disorders and to assess the impact of insufficient sleep on functional quality of life. In addition, the National Center for Chronic Disease Prevention and Health Promotion, in consultation with NSART and the NCSDR, has initiated a new sleep module in the Behavioral Risk Factors Surveillance Survey that will allow community-based analyses of sleep status. Data collection and analysis is anticipated to continue through 2008.

To facilitate the public dissemination of new findings, the NCSDR is organizing a national conference at the NIH in April 2009 on the topic “Sleepiness and Health-related Quality of Life.” Developed in partnership with the trans-NIH Sleep Research Coordinating Committee, the CDC, the National Highway Traffic Safety Administration, and the Office of the Surgeon General, this conference will include presentations from NIH-funded researchers. A major focus will be on the findings that are emerging from the partnership with CDC health surveillance activities.

Item

Thalassemia - The Thalassemia Clinical Research Network (TCRN) is a core program that has advanced physicians' understanding of how to diagnose, treat and manage this fatal genetic blood disease. The Committee suggests that additional protocols be adopted, particularly related to gene therapy, to advance the field further and lead to a cure in the shortest possible time. (p. 142)

Action taken or to be taken

The NHLBI shares the Committee’s interest in the conduct of high-quality clinical research on thalassemia via the TCRN and other avenues. The Institute will hold a conference in 2009; open to the health-care community and advocacy groups, for discussion of the future direction of NHLBI-sponsored clinical trials in this

disease. Gene therapy is currently an active area of investigation by many NHLBI-funded scientists. The field is advancing rapidly, however it has not yet matured sufficiently for gene therapy trials in humans to be undertaken.

Item

Lymphangioleiomyomatosis (LAM) - 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 international 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. 143)

Action taken or to be taken

NHLBI-funded scientists found that sirolimus (rapamycin) mimics the function of missing or abnormal proteins needed to control cell size and growth of LAM cells. Its potential as a therapy for LAM is being tested in the Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial, funded by the Office of Rare Diseases (ORD) and administered by the National Center for Research Resources (NCRR). The view that LAM behaves like a “cancer” suggests that multiple-drug therapy may be called for and that additional drugs need to be sought and tested. Also, the role of estrogen is being explored to help understand why LAM, but not tuberous sclerosis complex (TSC), affects women almost exclusively.

NHLBI intramural investigators collect pleural fluid for research use from LAM patients who are undergoing medically indicated procedures, and this fluid is now recognized as a rich source of LAM cells. Intramural and extramural investigators are working together on procedures to isolate LAM cells from body fluids for diagnosis and research. Intramural investigators have shown effects of sirolimus on gene expression. 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. Also, they have recently shown that hypoxemia is associated with accelerated disease progression. Hypoxemia can be treated by use of supplemental oxygen.

NHLBI transferred the collection, processing, and distribution of LAM tissue to the National Disease Research Interchange (NDRI), a NIH-supported not-for-profit corporation that specializes in human tissues needed to facilitate research on rare diseases. The new system for managing LAM tissue has a Web-based inventory and provides easier, faster access to tissue.

Several mechanisms of support are available for increasing research efforts on LAM. Regular investigator-initiated research grants are supporting LAM research, and an initiative on ancillary studies initiative provides another avenue.

Two new lung translational initiatives scheduled for release in 2009 may offer additional opportunities to LAM researchers. NHLBI would like to see these mechanisms fully utilized before LAM centers are considered.

The NHLBI continues to co-fund the annual scientific conference organized by the LAM Foundation and participates in the trans-NIH TSC coordinating committee meetings, organized by the National Institute of Neurological Diseases and Stroke. The NHLBI is revising and updating the LAM Fact Sheet on its Diseases and Conditions Index Web page.

Senate Significant Items

Item

Alpha-1 Antitrypsin Deficiency - The Committee encourages the NHLBI to work with the Office of Rare Disorders to establish a treatment algorithm for Alpha-1 antitrypsin-related disease to help assist physicians in correctly diagnosing it. (p. 93)

Action taken or to be taken

Please refer to page 20 of this document for NHLBI's response to this item on Alpha-1 Antitrypsin Deficiency.

Item

Bleeding and Clotting Disorders - The Committee encourages the NHLBI to continue its commitment to research in bleeding and clotting disorders by focusing on improved and novel therapies and maintaining its collaborative relationship with patient advocacy groups and the scientific and medical research community. (p. 94)

Action taken or to be taken

NHLBI maintains a strong commitment to research on bleeding disorders and continues to collaborate with the National Hemophilia Foundation (NHF) in supporting studies that offer promise for improved therapy of hemophilia, von Willebrand disease, and other hereditary bleeding disorders. Through the jointly developed initiative Improved Therapy for Hemophilia and Hereditary Bleeding Disorders, NHLBI funded five grants in 2005 and the NHF funded three. NHLBI funding ended in 2008. NHF funding ends in 2009. The program includes studies on factor VIII immunity and tolerance, engineered factor VIII molecules with improved stability or reduced immunogenicity, novel hemostatic agents and delivery systems, and the safety of and immune response to gene-transfer and cell-based therapies for hemophilia.

In 2006 the NHLBI began its Specialized Centers of Clinically Oriented Research in Hemostatic and Thrombotic Diseases, a five-year program, ending in 2011, fosters multidisciplinary research on clinically relevant questions. Awards were made to three centers for studies of clinical and basic aspects of platelet biology

and their role in the pathogenesis of thrombotic disorders, investigations of genetic and cellular determinants of altered platelet function in systemic inflammatory states such as atherosclerosis and diabetes, and research into the contributions of insulin resistance and type 2 diabetes to the development of arterial thrombosis.

In 2007, NHLBI collaborated with the National Institute on Aging (NIA) and the Office of Dietary Supplements (ODS) on the initiative Venous Thrombosis and Thromboembolism in the Elderly, an RFA based on a workshop held by the American Society of Hematology (ASH). NIA funded five grants, and NHLBI funded three. NHLBI also issued a new RFA in 2008 on Deep Vein Thrombosis and Venous Disease to stimulate exploration of the mechanisms of venous thromboembolism initiation, progression, and recurrence and to support clinical/translational studies to improve diagnosis and therapy. Interactions between this program and the ongoing Thrombosis and Hemostasis program at the CDC are planned to increase resources and enhance the potential for advances. The Institute continues to work with ASH, NHF and the Hemophilia and Thrombosis Research Society to identify and address the needs of the bleeding and clotting disorders community.

Item

Chronic Obstruction Pulmonary Disease (COPD) - The Committee applauds the NHLBI for implementing the COPD Awareness Campaign and increasing its investment in COPD research. The Committee is concerned about the growing number of women dying from COPD, and it encourages additional research on the role that gender plays in this disease. (p. 94)

Action taken or to be taken

The NHLBI shares the Committee's enthusiasm for the NHLBI COPD Awareness Campaign, "*Learn More/ Breathe Better*," which is increasing knowledge among Americans about the risk factors and symptoms of COPD. As emphasized in that campaign, COPD is now as much a problem for women as it is for men. In fact, in the United States today more women than men die of COPD. The NHLBI is actively striving to recruit women in its clinical studies and trials of COPD. It is having success in achieving good representation of women in such studies, and anticipates that analyses of possible gender differences in genetic susceptibility to COPD and in responses to treatments will be possible. In addition, the NHLBI plans to conduct a workshop in FY 2009 to evaluate current research gaps and opportunities in COPD, which will include the role gender plays in this disease.

Item

Congenital Heart Disease- - The Committee continues to urge the NHLBI to work with patient associations, other appropriate NIH Institutes, and the CDC to develop education and research initiatives targeted to the life-long needs of congenital heart defect survivors. (p. 94)

Action taken or to be taken

The NHLBI has taken a leadership role in research and education for congenital heart defect survivors and their families. The Pediatric Heart Network (PHN), established in 2001, conducts multicenter clinical studies on children and young adults with heart conditions such as single ventricle physiology, Kawasaki disease, and Marfan syndrome. The network's public web site at www.PediatricHeartNetwork.org has a special section for patients and families which provides information about topics that affect their lives, including exercise and nutrition.

In June 2008, the PHN randomized the last of 555 patients into a surgical trial that many seasoned researchers said could not be done. It was a randomized comparison of two surgical procedures for newborns with congenital heart disease so severe as to require life-saving surgery in the first week of life. This is the first time in the history of the specialty that a new surgical procedure was compared systematically to the standard procedure in a multicenter fashion.

The NHLBI works with patient associations representing a broad range of diseases and conditions. Once a year, the NHLBI holds a meeting of public interest organizations with concerns relevant to the Institute's mission to provide an opportunity for such groups to speak with each other and NHLBI staff about topics of mutual interest and to hear scientific presentations.

This year, NHLBI, with other NIH components and the National Marfan Foundation, created a comprehensive award-winning website designed to provide parents and healthcare providers information to understand clinical research in children and make informed decisions about participating in a study. The site is formatted to many educational levels by combining text, graphics and documentary film footage of experts, parents and children themselves sharing their experiences in clinical research. It can be viewed at: www.ChildrenAndClinicalStudies.nhlbi.nih.gov

The NHLBI and the Centers for Disease Control and Prevention (CDC) share many common interests in congenital heart disease. Recently, the CDC participated in a Working Group on research in adult congenital heart disease. As part of an effort to study growth patterns in infants affected by congenital heart disease, the NHLBI uses CDC data to update estimates of normal birth weight by gestational age. The NHLBI collaborates with CDC staff on analysis of these data and other congenital heart disease issues.

The NHLBI-supported Specialized Centers for Clinically-Oriented Research (SCCOR) in Pediatric Heart Disease have bridged clinical and basic research by identifying mutations in genes involved in heart development. The NHLBI uses lessons learned from the SCCOR program and PHN to transform the SCCOR into a broader pediatric translational program which will launch in the next year.

Item

Diamond-Blackfan Anemia [DBA] - The Committee encourages the NHLBI to continue and expand its research initiative into DBA. (p. 94)

Action taken or to be taken

In September 2004, the NHLBI awarded 16 grants related to "Molecular Mechanisms Underlying Diamond-Blackfan Anemia (DBA) and Other Congenital Bone Marrow Failure Syndromes," to encourage research on the genetics and basic mechanisms of these rare disorders. Grantees have since identified numerous new genes (ribosomal proteins) for DBA and other related marrow failure syndromes. It also generated interest among other NIH components and stimulated establishment of an Interagency Coordinating Committee for Hematology. In January 2007, the Committee sponsored the NIDDK-led workshop "Inherited Marrow Failure Disorders." Early in 2008 a clinical consensus document was published that set forth guidelines for DBA diagnosis. The document had been developed during the DBA International Consensus Conference held in 2007. Related fact sheets are planned for publication on the CDC Web site.

More recently, a meeting of expert hematologists and scientists was convened to identify critical questions in the field of DBA, specifically in the areas of genetics, genomics, animal models, and stem cells. In August 2008, the NHLBI and the NIDDK collaborated in a workshop, "Ribosomes and Their Role in Diseases," at which the recent discovery of ribosomal protein defects in patients with DBA and other bone marrow failure disorders was highlighted. The impact of all these activities is reflected in the impressive rise in peer-reviewed publications of rare bone marrow failure disorders.

Item

Lymphangioleiomyomatosis (LAM) - The Committee commends the NHLBI for supporting the MILES trial, and encourages the support of phase I and phase II clinical treatment trials to capitalize on the LAM patient populations that the NHLBI and the Rare Lung Disease Consortium has assembled. The Committee is also aware of the potential benefit of establishing regional LAM centers, and suggests the NHLBI consider supporting these activities. (p. 94)

Action taken or to be taken

Please refer to page 26 of this document for NHLBI's response to this item on Lymphangioleiomyomatosis.

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 to work with the Marfan syndrome community on strategies for establishing specialized treatment centers. (p. 94)

Action taken or to be taken
Please refer to page 23 of this document for NHLBI's response to this item on Marfan Syndrome.

Item
Myelodysplasia - The Committee urges the NHLBI, working in collaboration with the NCI and NIA, to establish a sustainable research program on myelodysplasia, a bone marrow failure disorder that primarily affects the elderly and individuals who have undergone chemotherapy and/or radiation therapy. The Committee requests a response in the fiscal year 2010 congressional budget justification. (p. 94)

Action taken or to be taken
The NHLBI remains firmly committed to collaborating with other NIH Institutes, including NCI and NIA, in supporting research on myelodysplastic syndromes (MDS) and other related bone marrow failure diseases, including aplastic anemia (AA). The Institute is pleased to provide the following update on its activities in this area.

NHLBI and NCI jointly issued the request for applications (RFA) "MDS: Seeking Cure through Discovery on Pathogenesis and Disease Progression" in FY2005. Its goals are to stimulate research on MDS; identify critical genetic, biochemical, and molecular pathways that affect the emergence and progression of these diseases; and study the mechanisms of disease mutagenesis, evolution, and progression. The NHLBI continues to support the research grants awarded in response to this RFA, as well as multiple investigator-initiated grants on MDS. These studies focus on understanding basic stem cell biology, and it is hoped that they may reveal mechanisms of stem cell mutagenesis, abnormal proliferation, and deregulated cellular physiology or identify molecular targets that may be exploited for either preventive or therapeutic intervention.

Following a research agenda–setting workshop sponsored by the American Society of Hematology (ASH) in January 2004, NIA and the NHLBI collaborated in issuing the RFA "Anemia in the Elderly." Its goal was to stimulate research into the epidemiology, etiology, diagnosis, management, and consequences of anemia in older persons. A primary focus of the RFA was "unexplained" anemia, a diagnosis given when no cause of anemia is apparent after hematological evaluation. Several studies supported through this solicitation explore the role of myelodysplasia in the etiology of unexplained anemia in older persons.

In November 2008, NHLBI, NCI, and NIA staff participated in a second ASH-sponsored research-agenda–setting workshop for MDS. This activity focused on identifying key research questions, determining gaps that need to be addressed, pinpointing opportunities for new investigation, and establishing a list of priorities that may form the basis for future funding opportunities.

Also, the Blood and Marrow Transplant Clinical Trials Network, co-sponsored by the NHLBI and the NCI, is leading a national clinical trial to treat patients with severe AA. Such patients often fail to benefit from conventional treatments and die from infection or bleeding. However, hematopoietic stem cell transplantation (HSCT) offers a potential cure. This Phase I/II trial is designed to optimize HSCT conditioning regimens for high-risk patients with severe AA receiving transplants of marrow from HLA-compatible unrelated donors.

Item

Sickle Cell Disease - The Committee commends the NHLBI for developing a strategic plan, with input from public stakeholders, to enhance its research program on sickle cell disease and asks that the final research plan and proposed implementation steps be provided to the Committee when completed**.** (p. 95)

Action taken or to be taken

The NHLBI research plan for sickle cell disease (SCD) and steps that will be taken to implement it are described in an editorial in the May 15, 2008, issue of the journal *Blood* ("A Recommitment to Sickle Cell Disease Research," by Elizabeth G. Nabel and Susan B. Shurin, Vol. 111, No. 10, pp. 4852-4853). Many implementation activities are under way. For example, the scope of NIH-sponsored clinical research trials is being broadened to allow a greater number of people with sickle cell disease to participate. The NHLBI is collaborating with the National Human Genome Research Institute to develop databases that will provide new avenues for understanding the disease and new approaches for therapy. It is also working closely with the CDC as it creates the first national surveillance system for hemoglobinopathies to ensure that the system will be able to enhance the research agenda and improve care for patients. The Institute is developing care guidelines for use by primary care physicians and also by patients and families to enhance their ability to advocate for their own care. Finally, NHLBI is preparing several funding opportunity announcements for basic and clinical research in SCD.

Item

Omega-3 Fatty Acids. - The Committee urges the NHLBI and the Office of Dietary Supplements in collaboration with the CDC, through the Heart Disease and Stroke Prevention Program, to develop and implement an education and awareness campaign for the public, patients and providers about the overall health benefits of consuming omega-3 fatty acids. (p. 95)

Action taken or to be taken

The NHLBI supports extensive research on prevention and management of cardiovascular disease (CVD) risk factors and healthy lifestyle change. Included are studies of omega-3 fatty acids and their role in prevention and treatment of CVD. Recent findings from these studies continue to support the federal nutrition

policy recommendation to consume fish and plant sources of omega-3 fatty acids, based on limited evidence suggesting an association between consumption of fatty acids in fish and reduced risks of mortality from CVD for the general population. The Office of Dietary Supplements and the NHLBI provided funds for the Agency for Healthcare Research and Quality to conduct an evidence-based review of the effect of omega-3 fatty acids on CVD. The review found little or no consistent effect of omega-3 on CVD and its risk factors, except for triglycerides, and concluded that more research is needed.

The NHLBI has a long history in developing CVD clinical guidelines, along with providing practical outreach and education programs for health care professionals, patients, and communities. The third report of the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults found the evidence regarding omega-3 fatty acids to be only moderate and, thus, provided an option to recommend higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils for reducing risk for heart disease. The panel found insufficient evidence to support recommendations for a specific amount of omega-3 fatty acids. The NHLBI currently implements these recommendations in its consumer education materials and campaigns such as Lowering Your Cholesterol with TLC (Therapeutic Lifestyle Changes) and The Heart Truth for Women. The Institute is embarking on a new effort to develop an evidence-based, comprehensive, integrated set of clinical guidelines directed principally at primary care practitioners to help adult patients reduce their risk for CVD. That review includes evaluating the newer evidence on the role of diet and its components, including intake of omega 3- fatty acids, in CVD risk reduction.

Item

Pulmonary Fibrosis. - The Committee continues to urge the NHLBI to increase funding for lung research, particularly in the area of pulmonary fibrosis, and to convene a consensus conference of experts and other stakeholders to lay the groundwork for a formal pulmonary fibrosis disease action plan for prevention and control of this deadly disease. (p. 95)

Action taken or to be taken

NHLBI support for basic and clinical research in pulmonary fibrosis has increased over the past decade. The idiopathic pulmonary fibrosis (IPF) clinical research network was established in 2005 to explore treatment of patients with newly diagnosed IPF using combinations of existing and relevant drugs at multiple points that could stabilize or improve the disease. The network includes 11 clinical centers (with multiple satellite sites), a data coordinating center, and a clinical research skills-development core. The first protocol to treat advanced IPF patients with pulmonary vasculature hypertension began in 2007 and is actively enrolling patients, a second protocol will begin in early 2009, and a third protocol is under development. Additionally, the network has enabled support of a number of new ancillary mechanistic studies that are conducted in conjunction with the main intervention trials.

In 2001 the NHLBI sponsored a workshop to assess future research directions in IPF (Crystal, RG et al, *Am J Respir Crit Care Med 2002, 166:236-246*), which provided a strategic plan for future research in IPF. The NHLBI has implemented a number of recommendations from this plan. We will continue to review the remaining areas in the report and update it as new information becomes available to continue to advance the science related to IPF.

Item
Pulmonary Hypertension (PH) - The Committee encourages the Institute to work with the PH community to support the establishment of a clinical research network that would provide for expanded clinical trials and facilitate collaboration and data sharing among PH investigators. (p. 95)

Action taken or to be taken
Please refer to page 29 of this document for NHLBI's response to this item on Pulmonary Hypertension.

Item
Sleep Disorders - The Committee continues to encourage the National Center on Sleep Disorders Research to work with other partners to implement a sleep education and public awareness project. (p. 95)

Action taken or to be taken
Please refer to page 30 of this document for NHLBI's response to this item on Sleep Disorders.

Item
Thalassemia - The Thalassemia Clinical Research Network (TCRN) is a core program that has advanced physicians' understanding of how to diagnose, treat and manage this fatal genetic blood disease. The Committee urges additional protocols, particularly related to gene therapy, to advance the field further and lead to a cure in the shortest possible time. (p. 95)

Action taken or to be taken
Please refer to page 25 of this document for NHLBI's response to this item on Thalassemia.

Item
Women and Heart Disease. - The Committee requests the NHLBI to place a higher priority on: the best strategies for assessing, preventing, and treating heart disease in women; why women receive significantly fewer referrals for rehabilitation programs, advanced diagnostic testing and treatments for heart disease than men, and how the referral rate for women can be increased; the most effective methods and treatments for diastolic heart failure; the biological differences between men and women in the location, type, and heart disease risk

level associated with fat deposits; the role of inflammation in heart disease in women; how sex differences in the regulation of heart rhythm affect risk of heart disease and response to treatment; why women ages 50 and younger are more likely to die following a heart attack than men of the same age; and how the heart disease diagnosis and care disparities between women of different races can be eliminated.

Action taken or to be taken

The NHLBI continues to place a high priority on improving the cardiovascular health of women through support of fundamental and clinical research. Progress has been made via targeted initiatives, investigator-initiated research, and a strong commitment to the inclusion of women in clinical studies. Improved strategies for diagnostic evaluation and prevention of heart disease continue to be the focus of research. Published reports from the NHLBI-supported Women's Ischemia Syndrome Evaluation study have identified clinical symptoms, new and conventional risk factors, and comorbid conditions that are more common in women, as well as diagnostic approaches that are more effective in women. These findings have led to improved awareness and better methods for the identification of ischemia in women, and they have underscored the need for sex-specific treatment guidelines. Similarly, NHLBI-supported studies have reported that women, compared with men, have differences in cardiac electrical activity (i.e., prolonged Q–T interval) that predispose them to potentially untoward cardiac rhythm disturbances as a side effect of prescription and nonprescription drugs.

The use of the drug spironolactone to treat diastolic heart failure is under evaluation in the NHLBI-supported clinical trial Treatment of Preserved Cardiac Function in Heart Failure with an Aldosterone Agent. Diastolic heart failure is a condition that commonly afflicts elderly women.

Cardiac rehabilitation has been shown to improve outcomes in women following a cardiac event, but only a small proportion of eligible women participate. There is evidence that logistic, financial, social, and personal barriers to participation exist. Longitudinal studies in women from various walks of life would be an approach to determine health care intervention approaches that may improve their participation. Heart Failure-Action, an NHLBI-supported randomized clinical trial that evaluates exercise training in patients with heart failure, is expected to provide additional insights.

The NHLBI is participating in an initiative to develop Population Health and Health Disparity Centers in collaboration with NCI and OBSSR. A major advantage of this approach to the problem of health disparities is the potential for integrating multiple levels of influence such as the medical system, providers, patient, community, social context, and policies in the review and development of practical interventions.

National Institute of Dental and Craniofacial Research (NIDCR)

House Significant Items

Item

Dental Caries - The Committee understands that early childhood caries is at high levels in American Indian/Alaska Native (AI/AN) populations. Because of this continuing large health disparity, additional research is needed on the causes and best methods to eradicate this disease among AI/AN children. The Committee encourages NIDCR to support clinical research in collaboration with the Indian Health Service to find effective anti-caries preventions, including new education and intervention modalities (p.143).

Action taken or to be taken

NIDCR's response is in Early Childhood Caries in the Senate section shown below.

Senate Significant Items

Item

Early Childhood Caries - The Committee notes the urgent need to eradicate early childhood caries among American Indian/Alaska Native [AI/AN] populations. The Committee urges the NIDCR, in collaboration with the Indian Health Service, to increase support for clinical research to find effective anti-caries preventions, including new education and intervention modalities (p. 96).

Action taken or to be taken

Early Childhood Caries (ECC) rates are disproportionately high in low-income racial/ethnic minority populations of young children, including American Indian/Alaska Natives (AI/AN). NIDCR is committed to reducing these disparities, and recently renewed funding for Centers for Research to Reduce Disparities in Oral Health. One of the new Centers, the Center for Native Oral Health Research (CNOHR) at the University of Colorado Denver, focuses solely on American Indians and Alaska Natives. The interdisciplinary team will conduct two trials designed to investigate methods to reduce ECC. Because access to dental services remains a challenge in many AI/AN communities, both studies will test the effectiveness of preventive interventions delivered by non-traditional dental workers to prevent ECC. One study will determine whether children whose mothers receive culturally appropriate educational and health promotion materials (including dental aids and brochures) in addition to home-based, motivational counseling sessions have less ECC than those who parents receive only educational and health promotion materials. Trained motivational interviewers from the AI community will deliver the intervention.

A second study focuses on the oral health of Head Start children. In this study, Community Oral Health Specialists (COHS) will provide oral health education

materials to parents and apply fluoride varnish to the children's teeth. This intervention will be compared to a group of children receiving fluoride varnish treatments alone. In addition to the interventional research conducted by the Center, other scientists with NIDCR support are exploring biological and behavioral risk factors for ECC in rural and urban AI communities.

In research involving oral health of American Indian/Alaska Natives, the NIDCR collaborates with care providers in the communities. This includes both the Indian Health Service (IHS) as well as providers supported by Tribal Corporations.

Item

Temporomandibular Joint Disorders [TMJDs] - The Committee encourages the NIDCR, along with the NIAMS and NIBIB, to put a higher priority on using noninvasive imaging technologies to establish, validate, and standardize clinical diagnostic criteria for TMJDs and to better understand the etiology and mechanisms underlying the symptoms of biomechanical pain and dysfunction. The Committee also calls on the NIDCR to initiate interdisciplinary partnerships within the NIH on chronic pain that is associated not only with TMJDs but other conditions as well. To address these collaborations extramurally, the Committee urges NIDCR to follow the recommendation of the Fourth Scientific Meeting of the TMJ Association calling for the establishment of regional centers of excellence. Finally, the Committee calls upon the TMJ Interagency Working Group to step up its level of activities and work more effectively to assess the state of science of TMJDs and their comorbidities, and to develop short- and long-range research plans (p. 96).

Action taken or to be taken

Temporomandibular muscle and joint disorders (TMJDs) are a heterogeneous set of conditions affecting the muscles, nerves, and bones of this complex joint. Most individuals with acute TMJ pain or dysfunction recover with no or minimal intervention. However, some will develop chronic TMJD characterized by persistent jaw and craniofacial pain, difficulties with chewing and swallowing, and an increased incidence of psychological disorders. NIDCR is pursuing a research agenda focused on better understanding the biological and behavioral mechanisms underlying the etiology and pathology of these disorders. Molecular, cellular, genetic, and cognitive approaches as well as clinical studies using state of the art technologies are being utilized towards this end. The complex structure of the temporomandibular joint and the intricate neuronal pathways that control the mechanics and sensation of the joint require the integration of non-invasive real-time imaging techniques with these other approaches in order to advance our understanding of TMJDs.

NIDCR has shared interests with National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and National Institute of Biomedical Imaging and Bioengineering (NIBIB) in the use of novel imaging technologies to

study the structure and function of the musculoskeletal system. The use of structural and functional MRI will enable researchers to uncover abnormalities in joint tissue architecture and identify changes in brain function that lead to persistent pain and joint dysfunction. Application of emerging imaging technologies such as diffusion spectrum imaging will enable researchers to decipher the complex neuronal circuitry of pain sensation in humans. Optical imaging techniques, currently used primarily in preclinical studies, offer improved sensitivity and structural resolution for understanding molecular and cellular mechanisms of disease. NIDCR continues to support and encourage research that will determine the best use of imaging technologies for the improved clinical diagnosis of TMJDs and for monitoring the outcomes of novel therapeutic interventions.

NIDCR, along with National Institute of Neurological Disorders and Stroke (NINDS) and The National Institute of Nursing Research (NINR), chair the NIH Pain Consortium, a partnership of 22 Institutes, Centers, and Offices at NIH that have a significant programmatic interest in chronic pain conditions. Consistent with recommendations of the Fourth Scientific Symposium of the TMJ Association as well as from prior Temporomandibular Joint Disorders Interagency Working Group (TMJDIWG) recommendations on systems approaches to studying TMJDs, NIDCR recognizes the importance of fostering interdisciplinary research on TMJDs and other comorbid chronic pain conditions. NIDCR supports efforts of principal investigators to assemble teams of scientists into research networks that will investigate these disorders.

The TMJDIWG facilitates collaboration among agencies that conduct TMJD-related activities as well as offers a forum for the exchange of information. For example, in September 2007 the TMJDIWG held a three-day workshop titled “A Systems Approach to Understanding TMJDs” that explored use of systems biology approaches to improve our understanding of the etiology, pathology, and treatment of TMJDs. Recommendations derived from this workshop will be posted on the TMJDIWG web site.

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

House Significant Items

Item

Animal Models for Diabetes-The Committee commends NIDDK for its efforts in the Animal Models of Diabetic Complications Consortium (AMDCC), which has created more than fifty new animal models for diabetes research. The Committee encourages NIDDK to expand the efforts of the AMDCC, particularly with respect to generating new animal models to study diabetic nerve damage. (p. 143)

Action taken or to be taken

The NIDDK appreciates the Committee's commendation of the interdisciplinary Animal Models of Diabetic Complications Consortium (AMDCC). This Consortium is pursuing several efforts in the area of diabetic nerve damage. For example, an AMDCC research site is working to improve animal models of diabetic nerve damage by utilizing a method to accelerate diabetes-related stress on cells in the nervous system and subsequent nerve damage. The AMDCC has also formed partnerships to ensure that interesting mouse models are screened for all other diabetic complications (including diabetic nerve damage) so that data and resources produced by the AMDCC are used to their full potential.

The NIDDK has made several efforts to bolster research in this field. For example, a workshop was held in April 2007 to review and promote advances in the field. In addition, the NIDDK co-sponsored a meeting in September 2008 to address the creation of standards for animal models of diabetic nerve damage. Scientific experts produced a list of definitions to characterize the animal model's similarity to the human disease. These standards and a planned compendium of best practices and methodologies for measuring diabetic nerve damage will be made available to the research community through publication of the standards (to be submitted to the journal *Diabetes*) and of the compendium on the AMDCC website (www.amdcc.org). Finally, the NIDDK sponsored a Pilot and Feasibility Grant Program to promote and stimulate the development of new techniques and progress in the characterization of rodent models of diabetic nerve damage.

The NIDDK is also fostering efforts to use new animal models of diabetic nerve damage to screen potential novel therapeutics. Investigators, as part of the NIDDK's and NCI's Type 1 Diabetes-Rapid Access to Intervention Development program, are accelerating promising findings in the laboratory to preclinical testing in these animal models. Led by an internationally recognized expert in experimental diabetic nerve damage, the scientists can use this resource to test novel interventions in established animal models of diabetic nerve damage and other diabetes complications. Potential new therapies are tested for their ability

to reduce or reverse nerve conditions associated with diabetes and promising therapies are further developed for future testing in clinical trials.

Item

Beta Cell Biology - The Committee encourages NIDDK to extend and expand its vigorous support of the Beta Cell Biology Consortium (BCBC) that promotes collaborative research relevant to understanding and treating type 1 diabetes. Particularly important is the creation of diabetes research resources and reagents that can be accessed by the entire diabetes research community. In addition, the Committee requests NIDDK to work with NCRR to ensure the viability of the regional Islet Cell Resources Centers or equivalent infrastructure that can efficiently produce and distribute purified human islets for beta cell biology research. (p. 144)

Action taken or to be taken

The NIDDK's Beta Cell Biology Consortium (BCBC) is an extremely productive group of scientists studying how insulin-producing beta cells develop and function. A major goal of the BCBC is to generate research resources for the scientific community. The Consortium has generated mouse models, antibodies, cell lines, gene chips, and other resources/reagents that are broadly available to the entire scientific research community. Not only are diabetes researchers using these resources, but scientists studying pancreatic cancer are also using them. Therefore, these resources are propelling research progress within the BCBC, as well as in the larger diabetes and cancer research communities. Scientists can access information on resources through the comprehensive BCBC website: www.betacell.org.

The BCBC is also continuing and expanding its Collaborative Bridging Project program. This program encourages collaboration among BCBC investigators, as well as with scientists outside of the Consortium. The goal of the program is to accelerate the development of cell replacement therapy for type 1 diabetes and to apply new technologies that can enhance research on beta cell biology.

In 2004, the BCBC attracted new talent through a Seeding Collaborative Research Program. This program permitted investigators outside of the BCBC to collect preliminary data and form collaborative research teams prior to applying for full-scale grants in the second competitive funding cycle of the BCBC in 2005. Those that went on to successfully compete for BCBC funding in the second funding cycle greatly strengthened the Consortium. In fact, these researchers are responsible for much progress. Because of the success of the program, the NIDDK is supporting another Seeding Collaborative Research Program, which was announced in August 2008. In addition, the NIDDK is supporting a Pilot and Feasibility Program for 2008 and 2009 to enable investigators outside of the BCBC to test highly innovative ideas and explore the feasibility of novel concepts related to the mission of the BCBC. This program is particularly targeted at new

investigators and at established investigators with no previous work in beta cell biology who wish to apply their expertise to this area of research.

The NIDDK appreciates the importance of ensuring the availability of human islets for basic research on beta cell biology. Because the awards for the Islet Cell Resource Centers, which were led by the National Center for Research Resources, ended in Fiscal Year 2008, the NIDDK is continuing this important resource through a research contract beginning in Fiscal Year 2009. This contract will support the infrastructure that is necessary to produce and distribute islets for basic research, thereby ensuring that scientists studying beta cell biology have access to these precious cells.

Item

Beta Cell Regeneration for Diabetes - Recent studies have revealed the presence of residual insulin-producing cells in some patients with longstanding type 1 diabetes. The Committee encourages NIDDK to support additional research on this important discovery and its potential to point to regenerative strategies for the treatment of type 1 diabetes. The Committee encourages NIDDK to foster collaboration and communication within the diabetes research field on this subject. (p. 144)

Action taken or to be taken

The NIDDK vigorously supports research on beta cell regeneration, which has the potential to benefit people with both type 1 and type 2 diabetes. For example, research in this area is conducted through the NIDDK's Beta Cell Biology Consortium (BCBC), which began in 2001. In 2005, the BCBC was expanded in scope to include research projects focused on beta cell regeneration. BCBC researchers developed a mouse model that is being used to study beta cell regeneration and how this process is affected by different drugs. Using the mouse model, BCBC researchers showed that drugs commonly used to suppress the immune system after islet transplantation have an adverse effect on beta cell regeneration. This observation may help to explain why transplanted islets lose function over time in people. The mouse model is serving as an important resource to increase understanding of beta cell regeneration.

The BCBC also communicates and collaborates with researchers outside of the consortium to enhance research on various topics in beta cell biology, including beta cell regeneration and other aspects of beta cell biology that can inform research on beta cell regeneration. For example, in 2008, the BCBC funded new research under a pilot and feasibility program. The program supported scientists testing the feasibility of concepts related to the mission of the BCBC. Research through this program relates to beta cell regeneration. In addition, the BCBC is continuing and expanding its Collaborative Bridging Project program, which encourages collaboration among BCBC investigators, as well as with scientists outside of the Consortium. A Seeding Collaborative Research Program,

announced in August 2008, will support scientists outside of the BCBC studying beta cell biology, to help them acquire preliminary data to be competitive for future funding. A similar program was conducted in 2004 and was a great success; several researchers funded through the program went on to acquire full-scale BCBC funding and have made tremendous progress. These programs are open to scientists outside of the BCBC, in order to attract new talent to studying beta cell biology, including beta cell regeneration.

NIDDK-supported researchers made an exciting discovery that some adult cells in the mouse pancreas, called exocrine cells, can be reprogrammed into insulin-producing beta cells. Remarkably, this reprogramming only required the delivery of three proteins that were previously found to be important in pancreatic development. If the same type of approach works in humans, this discovery can have a dramatic impact on the ability to increase beta cell mass in people with diabetes. The findings are also broadly applicable to the field of regenerative medicine, as the approach of turning adult cells into other cell types could be useful for treating other diseases.

In 2008, the NIDDK launched a new program called the Type 1 Diabetes Pathfinder, to support new investigators proposing creative research approaches to study type 1 diabetes or its complications. One of the ongoing research projects supported through this program focuses on beta cell regeneration. Thus, the NIDDK supports multifaceted research on this important area of science.

Item

Chronic Pediatric Kidney Disease - Translational and clinical research to understand the mechanisms involved in kidney injury and progression are important to develop and test new therapies in children. The Committee encourages NIDDK to initiate multi-center pediatric nephrology translational studies or treatment trials as 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. 144)

Action taken or to be taken

The NIDDK recently began a study on the natural history of acute kidney injury (AKI). One study site is enrolling approximately 100 children as part of this cohort. Because children with AKI often differ from adults in terms of underlying disease, mechanisms of injury, and response, this element of the study will provide important information about AKI in the pediatric population. The overall goal of this study is to determine the long term outcome after AKI, and to identify and validate new biomarkers (indicators) of kidney damage, recovery, and long term outcome in patients with AKI. Because there are virtually no effective therapies to reverse AKI, the identification of biomarkers of early-stage injury, when this condition may be responsive to intervention, is of critical importance.

The identification of such biomarkers may improve approaches to protecting the kidneys and preventing damage.

The NIDDK also supports a broad range of investigator-initiated clinical studies of kidney disease in children and adolescents. Research areas currently funded include pediatric transplant infections and outcomes; primary prevention of hypertension in obese adolescents; early detection and/or prevention strategies for hemolytic uremic syndrome; the genetics of and various therapeutic approaches to focal segmental glomerular sclerosis; and non-invasive diagnostics for IgA nephropathy.

In addition to these studies, the NIDDK continues to support the Study of Chronic Kidney Disease in Children (C-KiD), an observational study of over 500 children with mildly to moderately impaired kidney function. The goals of the C-KiD study are to determine the risk factors for progression of pediatric chronic kidney disease and to examine the impact of CKD on neurocognitive development, risk factors for cardiovascular disease, and growth. The NIDDK is also supporting a study of vesicoureteral reflux in children to determine whether antibiotic treatment prevents urinary tract infections and renal scarring in children with reflux. This study, RIVUR, has the potential to help researchers and physicians better understand how the best care for the tens of thousands of children who are diagnosed each year with reflux and urinary tract infections.

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 looks forward to the recommendations of the National Commission on Digestive Diseases and urges NIDDK to consider the Commission's recommendations (p. 144).

Action taken or to be taken

The Commission completed its research plan in September 2008, for transmission to the Congress through a Congressional Appropriations Committee Report. The research plan reflects the consensus of external scientists and patient advocates serving on this independent body. While the NIDDK provided leadership and support for this planning effort, the Commission's research plan is addressed to all stakeholders across NIH, as well as in the broader digestive disease research community. The Commission outlines steps for NIH and other stakeholders to take toward implementing the plan including the following recommendation for NIDDK:

> NIDDK-led investigator-initiated research, sample repository, clinical trials, and consortia on a host of digestive conditions such as inflammatory bowel diseases (IBD); viral hepatitis; drug-induced liver injury; and gastroparesis.

The Commission's Research Plan also had recommendations for NCI, NIAID, NIEHS, NIAAA, NICHD, NCCAM, NINR, NIA, ORWH, NIBIB, NCMHD and NIGMS.
Access this link for more information about the Commission and its Research Plan.
http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/.

Item
Glomerular Disease Research - The Committee continues to be pleased with the work of NIDDK in the area of glomerular disease research, particularly as it relates to focal segmental glomerulosclerosis, and commends the institute for the recent release of a program announcement on glomerular diseases. The Committee continues to be interested in the establishment of a patient registry for glomerular diseases. (p. 144)

Action taken or to be taken
The NIDDK supports a robust portfolio of research into glomerular diseases, including both investigator- and NIDDK-initiated research projects. Throughout 2008, the NIDDK solicited research under Program Announcements for "Grants for Basic Research in Glomerular Diseases" and "Pilot and Feasibility Clinical Research Grants in Kidney or Urologic Diseases." Projects funded in response to the first announcement include studies of basic glomerular cell biology, the development of new animal models or new imaging techniques, and the identification and characterization of novel biomarkers. Through the latter announcement, NIDDK funded pilot and feasibility clinical and translational research studies that are designed to address important scientific questions and are potentially of high impact.

There are many distinct forms of glomerular disease, most of which occur as rare diseases. The NIDDK has supported several efforts regarding registries for some forms of glomerular disease, including thrombotic microangiopathy-related glomerular disease, ANCA-related glomerular disease, and membranoproliferative glomerulonephritis type II. Complementing these activities, the NIDDK-supported focal segmental glomerulosclerosis clinical trial has collected a large amount of clinical data and samples for a cohort of subjects who have this form of glomerular disease. These samples will ultimately be made available to the wider research community.

Item
Hepatitis B Consensus Conference - The Committee is pleased with the scientific progress and development of numerous medications which now make it possible to develop a consensus on the best treatment protocols for hepatitis B. The Committee requests to be kept informed of the outcome of the October, 2008 Hepatitis B Consensus Conference. (p. 145)

Action taken or to be taken

To resolve issues concerning optimal use of the many available therapies against hepatitis B, in October 2008, the NIDDK convened an NIH Consensus Development Conference on management of hepatitis B, together with the Office of Medical Applications of Research, and the Johns Hopkins University School of Medicine, with additional support from the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA). The purpose of this 3-day conference was to examine important issues in hepatitis B therapy, including which groups of patients benefit from treatment and at what point during treatment is the benefit achieved, as well as which groups do not show a benefit from currently available treatments. The external experts serving on the conference panel addressed major questions regarding hepatitis B management related to current burden, disease development, benefits and risks of current treatment options, who should or should not be treated, appropriate measures to monitor treatment, and the greatest challenges and opportunities for future research on hepatitis B. Their recommendations 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

Incontinence - The Committee is pleased that NIDDK collaborated with NICHD on the recent state-of-the-science conference on incontinence and urges the institute to prioritize the recommendations of this conference. (p. 145)

Action taken or to be taken

The NIDDK, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Office of Medical Applications of Research, sponsored a State-of-the-Science conference on Incontinence in Adults in December 2007. 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, is beginning to lay the groundwork for an awareness campaign for fecal incontinence. Regarding urinary incontinence, the NIDDK supports the Urinary Incontinence Treatment Network (UITN) to conduct a series of 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 by late 2009. The UITN addresses a recommendation of the State-of-the-Science conference to determine the effects of interventions in women with urinary incontinence.

Item

Inflammatory Bowel Disease (IBD) - The Committee commends NIDDK for its leadership on 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. 145)

Action taken or to be taken
The NIDDK supports a broad range of inflammatory bowel disease (IBD) research. For example, the Institute recently strengthened its support for the IBD Genetics Consortium by renewing funding for this effort. Building on its previous successes, the Consortium, in collaboration with other scientists, recently published the discovery of 21 new genes or regions of the genome associated with susceptibility to IBD. These findings not only open new avenues to advance understanding of IBD, but also, the newly-identified genes (and genes in the identified genomic regions) represent potential targets for the development of novel diagnostic or therapeutic strategies. Analysis of the results also suggests that there may be many more genes that also influence the development of IBD. The IBD Genetics Consortium is exploring the potential for genetic analyses of various subgroups of patients so as to identify other IBD genes.

A major study by another group of scientists, supported in part by NIDDK, led to the recently-published finding of two additional regions of genomic variation, which are associated with pediatric-onset IBD. Other NIDDK-funded basic and clinical research on IBD is addressing such key areas as inflammation and interactions between gut bacteria and the immune system. The NIDDK has also co-sponsored a request for applications for a rare diseases clinical research network that will encourage research in many areas, including IBD in children. The topics of the grants to be funded will depend upon the nature and scientific merit of the applications. The Institute’s support of IBD research is consistent with the scientific opportunities outlined in the “Challenges in IBD Research” agenda of the Crohn’s and Colitis Foundation of America. The Institute continues to welcome and value the input of the IBD community.

Item
Irritable Bowel Syndrome - The Committee is pleased that NIDDK has formulated an action plan for digestive diseases through the National Commission on Digestive Diseases and that irritable bowel syndrome has been included. The Committee encourages the Institute to prioritize the recommendations of the Commission and expedite their implementation. (p. 145)

Action taken or to be taken
The independently developed research action plan of the National Commission on Digestive Diseases (NCDD), “Opportunities and Challenges in Digestive Diseases Research: Recommendations of the National Commission on Digestive Diseases,” will serve as a critical scientific guidepost for the NIH, other funding and professional organizations, industry, and the broader investigative community in advancing research on irritable bowel syndrome (IBS) and other digestive diseases over the next decade. The NIDDK currently supports a

dynamic research portfolio on IBS and other functional gastrointestinal disorders. Abdominal pain is a critical symptom in IBS, and important recent advances in our understanding of IBS supported by NIDDK include a series of insights into the brain-body interactions influencing visceral pain perception, sex and gender differences in these perceptions, and how a history of sexual and physical abuse heightens pain perception for many IBS patients. The NCDD plan includes a broad array of basic, clinical, and behavioral research recommendations for areas of further IBS research in a chapter devoted to IBS and other functional gastrointestinal disorders. Other sections of the NCDD plan also provide important recommendations for research relevant to preventing, treating, or reversing IBS. One example of a recommended area of study is research that can lead to an improved understanding of the gut mucosa and musculature. Relevant to this recommendation, the basic biology of muscle cells of the gastrointestinal tract is a focus of a new scientific workshop the NIDDK is planning for spring 2009. The NIDDK will continue to solicit broad stakeholder input as it oversees implementation of recommendations for IBS research included in this long-range research plan for digestive diseases, within available resources and in response to scientific opportunity.

Item

Islet Transplantation - The Committee encourages NIDDK to continue its support of innovative clinical trials for pancreatic islet transplantation. The Committee encourages two important areas of focus: the development of innovative strategies to monitor islet mass and function before and after transplantation as well as research on the potential of encapsulating islets as a means to improve transplantation efficiency. (p. 145)

Action taken or to be taken

The NIDDK and National Institute of Allergy and Infectious Diseases co-lead a Clinical Islet Transplantation (CIT) Consortium that is currently recruiting eligible patients for its seven clinical trials in pancreatic islet transplantation to be conducted in the U.S., Canada, Norway, and Sweden. The CIT has created a means by which to rigorously study new and innovative approaches to islet transplantation as a therapy for type 1 diabetes. The NIDDK is issuing a solicitation to extend the CIT through 2011 to allow these important trials to be completed.

The NIDDK continues to support inventive strategies to monitor islet mass and function before and after transplantation. The NIDDK has made a concerted effort to advance the field of beta cell imaging through scientific workshops, requests for applications, supplements to its Diabetes Centers Program, and through its Intramural Research Program. For example, the NIDDK, in collaboration with the Juvenile Diabetes Research Foundation and the European Commission, will host an international workshop on islet imaging in April 2009. The sustained efforts of NIDDK to build research on imaging beta cell mass and

function have been successful in substantially enlarging this research community and additional planned efforts will further develop this promising field of research.

The NIDDK also continues to support innovative approaches to decrease the dependence of transplant patients on long-term immunosuppression, which is currently used in islet transplantation to protect newly transplanted islets from attack by the patient's immune system. Immunosuppression, however, presents the risk of multiple adverse effects. An alternative to immunosuppression is to coat or to "encapsulate" the islets with a biomaterial to prevent the islets from attack by the patient's immune system, yet allow necessary nutrients to reach the islets. The NIDDK has supported research in islet encapsulation by both academic and small business investigators for many years. In a recent effort encompassing islet encapsulation and other areas of type 1 diabetes research, the Type 1 Diabetes Pathfinder Award was created in 2008 to support exceptionally creative new investigators in type 1 diabetes research who have the potential to produce a major impact in biomedical and behavioral research relevant to type 1 diabetes and its complications. One of these new awards will support an investigator researching islet encapsulation.

Item

Polycystic Kidney Disease (PKD) - The Committee urges NIDDK to function through 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. The Committee suggests these centers work in collaboration with General Clinical Research Centers, Clinical and Translational Science Awards and PKD Centers of Excellence to ensure that PKD patients receive the most appropriate diagnostic tests and therapeutic treatments. The Committee also encourages NIDDK to consider establishing a centralized facility for the volumetric analysis of kidney images, PKD genotyping and surrogate marker analysis. (p. 145)

Action taken or to be taken

The NIH Public-Private Partnership Program is designed to facilitate collaborations to improve public health though biomedical research. This Program allows the NIH to leverage its resources to work collaboratively with partners sharing similar goals. The NIDDK would welcome interested potential partners to join the Institute in research efforts in a broad range of disease areas, including research relevant to diagnosis and treatment of PKD.

Two large NIDDK-funded studies of PKD—HALT-PKD and CRISP—have worked with General Clinical Research Centers (GCRCs) and Clinical and Translational Science Awards (CTSAs) institutions to identify and enroll patients. The participation of these facilities has been invaluable to successful implementation of these studies. Together, these studies seek to identify better imaging and monitoring approaches as well as improvements in patient care for individuals with PKD. The HALT-PKD study, for which recruitment is ongoing, is testing

whether optimum blood pressure management, in combination with drugs that target the renin-angiotensin system will slow the progression of the more common form of PKD. The Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for the common form of the disease. An extension, CRISP II, continues to follow this valuable cohort of patients. The image analysis methods developed in CRISP and currently being implemented in HALT-PKD and have been implemented by industry-sponsored trials that were recently initiated 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 CRISP, CRISP II, and HALT-PKD. The Institute plans to make these data and samples available to the greater research community through the NIDDK Repository.

In addition, the Institute is planning a new initiative in Fiscal Year 2009 to identify and validate biomarkers and risk assessment tools for kidney function, injury, and disease progression in people with chronic kidney disease. Improved biomarkers for screening, monitoring kidney function, and managing chronic kidney disease would be of benefit to people with PKD.

Item

Thalassemia - The Committee urges NIDDK to play a significant role in the Thalassemia Clinical Research Network (TCRN) since the iron chelation and non-invasive iron measurement issues addressed by the Institute are important to the quality of life of thalassemia patients. (p. 145)

Action taken or to be taken

The NIDDK is 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. NIDDK research has led to greater understanding of how different iron chelating drugs remove iron from body tissues which has, in turn, led investigators to investigate potential "smart" combinations of chelators that may enhance the effectiveness of iron removal, while decreasing the doses of drugs needed for effective treatment. The Institute also supports research to develop better methods to detect and measure iron overload non-invasively both for diagnosis and for monitoring a patient's response to chelation therapy. Noninvasive imaging approaches for measuring body iron stores will contribute greatly to the effective clinical management of patients with iron overload and will also facilitate the development of improved chelation treatment.

To bolster research advances in this area, the NIDDK organized a 2-day workshop on Iron Overload: Mechanisms, Measurement, and Management, held in October 2008. This workshop addressed evolving insights into genetic determinants and molecular mechanisms that promote iron overload. The workshop also reviewed advances in the noninvasive, organ-specific clinical

measurement of iron overload and the current state-of-the-art in the prevention and treatment of iron overload. This workshop will inform continuing collaborations between NIDDK and other ICs (in particular NHLBI and NIBIB) to address future research priorities in this important area, including the standardization of noninvasive imaging techniques to detect and measure iron overload and on the translation of these techniques to clinical practice.

Item
Type 1 Diabetes Clinical Trials - The Committee applauds NIDDK for establishing national clinical trial platforms, such as TrialNet for Type 1 Diabetes, and encourages the institute to accelerate the development and testing of innovative drugs and drug combinations to treat type 1 diabetes. (p. 145)

Action taken or to be taken
The NIDDK appreciates the Committee's commendation of the Type 1 Diabetes TrialNet. TrialNet investigators are working toward the goal of preventing or delaying progression of type 1 diabetes through clinical evaluation of potential new therapies. For example, at the 2008 Annual Scientific Sessions of the American Diabetes Association, TrialNet researchers announced the results of a clinical trial in patients with new-onset type 1 diabetes. These researchers determined that the drugs mycophenolate mofetil (MMF) and daclizumab (DZB) are not able to stop the ongoing destruction of beta cells in these patients. Although this particular therapy was not beneficial, there is a robust pipeline of potential new therapies to be tested to try to preserve the function of insulin-producing beta cells in newly-diagnosed patients. Researchers participating in TrialNet have completed recruitment for a clinical trial to determine whether the drug rituximab can preserve insulin production in newly diagnosed type 1 diabetes patients. A TrialNet study of another agent, CTLA-4 Ig (abatacept), recently began recruitment. Finally, a fourth study, to determine whether administration of glutamic acid decarboxylase (GAD) can preserve insulin production, has been approved and is in development. TrialNet is also testing or soon to begin testing several new therapies—including oral insulin, GAD, anti-CD3, and omega-3-fatty acid docosahexaenoic acid (DHA)—to prevent type 1 diabetes in patients at high risk for developing the disease.

The NIDDK also has created a critical pipeline for the discovery and preclinical testing of novel therapies. An NIDDK-sponsored resource provides standardized testing of therapeutic potential in animal models. Agents showing promise in animal models must then be manufactured and assessed at the high standards required for human research—a challenge for many academic and clinical scientists. In order to help scientists overcome these challenges, the NIDDK, in collaboration with the NCI, implemented a program called the Type 1 Diabetes-Rapid Access to Intervention Development Program. This program provides key resources to make and test potential new therapeutics, expanding the pipeline of therapies to be tested and accelerating the delivery of these agents to clinical trial platforms. 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.

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, the Environmental Determinants of Diabetes in the Young Study, and the natural history study of TrialNet. The Committee urges NIDDK to advertise widely to the diabetes research community the availability of samples, take steps to ensure that the biorepositories implement efficient procedures to disseminate rapidly those samples to qualified researchers, and develop policies to expedite the availability of samples from other clinical trials in type 1 diabetes. (p. 146)

Action taken or to be taken

The NIDDK appreciates the Committee's commendation for establishing biorepositories and the desire to ensure that samples and data from type 1 diabetes clinical research studies are made available to qualified researchers. To facilitate sharing of samples and data collected in its clinical studies, the NIDDK established the Central NIDDK Repositories in 2003. The Central Repositories permit the broad research community to access biosamples and data from many studies, including type 1 diabetes clinical research studies. Data from several genome-wide association studies (GWAS) 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 (dbGaP). Therefore, the data from these GWAS studies are available in one place, making them easy to find and access. Scientists can find information on available samples and data, as well as procedures to request materials, on the Central Repositories' public website: www.niddkrepository.org.

The NIDDK has developed a public website (www.T1Diabetes.nih.gov) that has information on research resources, including data and samples, that are available through research consortia supported by the Special Statutory Funding Program for Type 1 Diabetes Research. The NIDDK is in the process of enhancing this website, in order to provide additional information on the availability of samples and data. The enhanced public website will have information on: samples and data that are currently available, timeframes when additional data and samples are expected to become available, access policies established by the clinical research consortia, and funding opportunities that may be available to conduct ancillary studies to ongoing clinical studies. In addition to including information on the T1DGC, The Environmental Determinants of Diabetes in the Young, and Type 1 Diabetes TrialNet, the enhanced website will include information on, and sharing policies from, additional type 1 diabetes

clinical research studies supported by the Special Statutory Funding Program for Type 1 Diabetes Research.

The NIDDK also uses the NIH Guide for Grants and Contracts to broadly advertise the availability of samples in its type 1 diabetes clinical research studies. 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 (biomarkers) of type 1 diabetes. The NIDDK will continue to use a variety of methods to ensure that the scientific research community is aware of samples and data available through its type 1 diabetes clinical research studies, in order to accelerate research progress and to maximize the usefulness of the studies.

Senate Significant Items

Item

Acute Liver Failure - The Committee supports the Institute's plan to renew funding for the Acute Liver Failure Study Group for an additional 5 years, and it urges the NIDDK to provide additional resources in this area. (p. 96)

Action taken or to be taken

The NIDDK supports two multi-center, clinical study groups focusing on acute liver failure: the adult Acute Liver Failure Study Group, and the pediatric Acute Liver Failure Study Group. The adult Study Group was initiated in 2000 for five years; funding was then renewed for an additional 5 years, through 2010. The pediatric Study Group is also funded through 2010.

The Adult Study Group has collected data and samples at 24 U.S. sites for studies to define the causes of acute liver failure and to identify factors that impact outcome and predict survival. The adult Study Group recently completed a clinical trial of a potential therapy (N-acetylcysteine or NAC) for acute liver failure due to causes other than acetaminophen toxicity, and is analyzing the results. The extended study plans to add international sites and to conduct additional research on acute liver failure disease processes, as well as optimal management and therapy.

In the pediatric Study Group, 24 sites in the U.S., Canada, and U.K., are collecting data to develop management strategies for acute liver failure in affected infants, children, and adolescents. Research being conducted includes studies to identify the causes and processes of acute liver failure that are unique to these age groups. A clinical trial is ongoing in this study population of a potential therapy (NAC) for acute liver failure not due to acetaminophen. With the funding provided through 2010, this pediatric Study Group is conducting additional studies of outcomes, predictors of prognosis, disease mechanisms, and novel treatment strategies in children with acute liver failure.

Item

Alpha-1 Antitrypsin Deficiency - The Committee encourages the NIDDK to maintain its support of Alpha-1 research and to collaborate with the NCI and other Institutes on this effort. (p. 96)

Action taken or to be taken

The NIDDK has sought not only to maintain, but expand its portfolio on alpha-1 antitrypsin deficiency research. To encourage research interest in this and related areas, the NIDDK, along with the NCI, the National Institute of Biomedical Imaging and Bioengineering (NIBIB), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) released a program announcement on "Etiology, Prevention, and Treatment of Hepatocellular Carcinoma." Among the NIDDK-funded grants from this solicitation is one on hepatocellular carcinoma in antitrypsin deficiency. It is hoped that this study will advance knowledge of how antitrypsin deficiency and other genetic diseases of the liver lead to liver cancer.

Another solicitation, entitled "Targeting Diseases Caused by Protein Misfolding and Misprocessing" (such as alpha-1 antitrypsin deficiency), was issued by the NIDDK along with National Institute of Neurologic Disorders and Stroke (NINDS) and the National Institute on Aging (NIA). Among the grants funded by NIDDK is an innovative study to identify potential therapeutics based on a high throughput screen for drugs that rescue the mutation in roundworms engineered to have the human alpha-1 antitrypsin mutation.

Item

Beta Cell Biology - The NIDDK is urged to extend and expand its vigorous support of the Beta Cell Biology Consortium, which promotes collaborative research relevant to understanding and treating both type 1 and type 2 diabetes. Particularly important is the creation of diabetes research resources and reagents that can be accessed by the entire diabetes research community. In addition, the Committee asks the NIDDK to work with the NCRR to ensure the viability of the regional Islet Cell Resources Centers or equivalent infrastructure that can efficiently produce and distribute purified human islets for beta cell biology research. (p. 96)

Action taken or to be taken

Please refer to page 45 of this document for the NIDDK's response to this significant item regarding beta cell biology.

Item

Biosamples for Type 1 Diabetes Research - The Committee commends the NIDDK for establishing biorepositories to house data and biological specimens collected by studies such as the international Type 1 Diabetes Genetics Consortium [T1DGC], The Environmental Determinants of Diabetes in the Young [TEDDY] Study, and the natural history study of TrialNet. The Committee urges

the 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. 97)

Action taken or to be taken
Please refer to page 51 of this document for the NIDDK's response to this significant item regarding biosamples for type 1 diabetes research.

Item
Chronic Pediatric Kidney Disease - Translational and clinical research to understand the mechanisms involved in kidney injury and progression are crucial to develop and test new therapies in children. The Committee urges the NIDDK to initiate two new prospective multicenter pediatric nephrology translational studies or treatment trials over the next 2 years. (p. 97)

Action taken or to be taken
Please refer to page 43 of this document for the NIDDK's response to this significant item regarding chronic pediatric kidney disease.

Item
Diamond-Blackfan Anemia [DBA] - The Committee is aware of important breakthroughs in DBA research and the link with a ribosomal protein defect. The Committee understands that the NIDDK is planning a workshop regarding the implications of ribosome biogenesis in hematological diseases. The Committee commends the NIDDK for its attention to DBA and encourages cross-Institute research initiatives related to ribosomal protein defects found in DBA and their implication in disease areas important to the NIDDK. (p. 97)

Action taken or to be taken
With the recent discovery of a ribosomal protein defect in some cases of Diamond-Blackfan Anemia, the NIDDK, along with the National Heart, Lung, and Blood Institute (NHLBI) and CDC, sponsored a workshop titled "Ribosomes and Their Role in Disease" in August 2008. Among the topics discussed were ribosomal structure and function, production of the ribosome, and disease. The Institute is currently reviewing the input garnered from the workshop to assess potential research opportunities.

Item
Digestive Diseases - The Committee looks forward to the recommendations of the National Commission on Digestive Diseases and encourages the NIDDK to consider them strongly. The Committee notes that the draft plan lacked specificity, and it urges the NIDDK to identify the programs, structures and resources that are necessary to implement a long-range plan. (p. 97)

Action taken or to be taken
Please refer to page 44 of this document for the NIDDK's response to this significant item regarding digestive diseases.

Item
Glomerular Disease Research - The Committee commends the Institute for the recent release of a program announcement on glomerular diseases, and it encourages the establishment of a patient registry in this area. (p. 97)

Action taken or to be taken
Please refer to page 44 of this document for the NIDDK's response to this significant item regarding glomerular disease research.

Item
Incontinence - The Committee is pleased that the NIDDK collaborated with the NICHD and the Office of Medical Applications of Research on the recent state-of-the-science conference on incontinence, and it urges the Institute to prioritize the recommendations of this conference. (p. 98)

Action taken or to be taken
Please refer to page 46 of this document for the NIDDK's response to this significant item regarding incontinence.

Item
Inflammatory Bowel Disease (IBD) - The Committee encourages the Institute to increase support for genetic and clinical IBD research and other opportunities outlined in the research agenda, `Challenges in Inflammatory Bowel Disease.' The Committee particularly encourages the NIDDK to expand support for pediatric IBD research. (p. 98)

Action taken or to be taken
Please refer to page 51 of this document for the NIDDK's response to this significant item regarding inflammatory bowel disease.

Item
Polycystic Kidney Disease (PKD) - The Committee urges the NIDDK to work through 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. The Committee urges that these centers work in collaboration with General Clinical Research Centers, Clinical and Translational Science Awards and PKD Centers of Excellence to ensure that PKD families receive the best diagnostic tests and therapeutic treatments and the opportunity to participate in promising clinical trials and pilot studies. The Committee also encourages the NIDDK to facilitate the establishment of a centralized facility for the volumetric analysis of kidney images, PKD genotyping and surrogate marker analysis. (p. 98)

Action taken or to be taken
Please refer to page 49 of this document for the NIDDK's response to this significant item regarding polycystic kidney disease.

Item
Thalassemia - The Committee urges the NIDDK to play a larger role in the Thalassemia Clinical Research Network [TCRN], as the iron chelation and non-invasive iron measurement issues addressed by the Institute are essential to the quality of life of thalassemia patients. (p. 99)

Action taken or to be taken
Please refer to page 50 of this document for the NIDDK's response to this significant item regarding thalassemia.

Item
Hepatitis B Network - The Committee supports the Institute's plan to fund and create a network of hepatitis B clinical research centers and urges that these centers be established to address the major research questions identified by the upcoming Hepatitis B Consensus Conference and the priorities identified for hepatitis B in the NIH Liver Disease Research Action Plan. The Committee expects to be kept informed on the outcome of the October 21, 2008, conference. (p. 97)

Action taken or to be taken
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. Research conducted by the Network will address hepatitis B research questions and goals identified through past NIH-sponsored meetings on hepatitis B management, as well as in the trans-NIH *Action Plan for Liver Disease Research*.

For example, research recommendations from the NIH Consensus Development Conference on management of hepatitis B, held in October 2008, are informing research conducted by the Network. The NIDDK convened this Conference together with the 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, 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 continues to strongly support the HALT-C clinical study on hepatitis C. The Committee also understands that nearly one-half of all persons with hemophilia have contracted the hepatitis C virus, and many of these individuals are co-infected with HIV. The NIDDK is encouraged to pursue research initiatives on co-infection and the progression of liver disease in this population. (p. 97)

Action taken or to be taken
Consistent with the stated goals of the trans-NIH *Action Plan for Liver Disease Research*, the NIDDK and other NIH Institutes and Centers continue to support research on liver disease associated with hepatitis C virus (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 a screening program for these pathogens in donor blood.

In a recent review of progress made toward achieving the goals of the *Action Plan*, advances were noted in research on HCV/HIV co-infection. For example, the Adult AIDS Clinical Trials Group funded by the 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 co-infected individuals. Several NIH-funded prospective studies that are actively assessing factors associated with progression of liver disease in patients with HIV/HCV co-infection include: 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 the 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 NCI. Additionally, the NIDDK has helped support research on genetic factors contributing to liver disease progression in persons 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.

The NIDDK also continues to support 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. However, the HALT-C trial is being

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.

Item

Interstitial Cystitis [IC] - The Committee is concerned by the projected declines in research funding for IC at the NIDDK. It urges the Institute to provide enough funding to implement the goals of the MAPP initiative and to support more basic research on the etiology, pathogenesis and pathophysiology of IC. In addition, the Committee notes the growing body of scientific evidence documenting the overlap between IC and vulvodynia, two highly prevalent, distressing conditions characterized by chronic pelvic and urogenital pain. The Committee, therefore, urges the NIDDK to establish a center for research and education on urologic/urogenital chronic pelvic pain syndromes that will focus specifically on IC and vulvodynia, and related comorbid disorders, and will establish collaborative initiatives among the ORWH, NIAID, NIAMS, NINDS, and NICHD. (p. 98)

Action taken or to be taken

The NIDDK is committed to fostering research that can lead to effective therapies for preventing, treating, or reversing the painful and not well understood urologic condition, interstitial cystitis/painful bladder syndrome (IC/PBS). In September 2008, the NIDDK initiated the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. This multi-center Network will conduct collaborative studies to determine the causes of the two most common chronic urologic pelvic pain disorders, IC/PBS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Building on recent scientific findings, the Network will explore the relationship of IC/PBS and CP/CPPS to other chronic pain disorders. The goal is to find out whether these conditions share common underlying disease processes. This innovative research approach is expected to lead to critical new insights into the underlying causes of urologic chronic pelvic pain, and potentially to new therapeutic targets for IC/PBS and CP/CPPS. The Network includes six Discovery Sites across the nation that will conduct research studies, and two separate Core Sites that will coordinate data collection and provide other services. Network studies will be developed in consultation with NIDDK scientific staff, and will include basic research on the etiology, pathogenesis, and pathophysiology of IC. The NINDS, NICHD, and the NIH Office of Research on Women's Health (ORWH) will also contribute scientific expertise to help shape the Network's research focus. The NIDDK expects to invest up to $37.5 million in this new initiative over the five-year course of the project, including $7.5 million each in FY 2008 and FY 2009. The ORWH expects to contribute funding to the Network in FY 2009. At the current funding level, the Network is expected to support both large research projects aimed at the primary MAPP goals, and additional ancillary studies to explore related research questions.

In exploring the relationship between urologic chronic pelvic pain syndromes and other chronic pain conditions, MAPP Network scientists 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. NIH is also conducting 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. Currently, NICHD and ORWH are cosponsoring an initiative to address basic, clinical, translational, epidemiologic and/or behavioral research that concentrates on studies of relevance to vulvodynia and that may lead to prevention and therapeutic opportunities. 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. 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

Non-Alcoholic Fatty Liver Disease - The Committee encourages the NIDDK to renew and expand its research network for non-alcoholic fatty liver disease, increase the involvement of non-Federal funding sources, and include adult and pediatric patients in research and clinical trials. (p. 98)

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 will be renewed in FY 2009 to continue this research for an additional five years, 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 potential treatments for NASH, the drug pioglitazone or vitamin E, as compared to a placebo. Results of this trial are expected in 2009. 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, with results expected in 2010. Renewal of funding for the Network is enabling expansion of a database to collect samples from additional adult and pediatric participants. Non-Federal sponsorship by industry partners has been significant for this Network and the NIDDK is exploring the possibility of involvement by several potential industry sponsors who have expressed interest in supporting additional clinical trials within the Network.

Item

Urological Research - The Committee encourages the NIDDK to establish a urological disease research branch and requests a response in the fiscal year 2010 budget justification. The Committee also urges the Institute to prepare a trans-NIH action plan for urological disease research. (p. 99)

Action taken or to be taken

Through efficient use of its current organizational structure, the NIDDK is actively involved in strengthening benign urologic diseases research and addressing challenges experienced by the urology research community. Several senior NIDDK scientific program staff lead a multi-faceted urology research program ranging from basic research to clinical trials. Through its chairmanship of the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, which has a specific subcommittee for urology, the NIDDK provides leadership and coordination for trans-NIH urologic diseases research. Because current gaps in urologic diseases research threaten the development of future therapies, the NIDDK has spearheaded strategic planning efforts with the urology research community to discuss barriers and develop solutions to the global issues that have hindered progress in urology research—including less than optimal academic structures, funding and research training issues, and professional development.

In February 2007, the NIDDK held a meeting on these issues with leaders in academia and professional societies, and is planning a second meeting for February 2009. NIDDK is also working closely through regular communications of its senior urology scientific staff with the American Urological Association (AUA) to work on these gaps and issues, and members of the NIDDK's National Advisory Council are also helping in this regard. Building on these efforts, the NIDDK has issued several Requests for Applications focused on revitalizing the urology research community, and funded new programs including an innovative research network to study chronic urologic pelvic pain syndromes, a new multidisciplinary career development research training program for urology researchers, and a revised O'Brien urology research centers program. The NIDDK continues to enhance research training opportunities for urologists through an agreement with the AUA for joint sponsorship of candidates.

Finally, the NIDDK continues to plan strategically to address current and future challenges and opportunities in NIH-supported urology research. Recent efforts include the aforementioned strategic planning efforts with the urology research community to discuss barriers and develop solutions to the global issues that have hindered progress in urology research (Feb 2007 and Feb 2009), a strategic plan for pediatric urology research published in February 2006, and a prostate disease research strategic plan published in 2008. Moreover, recent scientific meetings on urinary tract stones, urologic pain syndromes, and benign prostatic hyperplasia will contribute to the NIDDK's planning process by

identifying gaps in the current knowledge base. These examples of new and ongoing program enhancements in urology research studies, strategic planning, and research training, demonstrate the NIDDK's continuing commitment to effectively bolstering support for 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

House Significant Items

Item

Diabetic Complications - The Committee encourages NINDS to accelerate research on the underlying causes of neurological damage in diabetes patients, including both acute complications, such as hypoglycemia, and long-term complications like autonomic neuropathy. (p. 146)

Action taken or to be taken

Neurological complications are central problems in diabetes mellitus. The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide array of research projects aimed at understanding the mechanisms by which diabetes and altered blood glucose levels may cause cerebrovascular disease, stroke, neural injury (including neuropathies), and cognitive impairment.

Some of the research NINDS supports is elucidating the frequency and clinical heterogeneity of diabetic neuropathies in various populations and ethnicities, developing new disease model systems to better understand the neural causes of neuropathy-related chronic pain or ulceration, and developing better clinical tools to help doctors assess the condition of patients at risk of autonomic neuropathy and develop tools to determine the best way to control and manage the disease. In terms of the relation between diabetes and stroke, NINDS supports research to determine the effects of Type-2 diabetes hyperglycemia on the integrity of blood vessels, several studies aimed at developing high-throughput screening assays for drugs which may protect the brain from the effects of insulin resistance, and clinical studies to test the effects of insulin resistance inhibitors or insulin therapy on stroke outcomes. Patients undergoing diabetic treatment are also at risk for hypoglycemia, which may have harmful effects on the nervous system and has been associated with neuronal toxicity and cognitive impairment. Studies funded by NINDS are examining the molecular mechanisms of hypoglycemia-induced neuronal death in order to identify molecular targets for therapeutic development. In collaboration with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute on Diabetes and Digestive Kidney Diseases (NIDDK), NINDS also participates in a Request for Applications to develop Cooperative Multicenter Diabetes Research Networks for Hypoglycemia Prevention. This initiative is meant to develop research centers dedicated to exploring approaches for reducing the incidence of hypoglycemia and associated complications in children and young adults with type I diabetes.

The central nervous system (CNS) plays an important role regulating the body's blood glucose levels, and understanding this interaction may thus lead to means of preventing neural injury and other diabetes complications. To this end, in 2008 NINDS began planning a workshop on the CNS and glycemic control to be held

in 2009. The workshop, led by NINDS, and in collaboration with the NIDDK, the National Heart Lung and Blood Institute (NHLBI), the NICHD, the National Eye Institute (NEI), and the Juveniles Diabetes Research Foundation, will identify research opportunities, key needs of the relevant research communities, and develop collaborations between diabetes and neuroscience researchers.

Item

Headache Disorders - The Committee encourages intensified- efforts by NINDS to produce breakthroughs in understanding the causes, prevention, treatment, and eventual cure of headache disorders, including migraine, cluster headache, and chronic daily headache. The Committee encourages NINDS to increase its research effort in headache disorders with requests for application and career training and transition awards; and taking any other steps to ensure that vigorous intramural and extramural headache research programs are established. To identify consensus research targets, the Committee further encourages NINDS to collaborate with the national and international research community to develop Headache Disorders Research Benchmarks, similar to the Epilepsy Research Benchmarks initiative. To improve the transparency of NIH research funding allocations, the Committee suggests that "migraine" and "headache disorders" be included as individual categories in the annual NIH estimates of funding for various disease areas, as well as in the forthcoming Research, Condition, and Disease Categorization program. (p. 146, 147)

Action taken or to be taken

NINDS recognizes the considerable public health burden caused by headache disorders, including migraine, and thus is employing multiple strategies to stimulate research in this field. In FY07, NINDS, with the NIDCD, the NIDCR and the NIEHS, released a Funding Opportunity Announcement (FOA) on the Neurobiology of Migraine. This FOA is intended to stimulate innovative research to expand the current base of knowledge on the neurobiological mechanisms underlying migraine and to understand the role of neuromodulators (e.g. hormones) on migraine pathophysiology. One project funded under this announcement aims to fill a gap in the headache research field by developing an animal model for Chronic Daily Headache (CDH), which often evolves from episodic migraines. Successful development of this resource will allow for subsequent investigations into the pathophysiology of this disorder, and will provide a tool for researchers to test potential CDH therapies. NINDS also supports a variety of investigator-initiated research projects on headache disorders. A study by one team of NINDS-supported investigators focuses on Cortical Spreading Depression (CSD), a phenomenon common in migraines. CSD occurs when a slow wave of potassium ions causes a large number of neurons to fire at once, leading to a prolonged period of neuronal “silence” in the area. Investigators determined that CSD resulted in a drop in oxygen in the region, causing the neurons to swell and temporarily lose dendritic spines, tiny projections on neurons that form connections (synapses) with other neurons.

These findings suggest that drugs that inhibit CSD may be effective in the treatment of migraine.

Training the next generation of researchers is crucial to reducing the burden of neurological disorders, including headache. NINDS currently supports several trainees through career development awards with research focused on headache disorders. These trainees are focused on a diverse array of research topics including: gender differences in the pathophysiology of migraine, emergency department diagnosis and treatment of migraines, dissemination of behavioral treatment for migraine, and the molecular mechanisms involved in pain processing during migraine.

In October 2008, the 6th Headache Research Summit will convene on the NIH campus. Partially funded by NINDS, this conference will convene leading headache researchers to discuss issues such as translational research and migraine, neuroimaging of headache, mechanisms and neurogenetics of headache, epidemiology and risk factors of headache, and clinical trial design and interpretation. During this conference, NINDS will initiate preliminary discussions to determine the best way to establish research priorities and identify research opportunities for the field.

Item

Mucopolysaccharidoses - The Committee commends NINDS for taking the lead role supporting the scientific meeting entitled, "Towards Clinical Progress in the Mucopolysaccharidoses." NINDS is encouraged to pursue findings of the meeting, including the need for collection of natural history data to move novel therapies into the clinic and the growing evidence that combining various therapeutic modalities can dramatic increase efficacy. (p. 147)

Action taken or to be taken

NINDS invests in basic, clinical and translational research to understand the mucopolysaccharoidoses (MPS) and other lysosomal storage disorders (LSDs) and to develop therapies to treat their neurological manifestations. In March 2007, NINDS sponsored the workshop, "Towards Clinical Progress in the Mucopolysaccharidoses," where researchers reported research advances and identified opportunities essential to moving new therapies into the clinic.

Enzyme replacement therapies available for some forms of MPS and other LSDs do not cross the blood-brain barrier (BBB) and therefore do not treat neurological symptoms. NINDS supports studies on new ways to deliver functional enzymes to the brain, such as efforts to tap into pathways the brain normally uses to transport other substances across the BBB. NINDS also supports research on gene therapy approaches, which have successfully replaced enzymes in the brains of animal models. The human brain's large size presents a major challenge to achieving gene expression sufficient for clinical benefit, and funded projects are optimizing methods for broad gene delivery. In a recent advance, an

early phase clinical trial funded by NINDS established feasibility and general safety for gene therapy in the LSD Batten disease. While preliminary, evidence of slowed disease progression in treated children suggests the potential for similar approaches in other LSDs, including MPS.

NINDS workshop participants noted growing evidence that combining therapeutic modalities may synergistically increase treatment efficacy. NINDS supports research to identify and develop additional strategies for treating MPS that could possibly be used in combination with enzyme replacement or gene therapy. One project is testing whether the antibiotic gentamicin can suppress the mutation that causes MPS-IH. Other research focuses on pathways secondary to enzymatic deficiencies that contribute to disease pathology, including a study on specific vulnerable neuronal populations in a mouse model of MPS-IIIB. By determining the role of secondary or downstream pathways in disease symptoms, this research may reveal new treatment targets.

In addition, NINDS continues to support scientific conferences in the LSD research community, such as the Lysosomal Disease Network's Annual WORLD Symposium. This international conference gives researchers an opportunity to share findings in basic, translational and clinical research and to establish collaborations that could enable multicenter studies in natural history and other areas of clinical research. NINDS program staff will take an active role in developing the agenda for the 2009 WORLD conference, with a focus on moving research advances toward clinical trials. This conference will also provide a forum for following up on other needs expressed at the March 2007 NINDS workshop, which included natural history studies, newborn screening programs, and meaningful clinical outcome measures. Finally, through participation in the NIH Office of Rare Diseases' initiative for Rare Disease Clinical Research Networks, NINDS helps create additional opportunities for small research communities, like that in MPS, to address some of these clinical research needs.

Item
Multiple Sclerosis - The Committee recognizes the efforts of NINDS to focus on axon damage in multiple sclerosis and encourages NINDS to further advance this research. (p. 147)

Action taken or to be taken
Multiple sclerosis (MS) is a chronic inflammatory disorder that leads to the destruction of myelin, a fatty sheath that surrounds and insulates nerve fibers, or axons. Demyelination and other pathological processes can also damage the axons themselves, leading to neurodegeneration, but available therapies do not target this aspect of the disease. To promote research to develop neuroprotective treatments for MS as well as technologies or biomarkers for monitoring their efficacy, the National Institute of Neurological Disorders and Stroke (NINDS) continues to invite applications through a Program

Announcement with set aside funds entitled, “Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair.”

In response to this initiative, NINDS supports efforts to develop new tools and methods for imaging demyelination and axonal damage in the brains of living animals. Such tools may one day allow earlier diagnosis in humans as well as the ability to track disease progression and the effects of treatments. The initiative also supports research in mouse models of MS to identify and test new targets for therapies that can reduce brain pathology and neurological symptoms. For example, one project focuses on signaling pathways that inhibit the generation of new oligodendrocytes, the cells that make up the myelin sheath. This research may lead to new strategies for promoting remyelination of axons, which fails with recurring or chronic damage in MS. Other research includes studies to test the ability of small molecule candidates to prevent or protect against oligodendrocyte damage and a project to determine whether inhibition of a signaling pathway implicated in axonal degeneration in other disorders can also protect axons in MS.

In addition to studies in response to the above initiative, NINDS continues to support investigator-initiated research on disease mechanisms in MS that also address aspects of axonal damage. For example, one study is using brain imaging and analysis of brain autopsy tissue from MS patients to understand how axonal damage in the hippocampus, a brain region important for learning and memory, may contribute to cognitive decline in MS. Demyelination also occurs in other diseases, and research advances in these areas may lead to progress toward treatments for MS as well. In a recent study, NINDS-supported researchers transplanted human oligodendrocyte precursor cells into mice with a severe inherited myelin deficiency. The treatment restored myelin throughout the brains of these mice, improved neurological function, and prolonged survival, providing the first successful demonstration that cell transplantation therapy can rescue mice from the effects of myelin deficiency in the brain.

Item

Stroke - The Committee commends NINDS for its work in developing an institute-wide strategic plan and continues to support the comprehensive and timely implementation of its Stroke Progress Review Group Report. The Committee encourages NINDS to direct its research efforts in this area toward the support of current studies in stroke prevention, diagnosis, treatment, and rehabilitation, and research to explore new and promising scientific opportunities. (p. 147)

Action taken or to be taken

NINDS continues its implementation of the recommendations made by the Stroke Progress Review Group (SPRG), which were updated at a meeting of the SPRG in September 2006. One of the Institute’s most successful programs, its Specialized Program of Translational Research in Acute Stroke (SPOTRIAS),

continues to advance relevant treatment recommendations of the SPRG, including the recent finding that telemedicine may be a safe and effective way to extend the use of clot-busting drugs for acute stroke beyond hospitals with specialist expertise.

With respect to prevention, epidemiological researchers in the Northern Manhattan Study (NOMAS) studies are revealing valuable information about risk factors for high-risk minority populations. In the past year alone, NOMAS investigators have provided data to link the metabolic syndrome (a group of risk factors including obesity, cholesterol and blood pressure characteristics) to an increased risk of ischemic stroke, and have found that measurement of carotid plaque thickness (the thickness of plaque buildup in the carotid artery) may also be a useful tool for assessing stroke risk.

Biomarkers were a critical need identified by the SPRG, and investigators at the University of California at Davis have provided initial evidence of altered gene expression in blood that may help clinicians distinguish between different causes of ischemic strokes. These differences are not easily appreciated in the clinical setting, but if these data develop into a reliable test that will help physicians make these diagnostic distinctions, it will significantly impact the delivery of appropriate therapies.

Rehabilitation is an essential component of the research continuum, and the Institute has addressed the rehabilitation priorities identified by the SPRG by exploring variables such as movement range and disability levels and how they predict recovery. These data suggest that careful assessment of a patient's pre-existing condition may yield important information about post-stroke outcomes, and may be useful in planning effective rehabilitation strategies. In addition, NINDS , along with the NICHD, NIA, and NIDCD, have also published two program announcements (in March 2008) to solicit grants on the "Mechanisms of Functional Recovery After Stroke," and are collaborating on a workshop focused on post-stroke rehabilitation, to be held in FY 2009.

Basic and translational research also continue to progress at an unprecedented pace.

For example, NINDS-supported researchers have recently published data indicating that the brain's blood vessels provide more support for the nervous tissue than was appreciated previously. Other recent NINDS research has explored the cellular causes of bleeding that can occur if a clot-busting drug is given beyond the first three hours of symptom onset. These and many other findings will help clinicians deliver acute stroke therapies more safely in the future.

Senate Significant Items

Item

Charcot-Marie-Tooth **[CMT]** - The Committee commends NINDS for issuing a program announcement to solicit grant applications on CMT with the goal of identifying and validating therapeutic targets for use in CMT and other peripheral neuropathies. The Committee requests an update on CMT and CMT-related research, and on the progress achieved by the program announcement, in the fiscal year 2010 budget justification. (p. 99)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke supports a broad portfolio of investigator-initiated grants that focus on understanding the basic biological processes that, when disrupted, lead to Charcot-Marie-Tooth disease. Many of these projects aim to identify genetic mutations that underlie the various forms of CMT disease, and to understand how these mutations affect various neuronal processes that are compromised in CMT disease (e.g. transport of proteins within a cell, transmission of electrical nerve impulses, and communication between nerve cells).

Translating basic research findings into therapies is essential to reducing the burden of neurological disease, the central mission of NINDS. In FY07, NINDS began supporting a project through the Small Business Technology Transfer (STTR) program that is ultimately aimed at developing an ultra-sensitive, multiplex diagnostic system for more than 1000 neurogenetic disorders. The pilot phase of this project is designed to demonstrate feasibility by distinguishing between two “micro-mutations” that cause two distinct peripheral neuropathies, CMT1A (one form of CMT) and hereditary neuropathy with liability to pressure palsies (HNPP). Successful development of this type of platform will greatly expedite accurate diagnosis, and will facilitate quality management of patients with CMT and other complex genetic disorders. In addition, NINDS, in cooperation with the National Institute of Arthritis and Musculoskeletal, and Skin Diseases (NIAMS), developed a translational research initiative designed to stimulate the development of drugs, biologics, and devices for CMT and other diseases of the motor unit (neuron and muscle). The first component of this program is intended to support the preliminary stages of preclinical therapy development, while the second component is designed to support more advanced stages of therapy development, leading to the submission of an Investigational New Drug (IND) application to the FDA.

In addition to these activities, NINDS has recently established a Neuromuscular Working Group to help in the coordination of Institute efforts on the basic biology and diseases of the motor unit, including peripheral neuropathies, amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), myasthenia gravis and muscular dystrophy. It is anticipated that this working group will help to facilitate earlier recognition of conserved mechanisms and potential common therapeutic targets for the neuromuscular disorders. This working group also includes

member of NINDS intramural program as well as program staff from other NIH Institutes, including the NIAMS, National Heart, Lung, and Blood Institute, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

Item

***Duchenne Translational Conference* -** The Committee is aware that NIH will be convening a conference focused on translational research opportunities for Duchenne and Becker Muscular Dystrophy (DBMD) in the Spring of 2009. The Committee applauds NIH for maintaining DBMD as a priority and reconvening this conference, which previously occurred in 2007, in order to keep DBMD researchers· aware of cutting edge· and emerging opportunities to improve patient care. The Committee looks forward to the publication and dissemination. of these findings. Pursuant to this conference, the Committee is pleased that the Muscular Dystrophy Coordinating Committee (MDCC) will be updating the MD action plan to reflect accomplishments related to the five broad categories in the plan, and supports continued efforts to track research goals, NIH funded grants, and areas of unmet opportunity for DBMD translational research. (p. 146)

Action taken or to be taken

Recognizing that translational research requires coordinated efforts and guidance, on June 25-27, 2007, NINDS, NIAMS, NICHD, NHLBI, and ORD hosted an NIH Workshop on Translational Research in Muscular Dystrophy to review the current state of translational research for the muscular dystrophies (MD), identify challenges, discuss collaborations and strategies that may facilitate progress, and move forward several action items of the MDCC Action Plan for MD. Participants discussed targets for MD drug discovery and strategies for attacking these targets, including the appropriate use of different animal models, and the development of biomarkers for preclinical studies. The status of therapy development strategies outlined in the Action Plan was also evaluated and specific recommendations were given for the development of nucleic-acid and cell-based therapies, and for muscle regeneration, anti-inflammation, and membrane repair treatments. A summary of the workshop is accessible online.

In addition to the 2007 workshop, on May 22-23, 2008, NINDS hosted the first Translational Research Grantee Workshop, to discuss with grantees in the NINDS Translational Research Program best practices for performing milestone-driven translational research, as well as partnering and funding paradigms. All current and prior awardees of the NINDS Cooperative Program in Translational Research were invited, along with grantees for exploratory projects that were close to entering into cooperative agreement applications. Several NINDS-funded MD researchers attended.

The NINDS continues its support for translational research for neuromuscular diseases including MD and, along with NIAMS, has recently launched two new funding solicitations. The “Exploratory/Developmental Projects in Translational

Research for Neuromuscular Disease (R21)" initiative requests applications to generate tools or proof-of-principle projects for neuromuscular disease therapeutics. The "Cooperative Program in Translational Research for Neuromuscular Disease (U01)" is a milestone-driven program that will fund preclinical development and testing of new therapies with the goal of producing Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications for FDA approval. These two programs are based on the success of similar funding announcements released in 2006, specifically targeted to MD, and on the broadly-focused NINDS Translational Research Program. Thanks to these efforts, the NIH program for translational research in MD has grown significantly in the past few years. NINDS currently supports exploratory projects developing gene-therapy to protect against muscle degeneration in Duchenne Muscular Dystrophy (DMD), investigating strategies to correct MD genetic mutations, identifying compounds that reduce a toxic RNA implicated in myotonic dystrophy, and identifying drugs that increase integrin gene expression to treat DMD. Large-scale NINDS-funded projects include a study that will develop several small molecule drugs to increase muscle strength and regeneration and which involves a public-private partnership with a patient voluntary organization and a biotech company, and research to establish the safety and efficacy of genetic therapy to correct the dystrophin gene defect which causes DMD. In addition, NINDS has recently funded a National Center for Canine Models of Duchenne Muscular Dystrophy that will develop and sustain dog models of DMD, expand country-wide collaborations with investigators pioneering translational research on the treatment of DMD, and provide high-quality facilities and services to support pre-IND applications.

Item

Dystonia **-** The Committee continues to support the expansion of research and treatment developments regarding dystonia. The Committee also notes that the intramural program at NIH continues to advance research activity in dystonia, and more support is encouraged. (p. 99)

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 2006 scientific workshop on dystonia, the NINDS issued a program announcement in 2007, 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), in conjunction with the Dystonia Medical Research Foundation (DMRF) and the Bachmann-Strauss Dystonia and Parkinson Foundation, Inc. The announcement, which is scheduled to be active through July 2010, invites research grant applications aimed at understanding or treating generalized and focal dystonias and encourages basic, translational and clinical studies. In the past year, NINDS has funded four new grants related to dystonia through this and other programs, including the NINDS Cooperative Program in

Translational Research. The overall research program now includes a wide spectrum of projects that include study of dystonia at the level of genes, molecular pathways, and brain systems, as well as studies of epidemiology and the development of therapeutic strategies. In September 2008, the NINDS, together with the NIH Office of Rare Diseases and the Dystonia Medical Research Foundation, sponsored a scientific workshop focused on advancing translational research in dystonia. The NINDS Intramural Research Program also continues to conduct research 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

Fibromyalgia **-** Whereas fibromyalgia has traditionally been considered a musculoskeletal disorder, the Committee notes that substantial evidence implicates pathology within the central nervous system in the development and expression of fibromyalgia symptoms, including abnormal brain activity, abnormal concentrations of a variety of neurochemicals in cerebrospinal fluid, dysautonomia and neuroendocrine dysfunction. The Committee, therefore, urges the NINDS to collaborate with the NIAMS in convening an international symposium to elucidate the state of the science with regard to fibromyalgia, and publish a consensus document within 1 year establishing a roadmap for future fibromyalgia research. The Committee also encourages the NINDS to support basic research into animal models of the disorder. (p. 99, 100)

Action taken or to be taken

The NINDS supports basic and clinical research to understand and treat fibromyalgia, and is committed to collaborating with other NIH institutes supporting research on fibromyalgia through the NIH Pain Consortium.

The NINDS will work with the NIAMS to support an international symposium organized by the fibromyalgia community. During a recent meeting with representatives from the fibromyalgia community, NIH encouraged attendees to consider use of the NIH Support for Conferences and Scientific Meetings (R13) funding mechanism in order to develop an international symposium focused on the disease and associated issues. The R13 mechanism has been successfully used by a wide variety of research communities for the development of a symposium, seminar, conference, workshop or any other organized, formal meeting where researchers could assemble to coordinate, exchange, and disseminate information or to explore or clarify a defined subject, problem, or area of knowledge.

The Program Announcement, “Mechanisms, Models, Measurement, and Management in Pain Research” is supported by the NINDS and several other member Institutes or Centers of the NIH Pain Consortium, and solicits a wide range of research on pain conditions, including fibromyalgia. The announcement highlights fibromyalgia as a pain condition of special interest, and encourages

studies in animal models coupled with molecular and cellular studies. The development of new animal models that adequately reflect chronic clinical pain conditions is also explicitly encouraged.

The NINDS has joined several other NIH institutes in soliciting research on fibromyalgia as a co-morbid condition. For example, the Program Announcement, "Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Co-morbid Conditions" encourages research on fibromyalgia and other chronic disorders occurring with TMJD, and specifically encourages the use of animal studies. Fibromyalgia is a multisystemic illness that has symptomatology similar to chronic fatigue syndrome. Epidemiological studies comparing these two syndromes, as well as animal studies, are emphasized in a recent Program Announcement, Chronic Fatigue Syndrome: Pathophysiology and Treatment, supported by several NIH institutes, including NINDS.

The NINDS supports numerous ongoing studies that focus on changes in brain activity in chronic pain patients. In addition to clinical research, the NINDS supports studies of changes in brain activity and neuroendocrine dysfunction in animals, and studies elucidating the mechanisms and modulation of pain transmission in animal models of persistent pain. An example of such a study, relevant to fibromyalgia, is one in which the investigators are using molecular, pharmacological, and behavioral approaches to study the mechanism by which inflammation leads to increased sensitivity to pain. They are exploring the effects of chemical mediators released after inflammation on descending neural pathways and the subsequent effects on pain signaling and pain behaviors in rat models of persistent pain.

Item

Headache Disorders - The Committee encourages intensified efforts to understand the causes, prevention, treatment, and eventual cure of headache disorders, including migraine, cluster headache, and chronic daily headache. Research on these disorders, to date, has not received funding commensurate with their prevalence or their costs to the economy. Therefore, the Committee strongly urges the NINDS to solicit grant applications in this area; encourage new investigators with career training and transition awards; provide fair peer review by headache scientists of submitted headache research grant applications; and collaborate with the research community to develop ''Headache Disorders Research Benchmarks.'' (p. 100)

The NINDS recognizes the considerable public health burden caused by headache disorders, including migraine, and thus is employing multiple strategies to stimulate research in this field. In FY07, the NINDS, with the NIDCD, the NIDCR and the NIEHS, released a Funding Opportunity Announcement (FOA) on the Neurobiology of Migraine. This FOA is intended to stimulate innovative research to expand the current base of knowledge on the neurobiological

mechanisms underlying migraine and to understand the role of neuromodulators (*e.g.* hormones) on migraine pathophysiology. One project funded under this announcement aims to fill a gap in the headache research field by developing an animal model for Chronic Daily Headache (CDH), which often evolves from episodic migraines. Successful development of this resource will allow for subsequent investigations into the pathophysiology of this disorder, and will provide a tool for researchers to test potential CDH therapies. The NINDS also supports a variety of investigator-initiated research projects on headache disorders. A study by one team of NINDS-supported investigators focuses on Cortical Spreading Depression (CSD), a phenomenon common in migraines. CSD occurs when a slow wave of potassium ions causes a large number of neurons to fire at once, leading to a prolonged period of neuronal "silence" in the area. Investigators determined that CSD resulted in a drop in oxygen in the region, causing the neurons to swell and temporarily lose dendritic spines, tiny projections on neurons that form connections (synapses) with other neurons. These findings suggest that drugs that inhibit CSD may be effective in the treatment of migraine.

Training the next generation of researchers is crucial to reducing the burden of neurological disorders, including headache. The NINDS currently supports several trainees through career development awards with research focused on headache disorders. These trainees are focused on a diverse array of research topics including: gender differences in the pathophysiology of migraine, emergency department diagnosis and treatment of migraines, dissemination of behavioral treatment for migraine, and the molecular mechanisms involved in pain processing during migraine.

In June, 2007 the NIH initiated an extensive review of the peer review process, committed to the goal of funding the best science, by the best scientists, with the least amount of administrative burden. This review resulted in the identification of four priorities for implementation, including: 1) Engage the best reviewers, 2) Quality and Transparency of Review, 3) Provide Balanced and Fair Reviews, and 4) Continuous Review of Peer Review. These changes will help to ensure that all applications, including those on headache disorders, will receive a fair and balanced review.

In October 2008, the 6th Headache Research Summit will convene on the NIH campus. Partially funded by the NINDS, this conference will convene leading headache researchers to discuss issues such as translational research and migraine, neuroimaging of headache, mechanisms and neurogenetics of headache, epidemiology and risk factors of headache, and clinical trial design and interpretation. During this conference, NINDS will initiate preliminary discussions to determine the best way to establish research priorities and identify research opportunities for the field.

Item

Hydrocephalus research - The Committee continues to place a high priority on increasing research on hydrocephalus, and it urges NINDS to expand its research through program announcements or requests for applications. The Committee also urges NINDS to collaborate with other Institutes to advance hydrocephalus research priorities, including the NIA, NICHD, NEI, NIBIB, and ORD, and requests an update on the progress of such collaborative efforts in the fiscal year 2010 budget justifications. (p. 100)

Action taken or to be taken

NINDS-funded research in hydrocephalus includes several efforts toward improved diagnosis or treatment. For example, NINDS supports the development of new non-invasive technologies that may make diagnosis easier and more rapid. Shunts to remove excess cerebrospinal fluid (CSF) are the principal treatment available for hydrocephalus, and NINDS supports a prospective clinical trial comparing two shunt valve types for normal pressure hydrocephalus (NPH) and another study in NPH to determine how different parameters of shunt treatment relate to cognitive outcomes. As a secondary goal, this latter study will compare features of NPH and idiopathic Parkinson's disease, a common misdiagnosis in people with NPH.

Unfortunately, shunts often become obstructed or infected, and multiple replacement surgeries are common. NINDS supports the development of wireless, implantable flow sensors for monitoring shunt function quickly and noninvasively, as well as research on ways to prevent infection or obstruction, such as antibiotic coatings for shunt tubing and a new catheter with a microelectro-mechanical system to resist blockage. Other NINDS-funded research may lead to alternatives to shunts, such as the development of an implantable device that mimics valve-like structures around the brain through which CSF normally exits into the bloodstream. This project was supported in response to a Program Announcement for Bioengineering Research from the NIBIB and other NIH Institutes. NINDS welcomes applications under this initiative for milestone-driven, multidisciplinary research on innovative technologies to treat or monitor hydrocephalus.

Better understanding of the causes of hydrocephalus may also suggest new strategies for early detection, treatment or prevention. NINDS supports research on human genetic variations associated with Dandy Walker malformation and other congenital brain malformations that often lead to hydrocephalus. NINDS also supports studies on cellular and molecular mechanisms underlying brain malformations and hydrocephalus in animal models. In addition, NINDS supports basic research on normal CSF production and regulation, which may lead to new ways to prevent CSF accumulation.

Research relevant to understanding and treating hydrocephalus spans multiple NIH Institutes, and NINDS leads a trans-NIH working group focused on hydrocephalus and related disorders. The group includes extramural program

staff from NINDS, NICHD, and NIBIB, and it first met in June 2008 to discuss the NIH portfolio in hydrocephalus research and opportunities for collaboration across NIH and with industry and private organizations. The group will meet regularly to identify research priorities and consider how best to address them, whether through program announcements or other means.

As a recent example of collaboration, the NIH Office of Rare Diseases, NINDS and NICHD funded a conference held in November 2008 on Chiari malformation, which often leads to hydrocephalus. The conference sessions were also relevant to the diagnosis and treatment of other congenital malformations associated with hydrocephalus. In addition, NINDS program staff members attended the Hydrocephalus Association's "Accelerating Hydrocephalus Research Workshop" in March 2008, where they contributed to discussions on research and development opportunities.

Item
Mucopolysaccharidoses - The Committee commends NINDS for taking the lead role supporting the scientific meeting on the clinical progress of MPS. The Committee encourages NINDS to expand research into MPS, and to implement the recommendations from the meeting, including the need to collect natural history data to move novel therapies into the clinic, and to combine therapeutic modalities to increase efficacy. (p. 100)

Action taken or to be taken
Please refer to page 65 of this document for the response to this significant item regarding Mucopolysaccharidoses.

Item
Parkinson's Disease - The Committee encourages the NINDS to update the program announcement for the Udall Centers of Excellence for Parkinson's Disease Research Program to include the recommendations of the committee that evaluated the centers and to continue to fund and support this important program. The Committee also commends the NINDS for working to establish and make public lay-language research summaries for each Udall Center, which should be considered as a possible model for other NIH centers of excellence programs. (p. 100)

Action taken or to be taken
In late 2005, the National Institute of Neurological Disorders and Stroke (NINDS) assembled an external committee to evaluate its Udall Centers of Excellence for Parkinson's Disease Research Program. The committee completed its report, with recommendations, in August 2007. The recommendations included developing a coordinating committee to promote cooperation and collaboration among the centers, improving the review process for center applications, monitoring the progress of the centers, increasing administrative support, and

providing new opportunities for research training, multidisciplinary projects, and pilot studies. The NINDS presented its evaluation implementation plan to the current Udall center directors and the Parkinson's disease patient community at the annual Udall centers meeting in October 2008. The NINDS has begun implementing many of these recommendations. In November 2008, the NINDS released a program announcement (PA) to renew the Udall centers program. This PA enacted several of the recommendations, including the creation of a coordinating committee. The applications received under this PA will be reviewed together in a single study section, consistent with recommendations in the evaluation report. The NINDS is also beginning to gather data on the research productivity of the Udall centers.

The NINDS is continuing to work with the Parkinson's Action Network (PAN) to encourage Udall center directors to prepare lay-language summaries of their grants for the internet. The centers have voluntarily provided summaries to PAN, which has posted them on its web site at http://www.parkinsonsaction.org/Udall-Lay-Summaries.html. The NINDS has shared the template for these summaries with other NIH Institutes and Centers as a possible model for them to consider for their own centers programs.

Item
Stroke - The Committee commends the NINDS for its work in developing an Institute-wide strategic plan and supports the involvement of stroke scientists and/or clinicians in every aspect of this initiative. The Committee continues to support the comprehensive and timely implementation of its Stroke Progress Review Group Report. The Committee also urges the NINDS to devote additional funding for stroke prevention, diagnosis, treatment, rehabilitation, and research to explore new and promising scientific opportunities. In addition, the Committee acknowledges studies suggesting significant gender differences concerning stroke; for example, women often receive fewer diagnostic tests and intervention procedures. The Committee encourages the NINDS to increase research in this area in order to understand the differences in treatment options for men and women and provide a means to optimize stroke care. (p. 100, 101)

Action taken or to be taken
The NINDS continues its implementation of the recommendations made by the Stroke Progress Review Group (SPRG), which were updated at a meeting of the SPRG in September 2006. One of the Institute's most successful programs, its Specialized Program of Translational Research in Acute Stroke (SPOTRIAS), continues to advance relevant treatment recommendations of the SPRG, including the recent finding that telemedicine may be a safe and effective way to extend the use of clot-busting drugs for acute stroke beyond hospitals with specialist expertise.

With respect to prevention, epidemiological researchers in the Northern Manhattan Study (NOMAS) studies are revealing valuable information about risk

factors for high-risk minority populations. In the past year alone, NOMAS investigators have provided data to link the metabolic syndrome (a group of risk factors including obesity, cholesterol and blood pressure characteristics) to an increased risk of ischemic stroke, and have found that measurement of carotid plaque thickness (the thickness of plaque buildup in the carotid artery) may also be a useful tool for assessing stroke risk.

Biomarkers were a critical need identified by the SPRG, and investigators at the University of California at Davis have provided initial evidence of altered gene expression in blood that may help clinicians distinguish between different causes of ischemic strokes. These differences are not easily appreciated in the clinical setting, but if these data develop into a reliable test that will help physicians make these diagnostic distinctions, it will significantly impact the delivery of appropriate therapies.

Rehabilitation is an essential component of the research continuum, and the Institute has addressed the rehabilitation priorities identified by the SPRG by exploring variables such as movement range and disability levels and how they predict recovery. These data suggest that careful assessment of a patient's pre-existing condition may yield important information about post-stroke outcomes, and may be useful in planning effective rehabilitation strategies. In addition, the NINDS, along with the NICHD, NIA, and NIDCD, have also published two program announcements (in March 2008) to solicit grants on the "Mechanisms of Functional Recovery After Stroke," and are collaborating on a workshop focused on post-stroke rehabilitation, to be held in FY 2009.

Basic and translational research also continue to progress at an unprecedented pace.

For example, NINDS-supported researchers have recently published data indicating that the brain's blood vessels provide more support for the nervous tissue than was appreciated previously. Other recent NINDS research has explored the cellular causes of bleeding that can occur if a clot-busting drug is given beyond the first three hours of symptom onset. These and many other findings will help clinicians deliver acute stroke therapies more safely in the future.

Lastly, the Institute continues to explore gender differences in stroke diagnosis and treatment, and relevant NINDS research will be detailed in a separate response to the Committee's language specifically on Stroke in Women (to the Office of the Director).

National Institute of Allergy and Infectious Diseases

House Significant Items

Item

Asthma - The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee encourages NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages NIAID to collaborate more actively with voluntary health organizations to support asthma prevention, treatment, and research activities. (p. 148)

Action taken or to be taken

NIAID continues its long-standing commitment to research to improve prevention and management of asthma, particularly in pediatric populations. The NIAID-supported Inner-City Asthma Consortium (ICAC) evaluates the safety and efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. ICAC researchers also investigate the mechanisms of action of the immune-based therapies; develop and validate biomarkers of disease stage, progression, and therapeutic effect; and investigate the immunopathogenesis of asthma. For example, the ICAC Asthma Control Evaluation trial recently demonstrated that monitoring levels of exhaled nitric oxide in adolescents with asthma and adjusting treatment accordingly does not improve the course of their disease although it did reaffirm the importance of managing the disease according to NIH asthma guidelines.

The Immune Tolerance Network (ITN), which is supported by NIAID, evaluates novel, tolerance-induction strategies and their mechanisms of action in immune-mediated diseases, including asthma and allergic diseases. The ITN is currently conducting a number of clinical trials and mechanistic studies in asthma. One such trial is evaluating whether sublingual immunotherapy containing house dust mite, grass, or cat allergens will prevent the development of allergic diseases and asthma in children with atopic dermatitis (a long-term skin disease) and food allergy. Another study is examining whether an investigational ragweed vaccine will prevent asthma symptoms that are triggered by increases in ragweed levels in the fall season. NIAID also supports fifteen Asthma and Allergic Diseases Research Centers (AADRC) that conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases; ten clinical trials are currently under development by the AADRCs.

To improve our asthma management efforts, especially as they relate to children, NIAID opened a Pediatric Allergy Clinic at the NIH Clinical Center in FY 2005. The clinic, lead by a physician with specialty training in pediatric asthma and allergy, is now a focal point for translational research conducted in collaboration

with NIAID intramural laboratories. During FY 2008, there were over 500 patient care visits to the clinic, which uses child-friendly, non-invasive clinical techniques to evaluate allergic inflammation. In collaboration with the National Heart, Lung, and Blood Institute (NHLBI) pulmonology service, exercise challenge pulmonary function testing is also available.

NIAID continues to collaborate with nonprofit and voluntary health organizations and charitable foundations. For example, NIAID collaborates with the Asthma and Allergy Foundation of America (AAFA) to identify scientific gaps in research activities as well as encourages investigators to seek research grant support from the AAFA. NIAID also conducts seminars at annual symposia with the American Academy of Allergy, Asthma and Immunology and the American Thoracic Society. Lastly, NIAID is coordinating a workshop with the National Institute of Environmental Health Sciences, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NHLBI, the Merck Childhood Asthma Network, and the Robert Wood Johnson Foundation to develop better tools for assessing asthma outcomes.

Item

Autoimmunity - The Committee encourages NIAID to work with the Autoimmune Diseases Coordinating Committee to develop plans for research programs to investigate common mechanisms of autoimmune diseases. (p. 148)

Action taken or to be taken

The NIH Autoimmune Diseases Coordinating Committee (ADCC) was established in 1998 to increase collaboration and facilitate the coordination of research among the NIH Institutes and Centers (ICs), other federal agencies, private organizations and patient advocacy groups with an interest in these diseases. The ADCC, which is chaired by NIAID, meets approximately twice each year, providing a forum for discussion of possible areas of collaboration among NIH ICs.

The most recent meeting of the ADCC was will be held in October 2008 and included presentations by representatives of NIAID, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Digestive and Diabetes and Kidney Diseases (NIDDK), the National Institutes of Neurological Disorders and Stroke (NINDS) , and the National Eye Institute (NEI) on recent activities in autoimmune disease research. In addition, representatives of patient advocacy groups will have the opportunity to make presentations regarding priorities in autoimmune disease research.

In addition to chairing the ADCC, NIAID supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. NIAID also supports and

conducts research to understand the common mechanisms that may trigger autoimmune diseases. Knowledge gained from this basic research provides the rationale for clinical strategies to diagnose autoimmune diseases and the development of novel treatments for these debilitating diseases.

NIAID, in collaboration with NIDDK and the NIH Office of Research on Women's Health, supports the Autoimmunity Centers of Excellence (ACEs) to encourage and enable integrated basic and clinical research that focuses on treatment or prevention approaches for autoimmune diseases. For example, the ACEs are currently enrolling participants in a study to determine the safety and effectiveness of lovastatin, a statin used for lowering cholesterol, in controlling inflammation in mildly active rheumatoid arthritis. In addition, the ACEs are conducting a study to determine the safety of rituximab, an antibody used to treat some kinds of lymphoma, in treating patients with Sjögren's syndrome. Lastly, the ACEs are conducting a study to determine the comparative effects of the therapeutic Copaxone, which is used to reduce the frequency of relapses in relapsing-remitting multiple sclerosis (MS), versus Copaxone plus albuterol, used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease, in patients with MS.

Item

Drug-Resistant Tuberculosis - The Committee commends NIAID for the release of its response plan to drug-resistant tuberculosis, including extensively drug-resistant tuberculosis (XDR–TB). The Committee encourages NIAID to allocate appropriate resources to effectively address this global health emergency (p. 148).

Action taken or to be taken

NIAID remains firmly committed to leading and supporting a robust program of tuberculosis (TB) research, including research on multidrug-resistant (MDR) and XDR-TB. For example, NIAID supports basic research to enhance understanding of *Mycobacterium tuberculosis* (Mtb) and how it causes TB, and to translate this knowledge into improved health care interventions for TB, including diagnostics, therapeutics and vaccines. NIAID-supported researchers recently demonstrated that drug-resistant TB strains differ from drug-susceptible strains at only a few dozen genetic sites. This insight into which genes give TB the ability to resist drugs may inform development of better diagnostic tests to distinguish drug-resistant and drug-susceptible strains and may lead to new drugs that can overcome this resistance.

NIAID supports and conducts research with colleagues in TB-endemic regions such as Africa, Latin America and Asia to address the challenge of MDR- and XDR-TB. Support through the NIAID Tuberculosis Research Unit is enabling researchers in South Africa and Uganda to examine the critical host factors associated with tuberculosis infection, re-infection, reactivation from latency, and the progression of clinical disease. In addition, since 2005, NIAID researchers

have collaborated with scientists in South Korea at the Masan National Tuberculosis Hospital, which has the largest population of inpatient MDR-TB patients in the world. This collaboration has led to several clinical studies including trials to evaluate the use of metronidazole for MDR- TB and linezolid for XDR-TB. In these studies, NIAID is effectively leveraging its resources with additional funding and resources from partners such as the Bill and Melinda Gates Foundation, the Wellcome Trust, and Pfizer.

The Institute also supports efforts to develop novel therapeutics to combat TB and the emergence of drug-resistant TB strains, including pharmacological studies to optimize use of current drugs to prevent the occurrence of resistance and research to re-evaluate second-line therapies for efficacy against MDR- and XDR-TB. For example, NIAID scientists were instrumental in the development of SQ109, a promising TB drug candidate; a Phase 1b clinical trial of SQ109 is currently being planned and will be conducted at an NIAID-supported contract site. In 2008, NIAID joined the not-for-profit Lilly TB Drug Discovery Initiative to help coordinate resources and facilitate new drug development for MDR TB. This collaboration seeks to make research resources, particularly expertise in medicinal chemistry, available to the research community to accelerate the development of new drug candidates.

NIAID is advancing the effort to develop and test effective new vaccines for the prevention of TB through its support of fundamental, translational, and clinical research. Through contracts, the Institute provides researchers with access to facilities and resources for screening TB vaccine candidates in appropriate animal models. NIAID also supports, through public-private partnerships, the development and optimization of advanced stage vaccine candidates for preclinical studies and studies to enable investigational new drug applications.

Item

Fungal Diseases - The Committee recognizes that NIAID supports research on fungal diseases toward the three goals of providing better means of diagnosis, treatment, and prevention of the most important human fungal infections, including Valley Fever. The Committee encourages NIAID to continue to make its research resources available to Valley Fever researchers, and to continue to encourage the community to direct research efforts toward the feasibility of a vaccine approach to combat life-threatening fungal infections (p. 148).

Action taken or to be taken

Fungal infections are recognized as a growing threat to human health, especially in persons whose immune systems are compromised in some way. Fungi present an especially complex challenge to researchers, in part because pathogenicity is often associated with a physiological change from a form that exists in the environment to a form that can infect a human host. NIAID supports research on fungal diseases with the goals of providing better means of diagnosis, treatment, and prevention of the most important human fungal

infections, including Valley Fever, which is caused by *Coccidioides immitis and C. posadasii*. In addition, NIAID is committed to making research resources available to researchers investigating infectious diseases. For example, through a contract, NIAID is providing resources to support a Phase I/II clinical trial to evaluate a potential therapy for Valley Fever. The planning of this clinical trial was also supported through a NIAID grant.

NIAID also supported the genome sequencing of several strains of *C. immitis and C. posadasii*. Genome sequencing provides information that can facilitate a better understanding of pathogens and allow researchers to target their research toward more effective approaches to prevent and treat disease. These genome sequences and other relevant information are available to researchers and other interested parties at no cost.

Through the Mycology Research Units (MRUs), NIAID supports a project focused on vaccine discovery and immunogenicity of *Coccidioides* antigens to enhance the efficacy of a vaccine candidate in preparation for eventual clinical evaluation. To date, the immunogenicity of this vaccine candidate has been demonstrated in mice, and efficacy has been corroborated in non-human primates. Other NIAID-supported researchers are studying alternative *Coccidioides* antigens as potential vaccine candidates. NIAID will continue to encourage organizations interested in Valley Fever research to direct research efforts toward the feasibility of a vaccine approach to combat life-threatening fungal infections.

Item

Global Health - Each year, HIV/AIDS, tuberculosis (TB), and malaria kill millions of people and disable many millions more causing social upheaval and political instability, and also hindering economic productivity and trade around the world. Effective vaccines to prevent these diseases are critically needed, along with microbicides to prevent transmission of HIV and other sexually transmitted infections, modern tools to rapidly diagnose TB, and new drugs to treat the new and emerging drug-resistant strains of these diseases. In addition, more than 1 billion people living in tropical and subtropical climates around the world are affected by neglected tropical diseases on which little research is being done even though there are no safe, effective treatments, no vaccines, and inadequate diagnostics. The Committee also encourages NIAID to continue research on the development of improved medical interventions for the following diseases: cholera, dengue fever, African trypanosomiasis (African Sleeping Sickness), American trypanosomiasis (Chagas disease), visceral leishmaniasis, and Buruli ulcer (p. 148-149).

Action taken or to be taken

NIAID remains committed to basic and clinical research to develop better diagnostics, therapeutics, vaccines, and other prevention approaches for HIV/AIDS, tuberculosis (TB), malaria and other infectious diseases of importance to global health.

NIAID supports the development of new and improved tools to more accurately diagnose infection, allowing optimization of treatment efforts, especially in the case of drug-resistant strains. Five new diagnostic tools for TB are currently being validated in clinical trials, and existing diagnostic platforms are being adapted for use in TB applications, including the detection of drug-resistant (XDR) TB. To help strengthen modern malaria diagnostics, NIAID has supported the discovery of parasite proteins that can be detected by sensitive, inexpensive, and field-deployable, rapid diagnostic tests.

The Institute also supports basic and clinical research on treatment strategies for global infectious disease killers. Through the *Partnerships with Public-Private Partnerships* (PPPs) program and Tropical Diseases Research Units (TDRU), NIAID is actively supporting the discovery and development of treatments for parasitic tropical diseases. For example, PPPs researchers are developing a low-cost treatment for visceral leishmaniasis and identifying new drugs for African trypanosomiasis and American trypanosomiasis (Chagas' disease). In 2008, NIAID announced a new research initiative — *Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors*. This initiative will bridge basic research and product development by encouraging preclinical development of new therapeutic agents for malaria and other tropical diseases such as Buruli ulcer, and support innovative approaches to limit transmission of these parasites at the invertebrate vector level.

Vaccine research remains a high priority for NIAID. NIAID continues to advance HIV/AIDS vaccine research through its Vaccine Research Center, its extramural HIV Vaccine Trials Network as well as the newly established Vaccine Discovery Branch within the Vaccine Research Program in the Division of AIDS. In July 2008, NIAID announced major new initiatives to support investigator-initiated grants to advance HIV vaccine discovery and identification of novel tactics to interrupt HIV transmission.

The Institute currently supports basic and clinical research on a wide variety of vaccine candidates against other infectious disease threats, including malaria and dengue and its commitment to support cholera vaccine research. Recent developments include the initiation of a safety-stage clinical trial of an investigational single-dose, oral vaccine designed to offer combined protection against both enterotoxigenic *Escherichia coli (ETEC) (a type of E-coli that can cause Traveler's diarrhea)* and cholera.

NIAID's HIV Topical Microbicide Research Program is actively supporting research to identify and develop safe, effective, and acceptable topical microbicides. NIAID's integrated microbicide research portfolio is organized around basic biomedical research, preclinical product development, and clinical evaluation, including behavioral research.

Item

Hepatitis B - The Committee supports NIAID's plans to fund experimental models of hepatitis B and to continue support for a specialized animal model of hepatitis virus. The Committee encourages additional work in the area of new intervention discovery for the treatment and management of hepatitis. (p. 149)

Action taken or to be taken

Research to develop new classes of drugs that are safe and effective in treating hepatitis B (HBV) infections remains a priority for NIAID. NIAID-supported investigators, through partnership initiatives, are targeting research to novel targets in the HBV replication cycle to develop different classes of drugs. For example, researchers are currently developing synthetic derivatives of helioxanthin, a natural product that exhibits antiviral activity against HBV. This class of drugs works via a different mechanism than currently licensed HBV drugs and has shown early indications that it may be effective against drug-resistant strains of HBV.

In addition, NIAID continues the support of contracts for the screening of preclinical candidate drugs for HBV in human liver cancer cells. NIAID also supports contracts that utilize HBV animal models for the evaluation of therapeutic candidates, including the woodchuck model. Through an investigator-initiated award, researchers created a simple test that allows investigators to look at the mechanism of hepatitis B virus assembly and identify novel agents that may be effective in blocking the assembly mechanism.

The development of resistance to drugs against HBV remains an obstacle to treatment success and results in the spread and proliferation of resistant virus strains. The development of new classes of drugs against HBV will help address the problem of drug-resistant HBV strains. Studies in non-human primates, conducted by NIAID scientists and their colleagues, determined that the replication rate for HBV is higher than previously thought. A higher replication rate increases the frequency of HBV genetic mutations, including those mutations that cause the virus to become resistant to drugs. This finding may help to accurately predict the ability of HBV virus to develop resistance to drugs and inform the use of existing antiviral therapies, including the use of a single antiviral drug versus combination therapies.

Lastly, in October 2008, NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) cosponsored a conference on the management of hepatitis B. The purpose of the conference was to review recent developments regarding management and treatment options for hepatitis B, which could inform future plans with regard to the evaluation of potential drug candidates for treatment.

Item

Hepatitis C - The Committee encourages NIAID to continue to develop standardized terminology to describe anti-viral drug resistance, as well as studies of the mechanism of resistance and methods to overcome it. (p. 149)

Action taken or to be taken
NIAID remains committed to supporting research to improve treatment of hepatitis C (HCV). For example, NIAID supports two *in vitro* screening contracts to evaluate preclinical candidate drugs for HCV. NIAID also continues to support contracts to test therapeutic drugs and vaccines against HCV in animal models, including a novel transgenic mouse model.

In 2010, NIAID plans to support the Hepatitis C Cooperative Research Centers program. These centers are studying the virus-host interactions that determine the outcome of HCV infection, and in particular, the mechanisms and key steps by which HCV mutates to evade the host immune response both at the time of initial infection and during chronic infection. These studies will provide important insights toward developing vaccines and therapeutic options for treating infections.

At the 2007 Annual Liver Meeting of the American Association for the Study of Liver Diseases, NIAID arranged two scientific sessions related to the issue of HCV drug resistance: “Antiviral Therapy Against Hepatitis Viruses: Understanding and Managing Drug Resistance” and “HCV Plasticity: Escape and Resistance.” Although there are currently no new licensed drugs to treat HCV infection, the clinical issues related to drug resistance are similar to those with HBV. Thus, the lessons learned in studying HBV drug resistance will be instructive in addressing HCV.

Item
Inflammatory Bowel Disease (IBD) - The Committee encourages NIAID to strengthen its inflammatory bowel disease research portfolio and explore partnerships with the IBD community aimed at fostering greater research on the role of the immune system in the development and progression of IBD in both adult and pediatric populations. (p. 149)

Action taken or to be taken
NIAID remains committed to research on inflammatory bowel disease (IBD), including Crohn’s disease and ulcerative colitis. For example, the Institute continues to support basic research to investigate the immunological and genetic factors that contribute to IBD. NIAID-supported research has recently identified an association between Crohn’s disease and a genetic region that plays a role in the body’s ability to destroy bacteria. Other NIAID-supported research has demonstrated the importance of an immune signaling system in maintaining the health of the mucosa in the gastrointestinal tract.

NIAID investigators conduct studies of mouse models of Crohn's disease and ulcerative colitis and were the first to identify the protein that drives the type of inflammation found in Crohn's disease. This discovery led to a clinical trial of an antibody to this protein in patients with Crohn's disease that showed great promise as a treatment for this disease. NIAID researchers are currently conducting basic studies of the genetic mechanisms underlying Crohn's disease and the immunologic mechanisms underlying ulcerative colitis. This research team is conducting a number of clinical studies of treatments for both Crohn's disease and ulcerative colitis. In addition, NIAID has a decade-long partnership with the IBD community through a study to investigate how the body's immune system controls inflammation in the gastrointestinal tract in patients with IBD, with the long term goal of identifying specific targets for development of novel therapeutics for IBDs.

In 2008, NIAID issued a Request for Applications to support basic research projects on immune defense mechanisms and immune regulation at respiratory, gastrointestinal, and urogenital tract mucosal surface. Awards under this initiative are expected to be made in 2009. Other Institute programs such as the Immune Tolerance Network, the Autoimmune Disease Prevention Centers, and the (Human Leukocyte Antigen) *HLA Region Genetics in Immune-Mediated Diseases* program, which aims to define the association between genetic markers and immune-mediated diseases, also contribute to the basic understanding of immune-mediated diseases such as IBD.

NIAID is also a member of the National Commission on Digestive Diseases, which developed a long-range plan for digestive diseases research. The Commission's diverse membership represents the academic, medical research and practice communities, patient/patient advocacy community, and the NIH and other Federal health agencies. As part of the Research Plan, the Commission is assessing the state-of-the-science in digestive diseases and the related NIH research portfolio, with a view toward identifying areas of scientific challenge and opportunity.

Item

Liver Transplantation and Immune System Reaction - The Committee encourages NIAID to strengthen research on the immune system reaction to liver transplants in children. (p. 149)

Action taken or to be taken

NIAID supports a broad portfolio of basic and clinical research in the immunology and outcomes of transplantation, including transplantation in children. The goals of this research are to understand how the immune system recognizes transplanted organs and cells; to characterize the immunologic components of acute and chronic rejection; to evaluate novel therapies for treating rejection and prolonging graft survival; and to develop and implement strategies for immune tolerance induction.

Among the research supported by NIAID is the Immune Tolerance Network (ITN), an international consortium of researchers focused on the development of therapies that re-educate the immune system to avoid injurious immune responses and graft rejection while preserving protective immunity against infectious agents and certain cancers. The ITN is conducting a clinical trial to determine whether immunosuppressive drugs can be safely withdrawn from children who received liver transplants at least four years ago. The study also aims to identify, quantify, and characterize donor-specific immune responses and immunologic interactions which may predict or correlate with tolerance of transplanted organs.

In FY 2008, NIAID and NHLBI made awards to initiate the *Clinical Trials in Organ Transplantation in Children* (CTOT-C), a consortium to conduct clinical trials with the goal of reducing the immune-mediated morbidity and mortality unique to pediatric transplant recipients. The results of the studies being conducted by the CTOT-C may inform future studies of pediatric liver transplantation.

In addition, NIAID, with NHLBI and NIDDK, continues to support the multi-site *Clinical Trials in Organ Transplantation* (CTOT) consortium to develop and implement clinical and mechanistic studies in human heart, lung, liver, and kidney transplantation. The CTOT is currently evaluating the impact of the immunologic state of the deceased liver donor on the early outcome of liver transplantation and the effect of post-transplant events on later transplant outcomes. The CTOT will be supported in FY 2009.

Item

Malaria - The Committee commends NIAID for its malaria research and, especially basic research. While progress in malaria research has been encouraging, the Committee is concerned about the spread of malaria in areas where malaria had previously been controlled and about the contribution of drug-resistant parasites to this problem. The Committee encourages NIAID to allocate research resources to increase the understanding of the complex interactions among malaria parasites, mosquito vectors and humans; to develop new diagnostics, drugs, and vaccines; and to continue its collaboration with global public-private partnerships to leverage malaria research efforts. (p. 149)

Action taken or to be taken

Basic and clinical research on malaria is a high priority for NIAID, the lead federal agency charged with supporting biomedical research on malaria. Released in 2008, the NIAID *Strategic Plan for Malaria Research* and *Research Agenda for Malaria* identify long-term strategic goals and opportunities in malaria and define priorities for the future.

NIAID supports and conducts research to advance the understanding of the host-parasite-vector interactions associated with malaria. This research includes

malaria pathogenesis, parasite and host genomics, and the immunologic and epidemiological factors that affect disease transmission and progression. NIAID also supports vector management research, including mosquito genomics, mosquito development, metabolic pathways, host-seeking behavior, and ecology. NIAID-supported malaria research is conducted by scientists in the United States and over 20 countries, including many malaria-endemic countries. NIAID coordinates its research activities with other federal agencies and non-governmental organizations involved in malaria research.

NIAID is supporting research to develop new and improved therapeutics to treat malaria by identifying potential drug targets, elucidating the mechanisms of drug resistance, identifying drug combinations that may be safe and effective while limiting drug resistance, and developing approaches to restore efficacy of known classes of antimalarial drugs. For example, NIAID is partnering with the Medicines for Malaria Venture (MMV) to screen for and test novel antimalarial compounds. NIAID also supports research and development of new diagnostic technologies for malaria, including PCR-based and immunodiagnostics approaches.

The Institute currently supports basic and clinical research on a wide variety of vaccine candidates targeted against different life-cycle stages of the malaria parasite, including both subunit and attenuated whole parasite vaccines. For example, NIAID scientists are collaborating with the Malaria Vaccine Initiative of the Bill and Melinda Gates Foundation to develop a vaccine composed of multiple components of the malaria parasite. Building on encouraging results of a NIAID-supported trial of a candidate malaria vaccine in Malian adults, an international research team of NIAID-supported investigators and collaborators recently began a preliminary efficacy trial of a candidate malaria vaccine in 400 Malian children. NIAID also recently completed early phase clinical trials of two other candidate malaria vaccines in U.S. adults and currently is planning trials of these candidates to be conducted in Africa.

In 2007, the *NIAID Partnerships with Public-Private Partnerships* (PPPs) program was launched to stimulate the development of new drugs, vaccines, and diagnostics for high-priority neglected tropical infectious diseases of global importance, including malaria. Two PPP cooperative agreements were awarded to support antimalarial drug discovery. In FY 2010, a new initiative, the *Partnership with Product Development PPPs*, will expand on the success of this program. In addition, a program planned for FY 2010 will establish international research centers to support multidisciplinary research on malaria transmission and pathogenesis.

Item

Pediatric Influenza Vaccine - The Committee is concerned about the availability of FDA-licensed and approved influenza vaccines that are indicated for use in the vaccination of children as young as 6 months of age, particularly when compared

with CDC's expanding recommendations in the pediatric population. The shortage of pediatric influenza vaccines becomes even more stark for parents opting for thimerosal-free vaccine. Therefore, the Committee encourages NIAID to make available appropriate resources in order to work with influenza vaccine manufacturers in the development of pediatric influenza vaccines. Such resources would include NIAID's Division of Microbiology and Infectious Diseases conducting pediatric Phase III comparative safety and non-inferiority immunogenicity studies with a U.S.-licensed comparison for potential new entrants onto the U.S. market. (p. 149-150)

Action taken or to be taken
According to the Centers for Disease Control and Prevention (CDC), the lead Federal agency responsible for issuing vaccination guidelines, the supply of thimerosal-free influenza vaccine for children less than two years of age appeared to be adequate for the 2007-2008 influenza season. The CDC projects that the vaccine supply for this age group will be adequate to meet demand for the 2008-2009 influenza season. On September 19, 2007, the Food and drug Administration approved the nasal influenza vaccine FluMist for use in children between the ages of two and five. Approval for this vaccine, which contains a weakened form of the live virus and is sprayed in the nose, was previously limited to healthy children five years of age and older. FluMist does not contain thimerosal or any other preservatives.

The development of novel influenza vaccines and vaccination strategies that are safe and effective is a high priority for NIAID. In particular, NIAID's role in influenza vaccine development is to focus on those areas, such as pandemic influenza, in which there is little engagement by industry and for which there is little or no market demand. Indeed, at this time, NIAID resources allocated for influenza vaccines are focused on these high priority needs.

NIAID will continue its strong commitment to the development of novel influenza vaccines and vaccination strategies including developing and evaluating new vaccine formulations, adjuvants, immune response stimulators, protective T-cell and antibody epitopes, new routes of delivery, common epitope vaccines, and alternatives to egg-based vaccine production technologies.

Item
Scleroderma - The Committee encourages NIAID to expand its research portfolio on scleroderma in partnership with the scleroderma community. (p. 150)

Action taken or to be taken
NIAID remains committed to understanding the cause and improving the treatment of scleroderma, an autoimmune disease. For example, the Autoimmunity Centers of Excellence (ACEs) conduct collaborative basic and clinical research on autoimmune diseases, including scleroderma. 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. The ACEs are cosponsored by NIAID, NIDDK and the NIH Office of Research on Women's Health.

In addition to the research supported through the ACEs, NIAID continues to pursue research to further understand the mechanisms of and treatment for autoimmune diseases including scleroderma. For example, the Stem Cell Transplantation for Autoimmune Diseases Consortium is conducting a clinical trial to assess the efficacy of hematopoietic stem cell transplantation to treat scleroderma. The consortium is also studying the immune mechanisms underlying scleroderma.

In FY 2007, NIAID, NIDDK and the Juvenile Diabetes Research Foundation (JDRF) renewed the Immune Tolerance Network (ITN). The ITN supports clinical trials and assay development for promising tolerance induction and immunomodulatory strategies to treat autoimmune diseases. Lessons from other autoimmune diseases may have relevance for scleroderma.

NIAID will continue to support research on autoimmune diseases through sponsorship of the Autoimmune Disease Prevention Centers, which conduct research on the development of new targets and approaches to prevent autoimmune diseases, and the *HLA Region Genetics in Immune-Mediated Diseases* program to define the association between human leukocyte antigen region genes or genetic markers and immune-mediated diseases.

In addition to these research activities, NIAID chairs the NIH Autoimmune Diseases Coordinating Committee (ADCC), which was established in 1998 to increase collaboration and facilitate the coordination of research among the NIH Institutes and Centers, other federal agencies, private organizations and patient advocacy groups with an interest in these diseases. At the October 2008 ADCC meeting, several NIH Institutes presented information about recent activities in autoimmune disease research. In addition, representatives of patient advocacy groups had the opportunity to make presentations regarding priorities in autoimmune disease research.

Item

Transplantation - The Committee urges expanded research to improve technology needed to evaluate and monitor organs from deceased donors to increase and maximize organ donation, and to improve immune modulation therapies to reduce graft rejection in the recipients. (p. 150)

Action taken or to be taken

Basic and clinical research to improve transplantation outcomes continues to be a high priority for NIAID. A major goal of the NIAID transplantation research

program is the induction of immune tolerance, which may ultimately address many of the barriers to short- and long-term success of transplant procedures. Immune tolerance is the reeducation of the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents.

The Immune Tolerance Network (ITN), which was renewed in FY 2007 and is cosponsored by NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), is an international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for immune-mediated disorders, including the rejection of transplanted organs, tissues, and cells. One ITN study evaluated the transplantation of both kidney and bone marrow from the same donor into recipients with end-stage renal disease. In four of the five patients, immunosuppressive therapy was discontinued 9 – 14 months after transplantation and renal function remained, demonstrating the benefits of achieving immunologic tolerance in human organ transplant recipients. In total, the ITN transplant trials have resulted in 19 transplant recipients completely off immunosuppressive drugs for a range of 2 – 64 months and an additional 11 patients on tapering amounts of immunosuppressive drugs. These results offer the potential to improve the health, health-related quality of life, and lifespan of transplant recipients.

NIAID, in collaboration with NHLBI and NIDDK, continues to support the multi-site *Clinical Trials in Organ Transplantation* (CTOT) consortium to develop and implement clinical and mechanistic studies in human heart, lung, liver, and kidney transplantation. CTOT investigators evaluate new therapeutic regimens to overcome immunologic barriers to graft acceptance and/or long-term graft and patient survival and to treat or prevent immune-mediated complications of transplantation; investigate underlying mechanisms; and develop diagnostic tests and/or biomarkers for routine surveillance, early diagnosis, and ongoing monitoring of processes that contribute to post-transplant morbidity and mortality. Another NIAID initiative, the *Genomics of Transplantation Cooperative Research Program*, seeks to understand the genetic basis of immune-mediated graft rejection and thereby improve long-term graft survival and quality of life for transplant recipients. The CTOT program will be recompeted in FY 2009.

Senate Significant Items

Item

Antimicrobial Resistance - The Committee encourages the NIAID to strengthen clinical, translational, and basic research addressing antimicrobial resistant infections, with emphasis on health care-acquired bacterial infections in hospitals, long-term care facilities, etc. Clinical trials should aim to define natural histories of infection for common bacterial diseases and determine optimal implementation of existing agents and therapeutic strategies. Translational research should emphasize antibiotic development, vaccine development, novel

antibacterial agents and therapies, and new diagnostics. Particular attention should be given to multi-drug resistant gram negative bacterial infections and methicillin-resistant S*taphylococcus aureus* [MRSA] infections. The Committee further encourages the NIAID to accelerate its basic research activities to advance the understanding of mechanisms of resistance and how resistant microbes impact human health (p. 101).

Action taken or to be taken

Research to respond to the public health threat posed by antimicrobial-resistant organisms remains a priority for NIAID. The Institute's research portfolio includes basic research on the biology of resistant organisms and applied research that seeks to develop new diagnostics and therapeutics and vaccines to treat and prevent infection. For example, rapid diagnostics tests are currently not available for many infections, leading to the overuse of broad-spectrum antimicrobial drugs, which has been attributed to the accelerated development of resistance. Through the *Sepsis and CAP [Community Acquired Pneumonia]: Partnerships for Diagnostics Development* initiative, NIAID partners with industry in the development of broad diagnostic technologies that would provide early detection of select major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia. In addition, the *Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections* initiative is supporting the development of therapeutics or rapid diagnostics for the most common healthcare-associated pathogens.

Health care-acquired *Staphylococcus epidermidis* infections of indwelling medical devices are often associated with biofilms, a slimy matrix in which the bacteria are less susceptible to both antimicrobials and the immune system. Research in NIAID labs is providing the scientific basis for the development of novel drugs that target biofilm formation. NIAID scientists also identified compounds produced at high concentrations by community-acquired methicillin-resistant S*taphylococcus aureus* (CA-MRSA) strains, accounting in part for its enhanced virulence. Future research will investigate the potential use of antibodies directed against these compounds as novel anti-staphylococcal therapeutics.

In FY 2008, NIAID awarded six grants through the *Pharmacological Approaches to Combating Antimicrobial Resistance* initiative. The research supported through this initiative will apply pharmacokinetic and pharmacodynamic principles to studies on the prevention of the emergence of antimicrobial drug resistance in Gram-negative bacteria, which are the type of bacteria that most easily develop drug resistance. This initiative is intended to stimulate and strengthen collaborations between antimicrobial pharmacologists and infectious disease researchers to provide a synergistic, integrated approach that will form the basis for future clinical management of antimicrobial drug resistance.

NIAID continues to support two contracts under the *Clinical Trial for Community-Acquired Methicillin-Resistant Staphylococcus aureus* initiative. These contracts

are supporting the conduct of trials to determine the optimal treatment of uncomplicated cases of skin and soft tissue infections caused by CA-MRSA using existing off-patent antibiotics.

NIAID is collaborating with the Department of Defense on the Infectious Diseases Clinical Research Program (IDCRP), a clinical trials network examining emerging infectious diseases in military personnel. In particular, the IDCRP is focusing on studies of the prevention and treatment of antimicrobial resistant infections, such as CA-MRSA.

Item

Career Development in Asthma and Allergic Diseases - The Committee encourages the NIAID to work with private sector organizations to develop programs for the training and career development of researchers focused on allergic diseases. (p. 101)

Action taken or to be taken

NIAID remains committed not only to supporting and conducting research on asthma and allergic diseases but also to training and developing of the next generation of researchers in this field. For example, in June 2008, NIAID awarded twelve grants, totaling $3.5 million, to new investigators under the *Exploratory Investigations in Food Allergy* initiative. Co-sponsored with the Environmental Protection Agency, the Food Allergy and Anaphylaxis Network, and the Food Allergy Project, this program will support high impact, innovative research to identify the mechanisms underlying food allergy, with the additional goal of encouraging new investigators to the field of food allergy research.

Through the Allergy and Immunology Clinical Fellowship Program, NIAID offers intensive training and career development for clinicians interested in research careers focused on asthma and allergic diseases. This three-year training program, which is fully accredited by the Accreditation Council for Graduate Medical Education, recruits physicians in clinical internal medicine and/or pediatrics through the National Residency Match Program. The program is designed to provide trainees with high quality clinical and laboratory research skills that will enable them to pursue careers in academic medicine, advancing the care of children and adults with asthma and allergic diseases. Fellows receive clinical training at the NIH Clinical Center, Walter Reed Army Medical Center, the Johns Hopkins Pediatric Allergy Clinic, Children's National Medical Center, and a local private practice. In addition, the fellows receive broad instruction in the science and clinical care of allergic and immunologic disorders through an extensive lecture series, journal clubs, and case conferences.

In August 2008, NIAID, the American Academy of Allergy, Asthma and Immunology, and the Clinical Immunology Society co-sponsored the third annual School in Hypersensitivity and Allergic Diseases. This program provides mentorship and networking opportunities to post-doctoral fellows and junior

faculty members from academic institutions who work in the areas of allergy and clinical immunology. The program included a session on career planning as well as a session on funding mechanisms and grant writing strategies provided by NIAID representatives.

Item
Food Allergy and Anaphylaxis - In addition, the Committee encourages a greater effort to facilitate and promote investigator-initiated research on food allergy and anaphylaxis. The Committee commends the NIAID for its research initiative "Exploratory Investigations in Food Allergy," which will support innovative pilot studies and developmental research on the mechanisms of food allergy, with a goal of attracting additional investigators to the field of food allergy research, and urges the continuation of this initiative. (p.101-102)

Action taken or to be taken
NIAID is strongly committed to reducing the burden of food allergy by continuing and expanding support for research to understand food allergies, including bringing new scientists into this field of research.

Cosponsored by NIAID, the Food Allergy and Anaphylaxis Network, the Food Allergy Project and the U.S. Environmental Protection Agency (EPA), the *Exploratory Investigations in Food Allergy* initiative supports innovative pilot studies and developmental research on the mechanisms of food allergy, with a goal of attracting additional investigators to the field of food allergy research. In June 2008, NIAID announced 12 two-year grants, totaling $3.5 million, to investigators to lead high-impact, innovative studies of food allergy. All of these awards were issued to investigators new to the field of food allergy research. The EPA is expected to issue separate awards under this research initiative.

The establishment of the *Exploratory Investigations in Food Allergy* program emphasizes the emergence of food allergy as a significant public health concern and addresses recommendations made by the NIH Expert Panel on Food Allergy Research in March 2006. Projects will address key questions aimed at improving treatment and preventing food allergy, including studies to predict which food proteins are likely to cause allergic reactions, the factors that trigger severe responses, and the contribution of other immune disorders to food allergy. Other projects will help define the genetics of human food allergy and the role of interactions between genes and the environment in food allergy pathogenesis.

NIAID will continue to advance the field of food allergy by engaging new and established scientists to work in this area. In FY 2010, NIAID plans to renew the *Exploratory Investigations in Food Allergy* program.

Item
Hepatitis B - The Committee supports the Institute's plans to fund experimental models of hepatitis B and to continue support for the woodchuck model of

hepatitis virus. The Committee urges more work in the area of new intervention discovery for the treatment and management of this disease (p. 102).

Action taken or to be taken
Please refer to page 86 of this document for NIAID's response to this significant item regarding hepatitis B.

Item
Hepatitis C - The Committee encourages the continued development of standardized terminology to describe anti-viral drug resistance, as well as studies of the mechanism of resistance and methods to overcome it. (p. 102)

Action taken or to be taken
Please refer to page 87 of this document for NIAID's response to this significant item regarding hepatitis C.

Item
Inflammatory Bowel Disease (IBD) - The Committee encourages the NIAID to expand its inflammatory bowel disease research portfolio and explore partnerships with the IBD community aimed at fostering greater research on the role of the immune system in the development and progression of IBD in both adult and pediatric populations (p. 102).

Action taken or to be taken
Please refer to page 87 of this document for NIAID's response to this significant item regarding inflammatory bowel disease.

Item
Liver Transplants - The Committee urges expanded research on the immune system reaction to liver transplants in children (p. 102).

Action taken or to be taken
Please refer to page 88 of this document for NIAID's response to this significant item regarding liver transplants.

Item
Lupus - The Committee urges the NIAID to expand and intensify genetic, clinical and basic research and related activities with respect to lupus, with particular focus on the identification of biomarkers and addressing the apparent health disparities associated with this disease (p. 102).

Action taken or to be taken
NIAID maintains its commitment to supporting basic research on autoimmune diseases, including lupus. For example, NIAID researchers are working to

identify genetic factors associated with increased susceptibility to autoimmune disease in mouse models of systemic lupus erythematosus (SLE). These scientists have observed that autoimmune disease can be aggravated or attenuated, respectively, by breeding the mice with other mice that are or are not susceptible to autoimmune disease and are identifying genes that play a role in the development of autoimmune disease. Identification of these genes may uncover potential routes for modifying ongoing disease in lupus or other autoimmune diseases as well as serve as biomarkers to predict disease susceptibility, progression, and severity.

NIAID-supported investigators have used cutting-edge technologies to perform genetic analyses comparing large cohorts of individuals with autoimmune diseases to healthy control subjects. These studies have revealed new genetic risk factors for individual autoimmune diseases including SLE, as well as gene variants that predispose an individual to more than one autoimmune disease. Recently, three new genetic regions associated with SLE have been found. NIAID also supports programs, such as the Multiple Autoimmune Diseases Genetics Consortium and the *HLA Region Genetics in Immune-Mediated Diseases* program, which contribute to efforts to identify those genetic factors that contribute to the development of autoimmune diseases.

The Autoimmunity Centers of Excellence (ACEs), which are sponsored by NIAID, NIDDK, and the NIH Office of Research on Women's Health, conduct collaborative basic and clinical research on autoimmune diseases. Currently, the ACEs are conducting a number of clinical trials and mechanistic studies of immunomodulatory therapies for lupus. For example, researchers are analyzing the data from a recently completed Phase I/II clinical trial of anti-CD20 for treatment for lupus nephritis, and a preclinical study of DNase treatment for lupus is in progress. The ACEs are also developing a new Phase I clinical trial of anti-TNF for treatment of lupus nephritis. The ACE program is being recompeted, with new awards anticipated in FY 2009.

Lastly, NIAID supports the Autoimmune Disease Prevention Centers to conduct research on the development of new targets and approaches to prevent autoimmune diseases, including lupus.

Item

Malaria - To support and sustain the global efforts to control and eliminate malaria, the Committee urges the NIAID to allocate additional resources for research to increase the understanding of the complex interactions among malaria parasites, mosquito vectors and humans, for development of new diagnostics, drugs, vaccines, and vector management, and for continuation of its collaboration with global public-private partnerships to leverage malaria research efforts (p. 102).

Action taken or to be taken

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

Item

Nontuberculous Mycobacteria (NTM) - The Committee is aware of the reports of increasing incidence of pulmonary NTM infections in women and children, particularly involving rapidly growing mycobacteria, an inherently resistant subspecies. The Committee commends the NIH 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 and as well as medical and surgical outcomes through the stimulation of multi-center clinical trials and promotion of health care provider education. The Committee encourages the NIAID to issue program announcements, an NIH partnership funding program, and other appropriate mechanisms to ensure the initiation of grant proposals and other activities for pulmonary NTM disease (p.102-103).

Action taken or to be taken

NIAID remains committed to basic and clinical research on nontuberculous mycobacteria (NTM) to improve the understanding, diagnosis and treatment of NTM infections. For example, NIAID researchers have just published a multi-year study of clinical, microbiologic, immune, and genetic aspects of NTM infection conducted in collaboration with NHLBI researchers, and are collaborating with health maintenance organization partners and the Agency for Healthcare Research and Quality to examine risk factors for NTM disease.

NIAID is currently supporting a clinical trial planning grant to create a NTM Research Consortium (NTMRC) and to design a Phase II trial to assess the safety, tolerability, and efficacy of the standard three-drug treatment regimen in previously untreated patients with pulmonary *Mycobacterium avium* complex (MAC) infection. MAC infections account for over 75 percent of pulmonary infections caused by NTM. The NTMRC will be coordinated by the National Jewish Medical and Research Center (NJC) and will include clinical sites that care for many NTM patients as well as microbiological reference laboratories highly experienced in NTM culture and identification. NIAID intramural scientists have been the key developers and remain central participants in this consortium.

In FY 2008, NIAID, NHLBI and NIDDK co-sponsored a scientific conference hosted by NJC and organized in close coordination with the NTM Information and Research, Inc. (NTMir), an advocacy organization. The conference addressed topics such as predisposing risk factors for NTM infection, immunologic aspects of NTM disease, current therapeutic modalities, and new directions for drug development. It is expected that novel research collaborations as well as grant applications to address specific topics in NTM research will be among the outcomes of the conference.

NHLBI also supports research focused on the association between NTM and the pathogenesis of bronchiectasis, a leading lung problem in cystic fibrosis and primary ciliary dyskinesia, two rare obstructive lung diseases. In addition, NHLBI is planning to release a new Funding Opportunity Announcement to promote research on the microbiome of the lung in HIV-infected and HIV-uninfected controls. The program is expected to stimulate research on the role of infectious agents in the development of lung diseases, including NTM–related disease.

While NIAID is not planning to issue a program announcement for research specifically designed to address NTM, the Institute will continue to support investigator-initiated research on NTM and to assess scientific opportunities in this field. In addition, to facilitate future research, NIAID is broadening its well established contract resources for tuberculosis to include NTM. Through these resources, genomic, biochemical, bacterial and other reagents will be available for researchers starting in 2010. The Institute hopes that these cumulative efforts will lead to more effective prophylactic and therapeutic approaches to the prevention and control of respiratory infections.

Item

Parasitic Tropical Diseases - The Committee urges the NIAID to expand and intensify research on vaccines, diagnostics, and treatments for parasitic tropical diseases including African sleeping sickness, Chagas disease, elephantiasis, visceral leishmaniasis, Buruli ulcer, and cholera. The Committee further requests the NIAID to report an estimate of its funding for research on these diseases in the fiscal year 2010 budget justification (p. 103).

Action taken or to be taken

The support and conduct of basic and clinical research to develop better diagnostics, therapeutics and vaccines to treat and prevent tropical parasitic infectious diseases remains a priority for NIAID. For example, in FY 2008, researchers supported by NIAID and the NIH Roadmap made a significant leap forward in the battle against schistosomiasis, a parasitic disease that affects over 200 million people worldwide. Using genomics and medicinal chemistry, the investigators identified potential therapies that are effective in inhibiting an important enzyme in the parasite that causes schistosomiasis. In laboratory mice, inhibition of this enzyme resulted in killing of the parasite at all stages of development.

The NIAID Laboratory of Parasitic Diseases (LPD) is focused on the identification of immunological and molecular targets for vaccines and other disease interventions for parasitic diseases, including studies to uncover the basic aspects of the host-pathogen interactions both in humans and in animal models as well as studies to understand the vectors such as flies and mosquitoes that transmit medically important parasites. The LPD conducts clinical studies at the NIH Clinical Center as well as at international sites in India, Latin America and

Africa, including a study of the natural history of leishmanial infection and its treatments; studies to evaluate, treat and follow patients with Chagas' disease, malaria, trypanosomiasis, and other parasitic infections; and evaluation of albendazole and diethylcarbamazine as a new treatment regimen for lymphatic filariasis (elephantiasis).

NIAID also continues its commitment to support cholera vaccine research. Recent developments include the initiation of a safety-stage clinical trial of an investigational single-dose, oral vaccine designed to offer combined protection against cholera.

In March 2008, NIAID announced the *Development of Novel Interventions and Tools for the Control of Malaria, Neglected Tropical Diseases and their Vectors* initiative, which aims to support translational research related to the discovery and development of new therapeutics or vector management strategies that will reduce or eliminate morbidity and mortality resulting from malaria and neglected tropical diseases. NIAID anticipates making awards under this initiative in spring 2009.

In addition, NIAID continues its long-standing support for three important initiatives: the Tropical Diseases Research Units (TDRU), the Tropical Medicine Research Centers (TMRC), and the International Collaborations in Infectious Disease Research (ICIDR). Of note, the TDRU program has made progress in the preclinical development of K777 as a possible oral treatment for Chagas' disease. Through the *Partnerships with Public-Private Partnerships* program, NIAID continues its support for two cooperative agreements that focus on the development of new drugs for leishmaniasis and African trypanosomiasis, respectively.

In FY 2009, NIAID support for parasitic diseases is estimated to be $251M.

Item
Scleroderma - The Committee encourages the NIAID to expand its research portfolio on scleroderma in partnership with the scleroderma community (p. 103).

Action taken or to be taken
Please refer to page 92 of this document for NIAID's response to this significant item regarding scleroderma.

Item
Tuberculosis [TB] - The Committee commends the NIAID for the release of its response plan to drug-resistant TB, including strains that are extensively drug-resistant. The Committee encourages the NIAID and other NIH Institutes to allocate appropriate resources to effectively address this global health emergency. The Committee also encourages the NIH to ensure that experts with an understanding of the scientific basis for the control of tuberculosis are

appropriately represented on study sections that review TB research grants (p. 103).

Action taken or to be taken

NIAID supports basic research to enhance understanding of *Mycobacterium tuberculosis* (Mtb) and how it causes tuberculosis (TB) and to translate this knowledge into improved health care interventions for TB, including diagnostics, therapeutics and vaccines. For example, NIAID-supported researchers recently demonstrated that drug-resistant TB strains differ from drug-susceptible strains at only a few dozen genetic sites. This insight into which genes give TB the ability to resist drugs may inform development of better diagnostic tests to distinguish drug-resistant and drug-susceptible strains.

The Institute also supports efforts to develop novel therapeutics to combat TB and the emergence of drug-resistant TB strains, including research to re-evaluate second-line therapies for efficacy against multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. For example, NIAID scientists were instrumental in the development of SQ109, a promising TB drug candidate; a Phase 1b clinical trial of SQ109 is planned. In 2008, NIAID joined the not-for-profit *Lilly TB Drug Discovery Initiative* to help coordinate resources and facilitate new drug development for MDR-TB. This collaboration seeks to make research resources available to accelerate the development of new drug candidates.

NIAID is advancing the effort to develop and test effective new vaccines for the prevention of TB through its support for fundamental and clinical research. Through contracts, the Institute provides researchers with access to facilities and resources for screening TB vaccine candidates in appropriate animal models. NIAID also supports, through public-private partnerships, the development and optimization of advanced stage vaccine candidates for preclinical studies and studies to enable investigational new drug applications.

NIH remains committed to maintaining the integrity of scientific peer review study sections, which conduct grant application review through the NIH Center for Scientific Review (CSR). Candidates nominated to serve on a study section must meet general and expertise requirements, which include recognition as an authority in their field and experience as a principal investigator on a research project comparable to those being reviewed. The NIH CSR makes detailed information on the peer review process available on the Center's web site at http://cms.csr.nih.gov/ .

National Institute of General Medicine Sciences (NIGMS)

House Significant Items

Item

Training Minority Scientists. - The Committee continues to, be pleased with the quality of NIGMS' training programs, particularly those that have a special focus on increasing the number of minority scientists such as the Minority Access to Research Careers [MARC] and Minority Biomedical Research Support (MBRS) programs. The Committee encourages NIGMS to continue to support these important initiatives, and is particularly pleased that NIGMS has supported biomedical career opportunity programs for high school and undergraduate college students in conjunction with historically black health professions schools. (p. 150)

Action taken or to be taken

NIGMS continues to support a portfolio of research training grants dedicated to the development of biomedical researchers from groups underrepresented in science through its Division of Minority Opportunities in Research (MORE). MORE does this through programs of its Minority Access to Research Careers (MARC) and its Minority Biomedical Research Support (MBRS) Branches. NIGMS remains committed to supporting programs to engage underrepresented undergraduates in preparing for careers in biomedical research.

To increase the enrollment of competitively trained underrepresented students in Ph.D. or MD/Ph.D. programs, the MARC Branch focuses on undergraduate research training, supporting both institutional research training grants and grants for ancillary training activities. In FY 2008, the MARC research training grants supported approximately 576 undergraduate students, many of whom attended historically black colleges and universities (HBCUs) or historically black health professions schools. Additionally, through its Ancillary Training Activities program, the MARC Branch supports partnerships with professional societies, and other scientific and educational organizations. For example, MARC partners with such organizations as Federation of American Societies for Experimental Biology, Society for the Advancement of Chicanos and Native Americans in Science, American Society for Microbiology, American Society for Cell Biology, American Physical Society and the Leadership Alliance.

The MBRS Branch supports undergraduates at minority/minority serving institutions through its Research Initiative for Scientific Enhancement (RISE). The purpose of the RISE program is to enhance the research training environment at minority serving institutions, such as HBCUs, and to increase the numbers of students who pursue and attain a Ph.D. degree in biomedical or behavioral research. In FY 2008, the research development of over 1,207

underrepresented minority students, primarily undergraduates was funded by RISE. The Special Initiatives Section of MORE, in conjunction with NCMHD, supports the development of students from underrepresented groups through the Bridges to the Future Programs that facilitate the transition of students from Associate to Baccalaureate degree granting institutions and from Masters to Doctoral granting institutions. It does this by promoting inter-institutional partnerships that permit improvement in the development of underrepresented minority students being trained as the next generation of scientists.

Senate Significant Items

Item

Behavioral Research – The Committee notes that after many years of requests, the NIGMS is supporting basic behavioral research training. While this is a step in the right direction, the Committee remains very concerned that the NIGMS program needs expanding, and that the NIGMS still is not funding investigator-initiated research by behavioral scientists as it is authorized to do so in its statute and has been requested to do so by Congress many times. The Committee also encourages the NIGMS to expand its support of basic behavioral and social science research with initiatives such as the MIDAS program to improve modeling and predictive capabilities regarding the effects of a pandemic flu outbreak, and collaborations with other Institutes and Centers and the OBSSR (p. 103).

Action taken or to be taken

In FY 2007, NIGMS supported $21.7 million of basic behavioral research and training with over 90% of these funds devoted to investigator-initiated research and the balance supported basic behavioral research training. In FY 2008, NIGMS pursued additional steps to expand its support of basic behavioral research and research training.

NIGMS continued development of the Behavioral-Biomedical Sciences Interface institutional predoctoral training grant program. After funding two grants in the first year, NIGMS funded three additional grants in FY 2008 plus continued support of institutional predoctoral training grants with significant behavioral components with the trans-NIH neuroscience training program.

NIGMS also continues to support investigator-initiated research in areas such as the genetics of behavior in model organism such as Drosophila and C. elegans. The Models of Infectious Disease Agent Study (MIDAS) program is due for re-competition and the funding opportunity announcements have been released and it is anticipated that some of the grants supported will include significant behavioral research components.

Finally, NIGMS sponsored a workshop in conjunction with the Office of Behavioral and Social Science Research (OBSSR) on “Modeling Social Behavior” in November, 2008. This workshop was intended to explore the field of social behavior modeling, identifying opportunities, challenges, and gaps in our collective knowledge to guide the development of future programs across NIH.

Item

Training Minority Scientists. - The Committee continues to be pleased with the quality of NIGMS’ training programs, particularly those that have a special focus on increasing the number of minority scientists such as the Minority Access to Research Careers [MARC] and Minority Biomedical Research Support [MBRS] programs. The Committee encourages the NIGMS to continue to support these initiatives, and is particularly pleased that the NIGMS has supported biomedical career opportunity programs for high school and undergraduate college students in conjunction with historically black health professions schools (p. 103/104).

Action taken or to be taken

Please refer to page 104 of this document for the NIGMS response to this significant item regarding training minority scientists.

EUNICE KENNEDY SHRIVER NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT (NICHD)

House Significant Items

Item

Demographic Research - The Committee is pleased that NICHD has completed its long range demographic and behavioral sciences planning study. The Committee encourages the Institute to capitalize on the report's recommendations by investing in future research on changing family dynamics; the causes and consequences of population health; and the effects of migration on the health and well being of communities and individuals. (p. 150)

Action taken or to be taken

NICHD continues to support the Fragile Families Study, the Los Angeles Family and Neighborhood Survey (FANS), the National Longitudinal Study of Adolescent Health, the National Longitudinal Survey of Youth (NLSY), and the National Survey of Family Growth (NSFG). These studies are used extensively by scientists throughout the U.S. to advance knowledge of how our population and families are changing, and how these changes affect the healthy development of children.

Recent research initiatives are described below:

Population Health -- Research support on the causes and consequences of population health include mortality, socioeconomic status, natural disasters, and HIV/AIDS and other sexually transmitted infections. For example, one study is determining how higher education affects health and mortality, and how it differs, by race/ethnicity, nativity, gender, age, and cause of death. Another study examines how health problems among pre-school children affect later educational outcomes. The NICHD also supports research on policy and health, including a study on whether or not state and federal laws mandating that insurance companies provide minimum postpartum stays improve health outcomes for mothers and infants.

Family Dynamics -- NICHD supports research on the roles that mothers, fathers, and other family members play in children's health outcomes. Other research studies examine transitions into and out of marriage. Reflecting the changing composition of the U.S. population, NICHD-supported studies examine family dynamics in Hispanic/Latino and African American families. Other studies are developing programs to strengthen marriage and parenting skills across ethnic and socioeconomic groups, such as those delivered through religious organizations or targeted at military families.

Effects of Migration -- The NICHD supports research that examines how both international and domestic migration affects health and well-being. Studies of international migrants include examining HIV risk factors among Mexican migrants in the U. S. and those who return to Mexico. Other studies examine changes in health insurance and health practices among immigrants across generations; and analyze the factors that lead the children of immigrants to grow up in socially advantaged or disadvantaged households. Recent findings from a longitudinal study of domestic migration found that of the students from families in public housing who were randomly assigned vouchers that allowed them to move to less poor areas, the move was beneficial to girls, but not to boys. The study will continue to assess whether these effects continue as the children become young adults.

Item

First Pregnancy Complications - Pregnancy complications can affect the entire life of both the mother and child. Nearly half of all pregnant women have no pregnancy history to guide the practitioner, and there is often little information to predict and intervene. The rate of preterm birth for this group of women increased 50 percent in the last decade. They are at highest risk for developing multiple devastating maternal complications, fetal death, and preterm delivery. The Committee encourages NICHD to target this understudied population of pregnant women (p. 151).

Action taken or to be taken

Preterm birth affects 1 in 8 women in the U.S., with nearly half a million preterm births each year. Women for whom the current pregnancy will lead to their first delivery (nulliparous) comprise about 40 percent of pregnant women in the U.S.A recent national registry study showed that the rate of preterm delivery among low risk women in this category increased 50 percent in the past decade. Nulliparous women are also at highest risk for developing preeclampsia, which puts them at risk for devastating maternal complications, fetal death, and preterm delivery. In addition, almost two-thirds of singleton fetal deaths are among nulliparous women. The risk for adverse outcomes occurs about twice as often for black women compared to white women. Once one of these adverse outcomes has occurred, these women are considered at increased risk in their next pregnancy and are monitored more intensively. However, the prediction and prevention of the first adverse outcome is far more difficult because of the lack of research on the causes and potential preventive interventions in this population.

The NICHD has identified adverse pregnancy outcomes in women experiencing their first pregnancy as an important area for further research. An initiative specifically targeted to this population has recently been announced, http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-08-029.html. Applications in response to this solicitation are due to the NIH on March 18, 2009, with successful projects beginning around December 1, 2009. This initiative is for a prospective cohort study of a racially, ethnically, and geographically diverse

population of 10,000 nulliparous women with singleton gestations to undergo intensive research assessments during the course of their pregnancies to study the prediction and prevention of adverse pregnancy outcomes. To examine the role of genetic and environmental exposures, biological samples will be obtained in each trimester and at delivery. This study will identify predictive markers in this under-studied population. The results of this research may eventually allow clinicians to be pre-emptive, interceding before preterm birth, preeclampsia and stillbirth take their personal and economic tolls.

This new initiative builds on the findings from the nationwide networks of researchers who focus on maternal and fetal health issues currently being funded by the NICHD, and addresses a critical group of at-risk women who are not currently being studied and who represent 40 percent of the population that will become pregnant in a given year.

Item

Hypoglycemia - The Committee commends the NICHD for progress made through the Diabetes Research in Children Network to test the use of new glucose monitoring technologies in children with diabetes and encourages the Institute to expand the focus of this research network to include research on the causes and prevention of hypoglycemia in diabetic youth. (p. 151)

Action taken or to be taken

Studies in adults and school-aged children have documented an association between severe hypoglycemia (which can cause seizures or loss of consciousness) and either cognitive deficits or neurological changes. Research has found that recurrent mild-to-moderate hypoglycemia during early childhood, when the brain is undergoing rapid developmental changes, may have deleterious transient effects that result in permanent cognitive deficits. Along with other medically valid reasons for preventing hypoglycemia, these observations have generated concern about minimizing hypoglycemia among young children with type 1 diabetes mellitus (T1DM) due to their vulnerability to central nervous system damage.

The NICHD is co-funding the Diabetes Research in Children Network (DirecNet) with the NINDS to pursue this vital area of investigation. The network's efforts include the development of protocols to test strategies for hypoglycemia prevention and utilizing state-of-the-art neuroimaging techniques and cognitive testing to assess the effects of diabetes on brain structure and function in young children with T1DM. DirecNet researchers will soon begin a longitudinal study to determine the effects of hypo- and hyperglycemia in three- to eight-year old children with diabetes, testing the hypotheses that each condition alters brain structure in different ways. In addition to this study, the DirecNet study group plans to evaluate cutting edge technological advances to improve blood sugar control, such as closed-loop insulin delivery systems and newly developed pharmacologic agents targeted toward reducing hypoglycemia.

Item

Infertility and Contraception - The Committee commends NICHD for its research on alleviating human infertility and uncovering new male and female contraceptive leads, including the next generation of non-hormonal methods. The Committee notes that infertility is a condition which affects over six million people in the U.S. and is concerned that the number appears to be growing as age, lifestyle, and environmental factors increasingly impact reproductive health outcomes. Of the six million pregnancies each year, an estimated one-half are unintended. The Committee urges NICHD to continue identifying behavioral factors affecting fertility, infertility and unintended pregnancies, and recognizes that due to decreased private support for reproductive health research, enhanced public support is even more critical to maintaining reproductive health and advancing contraceptive research. (p. 151)

Action taken or to be taken

Recognizing the important role that infertility and contraception play in addressing the quality of life for women and men in the U.S. and around the world, the NICHD supports a broad program of research aimed at alleviating human infertility and reproductive disorders, identifying new contraceptive leads, and expanding fundamental knowledge of the processes that underlie the success or failure of human reproduction. Through the Reproductive Medicine Network, the Institute is exploring a wide range of scientific questions, from how the brain regulates puberty and ovulation, to finding new insights into the relationship between obesity, androgen excess and polycystic ovary syndrome (PCOS) in adolescents, and the implications for predicting the prevalence of metabolic syndrome in adulthood. One recently developed program, focused on fertility preservation, is aimed at developing technology to measure ovarian failure, to develop research strategies to prevent the loss of fertility and to foster the scientific workforce needed to accomplish these goals. Another program focus is preconception care, which considers the importance of the pre- and peri-conception period on egg quality and the subsequent health of offspring.

The NICHD is also actively supporting research on potential contraceptive methods for both women and men. Through a collaborative network of contraceptive development centers and other grantees, potential products are being developed. The Institute-sponsored Clinical Contraceptive Trials Network then evaluates those products and others for safety and efficacy.

In addition, the Division of Epidemiology, Statistics and Prevention Research of the NICHD is currently conducting an epidemiologic study focusing on environmental factors that may affect couples' ability to conceive a woman's ability to deliver a healthy baby. This study was implemented in response to growing evidence that certain chemicals capable of disrupting endocrine function (so-called endocrine disruptors) in the body may be harmful for human reproduction and development. Specifically, the Longitudinal Investigation of

Fertility and the Environment (LIFE) Study, a prospective cohort study of approximately 500 couples who are attempting to become pregnant, will examine and compare information provided by the couples on the daily use of cigarettes, alcoholic and caffeinated beverages, and vitamins. The LIFE Study is assessing whether endocrine-disrupting chemicals affect the length of time required for conception and the risk of infertility and miscarriage. The gestational age and birth size of all infants are also being assessed in the LIFE Study. The data from this one-of-a-kind study are important for identifying environmental reproductive and/or developmental toxicants, and for advising couples about behaviors to maximize their chances of conceiving and carrying a healthy pregnancy to delivery.

Item

Mental Retardation Centers - The Committee recognizes the contributions of the recently renamed Eunice K. Shriver Intellectual and Developmental Disabilities Research Centers (IDDRC), formerly known as the Mental Retardation Developmental Disabilities Research Centers (MRDDRC). The work of these centers leads 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 the 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 IDDRC so that they can conduct translational research to develop effective prevention and intervention strategies for children and adults with developmental disabilities. (p.151)

Action taken or to be taken

The 14 recently renamed Intellectual and Developmental Disabilities Research Centers (IDDRCs) provide infrastructure (core facilities and services) for over 1,000 research projects funded by many of the NIH Institutes and Centers and other government agencies. Funding from the NICHD and their structure allows the IDDRCs to maximize support from their home institutions and have an impact on research well beyond specific research grants. The Centers have been successful in unraveling the genetic origins or causes of many developmental disabilities, and will be focusing on interventions for a number of these conditions throughout the lifespan. In addition, the NICHD created the “centers-within-centers” concept by arranging for other researchers to use the resources of the IDDRCs’ core structures, providing access to research tools and patients, as well as advice on developing research protocols and establishing databases. Currently, the Fragile X Syndrome and the Rare Disease Cooperative Research Centers take advantage of this arrangement.

The NICHD issued an announcement in 2007, inviting centers to re-apply for core grants that would support research to advance diagnosis, prevention, treatment, and amelioration of intellectual and developmental disabilities (IDD).

The announcement stated that administrative and scientific organization within a Center and across the network should enhance further opportunities for breakthroughs, and encouraged translation of basic research results into patient-oriented protocols whose ultimate aims are to develop new approaches for the prevention, diagnosis, and treatment of IDD. Further, the Institute encouraged Centers to facilitate the development of the infrastructure needed to conduct clinical trials.

The three funded centers will focus on research on inborn errors of metabolism, Rett syndrome, cerebral palsy and autism; biobehavioral research on Fragile X syndrome, lysosomal disorders and autism; and clinical and basic research in the areas of Rett syndrome, pediatric brain tumors, sickle cell disease and glial cell biology. [Glial cells are non-neuronal cells that provide support and protection for neurons.]

Item

Preterm Births - Preterm birth is a serious and growing public health problem that affects over 500,000 babies each year. The Committee applauds NICHD for planning and conducting the Surgeon General's Conference on Preterm Birth, which is scheduled to occur in June 2008. The Committee encourages NICHD to expand and coordinate research on the causes of preterm birth based on the public-private agenda that is produced at the Surgeon General's Conference. The largest component of preterm birth is those deliveries between 34 and 37 weeks of gestation. The morbidity is significant for these babies, including respiratory complications, difficulty transitioning after delivery, and feeding issues. Although many late preterm deliveries are due to maternal or fetal indications, some have no reason listed in vital records as to what triggered the delivery. The Committee encourages NICHD to address the causes of these late preterm births and identify interventions for their prevention (p. 151/152).

Action taken or to be taken

The NICHD supports a wide range of research to improve our understanding of preterm birth. The research questions highlighted at the Surgeon General's Conference on the Prevention of Preterm Birth are critical components for understanding this issue. The NICHD is actively pursuing plans to coordinate research efforts with other agencies to implement many of the recommendations made at the Conference, including working with HRSA to establish an interagency coordinating committee.

The NICHD supports research on preterm birth through investigator-initiated grants and through networks such as the Maternal Fetal Medicine Units (MFMU) Network and the newer Genomics and Proteomics Network. In 2008, MFMU Network researchers published in the *New England Journal of Medicine* results from a double-masked, placebo-controlled trial for the prevention of cerebral palsy. The results showed that antenatal magnesium sulfate, a simple and common treatment often used to delay labor, resulted in a reduction from 3.5% to

1.9% of moderate or severe cerebral palsy. Earlier, results from another trial showed that 17 alpha hydroxyprogesterone (which is known to reduce preterm labor in women who have had a previous preterm birth) did not prevent preterm birth in multifetal pregnancies. The Network just completed enrollment in a randomized placebo-controlled trial of Vitamin C and E in nulliparous women for the prevention of preeclampsia, a major cause of medically indicated preterm birth. Another network of researchers, the Neonatal Research Network, will soon begin an observational study on hypotension in term and late preterm infants to investigate the prevalence and treatment of low blood pressure in such infants.

More recently, the NICHD's new Genomic and Proteomic Network for Premature Birth Research aims to accelerate the pace of premature birth research by focusing on genomic and proteomic strategies. The Network's key goals are to identify new biomarkers that are predictive of a preterm delivery and to delineate molecular mechanisms responsible for a preterm birth. The network's first study will follow 500 women at high risk for a preterm birth throughout pregnancy to look for biomarkers of spontaneous preterm delivery. Such biomarkers could allow physicians to act early enough to help prevent preterm delivery. The second study will include 1,000 women who deliver spontaneously preterm and 1,000 women who deliver full term. This study will determine whether a DNA profile can be used to predict a woman having a spontaneous preterm birth. If successful, this would allow physicians to determine a women's susceptibility to a preterm birth even before she conceives.

To reduce disparity in health-related outcomes, the NICHD has embarked on a community-linked, maternal and child health research effort, the Community Child Health Network. The network will rely on cooperative agreements to implement a multi-site, multi-level study examining how community, family, and individual-level factors interact with biological influences to yield health disparities in pregnancy outcomes and in infant and early childhood mortality and morbidity. Findings from this study will improve our understanding of the complicated interplay among environmental and genetic factors in high-risk minority populations.

Item

Spina Bifida - The Committee is disappointed that the Institute has not seemed to expand or prioritize its research efforts in the prevention and treatment of spina bifida and its associated secondary conditions. The Committee urges NICHD to strengthen its investment in understanding the myriad co-morbid conditions experienced by children with spina bifida, including those associated with both paralysis and developmental delay (p. 152).

Action taken or to be taken

The NICHD is one of several Institutes at the NIH that is committed to research efforts in the prevention and treatment of spina bifida. Spina bifida is one of a group of structural birth defects known as neural tube defects (NTDs), in which

the neural tube does not completely close during pregnancy. Infants born with spina bifida have significant disruptions in the brain and spinal cord. Although surgery to close the neural tube can be performed, NTDs generally lead to permanent damage to the spinal cord.

The NICHD funds a multicenter network trial, the Management of Myelomeningocele study (MOMS) evaluating the safety and efficacy of fetal surgical repair compared to traditional postnatal repair of open NTDs. This unique study enrolls women with diagnosed isolated spina bifida in the midportion of their pregnancy. The 200 women are randomized to receive either prenatal surgery on the mother and fetus or to return at the end of pregnancy to undergo standard closure by the same surgical teams. Study endpoints will include evaluating the effect on the mother's health during the index pregnancy and in future pregnancies, fetal outcome, neonatal and infant need for shunting (treatment for orthopedic and urologic problems common to people with spina bifida), and early childhood neurologic and mental functioning. Information about the trial can be found at the website: www.spinabifidamoms.com. Addressing the critical concerns of the urologic complications associated with spina bifida, the NICHD has also funded a competitive supplement to the MOMS trial to assess the impact of in utero surgery on urologic outcomes as compared to the standard postnatal repair.

The NICHD vigorously supports additional basic, translational and clinical research on spina bifida including sensorimotor development and amelioration of deficits by exercise, cognitive development, physical and psychosocial co-morbidities. The goal of another NICHD-funded project is to create an extensive foundation of basic information about the intrinsic sensorimotor capacities of infants with spina bifida across the first year of postnatal life to help develop future intervention trials. Furthermore, among the projects in NICHD's special birth defects initiative are several that target NTDs. One study seeks to understand the mechanisms leading to NTDs, and others specially target genetic and nutritional factors.

Item

Vulvodynia **-** The Committee urges NICHD to increase its efforts in vulvodynia research, with a particular emphasis on etiology and multi-center therapeutic trials. In addition, NIH is encouraged to ensure that experts in vulvodynia, and related chronic pain and female reproductive system conditions, are adequately represented on peer review panels. (p. 152)

Action taken or to be taken

The NICHD appreciates and shares the Committee's concern about vulvodynia and will continue to increase its efforts to answer the many unexplored questions of this elusive and chronic pain syndrome. While the true prevalence remains unknown, several million women in the U.S. are estimated to have vulvodynia.

We understand that vulvodynia represents a complex clinical syndrome of unexplained vulvar pain and sexual dysfunction, one that may have many contributing factors. To this end, the NICHD is planning to reissue and modify its funding opportunity announcement to build a greater scientific knowledge base for this debilitating condition. Investigators have been slow to respond with applications to the four previous solicitations. Consequently, the NICHD is planning to further stimulate research in this area through an active and coordinated approach using a Program Announcement with Referral and special review (PAR). Experts in vulvodynia, related chronic pain, and female reproductive system conditions will be adequately represented on a special emphasis peer review panel. A PAR, which remains active for three years, could encourage an increased investigator-initiated response and will demonstrate the NICHD's continued focus and ongoing commitment to this underserved area. NICHD will invite applications that focus on basic science, translational, and clinical research and the multiple factors that are key to diagnosing and treating this complex pain syndrome. With this new approach, grant applications that expand and intensify vulvodynia research should be forthcoming.

The NICHD also continues its additional efforts to determine the underlying etiology and pathophysiology of this condition. Recent activities have included the NICHD's partnership with the NIDDK, the NINDS and the ORWH on an initiative entitled *Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network*, which included vulvodynia as a related pain condition with similarities to urologic chronic pelvic pain syndromes. The NICHD partnered with the ORWH, the NINDS, other NIH ICs, ACOG, the National Vulvodynia Association, and other organizations to implement a national educational program for health care professionals, patients and the general public on vulvodynia's symptoms, diagnosis and treatment options. The Vulvodynia Awareness Campaign was followed by the NICHD's participation in the Vulvodynia Podcast, part of the popular educational ORWH podcast series, "Pin Point on Women's Health." Additional access to information on vulvodynia occurred during "Women's Health Week at NIH," an event sponsored by ORWH.

Senate Significant Items

Item

Behavioral Research on Families - The Committee encourages the NICHD to support planned research on the changing nature of our Nation's families. Further understanding of family processes will help to address the causes of family structure changes.
(p. 104)

Action taken or to be taken

The NICHD continues to support critical studies that generate information on the changing nature of the nation's families, including the Fragile Families Study, the Los Angeles Family and Neighborhood Survey, the National Longitudinal Study

of Adolescent Health (Add Health), the National Longitudinal Surveys, and the National Survey of Family Growth. These studies are used extensively by scientists throughout the U.S. to advance knowledge of how our population and families are changing, and how these changes affect the healthy development of children. The newest wave of the Add Health study, funded by the NICHD and 14 federal partners, combines biomedical and social science to investigate the processes through which health disparities emerge during the transition to adulthood.

The NICHD also supports research on parental and family influences on children's outcomes, the role of fathers in child well-being, and transition into and out of marriage. The Institute recently completed a long-term project that examined three aspects of family change: parenthood, intimate unions, and the relationships between generations. The goal was to design new models for explaining how families change. The study yielded two reports: "An Assessment of Available Data and Data Needs for Studying Intra- and Inter-Generational Family Relationships and Behavior" and "Explaining Family Change-Final Report." Recommendations include collecting new information and augmenting existing data sets to address emerging questions and gaps in the research, and continuing methodological and interdisciplinary research on the family.

The Institute also supports studies examining the economic, policy, psychological, and sociological factors that influence whether and when men become fathers; how nonresidential fathers participate in the lives of their children, and how father involvement differs by race, ethnicity, and education levels. Plus, the NICHD supports studies on how increases in women's opportunity to work in the paid labor force since 1960 has affected marriage decisions for young men and women; and the processes through which divorced parents of young children make the transition into remarriage.

The NICHD supports research and interventions aimed at strengthening marriage and the family such as a study that examines the nature and antecedents of marital distress and disruption within an ethnically diverse sample of low-income couples. Intervention studies include improving parenting and relationship quality among first-time parents; a marriage education project for premarital couples involving religious organizations; and an intervention for Army families delivered by Army chaplains.

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 cytogenic (chromosomal) 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. 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. 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. Further research is needed to identify which deletions or duplications within specific regions of genes are responsible for various conditions.

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.

The NICHD is also the lead NIH Institute for newborn screening research, with initiatives currently in place that fund research on the development of new testing technologies and new treatments for screened conditions. Recently, the NICHD established a National Newborn Screening Translational Research Coordinating Center to provide the necessary research infrastructure to facilitate studies leading to early detection and treatment for intellectual and developmental disabilities.

Item
Demographic Research - The Committee applauds the NICHD Demographic and Behavioral Sciences Branch [DBSB] for completing its long-range planning study, ''Future Directions for DBSB.'' The Committee encourages the Institute to

capitalize on the report's recommendations and to do so by supporting a balanced portfolio of investigator-initiated research as well as large scale databases. The Committee also congratulates the NICHD on its involvement in the Work, Family, Health and Well-Being Initiative and looks forward to learning how the Institute plans to disseminate the results of this groundbreaking study. (p. 104)

Action taken or to be taken

The NICHD's Demographic and Behavioral Sciences Branch is capitalizing on the recommendations in "Future Directions for DBSB," by continuing to support research in the traditional areas of demographic and behavioral research, while placing new or continued emphasis on the three areas identified by a long-range planning study. The traditional areas of demographic and behavioral research include research on family, children, and intergenerational relations; fertility, infertility, and reproductive health; HIV and sexually transmitted diseases; health, health disparities, and mortality; immigrants, migration and population distribution; and race, ethnicity, population composition, and change. The NICHD continues to support a balanced portfolio of investigator-initiated research in demographic and behavioral research, including 56 new investigator-initiated research grants in FY 2008, 22 of which were to new investigators.

The NICHD continues to support long-term studies that are shedding light on children, their families, and their communities. These include the National Longitudinal Study of Adolescent Health, the most comprehensive study of the health and health-related behaviors of adolescents and their transition into adulthood ever undertaken; the National Longitudinal Survey of Youth, which collects data on children age 15 and over and the mothers of these children; the Los Angeles Family and Neighborhood Survey, a longitudinal study examining how neighborhoods, families, and peers affect children's development and how welfare reform affects neighborhoods; the New Immigrant Survey**,** the first comprehensive nationally representative study of immigrants and their children, which is collecting longitudinal data on health, demographic and socioeconomic background, housing, and child development and education; and Fragile Families**,** a longitudinal birth cohort study of approximately 3,700 unmarried parents and 1,200 married parents and their children, which is examining how children develop over time and how family resources influence children's health and development.

The NICHD supports large studies that can be used by the greater research community: U.S., Latin American, and European censuses, and the National Survey of Family Growth. The NICHD supports a large collaborative project that aids researchers in documenting and archiving their data in formats that are easily accessible while guaranteeing protections for human subjects; and helps researchers' access complex data from a variety of sources. The NICHD has also begun a scientific evaluation of an intervention designed to reduce

workplace stress, thereby increasing child and family well-being, increasing worker productivity, and reducing health insurance costs.

Item

First Pregnancy Complications - Nearly half of all pregnant women have no pregnancy history to guide the practitioner, and there is minimal to no information to predict and offer preventative interventions. The rate of preterm birth for this group of women increased 50 percent in the last decade. Were predictors known, not only would the outcome for the first pregnancy improve, but subsequent pregnancies would be at lower risk. The NICHD is urged to conduct more research in this area. (p. 104)

Action taken or to be taken

Please refer to page 108 of this document for the NICHD response to this significant item.

Item

Intellectual and Developmental Disabilities Research Centers [IDDRCs] - The Committee recognizes the outstanding contributions of the recently renamed Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers [IDDRCs], formerly known as the Mental Retardation Developmental Disabilities Research Centers. However, the Committee is concerned that the IDDRCs do not have sufficient resources to sustain the progress made in this critical area and is especially concerned with the 11 percent funding reduction for recently funded centers. The Committee urges the NICHD to restore these reductions and, to the extent possible, provide additional resources to the IDDRCs so that they can lead our national effort to develop effective prevention and intervention strategies for children and adults with developmental disabilities. (p. 104/105)

Action taken or to be taken

The 14 recently renamed Intellectual and Developmental Disabilities Research Centers (IDDRCs) provide infrastructure (core facilities and services) for over 1,000 research projects funded by many of the NIH Institutes and Centers and other government agencies. Funding from the NICHD and their structure allows the IDDRCs to maximize support from their home institutions and have an impact on research well beyond specific research grants. The Centers have been successful in unraveling the genetic origins or causes of many developmental disabilities, and will be focusing on interventions for a number of these conditions throughout the lifespan. In addition, the NICHD created the “centers-within-centers” concept by arranging for other researchers to use the resources of the IDDRCs’ core structures, providing access to research tools and patients, as well as advice on developing research protocols and establishing databases. Currently, the Fragile X Syndrome and the Rare Disease Cooperative Research Centers take advantage of this arrangement.

An announcement issued by the NICHD in 2007 invited centers to re-apply for core grants that would support research to advance diagnosis, prevention, treatment, and amelioration of intellectual and developmental disabilities (IDD). The announcement stated that administrative and scientific organization within a Center and across the network should enhance further opportunities for breakthroughs, and encouraged translation of basic research results into patient-oriented protocols whose ultimate aims are to develop new approaches for the prevention, diagnosis, and treatment of IDD. Further, the Institute encouraged Centers to facilitate infrastructure necessary for conduct of clinical trials.

Following the submission of applications and completion of the normal peer review process, the NICHD renewed three IDDRCs in 2008 at the recommended funding levels. The three funded centers will focus on research on inborn errors of metabolism, Rett syndrome, cerebral palsy and autism; biobehavioral research on Fragile X syndrome, lysosomal disorders and autism; and clinical and basic research in the areas of Rett syndrome, glial cell biology, pediatric brain tumors, and sickle cell disease.

Item
Infertility and Contraception - The Committee commends the NICHD for its research on alleviating human infertility and uncovering new male and female contraceptive leads, including the next generation of nonhormonal methods. The Committee urges the NICHD to continue identifying behavioral factors affecting fertility, infertility and unintended pregnancies. (p. 105)

Action taken or to be taken
Please refer to page 110 of this document for the NICHD response to this significant item.

Item
Liver Disease and Minority Health - Obesity-related chronic liver disease, also known as non-alcoholic steatohepatitis [NASH], disproportionately affects Hispanic-American children. To better understand the genetic and environmental factors associated with obesity-related chronic liver disease in children, the Committee urges the NICHD to include NASH as a study component within the National Children's Study. (p. 105)

Action taken or to be taken
The National Children's Study (NCS) is planned to be the largest long-term study of environmental and genetic effects on children's health ever conducted in the United States. As a longitudinal study, the NCS will provide ample opportunities to examine a range of childhood diseases and conditions over time and in relation to a variety of environmental (physical, chemical and biologic) exposures and their interactions between genes and those exposures. Led by a consortium of federal agencies, and with input from scientists across the country, the NCS will be a major resource for scientists, providing data and biospecimens from a

nationally representative sample of children across racial and ethnic groups, including over 20,000 Hispanic-American children, and allowing for investigation of numerous issues such as obesity and its related consequences for organ health.

Liver wellness in childhood and diagnoses related to liver diseases, such as NASH, are a focus area, especially in their relation to many increasingly prevalent conditions such as obesity and diabetes. Although the NCS is an observational study, biosamples (such as blood samples) will be kept in a national repository; additionally, de-identified data will be available to scientists who are not part of the NCS for use in adjunct studies going through the regular peer review process.

Item
Preterm and Late Preterm Births - The Committee applauds the NICHD for planning the Surgeon General's Conference on Preterm Birth and encourages the Institute to expand its research based on the public-private agenda recommended at the conference. As authorized by Public Law 109–450, the Committee strongly urges the establishment of an interagency coordinating council on prematurity and low birth weight, to be headed by the NICHD, to ensure that these recommendations are implemented. The Committee notes that although many late preterm deliveries (between 34 and 37 weeks of gestation) are due to maternal or fetal indications, many have no reason listed in vital records as to what triggered the delivery. The NICHD is urged to address the causes of these late preterm births and identify interventions for their prevention. (p. 105)

Action taken or to be taken
Please refer to page 112 of this document for the NICHD response to this significant item.

Item
Rehabilitation Research - The Committee commends the Institute's National Center for Medical Rehabilitation Research for the substantial scientific progress made in the basic and applied research on constraint-induced movement therapy for stroke patients as well as advanced prosthetics. The Committee encourages the center to explore the broader social, emotional and behavioral context of rehabilitation, including effective interventions to increase social participation and reintegrate individuals with disabilities into their communities. (p. 105)

Action taken or to be taken
The NICHD recognizes the need to expand the research portfolio in developing effective interventions to increase participation in the community. The National Center for Medical Rehabilitation Research appreciates the special difficulties investigators face in writing successful grant applications to propose such research. Studies are needed to develop a stronger knowledge base and a

toolbox for moving the results of clinical trials and laboratory-based studies out into the community. If research results are to achieve meaningful changes in the lives of individuals with disabilities, these results must ultimately be applied in community settings.

In collaboration with the NIH Rehabilitation Coordinating Committee, the NICHD's National Center for Medical Rehabilitation Research published an announcement, "Meetings, Conferences, and Networks for Research Partnerships to Improve Functional Outcomes." http://grants.nih.gov/grants/guide/pa-files/PAR-08-207.html. The goal of this announcement is to encourage investigators interested in rehabilitation and management of chronic diseases to attack problems in novel ways by providing the funds necessary to pull investigative teams together and perform preliminary analyses. Efforts towards community-based interventions and measurement of participation are highlighted in the announcement as examples of the kinds of research activities that could benefit from this kind of planning and that the Institute would encourage.

Item
Uterine Fibroids - The Committee continues to encourage additional research on uterine fibroids, especially with regard to increased prevalence rates in minority women. (p. 105)

Action taken or to be taken
The NICHD published a Funding Opportunity Announcement, "Leiomyomata Uteri: Basic Science, Translational and Clinical Research," PAR-08-012 in March, 2008. This initiative will encourage new and experienced investigators to submit high quality research grant applications with the goal of transforming advances in our understanding of the molecular basis of uterine fibroids into new therapeutic options for prevention, treatment, and cure of this common gynecologic disorder. The NIEHS and the ORWH joined the NICHD in supporting this initiative. Recent research activities have formed the groundwork and increased our knowledge base. Our expectation is that new research should build upon and expand the basic underpinnings of uterine fibroid pathophysiology and innovative treatment modalities. The purpose of this announcement is to continue stimulating relevant basic, translational, and clinical research strategies focusing on promising and innovative studies that will enhance our understanding of uterine fibroids, and confirm the NICHD's ongoing interest in and commitment to this field.

The burden of the disease and clinical manifestations of uterine fibroids dictate the need for more sophisticated therapeutic targets. Several studies estimate that 20 to 40 percent of reproductive age women have uterine leiomyomata, and according to some reports, they are diagnosed in African American women two to three times more frequently than in Caucasian women. Investigators who respond to this announcement are encouraged to address the high incidence in

African American women and to examine the factors influencing racial differences surrounding uterine fibroids. The long-term goal of strengthening research in this critical area of women's health is to help reduce the burden of this disease, and improve the quality of life for women affected with this disorder. Another objective of this announcement is to support outstanding research projects and investigators who are willing to communicate in a collaborative fashion about a condition that poses a reproductive threat to many women. To that end, after initiating the program, the NICHD will invite successful applicants to join other NIH-funded investigators to participate in uterine fibroid research conference to share recent findings and to discuss future research directions. This type of meeting can generate excitement among the investigators and stimulate the beginning of collaborative partnerships.

The NICHD continues additional efforts to strengthen the science base, and to increase knowledge and understanding about uterine fibroids and the biological processes that lead to their development and long-term sequelae. The NICHD supports a clinical research study on uterine fibroids at Meharry Medical College, which further supports our emphasis on finding answers about the pathogenesis of uterine fibroids in minority women. The NICHD Women's Reproductive Health Research (WRHR) Career Development Program, in collaboration with ORWH, is an ongoing research training and career development program for junior OB/GYN physician scientists, located at 20 medical schools and universities nationwide. One of the WRHR scholars has a research project with an emphasis on uterine fibroids. The NICHD also will continue to solicit applications for translational research centers that focus on human reproductive diseases and disorders, including uterine fibroids, through the Specialized Cooperative Centers Program in Reproduction and Infertility Research.

Moreover, the NICHD intramural investigators have continued to explore the mechanisms responsible for uterine fibroid development and growth through basic, translational and clinical research studies conducted on campus. Among the many research efforts, investigators are working to begin treating patients who are part of their study protocols using ultrasound. If successful, many women who have been diagnosed with fibroids may be able to be treated without the need for surgery. Further, in the past year, in collaboration with ORWH and major professional medical societies, the NICHD convened a panel of experts to develop a clinical classification system, a long-needed development in clinical practice. The panel developed the framework for the system. A second panel meeting will be convened this fall to finalize the scoring system.

Item

Vulvodynia **-** For the 12th consecutive year, the Committee has called on the NICHD to expand research efforts on vulvodynia, yet only 11 total awards have been made to date and only 3 in the last 3 fiscal years. This is especially discouraging given that, in 2006, an NICHD-funded study showed that up to 16 percent of American women suffer from vulvodynia. The Committee strongly

urges the NICHD to substantially increase the number of awards for vulvodynia studies in fiscal year 2009, with a particular emphasis on etiology and multi-center therapeutic trials. In addition, to ensure that experts in vulvodynia and related chronic pain and female reproductive system conditions, are adequately represented on peer review panels, the Committee recommends that the current program announcement on vulvodynia, PA–07–182, be reissued with ''special review.'' Finally, the Committee calls on the NICHD to employ the full range of award mechanisms available to expand research and research capacity in this area. (p. 105/106)

Action taken or to be taken

Please refer to page 114 of this document for the NICHD response to this significant item.

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, including identification of gene variants associated with an increased risk for AMD, which presents an opportunity to predict and preempt the disease. The Committee encourages further research into diagnostics for early detection and appropriate therapies. The Committee also applauds NEI for the second phase of its Age-Related Eye Disease Study, in which additional dietary supplements are being studied to determine whether they can demonstrate or enhance their protective effects against progression to advanced AMD, as shown previously with dietary zinc and antioxidant vitamins in the study's first phase. (p. 152)

Action taken or to be taken

The NEI continues its research efforts to understand the causes and genetic influences on AMD to enhance our capability for early detection and treatment of this blinding disease. Determining the role of inflammation in AMD is an important component of this effort. NEI established a new program area in Ocular Immunology, Inflammation and Infection, which is already producing results. In late FY 2008, NEI investigators reported an association between a toll-like receptor gene (TLR3), which encodes a viral sensor that activates immune responses, and AMD. TLR3 is thought to induce cell death in tissues infected by certain viruses. The study found that a low activity genetic variant of TLR3 may confer protection against AMD by suppressing the death of retinal cells. Discovery of this gene's role in AMD affords an opportunity to investigate the early biological events that lead to the disease and to develop presymptomatic diagnostics and new therapeutics to prevent this form of the disease. This study will also spur additional investigations of genes involved in the immune response and their role in AMD.

Item

Diabetic Eye Disease - The Committee supports the collaborative efforts of the diabetic retinopathy clinical research network to test innovative treatments for diabetic eye disease. The institute is encouraged to consider expanding and extending the network by increasing the number of clinical trials with new drugs and therapeutics that can treat and prevent diabetic retinopathy. In addition, NEI is urged to work with the Food and Drug Administration to seek better endpoints and functional biomarkers for diabetic retinopathy that could accelerate the conduct of clinical trials and the potential approval of new treatments. (p. 152/153)

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research to improve the treatment of diabetic retinopathy, diabetic macular edema, and associated conditions. DRCR.net currently includes more than 150 participating sites with more than 500 clinicians throughout the country. DRCR.net is currently recruiting patients for two recently initiated clinical trials. One trial is comparing the effectiveness of two treatments for diabetic macular edema, a complication of diabetes that causes swelling of the retina due to fluid that leaks from faulty blood vessels in the retina. Patients are treated with laser photocoagulation combined with either steroid treatment or a drug to prevent growth of the abnormal blood vessels (anti-neovascular agent). A second trial is evaluating these same therapies in proliferative diabetic retinopathy, an advanced and severe stage of diabetic retinopathy where blood vessels leak blood into the vitreous, the clear, jelly-like substance that fills the eye. Two new trials are slated to recruit patients in FY 2010 to evaluate the effects of cataract surgery on diabetic macular edema and to evaluate the reproducibility of visual acuity measurements in diabetic macular edema.

In addition, NEI and the Food and Drug Administration (FDA) held a symposium, titled "Ophthalmic Clinical Trial Design and Endpoints in 2006" where representatives from both federal agencies, the Center for Medicare and Medicaid Services, university scientists and clinicians, and others conferred on endpoints and clinical trial strategies for evaluating new treatments for diabetic retinopathy, AMD and other retinal disorders. The symposium evolved from a series of meetings between members of the eye and vision research community, the FDA's Center for Drug Evaluation and Research, and NEI senior investigators. The symposium addressed developing standards for clinical trials in ophthalmology, including the use of new imaging technologies such as Optical Coherence Tomography (OCT) as possible endpoints in vision research clinical trials. The FDA gave useful guidance on the research steps necessary to validate OCT as a useful endpoint and that work is now ongoing.

Item

Screening for Diabetic Eye Disease - The Committee encourages NEI to foster research on the development of effective screening programs for early detection of diabetic eye disease, especially in insulin-dependent patients who are at increased risk for blindness at a young age (p. 153).

Action taken or to be taken

Diabetes is a chronic disease that imposes a large public health burden, afflicting 8 percent of the American population, with one in 500 children and adolescents afflicted with Type 1 (insulin-dependent) diabetes. Diabetic retinopathy (DR) is a significant complication of diabetes and is the third leading cause of blindness in the US. Although annual eye exams are recommended for patients with diabetes, a considerable number of these patients are not adequately screened for DR. In addition, many people with diabetes may not be aware that the

disease can lead to blindness. Effective treatments for DR do exist, so early intervention is critical to prevent vision loss and blindness. Consequently, there is an important need to improve efforts to educate patients about diabetic retinopathy and to encourage regular eye exams.

The people who most need such services are quite varied. Individuals lacking adequate health insurance, minority individuals at greater risk for DR, and individuals living in geographically isolated regions are some examples. Often, they are not likely to visit an eye care specialist or do not have trouble-free access to such specialists. Thus, education and telemedicine provide two potentially efficient and economic means to better serve the health needs of diabetics.

The NEI currently supports grants to develop novel, low cost screening tools for diabetic eye disease suitable for use in community-based screening programs. In addition, the NEI is developing a Request for Applications, "Innovative Educational and Ocular Screening Initiatives to Improve Detection of Diabetic Retinopathy," through the Small Business Innovation Research program, to develop educational outreach programs regarding the blinding consequences of diabetes; and to develop tools and systems to be used for increasing patient access to eye exams to screen for DR.

Senate Significant Items

Item

Age-Related Macular Degeneration (AMD) - The Committee commends the NEI for its trans-Institute research into the cause, prevention, and treatment of AMD, including the identification of gene variants associated with an increased risk for the disease. The Committee encourages further research into diagnostics for early detection and appropriate therapies. The Committee also applauds the NEI for initiating the second phase of its Age-related Eye Disease Study [AREDS], in which additional dietary supplements are being studied to determine whether they demonstrate or enhance protective effects against progression to advanced AMD, as shown previously with dietary zinc and antioxidant vitamins (p. 106).

Action taken or to be taken

Please refer to page 125 of this document for NEI's response to this item on Age-Related Macular Degeneration (AMD).

Item

Diabetic Eye Disease - The Committee encourages the NEI to expand and extend the Diabetic Retinopathy Clinical Research Network by increasing the number of clinical trials with new drugs and therapeutics that can treat and prevent diabetic retinopathy. (p. 107)

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research to improve the treatment of diabetic retinopathy, diabetic macular edema, and associated conditions. DRCR.net currently includes more than 150 participating sites with more than 500 clinicians throughout the country. DRCR.net is currently recruiting patients for two recently initiated clinical trials. One trial is comparing the effectiveness of two treatments for diabetic macular edema, a complication of diabetes that causes swelling of the retina due to fluid that leaks from faulty blood vessels in the retina. Patients are treated with laser photocoagulation combined with either steroid treatment or a drug to prevent growth of the abnormal blood vessels (anti-neovascular agent). A second trial is evaluating these same therapies in proliferative diabetic retinopathy, an advanced and severe stage of diabetic retinopathy where blood vessels leak blood into the vitreous, the clear, jelly-like substance that fills the eye. Two new trials are slated to recruit patients in FY 2010 to evaluate the effects of cataract surgery on diabetic macular edema and to evaluate the reproducibility of visual acuity measurements in diabetic macular edema.

Item

Low Vision and Blindness Rehabilitation - The Committee encourages the NEI to prioritize research aimed at developing and assessing new methods for the rehabilitation of visually impaired individuals, including children. The Committee also urges the NEI to collaborate with the **National Center for Medical Rehabilitation Research at the NICHD** on developing improved assistive technology and training research scientists in the field of rehabilitation. (p. 107)

Action taken or to be taken

The Low Vision and Blindness Rehabilitation program of the NEI continues to support research aimed at creating and assessing new assistive technologies and rehabilitation programs for visually impaired and blind adults and children. As part of this effort, NEI works with the National Center for Medical Rehabilitation Research at the NICHD in encouraging assistive technology research. In addition, NEI uses the Small Business Innovation Research (SBIR) grant mechanism to recruit talent from the private sector to further the development of assistive technologies. Through these efforts, NEI is leveraging existing technologies such as cell phones and Personal Digital Assistants (PDAs), to develop navigational aids. Small, portable optical character recognition devices are also being developed that scan retail bar codes to provide audible pricing information on products. NEI grants support bioengineering efforts to create technological interfaces that augment residual vision in the visually impaired. Devices are being developed that will allow blind and visually impaired pedestrians to navigate complex environments such as congested sidewalks and busy traffic intersections. The goal is to improve

mobility and independence thereby allowing the visually impaired to achieve their full potential as productive and vital citizens. NEI also recognizes the need for training researchers in these important areas and continues its strong support of postdoctoral fellowships and physician-scientist career development awards to develop future research capacity in this area.

National Institute of Environmental Health Sciences (NIEHS)

House Significant Items

Item

Mercury - In order to properly research gaps in the area of mercury exposure and brain chemistry, the Committee encourages NIEHS to pursue studies of how inorganic mercury and organic mercury compounds (including ethyl, methyl, and other forms of mercury from all sources) are processed in the bodies of children and adults. NIEHS is also encouraged to support studies of the toxic effects of inorganic mercury and organic mercury compounds on the nervous systems of young children, adults, and the elderly and methods of properly removing mercury and mercury-containing compounds from the brains of affected humans. (p. 153)

Action taken or to be taken

NIEHS supports a broad array of mercury-related research. Examples of studies investigating mercury compounds include the following:

Neonatal Thimerosal Exposure**:** It has been suggested that ethyl mercury in thimerosal-preserved vaccines contributes to neurodevelopmental disorders such as autism. An NIEHS-supported study exposed neonatal mice to thimerosal, with and without combined diphtheria, tetanus, pertussis and hemophilus influenza B vaccines. Results provide little support to the hypothesis that thimerosal exposure contributes to the etiology of neurodevelopmental disorders.

Neurological outcomes in children exposed to amalgam-related mercury: Studies involving children demonstrated an absence of neurobehavioral effects from clinical exposure to mercury amalgam, but neurological findings were not reported. NIEHS supported a study examining the safety of dental amalgam-treated children. Results indicate that neurobehavioral or neurological effects from dental amalgam mercury exposure in children are inconsequential.

Developmental mercury exposure**:** An NIEHS-supported study found that methylmercury exposure in juvenile rats led to reductions in hippocampal size and cell numbers, suggesting that neurons might be particularly vulnerable. Perinatal exposure led to profound deficits in juvenile hippocampal-dependent learning during training on a spatial navigation task. This study indicates that exposure to one dose of methylmercury during the perinatal period acutely induces apoptotic cell death, which results in later deficits in hippocampal structure and function.

Multidrug resistance proteins and the renal elimination of inorganic mercury**:** Current therapies for inorganic mercury (Hg^{2+}) intoxication include administration of a metal chelator. After exposure to a chelator, Hg^{2+} is rapidly eliminated from the kidneys and excreted in the urine. NIEHS-supported scientists are studying the roles of transport proteins in chelation efficacy to be able to design better therapies for mercury poisoning.

Selenomethionine reduces visual deficits due to developmental methylmercury**:** Many micronutrients, including selenium, are involved in cellular defenses against oxidative stress and may reduce the severity of methylmercury-induced deficits. NIEHS-supported researchers have shown that in Zebrafish embryos selenium co-exposure in the form of selenomethionine helped ameliorate deficits in visual responses due to methylmercury exposure.

Enhancing methylmercury excretion**:** Since N-acetylcysteine (NAC) is effective at enhancing methylmercury excretion when given either orally or intravenously, decreases brain and fetal levels of methylmercury, has minimal side effects, and is widely available in clinical settings, NIEHS sponsored a study to evaluate NAC as a potential methylmercury antidote and biomonitoring agent in humans. Using NAC, a monitoring protocol for early detection of acute methylmercury exposure in rats was devised to test whether NAC reduces methylmercury levels in the developing embryo.

Item

Respiratory Disease - The Committee recognizes the contributions of the NIEHS to help protect and improve pulmonary health. It encourages the Institute to devote additional resources to study the effects of changes in occupational exposures and ambient and indoor air.

Action taken or to be taken

NIEHS will continue to support research to help protect and improve pulmonary health, including studies on the effects of changes in occupational exposures and ambient and indoor air. NIEHS is funding a project designed to improve our understanding of how workplace exposures to respiratory irritants and sensitizers in medical settings affect allergies, asthma and lung function in a population of health professionals. The project will evaluate workplace exposure to respiratory irritants and sensitizers among professional nurses employed in a range of industries and medical settings and assess whether exposures contribute to the incidence and severity of new onset asthma and allergy symptoms, exacerbation of symptoms in previously symptomatic individuals, sensitization of previously asymptomatic individuals, and behavioral consequences of the frequent and/or severe symptoms.

An NIEHS-sponsored study conducted by the Center for Childhood Asthma in the Urban Environment is investigating the effect of in-home particulate matter exposure on atopic asthmatic children. In addition, NIEHS and the US Environmental Protection Agency (EPA) are supporting a project conducted at the Center for Childhood Asthma in the Urban Environment and the Children's Environmental Health Center to focuses on how exposures to environmental pollutants and allergens cause airway inflammation and respiratory morbidity in children. NIEHS is supporting clinical studies to assess the effects of indoor and ambient air pollutants. The Lung Mucus Hypersecretion and NQO1 study will

identify host susceptibility factors that confer vulnerability to the prototypal air pollutant, ozone. The results will significantly aid in understanding the mechanisms regulating pro-oxidant lung injury, production and secretion of airway mucins, and clearance of respiratory mucus, as well as the adverse health effects that occur during and following exposure to airborne respiratory irritants.

The NIEHS-funded Asthma Severity in Children and Environmental Agents study will measure residential exposures to indoor allergens, mold, nitrogen dioxide and nicotine, and relate exposure levels to daily symptoms, including wheeze, persistent cough, chest tightness and shortness of breath, and medication use.

Two other ongoing NIEHS-supported clinical studies, Ambient Air Pollution, Preeclampsia, and Preterm Delivery; and Dust Mite Allergen Reduction Study design models that use local traffic, weather, and population characteristics to predict monthly ambient concentrations of fine particulate matter (PM2.5) and carbon monoxide (CO). These models will be used to estimate study participants' PM2.5 and CO exposures before and during pregnancy and will test whether these air pollutant exposures are associated with subsequent risk of preeclampsia and preterm delivery. The researchers will also test biological markers of maternal lipid peroxidation and inflammation in maternal blood samples drawn during early pregnancy and examine carboxyhemoglobin measured in early-pregnancy maternal blood samples as a marker of CO exposure.

Senate Significant Items

Item

Agricultural Health Study - The Committee urges that the scope of the Agricultural Health Study be expanded to permit a greater focus on reproductive issues to investigate the possibility that many chronic illnesses may be due to environmental exposures experienced while in utero.

Action taken or to be taken

The NIEHS-supported Agricultural Health Study (AHS) began in 1993 and includes a cohort of 4,916 commercial applicators from Iowa and 52,395 private applicators, mostly farmers, from both Iowa and North Carolina. More than 75% of spouses of married private applicators also enrolled in the cohort. AHS researchers have been investigating the influence of pesticide exposures on menstrual cycle, age at menopause, infertility, pre-term birth, and birth weight. Through record linkages, the scientists have attempted to collect enough information to study pesticide exposure effects on birth defects, although the cohort may be too small to provide definitive data. This is an older cohort, and many of the enrolled women are now past reproductive age.

NIEHS agrees that it is of great importance to study reproductive issues associated with environmental exposures and is funding other studies more directly focused on the effects of exposures while in utero and during childhood. The largest of these is the ongoing long term prospective Norwegian Mother and Child Cohort Study (MoBa) (Mothers and Babies), which includes a cohort of 100,000 pregnant women and their children in Norway. MoBa will provide a valuable opportunity to assess the role of environmental exposures in the health of women and their children.

National Institute on Aging (NIA)

House Significant Items

Item

Alzheimer's Disease - The Committee suggests that NIA target research funding to accelerate the translation of basic research findings into clinical studies and human trials, and to consider beginning 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. 154)

Action taken or to be taken

NIA, in partnership with NINDS and NIMH, has launched a Translational and Drug Discovery Initiative to expand and intensify the translation of basic research findings into clinical studies and human trials and expand its investment in Alzheimer's disease (AD) research. This initiative supports several program announcements, "Alzheimer's Disease Drug Development Program" and "Grants for Alzheimer's Disease Drug Discovery" 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 24 projects funded under these Program Announcements, exploring a wide array of approaches, including agents that inhibit the development of AD's characteristic amyloid plaques and neurofibrillary tangles, immunotherapies, antioxidant drugs, and neuroprotective agents. It is anticipated that additional meritorious projects will be funded. In March 2009, an investigators meeting for AD Translational Research to discuss the progress and challenges of individual projects is scheduled.

NIA-supported investigators involved in drug discovery and drug development can use the services of NIA's Toxicology Contract, "Investigational New Drug Toxicology for Drugs to Treat Alzheimer's Disease and Other Aging-Related Diseases."

NIA also recently established 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. This network, coordinated at Washington University (St. Louis), includes a number of sites in the United States, England and Australia. We anticipate recruitment will begin in early 2009.

Item

Demographic and Economic Research -The Committee urges the Institute to continue its current support for the Demography of Aging Centers and the demographic and economic components of the Roybal Centers. The Committee applauds the Institute's support of an initiative that will lead to a national survey

of disability trends and dynamics among the U.S. older population residing in community and institutional settings (p. 154).

Action taken or to be taken
NIA will continue to support the Centers on the Demography and Economics of Aging program in FY 2009. In FY 2008, NIA solicited applications for a new five-year center program and expects to fund between eight and 13 Centers in FY 2009.

The Roybal Centers are intended to improve the health, well being, and productivity of older people, through the translation of basic behavioral and social sciences research. The NIA will continue to support these centers in FY 2009. In FY 2008, NIA solicited applications for a new five-year center program; economic and demographic research is encouraged in the solicitation. NIA expects to fund between eight and 12 Roybal Centers in FY 2009.

Work is on the way with the Office of Behavioral and Social Science Research (OBSSR) and the Office of AIDS Research to continue their current level of support for the Demography and Economics of Aging Centers, and with OBSSR to continue their support of demographic and economic components of the Roybal Centers.

NIA funded a new National Study of Disability Trends and Dynamics in September 2008 to provide timely estimates of disability trends and dynamics, as well as data on antecedents, correlates and consequences of disability and long-term care, including comparisons among ethnic groups. It will compare data that can be compared to the 1982-2004 National Long-Term Care Surveys for analysis of long-term trends.

Item
Gerontology Centers - The Committee expresses its full support for the Edward R. Roybal Research Centers on Applied Gerontology. The centers are designed to move promising social and behavioral basic research findings out of the laboratory and into programs, practices, and policies that will improve the lives of older people and the capacity of society to adapt to societal aging. The Committee suggests that NIA consider expanding the numbers of centers, developing new topics for research, especially in the area of diversity and ethnic and minority communities, and providing opportunities for collaborative, Interdisciplinary research between the Roybal centers and other program initiatives such as the resource centers for minority aging research and the demographic centers. (p. 154)

Action taken or to be taken

There are ten Roybal Centers. In pursuit of their objectives, collaborative and interdisciplinary research with other program initiatives are highly encouraged. For example, the Resource Centers for Minority Aging Research (RCMARs) partner with the Roybal and other NIA-supported Centers to develop and implement strategies to improve recruitment and retention of minorities in clinical research. A recent review of NIA clinical trial recruitment activities concluded the strategies, including partnership activities between the RCMARs and other Centers, are making a significant difference in terms of methods and practices used in the recruitment and retention of minority elders in aging research.

In FY 2008, NIA solicited applications for a new five-year center program; in the solicitation, research is encouraged on the translation and diffusion of medical advances to explain and ultimately reduce disparities in effective care and health status of the elderly. NIA expects to fund between eight and 12 Roybal Centers in FY 2009.

Senate Significant Items

Item

Alzheimer's Disease - While past investments in Alzheimer's research have led to a far better understanding of the disease as well as earlier, more accurate diagnosis, the Committee is concerned that progress has slowed in recent years. The Committee therefore recommends that a portion of the additional funds provided for the NIA be devoted to accelerating 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. The NIA is urged to work closely with the NINDS and NIMH in these efforts. (p. 108)

Action taken or to be taken

See House Report language on page 134 of this document.

Item

Behavioral Research and Decision-making - The Committee encourages the NIA to support its Neuroeconomics and Aging research program, which will examine the changing motives that drive behavior in older adults and could lead to interventions that will help older Americans better manage financial planning. (p. 108)

Action taken or to be taken

In 2006, NIA released a research announcement to stimulate investigations in the area of Neuroeconomics of Aging, specifically the social, emotional, cognitive, motivational processes and neurobiological mechanisms of economic behavior as these (1) influence social, financial, and health-related decisions affecting the well-being of middle-aged and older adults, and (2) inform the development and refinement of integrative economic theories of utility, learning,

and strategic choice relevant to aging. Of particular interest are applications exploring the neurobiological underpinnings of economic behavior associated with life cycle decisions in domains such as health care, health and long-term care insurance, health behaviors, savings, and retirement, as well as those investigating age differences in socioeconomic phenomena that govern expenditures of social and economic capital, such as fairness, altruism, and trust.

Nine grants are active under this announcement, including a study of behavioral and neural responses during anticipation of financial risk and reward in young, middle-aged, and old samples; a study to investigate the effect of acute stress on learning and performance in investment tasks for younger and older adults; and a study of the neural basis for altruism among older and younger adults.

A meeting of Neuroeconomics of Aging grantees is scheduled for September 2009. This will be a forum for sharing emerging findings and for exploring future directions for neuroeconomics research on aging-relevant themes.

Item

Behavioral Research and Long-term Cognitive Improvement - The Committee commends the NIA on the success of the ACTIVE study, and it encourages follow-up studies on more varied populations. (p. 108)

Action taken or to be taken

Age-related cognitive decline exclusive of dementia will affect most older individuals to some extent and has a direct impact on their independence and vitality. Cognitive training, physical exercise, enhancement of self-efficacy, social engagement, diet, environmental enrichment, and stress reduction have all been shown to have positive effects on cognition. The NIA-supported Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Study was the first randomized, controlled trial to demonstrate long-lasting, positive effects of brief cognitive training in older adults. However, testing indicated that training did not improve the participants' ability to tackle everyday tasks. More research is needed to translate the findings from the laboratory into interventions that prove effective at home.

NIA is currently soliciting research grant applications to take insights from previous work in cognitive aging and convert them into feasible intervention strategies that can be tested in randomized clinical trials. Interventions may include cognitive training, lifestyle interventions, dietary interventions, behavioral change, or a combination of approaches. Proposed interventions are encouraged to address the role of individual differences in mediating or moderating intervention adherence and outcomes. We anticipate grant awards in FY 2009.

Item

Cognitive Health - The Committee encourages the NIA to follow up on recent findings that cognitive health appears to be improving in the over-70 population. In particular, further studies to determine how education, exercise, medications, cardiovascular health and lifestyle affect cognitive functioning are encouraged. (p. 108)

Action taken or to be taken

Studies on the maintenance of cognitive health into old age continue to be an integral part of NIA's research portfolio. Ongoing activities include:

- Continuing its fruitful collaboration with the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke on the Cognitive and Emotional Health ("Healthy Brain") Project (CEHP). In 2007, the Initiative produced the *National Public Health Roadmap to Maintaining Cognitive Health,* which includes a set of 41 recommendations that are grounded in science, emphasize primary prevention, assume a community and population approach, and are committed to eliminating disparities. The long-term goal of the Roadmap is to maintain or improve the cognitive performance of all adults.
- In 2007, NIA hosted a Cognitive Aging Summit to provide an opportunity for experts in different fields of research to discuss advances in understanding of age-related brain and behavioral changes and to develop recommendations for research directions that will facilitate development of interventions for maintenance of cognitive health throughout life.
- Working with the McKnight Brain Research Foundation, in conjunction with the Foundation for NIH, NIA is soliciting grant applications for research to examine the neural and behavioral profiles that characterize healthy cognitive aging and that allow distinction from pathological cognitive change in the older adult. Findings from this initiative will advance our understanding of the causes of age-related cognitive change; test theories of adaptation, compensation, and cognitive reserve; provide a foundation for development of biomarkers; and lead to rational development of therapeutics and help guide treatment of cognitive decline or maintenance of cognitive function. This solicitation is a direct result of the Cognitive Aging Summit, at which experts strongly recommended the development of "gold standard" profiles for brain health and cognitive function across the lifespan.
- NIA is soliciting research to identify feasible nondrug intervention strategies to enhance cognitive health among older people, with the goal of identifying strategies that can be tested in clinical trials. Interventions may include cognitive training, lifestyle interventions, dietary interventions, behavioral change, or a combination of approaches.

Item

Demographic and Economic Research - The Committee is aware that fiscal year 2009 is a critical planning year for the NIA Demography of Aging Centers, the Roybal Centers for Research on Applied Gerontology, and the Health and Retirement Survey [HRS]. The Committee urges the NIA, with support from the Office of Behavioral and Social Science Research and Office of AIDS Research, to continue its current level of support for the Demography of Aging Centers and the demographic and economic components of the Roybal Centers. The NIA is also urged to provide sufficient funding for the HRS to preclude a cut in the survey's sample size and to ensure that biological data, including DNA, are collected as part of the next wave. Finally, the Committee applauds the Institute's support of the National Study of Disability Trends and Dynamics, which will include the older population residing in community and institutional settings. (p. 108)

Action taken or to be taken

NIA will continue to support the Centers on the Demography and Economics of Aging program in FY 2009. In FY 2008, NIA solicited applications for a new five-year center program and expects to fund between eight and 13 Centers in FY 2009.

The Roybal Centers are intended to improve the health, well being, and productivity of older people, through the translation of basic behavioral and social sciences research. The NIA will continue to support these centers in FY 2009. In FY 2008, NIA solicited applications for a new five-year center program; economic and demographic research is encouraged in the solicitation. NIA expects to fund between eight and 12 Roybal Centers in FY 2009.

Work is on the way with the Office of Behavioral and Social Science Research (OBSSR) and the Office of AIDS Research to continue their current level of support for the Demography and Economics of Aging Centers, and with OBSSR to continue their support of demographic and economic components of the Roybal Centers.

NIA funded a new National Study of Disability Trends and Dynamics in September 2008 to provide timely estimates of disability trends and dynamics, as well as data on antecedents, correlates and consequences of disability and long-term care, including comparisons among ethnic groups. It will compare data to the 1982-2004 National Long-Term Care Surveys for analysis of long-term trends.

The current funding period for the Health and Retirement Study (HRS) supports data collection in2010. Co-funding with the Social Security Administration (SSA) has ensured that no cuts to sample size. SSA co-funding ensured half of the total HRS sample received in-person interviews in 2008. In person data collection in 2010, including biological data and performance measures, will depend on future

NIA and SSA support. The biological and DNA data, and the physical performance measures, will enhance the health content of the HRS, significantly improving our ability to understand age-related changes in health.

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

House Significant Items

Item

Fibromyalgia – The Committee encourages NIAMS to convene an international symposium to elucidate the state of the science with regard to fibromyalgia and to publish a consensus document establishing a roadmap for future fibromyalgia research. The Committee encourages NIAMS to explore the broad spectrum of neurotransmitter abnormalities and other potential problems, including sleep disturbances, abnormal cervical anatomy and genetic factors, which might contribute to symptom development and expression. The Committee also encourages NIAMS to collaborate with NIDDK in support of its multi-disciplinary approach to the study of chronic pelvic pain initiative (p. 154-55).

Action taken or to be taken

Fibromyalgia syndrome is a common and chronic disorder characterized by widespread muscle pain, fatigue, and multiple tender points. The NIAMS supports a wide range of efforts that are designed to address this public health issue. Furthermore, the NIAMS welcomes the opportunity to partner with other NIH Institutes or Centers to find collaborative solutions involving research in fibromyalgia relevant to our mission.

During a recent meeting with representatives from the fibromyalgia community, NIAMS encouraged attendees to consider use of the NIH Support for Conferences and Scientific Meetings to develop an international symposium focused on the disease and associated issues.

The Patient-Reported Outcomes Measurement Information System (PROMIS) is an NIH Roadmap initiative aimed at changing the way patient-reported outcome tools are selected and employed in clinical research and practice evaluation. Researchers supported by NIAMS are currently conducting an ancillary study to PROMIS focused on fibromyalgia. It proposes to use data generated through National Fibromyalgia Association (NFA) focus groups to test and validate fibromyalgia-specific items, along with the PROMIS item banks. 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.

In another effort, a tissue bank of brain and spinal cord samples from fibromyalgia patients is under development. This tissue bank will allow researchers to investigate evidence of glial activation and proinflammatory cytokine production in patients, in comparison with age-matched, pain-free controls. Glial activation or their inflammatory products could present promising targets for chronic pain treatment.

The effectiveness of chronic pain prevention, identification, and management, such as that stemming from fibromyalgia, was the topic of a session at the 2008 NIAMS Scientific Retreat. The aim of the session was to determine how the NIAMS could more effectively study and contribute toward treatment options for patients who suffer from chronic musculoskeletal pain.

Item
Lupus - The Committee encourages NIAMS to support and bolster lupus research to help make much needed gains in understanding the causes of lupus and, ultimately, discover a cure for the disease (p. 155).

Action taken or to be taken
Systemic lupus erythematosus (SLE or lupus) is a serious and potentially fatal autoimmune disease, often occurring in women (nine times more often than men) of child-bearing age and affecting many parts of the body. People of all races can have lupus, however, African American women have a three times higher incidence (number of new cases) than white women developing the disease at a younger age with more serious complications. It is also more common in women of Hispanic, Asian, and Native American descent.

To facilitate genetic studies in lupus research, NIAMS supports a large lupus registry and repository designed to accelerate the search for lupus susceptibility genes. This registry collects and updates clinical, demographic, and laboratory data on patients with lupus and their families. Researchers are able to use the information in the registry to analyze the repository's DNA samples and search for the presence of genetic markers. Additionally, the NIAMS provides support for the Research Registry for Neonatal Lupus. This registry provides material for basic research on the causes of this disease. For more information about the registry, access this link: http://clinicaltrials.gov/ct2/show/NCT00074373

Two decades of research has yielded a wealth of new information on the mechanisms and key elements involved in immune response. As a result, opportunities exist to identify potential genetic, environmental, and infectious causes of lupus, and to develop novel approaches for lupus treatment and prevention. NIAMS intramural and extramural investigators have previously identified a variant of the STAT4 gene, which more than doubles the risk of lupus in individuals who carry two copies of the variant. Building on this finding, these investigators have now established that this STAT4 gene variant is more specifically associated with disease that is characterized by severe clinical manifestations, such as those involving the kidneys. This finding may be useful for early identification of the likelihood of developing severe disease manifestations.

Other genetic discoveries in lupus research have come from studying mouse models of the disease. NIAMS-funded researchers transplanted a particular mutation of the coro1a gene into lupus-prone mice and discovered that this form

of the gene conferred lupus resistance on the mice. Identification of such new genes involved in lupus susceptibility may provide new targets for treatment. In a separate study, NIAMS investigators have identified transforming growth factor β (TGF- β) as a clinically important molecule in diagnosing and treating chronic kidney disease associated with lupus. This molecule may potentially serve as an important biomarker for the risk of fibrotic kidney disease that often occurs in lupus, and blocking it may prove to be a potentially effective treatment.

According to a study of children with lupus, NIAMS-funded investigators determined that children who are diagnosed with lupus before their 16th birthday often experience more severe disease activity and accrue more disease damage compared with adults with lupus. Further research on this finding may help to determine how children with lupus can be treated differently from adults, potentially reducing some of the damage from this disease.

Item

Marfan Syndrome – The Committee commends NIAMS for the leading role it has played in advancing basic research on Marfan syndrome. The Committee encourages NIAMS to strengthen its support for musculoskeletal orthopaedic research in this area and to partner with NHLBI and the Marfan patient community in support of NHLBI's pediatric heart network clinical trial on Marfan syndrome (p. 155).

Action taken or to be taken

Marfan syndrome is a heritable condition that affects the connective tissue. The primary purpose of connective tissue is to hold the body together and provide a framework for growth and development. In Marfan syndrome, the connective tissue is defective and does not act as it should. Because connective tissue is found throughout the body, Marfan syndrome can affect many body systems, including the skeleton, eyes, heart and blood vessels, nervous system, skin, and lungs. NIAMS welcomes highly meritorious applications relevant to the mission of the Institute, as well as collaborative partnerships with other NIH components in Marfan syndrome.

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. NHLBI's network provides an ideal structure to test new medical or surgical therapies in uncommon conditions, such as genetically-induced aortic aneurysms, which are commonly associated with Marfan syndrome.

NIAMS also participates in NHLBI's Genetically Triggered Thoracic Aortic Aneurysms and Other Cardiovascular Conditions (GENTAC): National Registry. The registry enables investigators to determine the best medical practices to advance the clinical management of genetic thoracic aortic aneurysms and other cardiovascular complications associated with connective tissue diseases such as Marfan syndrome.

Item

Musculoskeletal Conditions – The Committee notes that musculoskeletal conditions are among the most disabling and costly conditions suffered by Americans. These diseases affect over 107 million Americans, with females suffering a higher rate of occurrence than males. The Committee encourages NIAMS to focus research on women and musculoskeletal conditions, including research on gender differences (p. 155).

Action taken or to be taken

NIAMS supports a broad portfolio of research that investigates various musculoskeletal conditions. One of the most prevalent is osteoporosis, which is responsible for bone fracture in one out of every two women and one in four men over 50 in their lifetime. NIAMS has partnered with NIA to support two long-term epidemiologic studies of fracture risk in women (the Study of Osteoporotic Fractures, SOF) and men (the Osteoporotic Fractures in Men study, Mr. OS), which have provided information that can now be used to examine gender differences. Results from these investments have recently revealed that older people who suffer high-trauma fractures are likely to have low bone mineral density. This discovery provides evidence, that when someone aged 65 years or more appears at a doctor's office or hospital emergency department with a broken bone, that person should be screened for osteoporosis, even if the fracture occurred because of a highly traumatic injury that could hurt even a healthy young person. This altered approach could lead to simple changes to a person's lifestyle and diet that would prevent future fracture.

NIAMS, along with several other NIH components including the NIA, NIBIB, NIDCR, NCMHD, NCCAM, and ORWH, created the Osteoarthritis Initiative (OAI), a public-private partnership in the form of a multi-center, longitudinal, prospective observational study of knee osteoarthritis. For more information about OAI access the following link: http://www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative/. Osteoarthritis is by far the most common type of arthritis, and the percentage of people who have it grows higher with age. An estimated 27 million Americans age 25 and older have osteoarthritis. Before age 45, more men than women have osteoarthritis; after age 45, it is more common in women.

Injuries to the anterior cruciate ligament (ACL) are among those musculoskeletal conditions that show significant gender differences. This is a very common injury

in the United States and affects women who participate in high-risk sports, such as soccer and basketball, at a 4- to 6-fold greater rate than men. Due to its prevalence and dramatic gender disparity, ACL injury is of great interest to NIAMS-supported researchers. Recently, investigators discovered that the use of a protein scaffold in a dog model led to dramatic improvement in ACL repair, potentially opening the door for novel regenerative treatment options.

While the reasons for the increased risk of injury among women are multi-factorial, an instrument that could identify which women athletes are at increased risk of this injury has been lacking. NIAMS-supported researchers have recently filled this void by discovering that a small increase in knee laxity (looseness) significantly increased a woman's likelihood of suffering a debilitating ACL injury. If combined with other measures that also have been found to predict an increased risk of ACL injury, this finding could serve as a highly accurate and useful screening tool to identify high-risk athletes, especially young women, for targeted training to prevent these injuries.

Item

Osteoporosis – The Committee encourages NIAMS and NIA 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. Research is also needed to identify the parameters that lead to the better prediction, prevention and treatment of bone diseases. (p. 155)

Action taken or to be taken

Osteoporosis is a condition of low bone mineral density that affects 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.

Previous investments by the NIAMS have elucidated the pathophysiology of bone loss in diverse populations. Results from the Tobago Bone Health Study have shown that West African men have higher bone mineral density (BMD) than Caucasian men. Meanwhile, data from the Study of Osteoporotic Fractures in Men (Mr. OS) indicates that Asian men have lower BMD than Caucasian men, and that low BMD leads to bone fragility and higher risk of fracture. These observed differences could lead to more personalized preventative treatments of bone. Another study that investigated the proximal femur structure, across all ethnic groups, observed that African-American and Asian men over the age of 65 have femurs with greater thickness and BMD, which could possibly explain the lower hip fracture rates in these populations. Studies also continue on other groups including one focused on the Navajo Native American community.

Although clinicians often recognize osteoporosis as the cause of fractures resulting from a minor injury, those related to more substantial injury, such as a fall, are rarely attributed to underlying bone disease. However, NIAMS-supported researchers, using the results from two NIH-funded epidemiologic studies of fracture risk in women and men led by NIAMS and NIA – the Study of Osteoporotic Fractures (SOF) and Mr. OS – revealed that older people who suffer high-trauma fractures are likely to have low bone mineral density. This discovery provides evidence that, when someone aged 65 years or more appears at a doctor's office or hospital emergency department with a broken bone, that person should be screened for osteoporosis, even if the fracture occurred because of a highly traumatic injury that could hurt even a healthy young person.

Furthermore, in a separate study, NIAMS-supported researchers found that physical exercise by children, specifically jumping, results in increased skeletal growth. Since bone is responsive to mechanical loading, it has been assumed that physical activity and exercise contribute to achieving optimal bone mass during childhood and adolescence. It was found that the bone gains in children that result from 7 months of jumping exercises during regular physical education classes can be maintained for up to 8 years. This build-up of healthy bone is one of the best ways to combat the bone loss that is commonly faced later in life.

NIAMS has also supported research aimed at developing methods to predict fracture risk due to osteoporosis. Scientists have produced a method to simulate bone loss during and after perimenopause using microscopic image data on real human bone, and to relate the most significant decreases in bone strength to specific image markers. With continued advances in imaging technology, it may be possible in the near future to use this simulation technique to estimate bone strength and fracture risk more accurately.

Item

Scleroderma - The Committee is aware of emerging opportunities in scleroderma research and encourages NIAMS to partner with the scleroderma patient community in convening a state of the science conference in this important area. (p. 155)

Action taken or to be taken

Though it is often referred to as if it were a single disease, scleroderma is really a symptom of 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 growth. In other forms, however, the problem goes much deeper, affecting blood vessels and internal organs, such as the heart, lungs, and kidneys.

To provide researchers the opportunity to coordinate, exchange, and disseminate information on advances in scleroderma, NIAMS has supported several scientific

meetings in this area and will continue to do so through the NIH R13 grant mechanism (Support for Conferences and Scientific Meetings). This funding opportunity has been used by a wide variety of research communities for the development of symposia, seminars, conferences, workshops, and other formal meetings at which scientists can discuss ideas and insights on recent research.

For example, NIAMS has supported the International Workshop on Scleroderma Research, which took place August 2-6, 2008. The workshop focused on basic research related to the pathogenesis of scleroderma. Scientific sessions covered autoimmunity, genetics, gene expression, vascular injury, animal models, fibrosis, and matrix metabolism. Clinically-related areas such as novel therapeutics and the development of measures of disease were also covered. The workshop brought together investigators in scleroderma from throughout the world, along with prominent researchers in related disciplines.

Relevant research of note includes the NIAMS-funded National Family Registry for Scleroderma, which is collecting biological samples from patients and, when possible, their parents, so that genetic differences between patients and healthy individuals can be detected and potentially traced to a parent. Further research based on this registry may reveal genes that contribute to the development of scleroderma. The NIAMS also supports a Center of Research Translation (CORT) focused on scleroderma. Researchers at the center are studying the molecular basis of scleroderma to understand its underlying causes using functional genomics and gene networks. CORTs are designed to bring together basic and clinical researchers in a way that helps to translate basic discoveries into new drugs, treatments, and diagnostics.

NIAMS-funded researchers are also working to develop a composite response index (CRI) for patients with diffuse systemic sclerosis. This tool will capture information on organ involvement in scleroderma and patient response to treatment. Such an index is crucial in developing new treatments for this disease and evaluating the outcomes of clinical trials.

Senate Significant Items

Item

Arthritis - The Committee supports the establishment of a national data collection system to ensure that the safety and effectiveness of new arthritis treatments is understood and that they are applied in the most beneficial manner, especially in the case of childhood arthritis. The Committee also notes the strong need for a national network of cooperating clinical centers dedicated to the care and study of children with arthritis. (p. 109)

Action taken or to be taken

“Arthritis” refers to a group of diseases that cause pain, swelling, stiffness, and loss of motion in the joints. More generally its describes rheumatic diseases that

may affect the joints, but cause pain, swelling, and stiffness in other supporting structures of the body such as muscles, tendons, ligaments, and bones. Children can develop almost any type of arthritis that affects adults which are among the leading causes of disability in children. The NIAMS supports a wide-range of research that covers the spectrum, from basic research at the cellular and molecular levels, to clinical studies of new treatments.

The NIAMS contributes to efforts that track the safety and efficacy of care through its support of investigators who utilize existing research center networks. One of these networks is the Childhood Arthritis and Rheumatology Research Alliance (CARRA). CARRA is an organization of pediatric rheumatologists, who have formed a network of research centers across North America that work cooperatively on investigations in clinical research. The NIAMS supports several studies that use the CARRA network to explore possible treatments for childhood arthritis. For example, one study is examining the effectiveness of rilonacept in children with systemic juvenile idiopathic arthritis (SJIA). Rilonacept, a biologic medication, attaches to interleukin-1 (IL1), preventing it from attaching to cell receptors and causing inflammation. The purpose of this study is to determine whether a rilonacept regimen, initiated early in the course of disease, is more effective than a similar regimen initiated 3 weeks later in children and young adults with SJIA. Current standard treatments of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids do not completely control the disease in most patients. Rilonacept has shown promise as a drug that inhibits IL1, an important driver of inflammation.

In a clinical study supported by NIAMS and utilizing the CARRA network, investigators are researching the use of certain drugs for children with polyarticular JIA, a condition that affects five or more joints during the first six months of disease. Specifically, the work is centered on the safety and efficacy of methotrexate, a disease-modifying antirheumatic drug, in combination with etanercept, a biologic drug that blocks tumor necrosis factor alpha, which is involved in inflammation and prednisolone, a corticosteroid medication. Another NIAMS-funded study in the CARRA network investigates the use of rituximab in children with the inflammatory muscle diseases dermatomyositis and polymyositis. Rituximab has been shown to be effective in treating rheumatoid arthritis, and warrants further investigation for these other rheumatic conditions. Known as a monoclonal antibody, rituximab destroys both normal and abnormal B cells (a major component of the immune system) and is used to treat diseases characterized by having too many B cells, overactive B cells, or dysfunctional B cells.

The NIAMS also supports the Juvenile Rheumatoid Arthritis (JRA) Registry, which collects genetic information on sibling pairs affected by JRA (another term for JIA). The registry has collected DNA samples from over 1500 JRA patients and 4000 family members. Studying these patients provides an excellent

opportunity to uncover the genetic susceptibility factors for childhood arthritis, a first step in developing new targeted treatments for the disease.

Item
Fibromyalgia – The Committee is concerned by the lack of a sustained commitment to fibromyalgia-specific research at the NIAMS, and it strongly urges additional resources for this purpose. The Committee urges the Institute, in collaboration with the NINDS, to convene an international symposium to elucidate the state of the science with regard to fibromyalgia and to publish a consensus document within 1 year establishing a roadmap for future fibromyalgia research. In additions, it urges the NIAMS to establish a funded center with dedicated staffing to serve as a nexus for research on fibromyalgia and related disorders that will explore the broad spectrum of neurotransmitter abnormalities and other potential problems, including sleep disturbances, abnormal cervical anatomy and genetic factors, that might contribute to symptom development and expression. The Committee also encourages the Institute to support basic research into animal models of the disorder. Finally, the Committee urges the NIAMS to collaborate with the NIDDK in support of its Multi-disciplinary Approach to the Study of Chronic Pelvic Pain [MAPP] initiative. (p.109)

Action taken or to be taken
Please refer to page 147 of this document for NIAMS' response to the significant item on fibromyalgia.

Item
Lupus - The Committee continues to strongly urge the Institute to greatly expand and intensify genetic, clinical, and basic research and related activities with respect to lupus, with particular focus on understanding the underlying mechanisms of disease, gene-gene and gene-environmental interactions, epidemiological research, lupus and kidney disease, biomarkers, pediatric research, environmental factors, and factors related to the health disparities and comorbidities associated with lupus. (p. 109)

Action taken or to be taken
Please refer to page 142 of this document for NIAMS' response to the significant item on lupus.

Item
Marfan Syndrome – The Committee encourages the NIAMS to expand its support for musculoskeletal/ orthopedic research in this area and to partner with the NHLBI and the Marfan patient community in support of NHLBI's Pediatric Heart Network clinical trial on Marfan syndrome. (p. 109)

Action taken or to be taken

Please refer to page 143 of this document for NIAMS' response to the significant item on Marfan syndrome.

Item
Osteoporosis – The Committee urges the NIAMS and NIA 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. Research is also needed to identify the parameters that lead to the better prediction, prevention and treatment of bone diseases. (p. 109)

Action taken or to be taken
Please refer to page 145 of this document for NIAMS' response to the significant item on osteoporosis.

Item
Scleroderma - The Committee is aware of emerging opportunities in scleroderma research and encourages the Institute to partner with the scleroderma patient community in convening a state of the science conference in this important area. (p. 110)

Action taken or to be taken
Please refer to page 146 of this document for NIAMS' response to the significant item on scleroderma.

Item
Temporomandibular Joint Disorders [TMJDs] – The Committee calls on the NIAMS to work with the NIDCR and NIBIB to develop a research team involving bioengineers, computer scientists, basic and clinical scientists to study the jaw anatomy, physiology and the complex neural, endocrine and immune systems interactions that orchestrate jaw function and trigger pathology of the jaw joint. The Institutes should integrate the findings from interdisciplinary studies of the structure, mechanical function, metabolism, and blood flow of bone, joints, and muscles with studies of central and peripheral neural pathways, and the endocrine, paracrine, and cytokine factors that impact upon these craniofacial structures, as a means to understanding the underlying causes of pain and dysfunction. (p. 110)

Action taken or to be taken
Temporomandibular joint disorders (TMJDs) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. Pain in the chewing muscles and/or jaw joint is the most common symptom; others include jaw muscle stiffness; limited movement or locking of the jaw; painful clicking, popping or grating in the jaw joint when opening or closing the mouth; and a change in the way the upper and lower teeth fit together.

Along with NIDCR, NIBIB, and others, the NIAMS recently co-sponsored a meeting of basic and clinical scientists, physicians, dentists and other health professionals, along with patients and patient advocates, to determine if there are common roots and physiological pathways between TMJDs and other pain-related conditions. The goal of the meeting was to stimulate cross-collaborative studies and to identify novel targets for diagnosis and therapy.

Additionally, the effectiveness of chronic pain prevention, identification, and management, such as that stemming from TMJDs, was the topic of a session at the 2008 NIAMS Scientific Retreat. The aim of the session was to determine how the NIAMS could more effectively study and contribute toward treatment options for patients who suffer from chronic musculoskeletal pain. The session intended to position the NIAMS to capitalize on and contribute to what is known about how to prevent, identify, and manage chronic pain.

The scale and complexity of today's biomedical research problems demand that scientists move beyond the confines of their individual disciplines and explore new organizational models for team science. Integrating different disciplines holds the promise of opening up scientific avenues of inquiry and, in the process, may result in new disciplines with which to tackle increasingly complex questions. To promote this approach, the NIAMS recently launched its new Building Interdisciplinary Research Teams (BIRT) program, which provides NIAMS grantees with administrative supplements for the establishment of collaborations that are highly innovative and are of potentially high impact. Specific areas of interest include soft tissue biology and imaging technologies. Investigators studying TMJDs are encouraged to consider the use of this new program in order to establish research partnerships which could lead to the development of new diagnostic and treatment techniques.

National Institute on Deafness and Other Communication Disorders (NIDCD)

House Significant Items

Item

Tinnitus - The Committee continues to remain interested in research on tinnitus, particularly in light of continued large increases in this condition among returning military personnel. Because tinnitus affects people of all ages, including children and the elderly, the Committee strongly encourages NIDCD to continue to increase collaborative research efforts between NIH, the Department of Defense, and the Department of Veterans Affairs to support a multi-disciplinary research approach that promotes accurate diagnosis and treatment to cure tinnitus. (p. 155)

Action taken or to be taken

Individuals with tinnitus experience the sensation of a ringing, roaring, or buzzing sound. Although tinnitus can be associated with noise exposure and hearing impairment, chronic disability due to tinnitus appears to have similarities to chronic pain as well as phantom limb pain. Because the causes for these syndromes are not fully understood and current treatments for tinnitus typically do not offer a cure, research in this area remains a high program priority for NIDCD.

Based on recommendations from Tinnitus Research Workshop in 2005 also sponsored by NIH Office of Dietary Supplements, NIDCD published a Request for Applications (RFA) in 2007 to further support research on tinnitus. It specified a collaborative team approach consisting of at least two distinct disciplines focused on issues relevant to tinnitus.

As a result of the funds set aside for this special funding opportunity announcement, NIDCD has funded one new grant in FY 2008 and plans are underway to support a second application. These awards will support investigations into the brain processes responsible for chronic and disabling tinnitus through the use of animal models and sophisticated imaging technology. Treating individuals with tinnitus would be greatly assisted by identifying pathological neural processes in specific brain areas and the ability to use existing techniques or developing new therapeutic interventions to resolve or ameliorate those pathological processes. Animal models provide the ability to perform invasive studies, gather brain tissue samples that precisely determine the extent of specific lesions at different points in the pathway for auditory perception, and assess the strengths and weaknesses of novel therapeutic interventions.

Basic and clinical research is underway to develop medical technology such as devices that deliver therapeutic agents into the cochlea itself, as well as neural prostheses that could be used to directly modify the perceptual result from

dysfunctional neurons activity. NIDCD will continue to work within the NIH Blueprint for Neuroscience Research consortium of NIH institutes and centers to better understand the overall issues involved in chronic pain to ensure our mission areas benefit from advances in this field. Finally, NIDCD will continue looking for opportunities to collaborate on this research area through activities within the Department of Veterans Affairs and the Department of Defense.

Senate Significant Items

Item

Central Nervous System Plasticity - The Committee urges the NIDCD to promote research to discover the cellular and genetic mechanisms that are responsible for central nervous system plasticity— how hearing loss changes the central nervous system—and how these alterations constrain auditory performance. Analysis at the level of synaptic connections through studies of perceptual learning is recommended. (p. 110)

Action taken or to be taken

The NIDCD is actively supporting research to study the cellular, genetic, and structural mechanisms involved in neural plasticity, which are fundamental to both learning and behavioral rehabilitation. For example, NIDCD-supported scientists are using fluorescent imaging technology to observe brain activity in humans, in order to understand brain plasticity and the related concept of critical periods for learning. Such studies are comparing differences in brain structures related to hearing and reading between deaf and hearing individuals, and differences in speech perception between native and late learners of English language, which relate directly to plasticity and to critical periods for learning.

Understanding critical periods of brain plasticity are also important for recipients of cochlear implants. A study using both rodents and humans will test the hypothesis that the ability to detect differences in timing between two closely spaced sounds improves during the first 30 days of cochlear implant stimulation, thus establishing a critical period. The results of this study will help hearing health specialists optimize rehabilitation for individuals who have received cochlear implants. NIDCD also continues to monitor progress from two research contracts intended to improve the quality of auditory perception derived from a multichannel cochlear implant. The scientists are developing techniques to support neural survival and function based on electrical stimulation and/or drug administration. They are required to identify neural properties that support perception from the cochlear implant in humans, develop treatments that improve function, and perform behavioral studies to confirm the functional impact of the treatment.

NIDCD is also supporting research on plasticity of the central auditory system within its intramural research program. One laboratory is investigating how neural connections and plasticity in the auditory system change as a result of congenital and early-onset deafness. For individuals with normal hearing,

sensory stimulation plays an important role in development of synaptic transmission. This research is directed towards understanding how synaptic transmission is affected by hearing loss and whether or not there is a critical period in development during which auditory experience is required for normal development of synaptic transmission. The data from these studies will help guide treatment strategies, such as determining the optimal time for cochlear implantation in deaf children. NIDCD intramural scientists are also investigating plasticity in the human central auditory system using various imaging techniques to visualize neuronal activity in the brain. Together, this research will address the molecular, cellular, and systems level components of neuronal plasticity that we expect to lead to a better understanding of plasticity in the human nervous system.

Item

Environmentally Induced Hearing Loss - The Committee urges increased efforts by the NIDCD to raise awareness of the threats to the auditory system posed by environmental noise. Risks to hearing in the workplace, and through recreational activities and by loud consumer products should be publicized. The Committee urges the dissemination of information emphasizing the dangers to hearing from these sources, as well as protective measures, through such means as the Wise Ears! Campaign, the NIDCD website and publications. Research studies to increase understanding and treatment of hearing loss and central auditory processing disorders resulting from noise are also recommended. The Committee also understands the potentially deleterious effects of environmental chemicals in water and air, like lead, mercury and carbon monoxide, on the inner ear. The NIDCD is urged to support studies in this area, especially of chemicals' impact on hearing during prenatal and early postnatal development. (p. 110-111)

Action taken or to be taken

In 1999, the NIDCD and the National Institute for Occupational Safety and Health launched WISE EARS! a national campaign to prevent noise-induced hearing loss (NIHL) in the general public and in people who work in noisy environments. The campaign's objectives were to educate the public about the risks of NIHL and to motivate individuals and organizations to increase awareness about preventing NIHL. Central to the effort was the development and distribution of free educational materials, available online and through a toll-free information clearinghouse.

NIDCD is continuing its education efforts and now refocusing a new campaign to reach children ages eight to 12 (the "tweens"). This new national public education campaign, called "*It's a Noisy Planet. Protect Their Hearing*" is designed to increase awareness among parents of tweens about the causes and prevention of NIHL. With this information, parents and other adults can encourage children to adopt healthy hearing habits before and during the time that they develop listening, leisure, and working habits. To find out more about the Noisy Planet campaign, visit www.noisyplanet.nidcd.nih.gov.

NIDCD also supports research to increase understanding and treatment of hearing loss caused by chemicals that damage the inner ear. NIDCD-supported scientists have developed a research method that relies on a zebrafish's lateral line—the faint line running down each side of a fish that enables it to sense its surroundings—to quickly screen for genes and chemical compounds that make the zebrafish susceptible to hearing loss. The fish's lateral line contains sensory cells that are functionally similar to those found in the inner ear, except these are on the surface of the fish's body, making them more easily accessible. When people are exposed to some antibiotics and chemotherapy agents, the sensory structures in the inner ear, called hair cells, can be irreversibly damaged, resulting in hearing loss and balance problems. Such medications are called ototoxic. People vary widely in their susceptibility to these agents as well as to damage caused by other chemical agents (such as environmental pollutants), loud sounds and aging. Using the new zebrafish screening model, researchers can very efficiently analyze the sensory structures under different conditions to find out what is likely to cause damage to these structures and, conversely, what can protect them from damage. The scientists suggest that their research technique, which combines chemical screening with traditional genetic approaches, offers a fast and efficient way to identify potential drugs and drug targets that may one day provide therapies for people with hearing loss and balance disorders.

Item

Hearing Devices - While research into regeneration and stem cell replacement promises beneficial discoveries in the future, the Committee recognizes that hearing aids and other assistive devices, such as cochlear prostheses, provide an important means to restore hearing in the present to individuals with deafness and other communication disorders. It recommends that the NIDCD support research to develop, improve and lower the cost of hearing aids, as well as support studies to allow the cochlear implant to benefit a greater number of individuals with profound hearing impairment. In addition, the Committee urges development of new central auditory prostheses that will open the door to hearing for many who cannot be helped by cochlear prostheses. (p. 111)

Action taken or to be taken

Approximately 36 million (17 percent) American adults have some degree of hearing loss. This number is expected to increase as the baby-boomer population ages because hearing loss and aging are related. In 2030, nearly one in five U.S. residents is expected to be 65 and older. This age group is projected to increase to 88.5 million in 2050, which is more than double the number of adults over age 65 in 2008 (38.7 million). Yet, approximately 20 percent of individuals who could benefit from a hearing aid use one. There are 1.2 million hearing-impaired children and 23 million hearing-impaired adults in the U.S. who do not use hearing aids, and the high cost of the device is consistently cited as a

barrier to obtaining one. NIDCD is exploring obstacles and opportunities to make hearing aids more affordable.

Scientists continue to explore ways to improve hearing aid technology so a wearer can better understand speech in a noisy background, such as a crowded room. An NIDCD-supported scientist is using technology based on the ears of a parasitic fly to improve hearing aids. The fly's ears are able to rapidly pinpoint the location from which the sound of a potential host—a cricket—is coming, even in a noisy environment. The intriguing mechanism that enables this fly to accomplish this feat has provided a model for scientists and engineers to use in developing miniature directional microphones for hearing aids that can better focus on speech in a single conversation, even when surrounded by other voices.

The cochlear implant is the only sensory neural prosthesis in widespread clinical use today. Some individuals with severe to profound hearing loss are receiving two cochlear implants, one for each ear. Research is demonstrating that these cochlear implant users are significantly better at localizing sounds and hearing speech in a noisy room, when compared to individuals with a single implant. Advanced signal processing techniques are required to fully take advantage of these capabilities.

A significant number of basic research studies to develop more effective central auditory prostheses are underway to address gaps in our understanding of the code for speech in the many parallel neural pathways activated by sound. NIDCD supports research that seeks to understand the essential features of the natural neural code for speech and hearing at sites along the neural pathway from the cochlea to the brain. For example, NIDCD is supporting two projects specifically to accelerate the pace of development for novel neural prostheses to provide hearing to subjects that cannot be helped by cochlear prostheses. An interagency agreement with the Department of Energy (DoE) was awarded to support development of advanced fabrication techniques and produce electrode arrays suitable for tests of novel neural prosthesis designs in chronic animal studies. This type of long-term study would be used to address both safety and efficacy concerns before human studies can be attempted and builds upon technology developed for the artificial retina project supported by the DoE. Another contract project is underway to provide open source software which performs cochlear implant signal processing algorithms. This effort will provide a suite of customizable software that can be used by the research community for use in both animal and clinical studies seeking to encode speech stimuli for new central auditory prostheses.

Item

Inner Ear Hair Cell Regeneration - The Committee recognizes that restoration of hearing through regeneration biology has achieved scientific proof of concept and encourages further research to develop a human application. The NIDCD should build on promising new approaches in sensory cell regeneration and reparation. The Committee realizes that while studies of inner ear neuron loss indicate that residual hearing can be preserved with partial retention of these cells, more research is needed to elucidate the extent to which cell replacement would correlate with improved hearing. (p. 111)

Action taken or to be taken:
NIDCD intramural scientists have made remarkable progress in understanding hair cell structure, development and function. They have determined some of the genes and growth factor gradients that determine the fate and orientation of these cells within the developing cochlea. In addition, they have identified a number of genes whose mutation results in hearing impairment in human populations, providing important clues about the molecular mechanisms that underlie hair cell function. Two such genes, *protocadherin 15* and *cadherin 23*, encode proteins that interact to form the tip link structure critical for conversion of mechanical deflection of the stereocilia by sound into electrical impulses transmitted to the central nervous system. Stereocilia, in their staircase pattern, are key cellular organelles located in the inner ear that are responsible for hearing and balance. Although stereocilia are exquisitely sensitive to mechanical vibration and easily damaged by over-stimulation, to prevent hearing loss, they must maintain themselves to properly function for an entire lifetime. A third gene, *myosin 15*, discovered about ten years ago in NIDCD's intramural laboratories, appears to be critical for maintenance of the stereocilia, since mice with defective *myosin 15* genes have greatly shortened stereocilia. In another remarkable study, NIDCD intramural scientists showed that the stereocilia are maintained by rapid turnover of the bundle of actin filaments, with actin protein added rapidly at the base of the stereocilia and removed at the top of the bundle.

NIDCD also supports academic researchers outside of NIH (extramural) who are working to develop new approaches in sensory cell repair and regeneration. For example, NIDCD supported a grant to a scientist at the Oregon Hearing Research Center submitted in response to a funding opportunity announcement (FOA) entitled "Cell Lineage and Developmental Studies in Hearing and Balance." The scientist's latest publication reports the use of gene transfer in the mouse inner ear to generate extra hair cells, which seem to function. These extra hair cells make appropriate connections with neurons, express markers of active synapses, and are capable of conducting nerve impulses. This promising data brings us one step closer to developing a human application for regenerating inner ear hair cells.

NIDCD continues to encourage further research into how cell replacement might improve human hearing. In 2008, NIDCD issued a FOA titled "Integrative Systems Biology Approaches to Auditory Hair Cell Regeneration," which invites

scientists to submit grant proposals to study methods to restore lost auditory hair cells and their sensory function following damage to the inner ear from a variety of factors including disease, aminoglycosides, noise and aging.

Item
Presbycusis - The Committee encourages continuing studies of the declining stria vascularis metabolism, as well as investigations of the central mechanisms of presbycusis. (p. 111)

Action taken or to be taken
The stria vascularis is a highly vascularized patch of tissue within the cochlea of the inner ear that is involved in maintaining auditory hair cell function and inner ear metabolism. Conditions such as presbycusis may interfere with normal inner ear metabolism and can cause hearing loss. NIDCD intramural scientists are actively studying presbycusis by identifying genes in humans and animals models that lead to age-related hearing loss. Although progressive hearing loss associated with aging is a common condition afflicting approximately one third of the elderly population, the genetic risk factors that cause this variable and quantitative disorder have not been thoroughly explored. For example, there is one rare type of age-related, delayed-onset, progressive hearing loss caused by mutations of the *EYA4* gene. In most cases, mutations in this gene also cause cardiomyopathy. NIDCD intramural scientists, in collaboration with other scientists at NIH, identified a large family with presbycusis, but no cardiomyopathy, showing a distinct form of these disorders. NIDCD intramural scientists have also identified several strains of mice with presbycusis and are in the process of identifying the genes that cause this condition in mice. This information can then be used to determine if the same genes are responsible for causing presbycusis in humans.

NIDCD is initiating a new exploratory/developmental phased Innovation for improving intervention possibilities for communication disorders. It will specifically encourage research grants clarifying the role of the inner ear homeostasis, including the role of the vascular system in presbycusis and other forms of hearing loss. NIDCD-supported scientists are also using neuroimaging and evoked potential studies to examine the physical structure and metabolic function of the nervous system that are hypothesized to contribute to age-related declines in speech recognition in older adults and epidemiological studies to evaluate the contribution of cardiovascular disease to sensorineural hearing loss.

In addition, the NIDCD, (occasionally in conjunction with the National Institute on Aging) supports research projects to further our understanding of the role of the stria vascularis in hearing and in presbycusis, as well as central mechanisms of presbycusis. There is a large body of evidence citing the importance of spiral ligament fibrocytes in establishing and maintaining inner ear metabolism. Using mouse models, scientists are determining the potential role of human hematopoietic stem cells in the maintenance of these non-sensory cells in the

inner ear and characterizing the effects of aging and cochlear injury on this process. Other scientists seek to define the functions of tight junctions in the stria vascularis and to understand whether abnormal basement membranes in strial tissue results in a deterioration of metabolic homeostasis degrading cochlear function. The role of oxidative stress in age-related hearing loss and its impact on sensory cells and the stria vascularis is also under investigation. Further, blood flow to the cochlea is essential for normal hearing, and dysfunctions in the cochlear blood supply can cause serious hearing disorders, including sudden sensorineural hearing loss, presbycusis, noise-induced hearing loss and tinnitus. Research studying cochlear blood flow is ongoing and may shed light on the cause of presbycusis.

Item

Psychosocial Interventions - The Committee encourages continued research into behavioral and cognitive-behavioral studies validating, refining, and comparing approaches to the treatment of persons with autism and autism spectrum disorders and their families, as well as studies that analyze and define the critical features of effective interventions and the development of innovative methodologies and outcome measures. (p. 111)

Action taken or to be taken

One of the core symptoms of Autism Spectrum Disorder (ASD) is language and communication difficulties. Currently, NIDCD supports a number of research studies which are exploring the basis for these difficulties, and investigating interventions which can help individuals with ASD develop improved communication skills. A notable question in assessing language progress as a function of treatment has been the lack of consensus on the spoken language benchmarks and which measures of expressive language development were most appropriate and effective for young children with ASD. In response, NIDCD assembled a group of scientists with expertise in language disorders and language acquisition in young children with ASD. In 18 months the group achieved consensus on these aims: 1) To offer a set of recommended measures that can be used for evaluating the efficacy of interventions that target spoken expressive language acquisition in children with ASD as part of treatment research studies or for use in applied settings and 2) To propose and define a common terminology for describing levels of spoken expressive language ability in children with ASD and set benchmarks for determining a child's language level in order to establish a framework for comparing outcome measures following different intervention. Publication of these recommendations is forthcoming in a peer-reviewed journal and will have an impact on basic scientist physicians.

NIDCD participates with of other NIH institutes on the Autism Coordinating Committee (ACC), to enhance the quality, pace and coordination of efforts at the NIH to find a cure for autism. Several initiatives sponsored by NIH ACC have successfully solicited research projects focused on communication and autism. Specifically, NIDCD-supported scientists are documenting developmental

patterns of language development and behavior in children with ASD, developing language assessment measures, investigating brain-behavior aspects of communication and autism, and creating and expanding intervention strategies. NIDCD continues its strong research commitment to improving the language, and thus the lives, of children and families with autism.

Item

Tinnitus - The Committee continues to remain interested in research on tinnitus, particularly in light of continued large increases in this condition among returning military personnel. Because tinnitus affects people of all ages, including children and the elderly, the Committee strongly encourages NIDCD to continue to increase collaborative research efforts between NIH, the Department of Defense, and the Department of Veterans Affairs to support a multi-disciplinary research approach that promotes accurate diagnosis and treatment to cure tinnitus. (p. 111)

Action taken or to be taken

Please refer to NIDCD's response on page 152 in the House Significant Items.

National Institute of Mental Health (NIMH)

House Significant Items

Item

Borderline Personality Disorder - The Committee encourages NIMH to expand its research on borderline personality disorder, including its genetic basis and the development of early detection and effective treatments (p. 158).

Action taken or to be taken

Borderline Personality Disorder (BPD) is a serious mental illness characterized by pervasive instability in moods, interpersonal relationships, self-image, and behavior. NIMH is committed to supporting research on all aspects of this disorder, including discovering its potential causes and genetic risks; understanding its developmental trajectory; and developing improved diagnostic tools and effective interventions. Several large twin studies have revealed a significant genetic contribution to BPD, stimulating interest in the field to determine the specific genes that may be involved. As a result, a number of NIMH-funded investigators have added genetic analysis as a component of their BPD studies. One project is the first and only prospective study of the relationship between borderline and other personality disorder features from age six to adulthood. The investigators have found that personality disorder features in children present as much if not greater risk for adult disorders and impairment.

Two NIMH-supported longitudinal studies on the course of BPD indicate it may not be an enduring disorder. These studies found an unexpected high rate of remission from the disorder, and when remission occurs, relapse is rare. However, impairments in functioning often persist after remission. Another study identified brain activity that may be fundamental to the interpersonal deficits that are characteristic of the disorder, which may be the basis for the impaired social functioning that often remains even as BPD remits. Other supported neuroscience research provides insights on emotional instability, one of the hallmarks of BPD. Significant advances have been made to predict self-harming behaviors highly prevalent in BPD. Together with NIDA, NIMH supported a study to develop a treatment called dialectical behavior therapy that is effective in reducing self harming behavior. Clinical investigators, encouraged by positive results from evaluations of treatment with adults, are examining the validity of the diagnosis of BPD and the effectiveness of treatment in adolescents.
In other NIMH-funded treatment research, group psychotherapy for BPD patients and family members was effective; this is being adopted in the United States and abroad.

Over the past decade, NIMH has entered into partnerships with private entities to promote BPD research, and to disseminate significant research findings. The Institute cosponsored a series of meetings to increase scientific interest and engagement in BPD research.

Item

Teen Suicidal behavior - The Committee is aware that a recent study funded by NIMH found that depressed teens who had not responded sufficient to the first antidepressant medication they were prescribed subsequently improved when they were switched to a different antidepressant medication, coupled with psychotherapy. The Committee encourages NIMH to strengthen its support for evidence-based behavioral interventions to reduce the burden of suicidal behavior (p. 158).

Action taken or to be taken

NIMH supports a range of research on suicidal behavior in youth in order to define the risk and protective factors for which interventions can be developed, as well as to refine treatment strategies for youth who have exhibited suicidal behavior. For example, NIMH-funded research has shown that parental history of suicide attempts is a significant predictor for suicide attempts in offspring and is associated with attempts occurring at a younger age. In addition, impulsive aggression, early-onset mood disorders, and a parental history of childhood sexual abuse are significant predictors of suicide attempts in youth. Understanding these risk factors is essential for knowing when to intervene to preempt suicidal behavior.

Depression is also a major risk factor for suicide. According to the recently completed Treatment of SSRI-resistant Depression in Adolescents (TORDIA) trial, teens with difficult-to-treat depression who do not respond to a first antidepressant medication are more likely to get well if they switch to another antidepressant medication and add psychotherapy rather than just switching to another antidepressant. Another study, Treatment for Adolescent Suicide Attempters (TASA), is investigating the use of antidepressant medications, cognitive-behavioral therapy (CBT), or both to treat adolescents who have attempted suicide. For this study, CBT was modified and adapted to the clinical needs of these at-risk adolescents. The study data are being analyzed and results are forthcoming.

NIMH is supporting research to determine the effectiveness of school-based suicide prevention efforts. For example, a recent NIMH-funded study tested the effectiveness of gatekeeper training across 32 middle schools and high schools. This training instructed administrative, health/social service, and support staff on how to recognize and talk to students who may be at risk for suicide and refer them to a service provider. As a result of the training intervention, staff had increased knowledge of risk factors and self-assessed appraisal of being able to refer youth. However, the actual referral of youth increased only slightly, and referrals varied based on the position of the school staff member involved. While teachers improved in referral skills, support staff did not increase their number of referrals. Another challenge was that youth in the intervention schools reported they would rather seek help from a peer than an adult. These findings suggest

that school-based suicide prevention programs need to consider carefully school staff capabilities and also include peer interventions.

Senate Significant Items

Item

Behavioral Research - The Committee urges the NIMH to put a greater emphasis on behavioral research in accordance with the first objective of its preliminary strategic plan, to ''promote discovery in the brain and behavioral sciences.'' In particular, the Committee urges a greater focus on the study of personality and social psychology, and basic animal behavior. In the area of HIV/AIDS, the Committee notes that behavioral research aimed at reducing the likelihood of HIV infection should include structural, environmental, and socio-economic variables to ensure that research based interventions can be evaluated as appropriate for racial and ethnic minority populations (p. 114).

Action taken or to be taken

Behavioral science research provides fundamental contributions towards the fulfillment of NIMH's mission to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery and cure. As described in its recent Strategic Plan, NIMH must ensure that the full array of novel scientific perspectives are used to further discovery in the evolving science of brain, behavior, and experience. The Plan describes four objectives in support of this mission: 1. Promote discovery in the brain and behavioral sciences to fuel research on the causes of mental disorders; 2. Chart mental illness trajectories to determine when, where, and how to intervene; 3. Develop new and better interventions that incorporate the diverse needs and circumstances of people with mental illnesses; and, 4. Strengthen the public health impact of NIMH-supported research.

In pursuit of these objectives, the Institute supports and promotes behavioral science research in a number of different areas. For example, NIMH continues its efforts to build upon findings in social psychology and integrate them into the multidisciplinary field of social cognitive neuroscience. The study of personality is included in many projects, including those that seek to identify people most at risk for developing mental illnesses. And basic animal behavior studies are used to inform any number of areas, such as models of the effects of early life stress.

NIMH supports a number of behavioral research studies aimed at reducing the likelihood of HIV infection that are responsive to trends in the epidemic. As a result, a substantial portion of the HIV/AIDS prevention research portfolio is devoted to understanding and devising innovative methods for intervening among those men and women at highest risk of contracting HIV. Approximately 70% of these grants are focused on ethnic minorities. This includes research on: socio-cultural and structural determinants of health disparities; devising new

research models, methods, and measures to accurately assess HIV risk behavior in these communities, and the development and testing of innovative structural and behavioral interventions in racial and ethnic minority communities to reduce HIV transmission. An example of one such study includes a multi-site trial in Atlanta, Philadelphia, New York, and Los Angeles to prevent STD and HIV transmission in heterosexual African-American couples where one individual is HIV-positive and the other is HIV-negative. Another involves the development and evaluation of an Internet-based HIV prevention intervention for young African-American students at historically black colleges in North Carolina.

Item

Minority Training - The Committee is disappointed to learn that the NIMH intends to reduce funding for its diversity training programs at a time when reducing health disparities for vulnerable and underserved populations should be a high priority. The Committee understands that a National Advisory Mental Health Council workgroup is studying the issue, and it requests to be notified when the group's report is completed. (p. 115)

Action taken or to be taken

Training the next generation of investigators, including those from a diversity of backgrounds, such as new minority investigators, continues to be a high priority for the NIMH. NIMH supports research training programs, including diversity training programs. NIMH continues to strike a strategic balance between building the pipeline of potential new investigators through research training and maintaining a viable pay line that will allow newly independent researchers to successfully compete for research project grants.

NIMH currently supports a number of programs specifically designed to increase the diversity of the mental health research workforce. For example, NIMH continues to promote diversity through the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research, the Mental Health Dissertation Research Grants to Increase Diversity, and the NIH Research Supplements to Promote Diversity in Health-Related Research program. NIMH also supports the Career Opportunities in Research Education and Training Honors Undergraduate Research Training Program, which provides institutional research training support for undergraduate minority students and others in scientific disciplines related to mental health. NIMH also supports an institutional training program titled: Institutional Research Training Programs: Increasing Diversity. The objective of the program is to support national or regional research training programs that will recruit, train, and retain pre- and/or postdoctoral trainees from underrepresented groups conducting research in areas relevant to NIMH.

In order to focus and enhance research training priorities, the National Advisory Mental Health Council (NAMHC) recently convened a workgroup on research training. The workgroup advised the NAMHC on NIMH's investment in research

training and provided strategic recommendations about how the Institute could better achieve its training goals, including diversity research training. Within the context of diversity research training, the workgroup made a number of specific recommendations describing ways in which NIMH could enhance the recruitment, training, and retention of trainees from diverse populations, as well as other recommendations encouraging NIMH to modify its approach regarding how it administers some of the Institute's long-standing diversity training programs. A full report of the NAMHC workgroup proceedings is available on the NIMH website at http://www.nimh.nih.gov/about/advisory-boards-and-groups/namhc/reports/investing-in-the-future.pdf.

Item

Older Adults - For the past several years, the Committee has recommended that the NIMH increase the amount of research grant funding devoted to older adults over the age of 65. Nevertheless, that funding has decreased significantly (both in real dollars and as a percentage of the total NIMH budget) at a time when the number of Americans over age 65 is increasing. The Committee strongly urges the NIMH to reverse that trend. The Committee also urges the Director of NIH, through the DCPASI, to examine the NIH's commitment to the treatment of late-life mental disorders and to identify potential areas of collaboration among the NIMH, NIA, and NINDS. Finally, the Committee urges the NIMH to develop additional outreach programs to stimulate growth in this field, both in terms of the number of research grant applications in aging as well as the number of researchers focused on aging and mental health. (p. 115)

Action taken or to be taken

NIMH invests significantly in geriatric mental health research and is committed to the continued growth of this research portfolio. NIMH-supported investigators are studying a diversity of topics in aging research, including projects to understand brain mechanisms that may contribute to late-life mental disorders; projects to improve diagnosis and treatment; studies to identify risk factors, with the ultimate goal of preempting illness; and clinical trials that evaluate how treatments affect real-world functioning.

In 2004, NIMH established a new Geriatrics Research Branch as a focal point for much of its clinical research on issues of aging. This branch supports programs of research, research training, and resource development in the causes and pathophysiology of mental disorders of late life, the prevention of these disorders and their consequences, and the treatment and recovery of persons with these disorders. To further strengthen and expand its translational neuroscience program, the Branch conducted a portfolio review and analysis in 2007 and 2008. For more information about Branch programs access the following link: http://www.nimh.nih.gov/about/organization/datr/geriatrics-research-branch/index.shtml

Through trans-NIH initiatives and funding opportunity announcements (FOAs), NIMH supports investigator-initiated grants, research centers, and multi-site clinical trials focused on geriatric mental health. These efforts are often done in collaboration with other NIH Institutes that support aging-related research. In FY 2007, NIMH reissued two Program Announcements (PAs) entitled "Clinical Research in Mental Illnesses in Older Adults" (http://grants.nih.gov/grants/guide/pa-files/PA-07-163.html), and "Pathophysiology and Treatment Response in Late-Life Mood and Anxiety Disorders" (http://grants.nih.gov/grants/guide/pa-files/PA-07-077.html). NIMH also cosponsors several relevant FOAs with other ICs, such as "Cost Effective Health Promotion Interventions/Programs for Older Workers" (NIA, NIMH); "Angiogenesis in the Nervous System in Health and Disease" (NINDS, NIMH, NIA, NEI, NCI); "Grants for Alzheimer's Disease Drug Discovery" (NIA, NIMH, NINDS); and "Biomarkers for Older Controls at Risk for Dementia (BIOCARD) Study Extension" (NIA, NIMH).

NIMH continues efforts to expand the pipeline of future generations of scientists in the field of mental health and aging research through support of institutional research training programs, pre-and postdoctoral individual fellowships, mentored career development awards for junior investigators, and research education grants. For example, in FY 2007, NIMH supported a number of institutional training programs focused on late life mental disorders, geriatric mental health services, and psychiatric-medical comorbidity in aging. Career award recipients are also investigating a diversity of topics, including interventions to prevent post-stroke depression; diagnosis and treatment of depression in Parkinson's disease; antidepressant adherence in late life depression; intervention for older adults with bipolar disorder; and prevention of psychiatric morbidity in Alzheimer's disease caregivers.

Item

Postpartum Depression - The Committee urges the NIMH to develop a research plan for postpartum depression and psychosis; expand basic research on the etiology and causes of postpartum conditions; expand epidemiological studies to address the frequency and natural history of postpartum conditions and the differences among racial and ethnic groups with respect to such conditions; expand the development of improved screening and diagnostic techniques; and increase clinical research for the development and evaluation of new treatments. (p. 115)

Action taken or to be taken

NIMH continues to support research on postpartum depression and psychosis through the program announcement (PA), "Women's Mental Health in Pregnancy and the Postpartum Period." This PA fosters research on perinatal mood disorders (psychotic and nonpsychotic) in four areas: clinical course, epidemiology, and risk factors; basic and clinical neuroscience; interventions; and services. In addition, the PA encourages studies exploring the effects of

current or lifetime drug abuse, including treatment status and comorbid conditions; the onset and course of mental disorders during the perinatal period; and health care disparities among different racial and ethnic groups.

NIMH currently supports extramural and intramural research projects on the causes of postpartum depression, including the genetic risk for developing the disorder; differences in neurotransmitter systems in women with postpartum depression compared with those without the disorder; and the involvement of factors such as reproductive hormones and proinflammatory cytokines (signaling proteins that act as intercellular mediators of the immune response). The NIMH Intramural Research Program supports a study that is following women during the postpartum period to assess whether the onset of depression is associated with a change in reproductive hormone levels. A companion study will determine whether estradiol administration can relieve symptoms of postpartum depression. In addition to studies examining the causes of postpartum depression, NIMH supports research on screening for and the prevention of this disorder in diverse, at-risk populations, including adolescents and low-income minority women. A number of studies are examining the use of pharmacotherapy and psychotherapy for the treatment of postpartum depression. Innovative delivery of treatments, such as self-help programs involving use of the internet, are also being investigated.

NIMH also supported a study in which researchers pinpointed a GABA receptor component, called the *delta* subunit, that fluctuated conspicuously during pregnancy and postpartum in the brains of female mice, hinting that it might have pivotal behavioral effects. This mechanism in the brains of mice could explain why some human mothers become depressed following childbirth. For more information, access the following link: http://www.nimh.nih.gov/science-news/2008/mechanism-for-postpartum-depression-found-in-mice.shtml

Item

Preventing Suicide - The Committee encourages the NIMH to increase the amount of funding it provides to develop practical, therapeutic approaches to reducing the burden of suicide, attempted suicide, and their attendant risk factors, by integrating biological, psychotherapeutic, service-based, and preventive interventions. The Committee continues to encourage the NIMH to support advanced as well as additional developing centers for the intervention and prevention of suicide, and to ensure that they are well distributed geographically. The Committee also notes that suicide remains the third-leading cause of death among teenagers and that depressive disorders continue to be very common in adolescence. The Committee therefore strongly encourages NIMH to increase its investment in finding ways to better identify the risk factors for suicide in adolescents, improving the criteria for identifying those at risk, and examining the outcomes of actions taken to assist those found to be at risk (p. 115).

Action taken or to be taken

NIMH continues to invest significantly in suicide prevention research. The Developing Centers for the Intervention and Prevention of Suicide (DCIPS), co-funded by NIMH, NIAAA, and NIDA, continue to develop and test important practical therapeutic and preventive interventions for individuals at risk for suicide across the life course. A public-private collaboration between the American Foundation for Suicide Prevention and the DCIPS sites facilitated a pilot project to determine the feasibility of implementing a multi-site emergency department study that would validate suicidal behavior assessments and related risk factors and examine the viability of a 6-month follow-up of more than 165 patients. One DCIPS site is working with another NIMH-funded center (Silvio O. Conte Center for Neuroscience Research) devoted to studying the biology of suicide. DCIPS research efforts are also coordinated with the Department of Veterans Affairs (VA). Specifically, DCIPS researchers collaborate with one of the Veterans Integrated Service Networks (VISN 19 in Denver) of the Veterans Health Administration. This network focuses on the biological basis of suicidal behavior in schizophrenia, post-traumatic stress disorder, and traumatic brain injury. All investigators from the DCIPS centers are applying evidence-based interventions within the VA health care system to improve suicide assessment and treatment. NIMH staff also served on the recent VA Blue Ribbon Workgroup on Suicide Prevention in the Veteran Population.

In addition to activities with the VA, NIMH coordinates efforts with the Substance Abuse and Mental Health Services Administration (SAMHSA), the Indian Health Service, and the Centers for Disease Control and Prevention to optimize federal suicide prevention activities. For example, a meeting organized by SAMHSA on suicide prevention within emergency departments has led to an FY 2009 NIMH initiative to improve the identification, evaluation, and appropriate referral by emergency department staff of individuals at risk for suicide. The initiative will also seek to develop practical interventions that can assist community providers who care for these high-risk patients.

NIMH continues to support research focused on reducing suicide risk among adolescents, with the identification of early risk factors, such as parental history of suicide; parental history of childhood sexual abuse; and impulsive aggression or early-onset mood disorders in children and adolescents. The Treatment for Adolescent Suicide Attempters (TASA) study is investigating treatments for adolescents who have attempted suicide, including antidepressant medications, cognitive-behavioral therapy (CBT), or both. The data from this study are currently being analyzed and results are forthcoming. Another recent NIMH-funded study tested the effectiveness of gatekeeper training across 32 middle schools and high schools. This training instructed administrative, health/social service, and support staff how to recognize and talk to students who may be at risk for suicidality and refer them to a service provider. As a result of the training intervention, staff had increased knowledge of risk factors and self-assessed appraisal of being able to refer youth.

Item

Tuberous Sclerosis Complex -- The Committee encourages the NIMH, working together with the NICHD and NINDS, to support research on the pathophysiology of autism spectrum disorder in tuberous sclerosis complex, and other known genetic disorders where autism has a significant impact on individuals with the disease (p. 115).

Action taken or to be taken

In 2006 NIMH, in collaboration with NINDS, NCI, NIAMS, and NIDDK, supported a Program Announcement with set aside funds (PAS) until 2008, "Understanding and Treating Tuberous Sclerosis Complex," (TSC) for projects addressing new and/or exploratory research in TSC. Applications submitted under this announcement were encouraged to include studies of the links between autism and TSC; assessment and treatment of TSC-associated cognitive and behavioral problems (including pharmacological and non-pharmacological interventions); and neurodevelopmental and longitudinal studies of TSC patients that investigated the progression and inherent variability of the disease. For more information about this PAS access the following link: http://grants.nih.gov/grants/guide/pa-files/PAS-06-206.html

NIMH currently supports a PA titled "Research on Psychopathology in Intellectual Disabilities," which focuses on disorders involving cognitive impairment, including TSC. This announcement encourages basic and clinical research that examines the epidemiology, etiology, treatment, and prevention of comorbid mental health conditions (e.g., anxiety and depression) in persons with intellectual disabilities. For more information about this PA access the following link: http://grants.nih.gov/grants/guide/pa-files/PA-06-431.html.

NIMH also supports a PA titled "Research on Autism and Autism Spectrum Disorders," encouraging research designed to elucidate the diagnosis, epidemiology, etiology, genetics, treatment, and optimal means of service delivery for individuals with autism spectrum disorders (ASD). One study funded in response to this PA is examining whether genes that influence mTOR signaling (an enzyme that plays an essential role in TSC) are associated with ASD.

In addition, NIMH has been actively participating in a trans-NIH working group to increase awareness of TSC and TSC-related activities across NIH. This working group includes representatives from NIMH, NINDS, NCI, NIDDK, NHLBI, NIAMS, NICHD, NIGMS, NHGRI and the Office of Rare Diseases, as well as representatives from the Tuberous Sclerosis Alliance.

In the fall of 2007, NIMH co-sponsored a scientific conference, "Tuberous Sclerosis Complex Conference: From Genes to New Therapeutics," with NINDS, NIDDK, NCI, NIAMS, and the Tuberous Sclerosis Alliance. This meeting brought

together the TSC research community with other key researchers working on overlapping areas of interest such as autism, epilepsy, and cancer.

National Institute on Drug Abuse (NIDA)

House Significant Items

Item

Asian American and Pacific Islander (AAPI) Behavioral Research – The Committee recognizes that there is a need for additional research to develop a body of knowledge addressing the bio-psycho-social aspects of substance abuse as well as co-occurring disorders among Asian American and Pacific Islander (AAPI) populations. The Committee urges NIDA, NIAAA, and NIMH to address the behavioral health research needs for AAPI populations, including studies focused on AAPI incidence and prevalence data for substance abuse and co-occurring disorders; research addressing the biological differences that may exist within AAPI populations; nature of substance abuse among AAPI populations; effective prevention and treatment strategies; and culturally appropriate ways to evaluate AAPI substance services; and the etiology, causes, and impact on AAPI populations as a result of substance use and abuse (p. 156-7).

Action taken or to be taken

NIDA established an AAPI Workgroup in 1999 composed of researchers, scholars, practitioners, and community advocates. The workgroup makes recommendations on research and outreach needed to enhance the knowledge base on drug abuse health effects and consequences in AAPI populations. Members also encourage AAPI students, researchers, and community-based organizations to participate in research. NIDA uses its Diversity Supplement program to support AAPI drug abuse researchers and scholars—currently NIDA supports seven AAPI students and investigators.

In 2007, NIDA offered administrative supplements for research focused on American Indian/Alaskan Native and Asian American/Pacific Islander Populations, with a primary goal of expanding analyses of existing samples in order to assess patterns of drug use, and potential adverse behavioral, social, and health consequences, or differential treatment outcomes within and across these specific populations. Five awards were made, including studies to examine ecstasy and other drug use among AAPI youth, motivational parent training in community corrections, and substance use and psychiatric disorder comorbidity. Notable findings include those showing Native Hawaiians to be at higher risk for licit and illicit substance abuse across datasets, as well as to experience childhood conduct disorder—a strong predictor of substance abuse—much more commonly than Asian Americans or Caucasians.

NIMH supports projects designed to address mental health needs in AAPI populations, including epidemiological studies, basic studies on cultural differences that may influence treatment outcomes, and clinical studies that focus on identifying specific risk and protective factors to inform intervention programs.

For example, the Asian American Center on Disparities Research conducts a research program that investigates how cultural factors work to either enhance or mitigate the implementation and effectiveness of evidence-based treatments for Asian American clients. In addition, NIMH diversity training continues to support students of AAPI heritage, given their under–representation in the mental health clinical sciences.

NIAAA supports research aimed at identifying genetic and/or psychosocial factors associated with alcohol dependence in AAPI populations. For example, one exploratory/developmental study is focused on the study of genetics in American Samoans. The indigenous Polynesians of American Samoa constitute an isolated population that have a high prevalence of obesity and alcohol use. This research is attempting to identify behavioral and genetic factors associated with alcohol consumption and the neurobiological control of behaviors associated with food consumption, areas with many commonalities. Another research project is looking at genetic and psychosocial vulnerability variables associated with alcohol involvement (alcohol consumption and alcohol-related problems) in 21-25 year old Chinese American and Korean American college students. The study of two Asian American subgroups with significantly different patterns of alcohol consumption and alcoholism offers a unique opportunity to control the influence of some specific genetic factors while searching for additional influences on alcohol use behavior and how these factors may relate to promote or protect against alcohol problems.

Item

***Prescription Drug Abuse*.** - The Committee commends NIDA for its leadership in addressing the issue of prescription drug abuse. Particular concern revolves around the inappropriate use of opioid analgesics, powerful pain medications, and stimulants routinely prescribed to treat attention deficit hyperactivity disorder. The Committee encourages NIDA to continue research aimed at reducing prescription drug abuse, especially among youth, and at developing pain medications with reduced abuse potential. (p. 157)

Action taken or to be taken

According to NIDA's 2007 "Monitoring the Future Survey (MTF),"nearly one in ten 12th graders reported past-year nonmedical use of the pain medicine Vicodin, making it among the most commonly abused drugs by high school seniors. Past-year OxyContin abuse was unchanged from the previous year in grades 8, 10, and 12.

NIDA continues to sponsor research to elucidate these worrying trends and develop effective counter strategies. Current NIDA-supported researchers are conducting large-scale epidemiological studies to investigate the patterns and sources of illicit prescription drug use in high school and college students. Results to date suggest that prevention efforts with adolescents should consider the importance of social influences, along with motivations for abusing drugs,

often biased by gender and age (e.g., adolescent girls tend to abuse prescription painkillers for perceived pain while boys tend to abuse them to get high and become part of a group). Other populations of interest include older adults, who are frequently prescribed psychotherapeutic drugs and who may be particularly vulnerable to the health consequences of misuse or abuse.

NIDA and the National Institute of Mental Health have joined to invite research applications to reduce prescription drug abuse while supporting the appropriate medical use of therapeutic agents with abuse liability. A Program Announcement, titled "Prescription Drug Misuse," applies to a broad range of research disciplines. Studies are particularly needed on all classes of prescription drugs with abuse liability, including analgesics, stimulants, sedative/hypnotics, anxiolytics, and muscle building, performance enhancing drugs, such as anabolic steroids. Researchers are encouraged to study the relationship between the prescription medication, the reason it was prescribed (e.g., pain, sleep disorder, anxiety disorder, obesity), and the environmental and individual factors contributing to its abuse.

NIDA also continues to investigate treatments for opiate addiction as well as less addictive alternatives to treating pain. NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN), for example, is sponsoring the first large-scale, multisite study to test the effectiveness of buprenorphine-naloxone—a medication used to treat heroin addiction—as a treatment for addiction to prescription pain medications, in combination with behavioral therapy. Additionally, NIDA's initiative—Prescription Opioid Use and Abuse in the Treatment of Pain—solicited multidisciplinary clinical and preclinical studies, to provide a scientific foundation to inform health care providers how to treat pain successfully while minimizing the risks of abuse and addiction to opioids.

Further, NIDA is undertaking a Physician's Outreach Initiative to engage the medical community in identifying substance abuse problems in their patients and to raise awareness of substance abuse and addiction as a primary care health issue. NIDA continues to (1) work with the Office of National Drug Control Policy (ONDCP) to increase drug abuse training for physicians; (2) partner with the American Medical Association to improve physician-patient communication about substance abuse; and (3) sponsor four National Centers of Excellence in Physician Information to conduct research and develop messages and dissemination avenues for medical students, primary care, and family practice residents to raise awareness of substance abuse issues and of NIDA as a resource.

Item

Pulmonary Hypertension (PH) - The Committee notes 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. (p. 157)

Action taken or to be taken

National surveys have shown a stabilization or decline in methamphetamine abuse for approximately the last 5 years, especially among young people. However, it remains a serious problem, particularly in western parts of the country and Hawaii. In addition, there have been reports of increases in the proportion of Hispanics in methamphetamine treatment in some areas of the country. 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, as the committee noted, 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 met with the investigators from this study to explore a larger survey to assess the frequency of pulmonary arterial hypertension in subjects who abuse methamphethamine.

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

State Substance Abuse Agencies - The Committee strongly supports NIDA's State substance abuse agency infrastructure grants that help State substance abuse agencies conduct research to create, implement, expand, and/or sustain science-based improvement in the publicly funded prevention and treatment

system. The Committee encourages NIDA to continue this initiative to allow additional State substance abuse agencies to benefit. (p. 157–158)

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," or SSAs, charged with managing the country's publicly funded substance abuse system. SSAs look to NIDA to obtain credible information about 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 fortifies our communications with Substance Abuse and Mental Health Services Administration (SAMHSA) and treatment practitioners in the field.

A collaborative initiative between NIDA and SAMHSA, "Enhancing State Capacity to Foster Adoption of Science-Based Practices," encouraged state agencies to team with research organizations to optimize their research capabilities and examine the delivery of publicly supported drug abuse treatment or prevention services. Grants awarded under this RFA are looking at ways to improve delivery of substance abuse treatment services and at the factors that influence their success and replication potential.

Another NIDA research solicitation, released in FY 06 with NIMH and SAMHSA, sought to enhance the capacity of community-based providers of prevention and treatment services, including services for individuals with co-occurring mental disorders. Among seven funded grants are those examining an integrated behavioral program for prescription opiate addiction and chronic pain, co-occurring disorder care in rural areas via technology enhancements, and ways to enhance substance abuse treatment for women offenders.

Efforts to systematically move science-based interventions and practices into community settings are occurring through the National Drug Abuse Treatment Clinical Trials Network (CTN), which involves practitioners from community treatment programs in formulating, adapting, and testing 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 products to date, including those on implementing a buprenorphine detoxification regimen, and using motivational incentives to encourage and maintain drug abstinence. NIDA's translation efforts are garnering growing support from state agencies and from treatment practitioners themselves. A post-conference evaluation of the "Blending Research and Practice: Enhancing Services Using Addiction Treatment and Prevention Research" meeting in June

2008 showed 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.

Senate Significant Items

Item

Behavioral Research – The Committee commends NIDA for supporting research on adolescent sensitivity to drug use, and encourages further research, both animal and human, on social and environmental influences that may be responsible for this increased vulnerability. The Committee also encourages research on how behavioral changes during adolescence may be unique to drug abuse, and it applauds the NIDA's continued support of behavioral research using animal models (p. 113*).*

Action taken or to be taken

Addiction is influenced by multiple factors including genes, brain development, and the social environment. Use of drugs or alcohol during adolescence has been identified as the single most important marker for long-term drug problems. Thus 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 place adolescents at increased risk. Animal studies have been particularly important in identifying age-dependent vulnerability to the effects of early drug exposure. For example, compared to adults, adolescent animals show differences in sensitivity to the rewarding and aversive effects of nicotine, are more likely to self-administer higher amounts of nicotine, and exhibit more persistent changes in learning, memory, and global brain functioning following drug exposure. Human studies of adolescent vulnerability are applying genetic techniques to study developmental effects of early nicotine exposure. A recent genome-wide association study found a specific genetic variant is linked to an increased risk for nicotine addiction, but only in individuals who began smoking before age 17. Researchers are also finding genes that may counter this vulnerability.

NIDA is also targeting the influence of social factors on individual decision-making in teens, a critical focus for understanding drug abuse. To this end, developmental and social neurobiological perspectives are being applied to investigate mechanisms underlying adolescents' increased sensitivity to social influences (e.g., peers, parents). 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.

Through Requests for Applications (RFA) such as "The Genes, Environment and Development Initiative" and "Brain Imaging Drug Use Prevention Messages," NIDA continues to stimulate research on drug prevention in adolescents. The latter is a call for studies using neuroimaging techniques to identify messages that will be most salient with distinct audiences, particularly teens that are at high risk for drug abuse.

Working with its partners, NIDA continues to focus research and community outreach on educating multiple audiences about adolescent drug use. Dissemination and translation of research findings at scientific meetings and sponsorship of programs and projects targeting teens are examples. In November 2008, NIDA sponsored the meeting on "Adolescent Development Following Prenatal Drug Exposure: Research Progress, Challenges, and Opportunities" bringing together scientists, clinicians, and public health specialists to discuss adolescent behavioral and health outcomes related to early drug exposure. Other adolescent-focused programs include our 2nd annual "Drug Facts Chat Day," a web-based event where high school students across the country interact with NIDA scientists to get information on drugs and their effects. Lastly, one of NIDA's science education projects received a Bronze Telly Award for outstanding youth programming, selected from among 13,000+ entries worldwide.

Item

Health Disparities and Education/Income Levels – The Committee notes that people with less education and lower incomes are disproportionately vulnerable to drug dependence. The Committee commends the NIDA for encouraging researchers to investigate mediators and moderators of such increased vulnerability on how to effectively tailor drug abuse prevention and treatment interventions to these at-risk populations. (p. 114)

Actions taken or to be taken

Research supported by NIDA has established that many risk factors are associated with drug abuse. These can include early aggressive behavior, poor social skills, lack of parental supervision, drug availability, co-morbidity with psychiatric disorders, and—as the Committee notes—poverty and poor academic performance. Risk factors exist in many domains such as the family, peer culture, school, and at the community and individual levels. NIDA research has supported the development of an array of drug abuse prevention programs designed for use in these areas.

NIDA has funded multiple studies focused on identifying interventions to prevent drug abuse among those who are vulnerable at an early age. One published study found that when new African American mothers with incomes at or below

the federal poverty level were provided with regular nurse visits—from pregnancy until their child turned two—many benefits were realized. Seven years after the program ended, participant outcomes revealed longer intervals between first and second children, more stable partner relationships, better academic adjustment for elementary school children, and reduced childhood mortality from preventable causes. Providing a stable home environment can be key to preventing drug abuse for at risk populations.

Research on interventions designed to improve parenting skills is another area showing signs of success. A recent study of 120 low-income, urban 2-year-old boys at high risk for conduct problems showed that a brief family-centered intervention that reduces disruptive behavior also led to increases in proactive and positive parenting. These parenting changes correlated with changes in children's disruptive behavior.

Long-term studies have provided information on outcomes associated with some school-based interventions as well. For example, the Good Behavior Game (GBG) was started in Baltimore during the 1985-1986 school year. The program focused on improving children's conduct within the school setting, and reducing early aggressive, behavior in order to lessen negative social behaviors, including drug abuse. This intervention showed a positive impact on problems with emotions, behavior, and drugs or alcohol—but only for *males*. By young adulthood, significant effects were found for males in reduced: drug and alcohol abuse/dependence disorders; regular smoking; and antisocial personality disorder, particularly in those who were more aggressive and disruptive in first grade. These results highlight the value of a first-grade universal prevention intervention on long-term outcomes, while they also point to the need for researchers to explicitly include an examination of sex/gender differences in their study designs, and to focus on interventions that will be effective in young girls; both of which NIDA strongly encourages. Finally, NIDA's release of its "Drug Abuse Prevention Intervention Research" Program Announcement in the summer of 2008 signals a continued investment in research designed to mitigate drug abuse risk factors and foster protective ones.

Item

Medications Development – The Committee encourages the NIDA to develop new, effective medications that could, either by themselves or combined with validated behavioral therapies, help alleviate the personal and social impact of addiction. (p.114)

Action taken or to be taken

NIDA has made the development of addiction medications a top research priority given the reluctance of pharmaceutical companies to invest in this area. NIDA's primary focus is on the development of medications for stimulant (cocaine and methamphetamine) and cannabis addictions. A secondary focus is on nicotine, opiates, and polydrug abuse.

For cocaine addiction, NIDA is funding studies of topiramate (TOPAMAX) and disulfiram (Antabuse), as well as ondansetron, for which promising results have recently emerged. NIDA is also interested in medications that could improve the compromised cognitive function of persons addicted to stimulants. This approach could improve treatment retention and outcomes for interventions such as cognitive behavioral therapy. For example, modafinil, a medication currently marketed for narcolepsy, has been shown to enhance cognition and—in combination with behavioral treatment—has recently been shown to reduce cocaine use. NIDA has begun to enroll patients in a study of modafinil for treating methamphetamine addiction, which should complete enrollment in early 2009. This study will evaluate multiple cognitive processes that are often dysfunctional in methamphetamine patients to determine whether modafinil helps to correct these deficits. .

In addition, NIDA researchers have recently shown that the antidepressant bupropion, reduced or eliminated methamphetamine abuse in low to moderate abusers (<18 days per month). NIDA is also testing two anti-seizure medications, TOPAMAX and vigabatrin, for their efficacy in treating methamphetamine addiction.

For cannabis, NIDA is funding both animal and human studies to evaluate compounds that facilitate abstinence. A combination of Lofexidine and tetrahydrocannabinol (oral THC), the primary psychoactive ingredient in marijuana, helped ease withdrawal symptoms as well as craving in one study, which is important since many cannabis users relapse during this phase.

For opiate addiction, NIDA is conducting clinical trials with depot naltrexone, a long-acting antagonist that blocks the effects of opiate drugs. A long-acting version of naltrexone may help surmount its main drawback as a medication—poor adherence, especially by patients who are ambivalent about stopping drug use. NIDA is also testing Lofexidine for opiate withdrawal, which has yielded positive results.

NIDA is also exploring novel strategies for treating drug addiction. For example, rather than targeting implicated neural pathways/receptors, NIDA is targeting the drug itself using immunotherapy. Addiction immunotherapies cause the body to generate antibodies that bind specific drugs while they are still in the bloodstream, blocking their entry into the brain. Cocaine and nicotine vaccines are both under study, the former having completed early trials, with a follow-up multicenter trial expected to start in 2009; the latter showing positive results in that the vaccine doubled the quit rate measured at 26 weeks. Six projects have been recently awarded under a 2007 RFA that seeks to develop a vaccine for methamphetamine addiction.

Item

Single State Authorities [SSA] – The Committee urges the NIDA to continue SSA Research Infrastructure Grants to allow additional State substance abuse agencies to benefit from the program. (p. 114)

Actions taken or to be taken

Please see House Significant Item titled State Substance Abuse Agencies on page 174.

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

House Significant Items

Item

Alcohol-induced Liver Damage - In an effort to improve treatment outcomes, the Committee encourages NIAAA to study the development of biomarkers in patients susceptible to alcohol-induced liver damage. The Committee also supports the study of medications development to treat alcoholic liver disease to reduce the incidence of liver transplantation. (p. 156)

Action taken or to be taken

Please refer to page 182 of this document for NIAAA's response to this item.

Item

Underage Drinking - The Committee continues to encourage NIAAA to study alcohol advertising issues as an underage drinking prevention research priority. The Committee requests a description of NIAAA's plans to conduct such research, as well as a detailed breakdown of NIAAA's research activity in the area of underage drinking prevention by subject area. (p. 156)

Action taken or to be taken

The general perception is that more advertising leads to more exposure to advertising, which leads to more underage drinking. However, it is very difficult to ascertain the effect of advertising on drinking behavior since its impact must be measured against a background dense in other alcohol messages and images. In addition, the influence of advertisements and alcohol-related messages depends on an individual's age and stage of development, his or her expectations about drinking, and the context in which messages are received, including an overall culture that supports alcohol use. Devising studies that tease out the effects of advertising is very difficult since virtually all youth in America are exposed to some alcohol messages through television, music videos, movies, and the Internet. The available evidence from the limited number of studies conducted to date indicates that advertising impacts young people's attitudes about drinking, but the direct effects on actual consumption seen in these studies are small. To expand our knowledge of the effects of advertising beyond what previous studies have been able to show, NIAAA will issue an announcement to solicit applications incorporating innovative, new approaches.

NIAAA's overall research activities in the area of underage drinking prevention encompass studies of children, adolescents, and college students. In addition, a number of studies are focused on minority, disadvantaged, and rural populations. The portfolio includes a wide range of individually and environmentally focused underage and college drinking prevention trials plus studies on the impact of

peers, siblings, family and neighborhood on underage drinking in general. More specific foci include underage drinking and driving, fraternity and sorority drinking, sexually related consequences of underage drinking including HIV risk, policy research, screening and brief interventions, as well as a small number of studies on exposure to, and effects of, advertising and media on young people and their drinking behavior.

Senate Significant Items

Item

Alcoholic Energy Drinks **-** The Committee is aware of NIAAA funded research showing that college students who consumed alcoholic energy drinks were at greater risk of engaging in risky behaviors and experiencing alcohol-related harms. The Committee urges the NIAAA to initiate and pursue further research in this area, including the impact of pricing, packaging and marketing of these beverages on youth consumption patterns. (p. 112)

Action taken or to be taken

NIAAA has explored the relationship of non-alcoholic energy drink consumption and other problem behaviors. Importantly, the use of energy drinks was found to be associated with a constellation of problem behaviors including marijuana use for the entire sample, and alcohol problems and prescription drug abuse for white, but not for black students. Of particular concern is that two-thirds of study participants reported using the drinks as mixers with alcohol. It is important to understand the many factors that influence underage drinking and other problem drinking behavior including emerging risks and product trends. NIAAA is especially concerned about the practice of consuming energy drinks with alcohol which may facilitate excessive drinking. NIAAA will encourage the alcohol research field to address this issue.

Item

Alcohol-induced Liver Damage **-** The Committee urges the NIAAA to study the development of biomarkers in patients susceptible to alcohol-induced liver damage. The Committee also supports the study of medications development to treat alcoholic liver disease to reduce the incidence of liver transplantation. (p. 112)

Action taken or to be taken

Alcoholic liver disease (ALD), and particularly cirrhosis, is one of the leading causes of alcohol-related death. NIAAA strives to develop biomarkers for identifying individuals who are prone to develop liver damage due to excessive alcohol consumption and for monitoring responses to treatment. Using the information developed from genomics and proteomics, NIAAA is hoping to foster the development of biomarkers, especially using the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs that translate science into marketable products. In addition, NIAAA is

encouraging the development of medications for ALD especially in view of the new findings of the role of cannabinoid receptors in liver fibrosis. NIAAA is co-funding early toxicology studies for an NIH Rapid Access to Interventional Development (RAID) application to develop a new compound that reverses liver fibrosis, thus alleviating the need for liver transplantation, which currently is the only treatment for end stage liver cirrhosis. By understanding mechanisms of ALD, NIAAA would help develop medications for treatment at various stages of the disease. In addition, as AIDS patients' life expectancy has increased since the introduction of highly active antiretroviral therapy (HAART) medications, liver disease has become a more prominent cause of mortality of these patients. Therefore, identifying how alcohol further contributes to liver damage in HIV-infected individuals is a priority of NIAAA.

Item

Hepatitis - The Committee urges the NIAAA to work with voluntary health organizations, to promote liver wellness, education, and primary prevention of both hepatitis and substance abuse. (p. 113)

Action taken or to be taken

NIAAA supports research to understand and prevent alcohol-induced damage to all organs, including the liver. Alcoholic liver disease is a leading cause of death from excessive and long term alcohol consumption. Over the past several years, NIAAA has provided scientific expertise about the harmful effects of alcohol to voluntary organizations as well as devoted two issues of *Alcohol Research and Health* (Vol. 27, 2003) and one issue of *Alcohol Alert* (January 2005) to the topic of alcoholic liver disease. These publications are available on the web at http://www.niaaa.nih.gov/Publications. Although it is imperative to find methods of preventing alcohol-induced liver or other organ damage in people who drink, the surest way to decrease risk of organ damage is to reduce alcohol exposure in children and adolescents. Reduced exposure lessens the probability of pursuing the harmful behaviors that may ultimately lead to alcohol use disorders and the associated health effects of excessive and long term alcohol use. The prevention of child and adolescent alcohol use and its consequences continues to be a focus of NIAAA's Underage Drinking Research Initiative. In addition, NIAAA provided the scientific foundation for *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* and continues to work with the Office of the Surgeon General to promote and disseminate it.

Item

Social Neuroscience and Behavior **-**The emerging field of social neuroscience holds promise for understanding and treating alcohol use disorders, and the Committee is pleased that the NIAAA plans to invest in this field. The Committee also urges the NIAAA to support complementary research on social behavior, as research is needed on the implicit cognitive, emotional, and social factors that influence the transition from moderate to uncontrolled drinking, and to support

studies on how socialization processes interact with neural aspects of emotion that either promote or protect against alcohol abuse.

Action taken or to be taken

NIAAA has invested in an ongoing initiative on mechanisms of behavior change (MOBC). This initiative is providing important information about desistance from drinking as well as the transition from controlled drinking to alcohol dependence. It is capitalizing on advances in social and affective neuroscience including new tools to better understand the initiation, escalation, maintenance and reduction of problem behavior such as harmful alcohol use. In formulating this interdisciplinary initiative, NIAAA incorporated findings from human and animal research on the neural and physiological mechanisms of affective and social factors that affect alcohol and/or other substance use behaviors. In addition, research was considered on how the neural underpinnings of emotional and social constructs may relate to health-promoting change, particularly intervention response and potential for relapse. Other relevant research from the fields of cognitive psychology, brain imaging, and affective neuroscience was also taken into account. While NIAAA currently does not have specific studies on the role of social networks, the Institute recognizes the potential of this line of research and is working to incorporate it into the MOBC initiative.

Item

Underage Drinking - The Committee commends the NIAAA for continuing to partner with the Office of the Surgeon General and SAMHSA to promote and disseminate ''The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking.'' The Committee urges the NIAAA to continue researching the effects of alcohol on the adolescent brain and to provide guidance on screening for, and diagnosis of, alcohol misuse in children and adolescents. The Committee also encourages the NIAAA to engage in additional study of alcohol advertising issues as an underage drinking prevention research priority, including analysis of data on youth brand and beverage preferences. (p. 113)

Action taken or to be taken

NIAAA looks forward to a continued partnership with the Office of the Surgeon General. NIAAA is supporting research to address the following questions: (1) do persistent changes in neural and behavioral function result from adolescent alcohol use; and (2) do the processes that confer adaptability of the adolescent brain to its environment also make it more vulnerable to alcohol-induced changes in structure and/or function, especially in terms of setting it up for future dependence? Complementing NIAAA's ongoing pilot studies with humans to determine if alcohol can disrupt, co-opt or alter normal developmental processes in the brain, NIAAA plans an initiative in FY 2010 to study alcohol-induced changes in the brain in animal models. Together these human and animal studies will set the stage for a larger scale initiative supporting longitudinal human studies to differentiate between direct effects of alcohol and common underlying mechanisms in alcohol dependence, as well as to more fully assess

other short- and long-term effects of alcohol exposure on the developing adolescent brain.

NIAAA has also supported studies on the relationship between alcohol advertising and underage alcohol use. The general perception is that more advertising leads to more exposure to advertising, which leads to more underage drinking. However, it is very difficult to ascertain the effect of advertising on drinking behavior since its impact must be measured against a background dense in other alcohol messages and images. In addition, the influence of advertisements and alcohol-related messages depends on an individual's age and stage of development, his or her expectations about drinking, and the context in which messages are received, including an overall culture that supports alcohol use. Virtually all youth in America are exposed to some alcohol messages (e.g. through television, music videos, movies, and the Internet); therefore, devising studies that tease out the effects of advertising per se is very difficult. The available evidence from the limited number of studies conducted to date indicates that advertising impacts young people's attitudes about drinking, but the direct effects on actual consumption seen in these studies are small. To encourage more research in this area and expand our knowledge of the effects of advertising beyond what previous studies have been able to show, NIAAA will issue an announcement to solicit applications incorporating innovative, new approaches.

National Institute of Nursing Research (NINR)

Senate Significant Items

Item

Nurse-Family Partnership Program – The Committee urges the NINR to expand Nurse-Family Partnership Programs affiliated with nurse-managed health centers and involve advanced practice nurses in research and demonstration projects. (p. 112)

Action taken or to be taken

As part of its overall efforts to find new and more effective ways to promote health and prevent disease, NINR conducts research on improving the health outcomes of newborn children and their parents and families. In FY 2008, NINR-supported investigators conducted studies on: designing an intervention to assist mothers of premature infants in feeding their child after discharge from the hospital; assessing a community-based, culturally relevant intervention to promote perinatal risk-reduction behaviors in first-time Native Hawaiian mothers; and developing methods to evaluate feeding readiness in preterm infants. NINR plans to continue its support of research to develop successful strategies for assisting parents in caring for their newborns, with the goal of ensuring the long-term, positive health outcomes for the children.

Item

Preterm Births – The Committee is aware of the increasing trend of preterm births, resulting in a gradual reduction over the last decade of the average gestation period from 40 weeks to 39 weeks in the United States. The NINR is urged to fund maternal-child research to help address the cause of the decreasing gestation period, the health impact of this trend, and any necessary interventions. (p. 112)

Action taken or to be taken

As part of the Institute's larger research programs in the areas of quality of life, health promotion, and disease prevention, NINR supports research projects focused on reducing the incidence of preterm birth and low birth weight (LBW), and promoting the growth and development of preterm/LBW infants. In one recently reported, interdisciplinary study[1], an NINR-funded investigator and a team of electrical and computer engineers explored a technique that could assist clinicians in detecting the early onset of, and possibly preventing, premature birth. Currently, clinicians can only attempt to delay delivery once the extensive uterine contractions of labor have been initiated in the final stages of the delivery process. However, because the cervix prepares for delivery weeks to months before labor in a process termed 'preterm cervical ripening', researchers

[1] Bigelow TA, McFarlin BL, O'Brien WD, and Oelze ML (2008). *In vivo* Ultrasonic Attenuation Slope Estimates for Detecting Cervical Ripening in Rats: Preliminary Results. Journal of the Acoustic Society of America 123(3): 1794-800.

theorized that a noninvasive ultrasound technique might be used to detect this early warning sign well in advance of premature delivery. Using computer simulations and mathematical algorithms, the research team was able to successfully detect differences in the ultrasound signatures of cervical tissue preparations. Future developmental work could lead to this technique becoming an effective means to detect and predict cervical ripening, which could potentially postpone preterm births, reduce mortality, and improve long-term health outcomes.

NINR currently supports a number of maternal-child health research studies focused on premature infants. These include investigations to: develop assisted-exercise techniques to promote weight gain and muscle development in premature infants; assess possible biological, behavioral, and cultural factors leading to increased levels of premature birth in Hispanic women; and determine the health benefit and cost-effectiveness of feeding human milk to very low birth weight infants in the neonatal intensive care unit. NINR plans to continue to support research to reduce the incidence of preterm birth and promote health outcomes in infants born prematurely.

National Human Genome Research Institute (NHGRI)

Senate Significant Items

Item

Gene-Environment Interactions (GEI). - The NHGRI is encouraged to invest in research on ways that gene expression is influenced by the physical and social environment. The Committee encourages the NHGRI, on its own and in partnership with other Institutes and Centers, 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. 116)

Action Taken or to be Taken

Through the Genes, Environment and Health Initiative, a joint NHGRI - NIEHS collaboration launched in 2007, NHGRI continues to investigate the relationships between genetic variation and other factors involved in health and disease, such as stress, diet, physical activity, and substance abuse. The new real-time environmental monitoring technologies and other tools and approaches developed through GEI should be critical to achieving better understanding of how environmental factors, including psychosocial stress, influence gene expression.

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 of NINDS, NICHD, NIAMS and NIGMS, as well as other relevant institutes, to ensure ongoing support of SMA research and drug development, including the development of a clinical trials network. The NIH Director will ensure that trans-NIH cooperation on SMA continues, including the development of a clinical trials network. With respect to each institute's distinct work on SMA: The Committee encourages NINDS to plan for each of the successive stages of SMA research, including preclinical testing of multiple compounds and the necessary clinical trials infrastructure on a national and coordinated level; the Committee 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.

The Committee continues to support the development of a pan-ethnic carrier screening program for SMA. The Committee is pleased that NHGRI and NICHD held a conference in February 2008 exploring the complexities of carrier screening programs for diseases such as SMA and that the conference included scientific, medical, and advocacy perspectives.

The Committee encourages NHGRI, NICHD, and NINDS to collaborate in further exploration of pan-ethnic carrier screening for SMA and on the development of specific recommendations and guidelines for providers and patients, and to continue working cooperatively with professional societies and the advocacy community in these efforts; and The Committee also encourages NICHD to support large scale pilot studies that support the development of a national newborn screening program for SMA. (p. 174)

Action taken or to be taken

Scientific and clinical staff cooperates across the NIH Institutes on SMA whenever issues intersect their missions and expertise, such as clinical trials design issues and carrier screening. The NIH Director will establish a trans-NIH working group on SMA that includes NINDS, NICHD, NIAMS and NIGMS, as well as other relevant institutes to ensure that trans-NIH cooperation on drug development, clinical trials, and other aspects of SMA research continues.

NINDS continues to support the SMA Project and is planning for successive stages of preclinical drug development and clinical trials, as well as continuing to fund basic and translational research on SMA through investigator-initiated grant programs. The SMA Project Steering Committee includes experts from academia, the FDA, and industry who guide the project on pre-clinical drug development, clinical trials, and regulatory issues. In 2004, the NINDS convened an international scientific workshop on clinical trials for SMA, which has published recommendations on the challenges and opportunities, and a pilot

NINDS clinical trial of phenylbutyrate for SMA is among the NIH supported projects that will provide information useful for future SMA clinical trials, including natural history data.

In August 2008, NINDS and NIAMS issued a translational research initiative for neuromuscular disease. This comprehensive preclinical therapy development program is designed to prepare novel therapeutics for clinical trials and complements the SMA Project by encouraging a broad spectrum of investigator-initiated preclinical therapy development strategies. Response has been encouraging, and NIH is working with SMA investigators to assist in the development of applications through this program and with non-governmental SMA groups to best coordinate the program with their efforts the overarching objective of the muscle biology and diseases program at the NIAMS is to advance the understanding of, and, ultimately, prevent and treat a wide range of diseases and conditions that directly affect skeletal muscle. Research supported in this area may help to identify new therapeutic approaches for preventing or reversing the loss of muscle mass, which could be applicable to SMA and other motor neuron disorders.

NICHD supports the development of both newborn and carrier screening tests for SMA, which will be critical for the success of clinical trials in infants, and supports research on testing muscle strength in SMA, a crucial outcome measure for clinical trials of therapies. NICHD also organized a scientific meeting in 2008 on the development of new drugs for treatment of SMA, and is developing a translational research network intended to validate interventions for several conditions, including SMA.

Following the NIH-sponsored February 2008 discussion of population-based carrier screening, NHGRI continues its analysis of carrier screening, specifically including carrier screening for SMA. NHGRI is actively engaged with NICHD in the discussion of research concepts for SMA newborn screening programs.

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

Senate Significant Items

Item

NIBIB Intramural Program - The NIBIB is urged to use a portion of the additional resources provided in the Committee's recommendation to support a new intramural research laboratory in translational radiologic research. (p. 116)

Action taken or to be taken

In FY 2009 NIBIB will support a translational research laboratory to evaluate improved diagnostics of cardiovascular disease using advanced radiological imaging techniques in the NIH Clinical Center. Novel biomarkers would be assessed to correlate image data with progression of disease with the overall goal of early characterization and detection of cardiovascular diseases such as coronary artery disease and heart failure. Imaging techniques would also be developed for improving specificity of diagnosis of oncological diseases, and for exploring the relationship between early diagnosis and early treatment of cancers.

National Center for Research Resources (NCRR)

Senate Significant Items

Item

Research Centers in Minority Institutions (RCMI)- - The Committee continues to encourage the NCRR to strengthen participation from minority institutions, especially those with a track record of producing minority scholars in science and technology. (p. 117)

Action taken or to be taken

The Research Centers in Minority Institutions (RCMI) Program continues to develop the research infrastructure at predominantly underrepresented minority institutions that award doctorates in the health professions or a health-related science. The Program also continues to expand the capacity for clinical and translational research by developing the appropriate infrastructure in minority institutions with affiliated medical schools through the RCMI Clinical Research Infrastructure Initiative and the RCMI Translational Research Network (RTRN). In addition, three of the RCMI institutions are serving as partners with Clinical and Translational Science Award programs.

The 18 institutions currently funded via this program have an outstanding track record of producing minority scholars in science, medicine, and technology. Twenty-seven percent of the Ph.D.s earned by minorities in the biomedical and behavioral sciences were awarded by these institutions in FY 2005, according to the most recent available data. The eight medical schools included in this group produced 18 percent of the minority M.D.s in the United States in FY 2007.

In FY 2008, NCRR continued to fund the RTRN, a cooperative research network to facilitate clinical and translational research in health disparity areas. This Network consists of a consortium of researchers from the various RCMI programs; other academic health centers; community providers; community organizations; and a Data and Technology Coordinating Center. The goal is to facilitate development of multi-site clinical and translational research in health disparity areas. NCRR will continue to provide the resources necessary to support the RTRN.

National Center for Complementary and Alternative Medicine (NCCAM)

House Significant Items

Item

Liver Disease Treatments -. The Committee notes that progress has been made in documenting the benefits of the active ingredients in milk thistle in animal trials to improve the outcomes of non-alcoholic steatohepatitis and hepatitis C, and urges continuing efforts to document its effectiveness in humans. In addition, the Committee notes that NIDDK is doing promising work with SAMe, an amino acid made by the liver to detoxify medications, and encourages NCCAM to collaborate with NIDDK on these studies (p. 159).

Action taken or to be taken

The National Center for Complementary and Alternative Medicine (NCCAM) will continue to collaborate with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on studies of the role of complementary and alternative medicine (CAM) in liver health. Together, NCCAM and NIDDK support the multicenter (University of North Carolina, Chapel Hill; University of Pittsburgh; Harvard University/Beth Israel Deaconess Medical Center; University of Pennsylvania; and Thomas Jefferson University) SyNCH Phase I/II randomized controlled trials to investigate the pharmacokinetics, safety, and efficacy of silymarin (milk thistle) for treatment of chronic hepatitis C. Outcomes from this synergistic research collaboration will determine whether larger (Phase III) clinical trials of silymarin for chronic liver disease should be conducted.

NCCAM continues to support a portfolio of basic, translational, and clinical research on the role of other CAM modalities for liver disease. For example, at the University of Southern California, NCCAM supports an animal model study of s-adenosylmethionine (SAMe) to enhance understanding of its role in liver health and pathology and to identify factors that may be important in understanding which patients could benefit from SAMe use. NCCAM also funds pilot studies investigating the potential role of omega-3 fish oil in treating non-alcoholic steatohepatitis (NASH) and garlic in regulating liver function.

Senate Significant Items

Item

Behavioral Interventions *-.* The Committee encourages NCCAM to continue exploring the combined effects of behavioral interventions and pharmacotherapies/biologics in the prevention and treatment of debilitating conditions across the lifespan, with research that elucidates and enhances the mind-body connections in health (page 117).

Action taken or to be taken

The National Center for Complementary and Alternative Medicine (NCCAM) funds a substantial portfolio of basic, translational, and clinical research on the role of mind-body medicine, including meditation, hypnosis, yoga, placebo, and tai chi, applied to a wide range of diseases and conditions. As part of the NCCAM Centers of Excellence for Research on CAM (CERC) program, investigators at the *Osher Center for Integrative Medicine* at the University of California, San Francisco, are studying a form of meditation to determine whether it might slow progression of early stage HIV infection and delay the need to initiate anti-retroviral therapy. In FY 2008, NCCAM added two new centers on mind-body research to its CERC program. The University of California, San Francisco center is studying the effects of mindfulness-based stress reduction on obesity and metabolic syndrome, and the University of Wisconsin, Madison center is examining how different forms of meditation affect the brain's regulation of emotion. The NCCAM-funded *Oregon Health and Science University Developmental Center for Research on CAM* is exploring mechanisms of mind-body interactions through studies on the placebo effect. In July 2008, NCCAM, in collaboration with several other NIH ICs, conducted a workshop on meditation for health purposes to assess the current state of the science in mediation research and consider future research directions.

Data from the 2007 National Health Interview Survey indicate that the most common reason for the use of complementary and alternative medicine among U.S. adults is chronic pain, most frequently, for back pain. To further encourage research on CAM for the management of chronic pain, NCCAM will support investigations of non-pharmacologic CAM practices, including mind-body medicine, under a new initiative*, Effectiveness Research -- CAM Interventions and Chronic Back Pain*. Funded studies will include a variety of outcome measures of effectiveness, such as reduction in the use of narcotic analgesics or medications with known side effects, as well as improved patient functioning. Another new NCCAM initiative, *Program for Translational Tools for CAM Clinical Research,* will support development of methodologies, metrics, and measurement tools to strengthen the conduct and comparability of clinical trials of mind-body approaches.

National Center on Minority Health and Health Disparities (NCMHD)

House Significant Items

Item

Glomerular Disease Research - The Committee understands that glomerular disease, a group of diseases affecting the filtering mechanisms of the kidneys, is more prevalent among African Americans than in the general population. The Committee encourages NCMHD to explore collaboration with NIDDK to support research activities related to glomerular injury

Action taken or to be taken

See Senate Report language on page 196 of this document.

Senate Significant Items

Item

Adolescents and Suicide - The Committee strongly encourages the NCMHD to expand and strengthen science-based research for minority populations at elevated risk for suicide. The Committee further urges the Center to issue a report identifying best practices for collecting and disseminating data on evidence-based suicide prevention programs for adolescents and young adults with the identified populations. (p. 165)

Action taken or to be taken

The overall suicide rates among American Indian/Alaska Natives are significantly higher than other racial/ethnic minority populations. In fact, among American Indian/Alaska Native adolescents and young adults ages 15- to 34-years, suicide is the second leading cause of death (21.7 per 100,000) and is 2.2 times higher than the national average for that age group (10.0 per 100,000). Suicide is a particular public health within the State of Alaska and the Alaska Native community. From year 2003 through 2006, the average suicide rate for Alaskan Natives was 51.4 per 100,000, in contrast to 16.9 per 100,000 for non-Alaskan Natives.

In FY2008, under the NCMHD Community Based Participatory Research Initiative, funds were awarded to the University of Alaska to initiate an intervention research project (*Elluam Tunglinun*: Toward Wellness) focusing on Alaska Native suicide. The project is a culturally-based preventative intervention to reduce the suicide risk and co-morbid underage alcohol abuse among Alaska Native Yup'ik Eskimo youth. The NCMHD plans to support the project for a 5-year period.

Item

Glomerular Disease - The Committee continues to urge the NCMHD to collaborate with the NIDDK on glomerular disease, a group of diseases that is more prevalent among African Americans than in the general population.

Action taken or to be taken

Glomerular disease continues as an area of research emphasis for NCMHD. For instance, the NCMHD Center of Excellence at Case Western Reserve University is conducting a 5-year research project (*Transplant Navigator Intervention to Overcome Barriers to Kidney Transplantation*) with total support of approximately $1 million. The project is testing a novel intervention that targets patients and nephrologists as they together make transplant-related decisions. In addition, NCMHD has provided $2 million since FY 2002 to NIDDK extramural research studies, including prospective studies of chronic renal insufficiency in minority populations and a cross-sectional epidemiologic study on urologic diseases. The primary objectives of the chronic renal insufficiency cohort studies are to examine risk factors for rapid progression of chronic kidney disease.

Item

Data on Training - The Committee endorses the recommendations put forward in the National Academy of Sciences' 2005 report on NIH minority research training programs, and it urges the NCMHD to collaborate with all Institutes and Centers to develop a coordinated response and to produce an integrated NIH-wide trainee data tracking system. The Committee further urges the Center to engage trainees actively in the data tracking process to document outcomes such as funding awards for trainees or fellows, including those programs that are targeted to underrepresented minorities.

Action taken or to be taken

The NIH has established the Minority Training Committee with representatives from each Institute and Center to address the recommendations of the NAS report. The Minority Training Committee was created to provide guidance and recommendations to the NIH Director on strategies for developing a diverse biomedical research workforce. The committee's report is being finalized and is expected to include advice on the development of a database that collects a minimum data set for all persons who receive funding as trainees, fellows, research assistants, or postdoctoral fellows, including those programs targeted or non-targeted to underrepresented minorities.

John E. Fogarty International Center (FIC)

House Significant Items

Item

Drug-Resistant Tuberculosis - - The Committee notes with concern the development of drug-resistant tuberculosis in middle- and low-income countries. The Committee urges FIC to continue and expand its support of tuberculosis training programs through the AIDS International Training and Research Program. (P. 11.

Action taken or to be taken

Currently, 18 of the 28 grants in the AIDS International Training and Research Program (AITRP) provide tuberculosis (TB)-related training for scientists in many low-and middle-income countries, including most of the 20 countries that account for 80% of the TB burden. Eight of these countries allocate at least 20% of their funds to research training on HIV-TB co-infection. In 2004, FIC funded a research training program called the International Clinical, Operations and Health Services Research Award for AIDS and TB (ICOHRTA AIDS/TB) to strengthen the in-country capacity to address the research agenda around the implementation of programs for TB and HIV prevention, care and treatment. To date, seven of the eight sites have a very strong TB-focused training, again in many of the high burden countries (Brazil, China, Haiti, Peru, Russia, South Africa, Uganda and Zimbabwe). Also, FIC supports research training for TB in the Global Infectious Disease (GID) Program. Currently three of the GID awards are focused 100% on TB. In 2007, FIC funded a supplement through a GID award to support training for scientists selected by the ICOHRTA AIDS/TB grantees in Uganda and Zimbabwe for the Microscopic Observation Drug Susceptibility (MODS) assay. MODS, a lab technique developed in Peru to more easily culture TB and test for drug resistance in low resource settings, was developed under Robert Gilman at Johns Hopkins University under the GID grant. This allowed true southern hemisphere training and scientific exchange between Peruvians and Africans. The Ugandans and Zimbabweans returned home to validate the technique in their countries and exchange their experiences with the Peruvians.

In 2009 and 2010, FIC expects to support the ICOHRTA AIDS/TB program that includes strong TB components. The FIC will continue to stress the need to include the relationship between the development of drug resistant TB in the context of HIV/AIDS research training.

Item

HIV Prevention Trials - HIV prevention research poses unique challenges for both the communities and researchers engaged in clinical trials. FIC has proven experience in working to address such challenges through programs such as the AIDS International Training and Research Program. The Committee encourages FIC to continue, and initiate where necessary, programs to strengthen the capacity of developing country partners to ensure that they are ethically sound and that site-level researchers, staff, and sponsors appropriately engage local communities. (P. 11).

Action taken or to be taken

Over the past ten years, the FIC has supported ethics and community participation training through the AIDS International Training and Research Program (AITRP). In addition to the NIH-required education in the Protection of Human Subjects that is required for all FIC trainees involved in training related research with human subjects, 15 of the 28 funded AITRPs grants supported additional bioethics training, either for specific individuals trainees or through workshops conducted in-country.

In addition, since 1999, FIC has supported scientists in low- and middle-income countries in a new biennial competition in its International Research Ethics Education and Curriculum Development Award Program. Planning grants or full awards are made directly to institutions in low-and middle-income countries and as full awards to institutions in developed countries that support ethics training. Currently, 16 U.S. and foreign institutions are funded and four have strong links to the AITRP awards. Over the past several years, the FIC website has included contact information for trainees from the Bioethics program to increase collaboration. See http://www.fic.nih.gov/programs/training_grants/bioethics/index.htm

FIC will continue to encourage AITRP grantees to support ethics and community participation training. In 2010, FIC expects to convert the competition of the bioethics training program to an annual announcement.

Senate Significant Items

Item

Drug-Resistant Tuberculosis - The Committee notes with concern the development of drug-resistant tuberculosis in middle- and low-income countries. The Committee urges the FIC to continue and expand its support of tuberculosis training through the AIDS International Training and Research Program. (P. 18)

Action taken or to be taken
Please refer to page 197 of this document for FIC's response to this item on Drug-Resistant Tuberculosis.

Item
HIV Prevention Trials - The Committee encourages the FIC to continue, and initiate where necessary, programs to strengthen the capacity of developing country partners to ensure that HIV prevention research has appropriate resources to conduct research that is ethically sound and that site-level researchers, staff, and sponsors appropriately engage local communities and other civil society stakeholders. (P. 18)

Action taken or to be taken
Please refer to page 198 of this document for FIC's response to this item on HIV Prevention Trials.

National Library of Medicine (NLM)

Senate Significant Items

Item

Communication of Research Findings - The Committee is pleased that NLM has followed through on its commitment to expand the distribution of NIH MedlinePlus magazine. The Committee strongly urges the NLM to put a high priority on supplying all physician offices with this valuable resource. (p. 119)

Action taken or to be taken

NIH MedlinePlus is a quarterly general interest consumer magazine published by NIH, NLM, and the friends of the NLM. It provides a compendium of the latest research from the NIH and useful health tips for the public. Launched in May 2006, it is distributed nationwide to doctor's offices, health centers, clinics, hospitals, medical libraries, and individual subscribers. Distribution increased from 50,000 copies per issue in 2006 to a distribution of more than one-half million copies of the summer 2008 issue and a readership of about 5 million. As we enter the third year, NIH Medline Plus magazine, NLM plans to expand the readership of this free consumer publication. Currently, 125,000 physicians regularly receive the magazine, up from 33,000 physicians in 2006. The distribution of the magazine to physician offices nationwide is expected to continue to increase with the continuing support of NIH and voluntary organizations,

Item

Drug-Induced Liver Disease - The Committee urges a redoubled effort to create an accessible and user-friendly website on drug-induced liver disease. (p. 119)

Action taken or to be taken

NLM and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are developing a Web resource on drug- and herbal medication-induced liver disease. Tentatively named LiverTox, the pilot version was shown at a NIH international symposium of experts that was held at NLM on December 1-2, 2008. Feedback from that meeting has proven useful to the system developers. Medical experts, including participants in NIDDK's Drug-Induced Liver Injury Network, are currently being selected to review and evaluate the current pilot system. In the meantime, further content and information technology development is necessary before public release. NLM and NIDDK anticipate releasing a fully operational system by early 2010.

This new database will offer a collegial forum for interaction and shared file building by experts in the field and a comprehensive, integrated resource of worldwide knowledge. It will be a source of information for primary care physicians and internists who are likely to see occasional cases of drug-induced

liver injury. The website will also help experts in liver disease and toxicology and patients seeking information.

Item

Native Hawaiian Healthcare Resources - The Committee continues to encourage the NLM to work with native Hawaiian organizations to provide health information and health resources for this population. (p. 119)

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 to develop a website on Native Hawaiian Health. Previously NLM had supported POL to develop its own websites for the Native Hawaiian health system. This new site development will become available to the public in late FY 2009. This is a collaborative activity. 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 Technology to map traditional Hawaiian factors with current health data. NLM has refined and expanded its collection development policy to include materials related to traditional Hawaiian (and other Native American) health and healing practices. The Library encourages the digitization and preservation of these materials by local institutions. NLM funded POL to work with the Miloli'i Native Hawaiian community 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 plans to mount a major exhibition on this topic in 2010. The Library is seeking input and participation from Native tribes and communities and hopes to interview Hawaiian traditional healers for in this exhibition.

Office of the Director

House Significant Items

Item:

Vulvodynia **-** The Committee commends ORWH for working with other institutes and centers, women's health offices in other HHS agencies, and patient and professional groups to plan an educational outreach campaign on vulvodynia, launched in October 2007. Because nearly five years have passed since the last NIH conference on vulvodynia, the Committee requests that ORWH convene, with the support of relevant institutes and centers, a consensus conference on vulvodynia in fiscal year 2009, with specific emphasis on co morbid conditions. Finally, the Committee encourages the Director to work with the Center for Scientific Review and institute and centers to ensure that experts in vulvodynia and related chronic pain and female reproductive system conditions, are adequately represented on peer-review panels. (p. 164)

Action taken or to be taken:

The Office of Research on Women's Health (ORWH) at the National Institutes of Health (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 as well as other partners within the U.S. Department of Health and Human Services such as the Health Resources Services Administration (HRSA), 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 educate women and their health care providers about the existence and impact of vulvodynia. For example, the materials of the Vulvodynia Awareness Campaign (VAC) launched by ORWH and its partners in October 2007 continue to be among ORWH's most popular resources accessed through the internet. Vulvodynia was the subject of the December 2007 ORWH podcast "PinnPoint on Women's Health". These podcasts are conversations between the ORWH Director and NIH experts concerning important topics in women's health. Further, HRSA, as a partner of ORWH on the VAC, will distribute, via email and other web-based technologies, the VAC materials to their network of over 3,700 Primary Care Health Centers. In 2007, these sites served over 16 million low-income patients.

As part of its strategic planning with the NIH ICs, ORWH was a co-sponsor with the National Institute on Diabetes and Digestive and Kidney Disease in a very successful meeting of NIH staff and advocacy groups that focused on multidisciplinary approaches to the study of the chronic pelvic pain syndromes, including vulvodynia. Discussion included where state-of-the-art research is presently, and what the future directions for research should be. The ORWH will work with other NIH ICs to develop a scientific workshop which can similarly

encourage a multidisciplinary approach to the identification, and treatment of chronic pain disorders of women such as vulvodynia.

The Center for Scientific Review (CSR) will work with the ORWH to identify researchers to review grant applications on vulvodynia and related chronic pain. CSR encourages scientific societies and related professional organizations to nominate well-respected investigators to serve on NIH peer review groups. Data on these investigators is placed in CSR's National Registry for Society-Recommended Reviewers so that CSR staff can identify qualified reviewers for their peer review groups.

Item

The Office of AIDS Research (OAR) - Coordinates the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program. Through its annual comprehensive trans-NIH planning, budgeting, and portfolio assessment processes, OAR sets scientific priorities, enhances collaboration, minimizes duplication, and ensures that research dollars are invested in the highest priority areas of scientific opportunity. OAR develops an annual trans-NIH strategic plan and budget for all HIV/AIDS research activities. The Committee expects the Director of NIH to use this plan and the budget developed by OAR to guide his decisions on the allocation of AIDS funding among the institutes. The Director of NIH also should use the full authority of his office to ensure that the institutes and centers spend their AIDS research dollars in a manner consistent with the plan. In addition, OAR allocates an emergency AIDS discretionary fund to support research that was not anticipated when budget allocations were made. (p. 164)

Action taken or to be taken

OAR developed the annual *Trans-NIH Plan for HIV-Related Research* (http://www.oar.nih.gov/strategicplan/) that articulates the scientific priorities for AIDS research and is a roadmap for investments to shape the comprehensive NIH program of basic, clinical, and behavioral research on HIV infection and its associated co-infections, opportunistic infections, malignancies, and other complications. The plan is developed through a unique and effective multi-step annual process that involves trans-NIH Coordinating Committees and non-NIH experts from academia, industry, foundations, other government agencies, and community representatives. The plan provides the framework for developing the trans-NIH AIDS research budget; determines the use of NIH AIDS-designated dollars; permits tracking and monitoring of those expenditures; and communicates the NIH AIDS research agenda to Congress, the scientific community, AIDS-affected communities, and the public. The planning process also included a comprehensive trans-NIH review of all grants and contracts supported with AIDS-designated funds scheduled to recompete in FY 2009. This process ensures that the AIDS research budget is supporting the highest priority science, initiatives are aligned with the research objectives of the strategic plan, redundancies are eliminated, collaborations occur across Institutes, and OAR is able to shift dollars to address the changing domestic and international AIDS

epidemic, as well as the evolving scientific priorities.

Through these processes, OAR identifies emerging scientific opportunities and public health challenges that require focused attention. OAR manages and facilitates multi-IC 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 convenes scientific workshops. These unique trans-NIH processes allow OAR to ensure that precious research dollars are invested effectively and efficiently and to develop a unified and coordinated AIDS research program. OAR then uses the results of these processes to work with the Institutes and Centers in developing final budget allocations once appropriations action is completed.

Item

National Institute on Aging (NIA) Demography of Aging Centers - The Committee is aware that in 2004 OBSSR played an instrumental role through co-funding of the NIA Aging Centers. The Committee encourages OBSSR to once again lend its support to these programs, which are generating important economic and demographic population research findings. (p. 165)

Action taken or to be taken

OBSSR continues to play an instrumental role in supporting the NIA Aging Centers. From 2004 through fiscal year 2008, in partnership with NIA, OBSSR has supported several aging centers around the U.S., including the UCLA's Center on Biodemography and Population Health; the RAND Corporation's Center for the Study of Aging; the University of Chicago's Center on Demography and Economics of Aging; and the University of California at Berkeley's Center on the Economics of Demography of Aging. As outlined in OBSSR's strategic prospectus, economic and demographic population research is a priority area for FY 2009.

Item

Adolescents and Suicide - The Committee strongly encourages the NCMHD to expand and strengthen science-based research for minority populations at elevated risk for suicide. The Committee further urges the Center to issue a report identifying best practices for collecting and disseminating data on evidence-based suicide prevention programs for adolescents and young adults with the identified populations. (p. 165)

Action taken or to be taken

The overall suicide rates among American Indian/Alaska Natives are significantly higher than other racial/ethnic minority populations. In fact, among American Indian/Alaska Native adolescents and young adults ages 15- to 34-years, suicide is the second leading cause of death (21.7 per 100,000) and is 2.2 times higher than the national average for that age group (10.0 per 100,000). Suicide is a particular public health concern within the State of Alaska and the Alaska Native

community. From year 2003 through 2006, the average suicide rate for Alaskan Natives was 51.4 per 100,000, in contrast to 16.9 per 100,000 for non-Alaskan Natives.

In FY2008, under the NCMHD Community Based Participatory Research Initiative, funds were awarded to the University of Alaska to initiate an intervention research project (*Elluam Tunglinun*: Toward Wellness) focusing on Alaska Native suicide. The project is a culturally-based preventative intervention to reduce the suicide risk and co-morbid underage alcohol abuse among Alaska Native Yup'ik Eskimo youth. The NCMHD plans to support the project for a 5-year period.

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. 165)

Action taken or to be taken

The Office of Rare Diseases (ORD) continues to stimulate NIH research and research-related activities to increase our knowledge about systemic amyloidosis. The ORD's Request for Application for the recompetition of the "Rare Diseases Clinical Research Network," specifically noted systemic amyloidosis as a rare disease category of interest for RDCRC application submissions.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is preparing a multi-institute program announcement on systemic amyloidosis research. In addition, The NIDDK continues to support amyloidosis research through grants and fellowships. One notable finding from NIDDK-supported research in the past year is the biochemical characterization of hybrid transthyretin molecules that has provided insight into the limitations of an important animal model of transthyretin amyloidosis.

In January 2009, the NIDDK and ORD sponsored a meeting on "Protein Misfolding and Misprocessing in Disease," which included discussion on systemic amyloidosis. The link to this meeting is: http://www3.niddk.nih.gov/fund/other/protein/index.htm.

In the past year, the proceedings of the "XIth International Symposium on Amyloidosis," co-supported by NIDDK and ORD, were published by CRC Press.

This important reference volume contains many articles on current basic and clinical research on all forms of amyloid disease, including systemic amyloidosis.

The National Institute of General Medical Sciences (NIGMS) is supporting a study on light chain amyloidosis proteins to identify the reason slightly different versions of the light chain protein cause differences in disease severity. Scientists found that one disease-causing mutant protein was more likely than the healthy protein to unfold, lose its shape, and lead to systemic amyloidosis. Three-dimension atomic structures of the normal and the pathological proteins showed that the overall structure of individual mutant proteins was much the same, but the way pairs of them fit together was completely different leading to disease.

The National Cancer Institute (NCI) has three projects on primary systemic amyloidosis. One grant has developed a transgenic mouse model that mimics human amyloidosis in order to (1) study the disease process; (2) refine imaging technology to detect amyloid deposits, which will lead to improved diagnosis; and (3) develop monoclonal antibodies to eliminate amyloid deposits. A recently funded small business grant has discovered a common feature found in plasma cells (antibody secreting B lymphocytes) of primary amyloidosis patients. They are developing a new, highly specific test for detecting malignant cells or their secreted proteins. NCI is also supporting a randomized clinical trial of high dose chemotherapy for the management of amyloidosis and analyzing the B cell populations and the kinetics of amyloid formation around the amyloid deposits to define and determine the mechanisms of disease progression and response to therapy.

Item

Bone Diseases – The Committee encourages NIH to expand genetics research on diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, Paget's disease, melhoreostosis, XLinked hypophosphatemic rickets, and fibrodysplasia ossificans progressiva. The Committee encourages NIAMS, NIA and other institutes to issue program announcements on the interaction of environmental and genetic factors in Paget's disease. The Committee encourages NIH to strengthen research on skeletal stem cell biology. (p. 166)

Action taken or to be taken

The NIH supports research in bone biology and bone diseases that is diverse in both application and approach. Working in association with the U.S. Bone and Joint Decade in partnership with the Rare Bone Disease Patient Network, the NIH, including ORD, NIAMS, and NIDDK, recently provided support for the organization of a new conference entitled, "*1st Advances in Rare Bone Diseases,"* which took place October 23-24, 2008, on the NIH campus. This conference brought together leading international authorities to share and debate the latest diagnostic and therapeutic advances in rare diseases of the musculoskeletal

system. The biologic and genetic mechanisms underlying each disease, as well as treatment options were discussed.

In addition to broad genetics studies, NIAMS is supporting researchers that are investigating Paget's disease, a condition that results in the growth of larger and weaker bones. In studying the pathobiology of Paget's disease, researchers are investigating how gene expression and signaling of young bone cells can influence bone growth. Other research funded by NIAMS is looking into the genetic basis for muscle weakness and its association with Paget's disease.

NIAMS-supported research continues to contribute to major advances in the understanding of the processes responsible for the mineralization of bone, and of genetic disorders such as 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 work toward developing new treatments. CORTs are designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics.

Additionally, NIA, NIAMS and NICHD participate in a program announcement to encourage basic research examining the changes in composition and organization of the extracellular matrix (the part of tissue that provides structural support to cells) that results from aging. This funding opportunity also promotes research in how the altered function of the musculoskeletal system and skin predisposes tissues to diseases. Advances from these studies could help to inform rare bone diseases by increasing the basic knowledge that is required to understand the cellular and molecular pathways of bone development, and find targets for new treatments.

Item

Bridging the Sciences – The Committee believes the "Bridging the Sciences" demonstration program fulfills a need not met elsewhere in the Federal government by supporting research at the interface between the biological, behavioral, and social sciences with the physical, chemical, mathematical, and computational sciences. The Committee encourages the Director to give high priority to developing a demonstration program and to collaborate with the Department of Energy, the National Science Foundation, and other agencies. The Committee notes the importance of compliance with the statutory provisions dealing with appropriate, multidisciplinary peer review panels and the unique type of research envisioned. (p. 166-167)

Action taken or to be taken

The Demonstration Oversight Group created last year to oversee development of demonstration projects has initiated an inventory of relevant bridging activities

already underway at NIH to avoid duplication and identify potential opportunities. The Implementation Group, charged with identifying candidate demonstration project concepts now has expanded representation from NIH, the National Science Foundation, the National Institute of Standards and Technology, the Department of Energy, and the United States Department of Agriculture. This group has developed several highly interdisciplinary concepts and is currently refining and prioritizing them, for presentation to the Oversight Group. Pending approval by the Oversight Group, the intent is to support new projects that demonstrate unique opportunities that Bridge the Sciences and can catalyze a major biomedical advance.

A variety of mechanisms will be used to ensure appropriate multidisciplinary peer review. For example, NIH will use the Program Announcement with review (PAR) that permits selection of an appropriate multidisciplinary review committee.

Item

Chromosome Abnormalities - The Committee requests NIH to convene a state of the science meeting on chromosome abnormalities, defined as chromosome deletions or duplications greater than 5 Mb of DNA. The purpose of the meeting would be to create a plan for collection of data regarding dosage sensitive and insensitive genes and to establish phenotyping and genotyping standards for data collection. (p. 167)

Action taken or to be taken

Chromosomal abnormalities greater than 5 Mb of DNA are directly visible with the use of a microscope, this is generally considered the field of cytogenetics. NHGRI supports genomic research related to the identification and analysis of DNA insertions or deletions; however these DNA changes are significantly smaller than 5Mb. State of the science conferences are designed to address and achieve consensus on controversial issues in medicine. This area of research at NHGRI is extremely premature for a state of the science conference.

Item

Dandy Walker Malformation – The Committee requests NIH to report historical annual funding levels for Dandy-Walker Syndrome research. (pg 168)

Action taken or to be taken

The NIH is committed to investing in research to better understand, treat and prevent Dandy-Walker and other congenital brain malformations and their associated symptoms. The NINDS and NICHD support ongoing clinical studies to identify genes and mutations associated with DWM and other congenital hindbrain malformations and to refine descriptions of their clinical features. Such studies may provide insights into new strategies for early diagnosis as well as information relevant to determining the risk of recurrence in families affected by these disorders. Additional studies supported by NINDS and NICHD are using animal models and in vitro experiments to examine mechanisms underlying

hindbrain development and malformations, including the role of genes associated with Dandy-Walker malformation. Improved mechanistic understanding may lead to the identification of new targets for treatment or prevention.

Dandy-Walker malformation and other congenital hindbrain malformations can disrupt the normal flow of cerebrospinal fluid (CSF) in the brain, often leading to hydrocephalus. NINDS leads a trans-NIH working group focused on hydrocephalus and associated disorders, including Dandy-Walker syndrome. The group includes extramural program staff from NINDS, NICHD and NIBIB, and it first met in June 2008 to discuss the overall NIH portfolio in hydrocephalus research and areas of need and opportunity. This group will continue to meet regularly to share information and to identify future opportunities for research investment and collaboration, both among NIH Institutes and with industry and private funding organizations.

The NIH annually reports funding levels for 215 categories of research areas, diseases and conditions. (The Dandy-Walker Syndrome is not one of the RCDC reported diseases.) NINDS supports the majority of NIH-funded research specifically focused on Dandy-Walker malformation, and spending levels for research during fiscal years 2005-2008 are reported below.

NINDS funding for Dandy-Walker malformation research (in thousands):
FY2005 (actual) $1,087
FY2006 (actual) $1,050
FY2007 (actual) $1,350
FY2008 (estimated) $2,032

Item
Facioscapulohumeral Muscular Dystrophy (FSHD) - The Committee urges NIH to further develop its research portfolio on FSHD. (p.168)

Action taken or to be taken
NIH supports research to identify the causes for the abnormal chromosome 4 deletion that is responsible for Facioscapulohumeral muscular dystrophy (FSHD), the effect of the genes that seem to be dysregulated in FSHD, and to evaluate potential animal models of FSHD, a critical step needed to develop a hypothesis about disease pathogenesis and to test potential therapeutic approaches. A recent Request for Applications for mechanistic research in understudied muscular dystrophies, released by NINDS, NIAMS, and the Muscular Dystrophy Association (MDA), produced a total of 9 grants, three of which focus on studies of FSHD.

Over the last five years, NINDS has also provided support to the University of Rochester, Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (Wellstone Center), which performs research on myotonic dystrophy (DM) and FSHD. This Wellstone Center has provided evidence that

the expression of genes adjacent to the deleted DNA region is not altered in FHSD, and is investigating whether over-expression of vascular smooth muscle genes contributes to the pathology. The University of Rochester is also home to the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy (FSHD) for patients and family, funded by the NINDS and NIAMS. This National Registry helps researchers and clinicians connect to those who are affected by FSHD or DM, provides important biological samples for research studies, and enables individuals affected by these diseases to participate in clinical trials if they so desire. Through the support of the Wellstone Center, and leveraging the resource of the FSHD Registry, the University of Rochester recently initiated collaboration with Leiden University Medical Center (LUMC) in the Netherlands. This partnership was recently awarded a private donation to establish a new Fields Center for FSHD and Neuromuscular Research. The Fields Center will continue the collaborative research initiated under the Wellstone Center and will focus on the biological and genetic causes of FSHD and on developing clinical practice guidelines for the care of affected individuals.

In FY 2008, NICHD funded a new Wellstone Center focused exclusively on FSHD at the University of Rochester Medical Center. (http://www.urmc.rochester.edu/MDCrc/index.cfm) The new Center will identify biomarkers to evaluate outcomes of clinical trials for FSHD. Objectives of the Center are: 1) to identify FSHD-specific chromosomal abnormalities using state-of-the-art transcript profiling, proteomics, and bioinformatics tools, 2) to investigate whether FSHD disrupts muscle gene regulatory and signaling mechanisms controlling muscle cell death (apoptosis), muscle differentiation, and/or regeneration, 3) to develop muscle tissue cell cultures and mouse models to investigate the epigenetic mechanisms that lead to the chromosomal abnormalities, 4) to conduct clinical research leading to the development of drug and cell-based therapeutics for the treatment of FSHD, and to the design and conduct of clinical trials to test the efficacy of such therapeutics, and 5) to develop and conduct a research training program for clinicians and researchers investigating FSHD.

Item
Fragile X - As part of the Fragile X collaborative, the Committee encourages NIMH to enhance its Fragile X translational research efforts by joining with NICHD and NINDS to develop cooperative research support mechanisms for controlled studies of existing and new pharmacological treatments for Fragile X and identification of key molecular targets which are likely candidates for designing drug treatments for Fragile X. (p. 168/169)

Action taken or to be taken:
The NIH Fragile X Research Coordinating Group (comprising representatives from NICHD, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, and NIDCD) along with representatives from the scientific and clinical research communities, representatives for affected individuals and family members and other pertinent

federal agencies formed three working groups in March of 2008 to provide input on proposed research objectives for Fragile X syndrome (FXS) and the associated disorders of Fragile X-associated Tremor/Ataxia (FXTAS) and Fragile X-associated Primary Ovarian Insufficiency (FXPOI). In addition, the NICHD, in collaboration with the Office of Rare Diseases (ORD), the NINDS, the NIMH, FRAXA, the National Fragile X Foundation (NFXF), and the Fragile X Clinics Consortium (FXCC), held a two-day scientific meeting on developing cognitive and behavioral outcome measures for clinical trials with children with FXS. The information gathered during these meetings was essential to the completion of the Research Plan for Fragile X, designed to be used by the NIH and the FXS, FXTAS, and FXPOI research communities, and to be shared with other federal agencies and outside organizations to facilitate coordinated research activities that will lead to timely detection, diagnosis, treatment, and prevention of disorders related to FXS.

Current NIH collaborative research activities relating to FXS and associated disorders include efforts aimed at developing treatments and novel interventions through an ongoing cooperative agreement for clinical trials of pharmaceuticals for FXS. This effort is led by NIMH in partnership with the NICHD, which is the NIH lead for research under the Best Pharmaceuticals for Children Act (BPCA), the NINDS, FRAXA Research Foundation (FRAXA), and Autism Speaks. The aim of the clinical trials is to develop therapeutics to treat FXS and autism. Compounds being developed through the NIH-supported cooperative agreement were shown to reverse many associated symptoms in mouse models of FXS. If further testing confirms the compounds' safety in animals, a Food and Drug Administration (FDA) permit will be requested for research to determine dosage and safety in non-affected human volunteers before moving forward with clinical trials in people with FXS.

The NIH focus on efforts to understand the relationships between FXS and autism continues through the Program Announcement (PA) soliciting research to study the "Shared Neurobiology of FXS and Autism." Originally issued in 2005 and reissued in 2007, the PA established a public-private partnership led by the NIMH in collaboration with the NINDS and the NICHD. The partnership also includes the Canadian Institutes of Health, the Health Research Board of Ireland, FRAXA, and the National Alliance for Autism Research, and Autism Speaks. The grants awarded through this mechanism range from examining language in FXS children to studies in mouse models on structural abnormalities in neurons observed in FXS

Item

Fragile X - The Committee encourages NHGRI to consider expanding its research activities on Fragile X to contribute to efforts to expand newborn screening to include Fragile X, and to contribute to efforts to understand the

ethical and psychosocial implications of detection of children and young women who are found to be carriers of Fragile X mutations. (p. 169)

Action taken or to be taken:
NHGRI supports research into the ethical and social aspects of fragile X screening, including newborn screening and carrier screening across the lifespan. This research is examining complex ethical issues pertaining to stigma and attitudes toward Fragile X newborn screening and FMR-1 carrier detection across the lifespan, the risks and benefits of diagnosis, and ways in which the implications of a diagnosis influences decisions about familial disclosure.

NHGRI also continues to support comprehensive research on the function of the human genome and the interplay between genetic variation and disease. While not focusing on specific diseases, this research provides an evolving framework for disease-specific research such as that on Fragile X. To further expand our understanding of the genome, NHGRI has continued expansion of the ENCyclopedia of DNA Elements (ENCODE) project that seeks to identify all functional elements of the human genome.

Item
Fragile X - FIC is encouraged to continue to identify opportunities for furthering Fragile X basic and translational research efforts, including the establishment of public private partnerships that will increase the number of international Fragile X research projects and collaborations. (p. 169)

Action taken or to be taken:
The Fogarty International Center (FIC) will be joining the Trans-NIH Fragile X Working Group (including such ICs and Offices as: NICHD, NIDDK, NIMH, NINDS, and Office of Rare Diseases) to assist in locating possible international partnerships and/or collaborations for Fragile X research. Fragile X is a pervasive syndrome that knows no geographical boundaries, and which is known as the most common inherited cause of mental impairment and autism. The synergy from a trans-NIH working group could produce expanded partnerships, nationally and internationally, and foster broader collaborations to increase progress toward effective treatments and perhaps contributing to the goal of a cure.

Item
Hydrocephalus research - In light of Congressional support for increased collaborative research efforts into the epidemiology, pathophysiology, disease burden and treatment of hydrocephalus, the Committee encourages the Director to establish a working group to intensify hydrocephalus research efforts and ensure collaboration among the institutes. The Committee requests an update on the progress of such collaborative efforts in the 2010 budget justifications, as well as projected spending on hydrocephalus research. (p. 169)

Action taken or to be taken

Research related to hydrocephalus spans multiple NIH Institutes, and NINDS leads a trans-NIH working group that focuses on hydrocephalus and related disorders. The group, which includes extramural program staff from NINDS, NICHD and NIBIB, first met in June 2008 and will meet regularly to share information and identify opportunities for research and collaboration across NIH and with industry and private organizations.

Several NIH-funded projects aim to improve diagnosis or treatment for hydrocephalus. NINDS supports the development of new non-invasive technologies for easier and more rapid diagnosis, a prospective clinical trial comparing shunt valves for normal pressure hydrocephalus (NPH) and a study on how different shunt treatment parameters relate to cognitive outcome in NPH. The latter study will also compare features of NPH and idiopathic Parkinson's disease, often misdiagnosed in people with NPH. NIBIB supports a project to build a telemetry volume sensor to monitor the brain's ventricles, where cerebral spinal fluid CSF accumulates in hydrocephalus. Patient-specific models of CSF and ventricle dynamics developed by the project may be used in new types of shunts with feedback regulation.

Shunts to remove excess CSF are the principal treatment for hydrocephalus, but they often become obstructed or infected, and multiple shunt replacement surgeries are common. NINDS supports the development of wireless, implantable flow sensors to assess shunt function quickly and non-invasively, as well as ways to prevent infection and obstruction, such as antibiotic coatings for shunt tubing and a catheter with a micro-electromechanical system to resist blockage. Other NINDS-funded research efforts may lead to shunt alternatives, such as an implantable device that mimics the valve-like structures through which CSF normally exits into the bloodstream.

Understanding the causes of hydrocephalus may suggest new strategies for early detection, treatment or prevention. For example, NINDS supports research on genetic variations associated with congenital malformations like Dandy Walker that lead to hydrocephalus, and NINDS and NICHD fund cellular and molecular studies on brain malformations and hydrocephalus in animal models. NINDS also supports research on normal CSF regulation that may lead to new ways to prevent accumulation. Finally, NIA supports a study on age-related changes in CSF dynamics that may be related to NPH and to impaired clearance of beta amyloid peptides in Alzheimer's disease.

The NIH annually reports funding levels for 215 categories of research areas, diseases and conditions. Hydrocephalus is not currently among the reported categories. NINDS supports the majority of NIH-funded research on hydrocephalus; current and projected spending for NINDS are (in thousands): FY2007 (actual) $1,784; FY2008 (estimated) $2,209.

Item

Limb-sparing Techniques – Targeted medical research is needed to help surgeons find new limb-sparing techniques to save injured extremities, avoid amputations and preserve and restore the function of injured extremities. The Committee suggests that the Director of NIH make this issue a trans-NIH priority and use the expertise of all of the institutes to fund research that will help surgeons save severely injured limbs. (p. 169)

Action taken or to be taken

The loss of a limb or its functionality is a life-altering experience, both physically and psychologically. The NIH, including NIAMS, NIBIB, and NIDCR, has partnered with the U.S. Military to launch the Armed Forces Institute for Regenerative Medicine (AFIRM). AFIRM aims to bring tissue engineering solutions to some of the key, life-compromising injuries sustained in modern warfare. Regenerative medicine utilizes therapies that prompt the self-regenerative capacity of the body, and integrates cells with biomaterials for the creation of engineered tissues or organs for therapy.

The Transformative Research Projects Program (T-R01), part of the NIH Roadmap for Medical Research, facilitates the submission and support of exceptionally innovative, high risk, original and/or unconventional research that has the potential to create new, or challenge existing, scientific paradigms. Researchers exploring novel approaches in treating injured extremities are encouraged to explore the use of this new funding opportunity. In addition, the topic of "complex 3-dimensional tissue models" has been highlighted as an area of emphasis and may result in research relevant to limb-sparing technologies.

The NIH works closely with representatives from the orthopaedic and mental health research communities to address issues associated with the loss of a limb or its functionality. For example, in January 2008, the NIH participated in a symposium hosted by the American Academy of Orthopaedic Surgeons, the Orthopaedic Trauma Association, and the Society of Military Orthopaedic Surgeons entitled, "Extremity War Injuries III: Challenges in Definitive Reconstruction." This meeting was the third in a continuing series, the first of which was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). The symposium assembled military and civilian orthopaedic surgeons and researchers to address issues pertaining to definitive reconstruction. NIAMS also hosted a roundtable discussion in 2007 on musculoskeletal injury and trauma. Representatives with diverse orthopaedic backgrounds participated in the roundtable, including a representative from the U.S. Army Institute of Surgical Research. Together, these meetings provide scientific staff at the NIH with information on the areas of greatest need and opportunity, and how best to incorporate these findings into the scientific planning process at relevant Institutes and Centers.

NIAMS also supports a variety of studies to reduce complications, disability, and mortality associated with traumatic injury. An example is the Lower Extremity Assessment Project (LEAP) which is a clinical study assessing the outcomes of amputation and reconstruction for severe lower leg injuries. Researchers have found that patient satisfaction is predicted more by conventional measures of function, pain, and the presence of depression, than by any underlying, a priori, characteristic of the patient, injury, or treatment. Consequently, severe injury to a person's lower-limb was found not to be what constitutes "successful recovery" for some medical conditions. Focusing on the patient's perspective to evaluate medical outcomes, a relatively innovative approach, could lead to treatment and rehabilitation strategies that enhance this satisfaction and overall patient quality of life.

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. 170)

Action taken or to be taken

The NIH, through its five-year Health Disparities Strategic Plan for all of the Institutes and Centers, is committed to strengthening the research infrastructure and capacity at minority health professions institutions. As the focal point for coordinating all NIH minority health and health disparities activities, the NCMHD will continue working with the NIH Office of the Director, the Institutes and Centers, the Health Resources and Services Administration (HRSA), the Office of Minority Health in the Office of the Secretary of Health and Human Services, the Indian Health Service, and other federal agencies to strengthen the research infrastructure at minority health professions schools. Some of the NIH programs that are helping to build the research capacity at these institutions are detailed below.

NCRR and NCMHD have partnered with minority health professions schools to address infrastructure needs. The partnership co-funds activities such as the RCMI Translational Research Network (RTRN), which includes a consortium of researchers from the Research Centers in Minority Institutions (RCMI)-funded Clinical Research Centers; researchers from other academic health centers; community health providers; community organizations; and a Data and Technology Coordinating Center (DTCC). The RTRN DTCC 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. These areas include cancer; cardiovascular

diseases (heart disease and stroke); diabetes; infant mortality; mental health disorders; HIV/AIDS and other infectious diseases; and chronic kidney disorders. In addition to addressing infrastructure needs, the RTRN consortium provides a structural context in which investigators from the minority health professional schools can pool their resources and expertise in order to focus their collective strengths on addressing health disparities.

In addition, the NCMHD has two other programs which address research infrastructure at minority health professions schools. The purpose of the NCMHD Research Infrastructure in Minority Serving Institutions Program (RIMI) is to establish, strengthen and/or improve the scientific infrastructure and environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities and programs for institutional and individual faculty initiated basic, biomedical, clinical and/or behavioral research and research training programs that contribute to building a cadre of research scientists in the elimination of health disparities. Also, the NCMHD Research Endowment Program provides grants to build research and training capacity at institutions that have been designated Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals by the Health Resources and Services Administration (HRSA) in order to facilitate minority health disparities research and other health disparities research.

Item

Mitochondrial Dysfunction and Autism - The Committee is aware of data suggesting that mitochondrial disorder or dysfunction may be present in a subset of children with symptoms that fall along the autism spectrum. The Committee encourages NIH to vigorously pursue research into the possible link between mitochondrial dysfunction, autism, and vaccines and, if a relationship is confirmed, to pursue the development of tools that will screen children with mitochondrial disorders who may be at risk from immunization. (p. 170)

Action taken or to be taken

On June 29, 2008, the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS) held a workshop entitled “Mitochondrial Encephalopathies: Potential Relationships to Autism?” (www.ninds.nih.gov/news_and_events/proceedings). Invited panelists discussed scientific evidence for overlap between mitochondrial disorders and autism. They noted that drawing conclusions from available data is difficult since studies have used small numbers of patients, many tests are not specific to mitochondrial diseases, and some results vary with test conditions and methods. However, the panelists agreed that their combined clinical experience and published reports suggest mitochondrial involvement in some autism cases, and they discussed

research needs to better understand this relationship and the extent of its contribution to autism.

Mitochondrial disease symptoms can appear episodically, and abrupt deterioration may follow infection or other stress to mitochondrial function. Workshop panelists discussed known or suspected triggers for deterioration, including infection, fever, dehydration, reduced caloric intake, exercise (sometimes), and some medications and environmental toxins. For many of these, mechanisms of deterioration are not well understood, and for infections, it is unknown whether the trigger is the infectious agent, fever, or other aspect of the inflammatory or immune response. Among many mitochondrial disease patients collectively seen by the panelists, few deteriorated after vaccination, and in those cases, it was difficult to rule out a role for other factors. To reduce the serious risk posed by infection, the panelists strongly encourage vaccinations in children they treat.

Workshop panelists also discussed difficulties in diagnosing mitochondrial disease. No single test or biomarker is both sensitive and specific, and full evaluation of a child with suspected mitochondrial disease may include a clinical exam and detailed medical history, analysis of metabolites in blood, urine, and cerebrospinal fluid, genetic tests, brain imaging, and tissue biopsies (most often muscle) for biochemical or histological analysis. To make matters worse, mitochondrial DNA mutations may not be present in all copies of mitochondrial DNA or in all body tissues, and may therefore elude detection in samples collected for testing. For these reasons, the diagnosis of a mitochondrial disorder is usually qualified according to consensus guidelines as either “definitive”, “probable” or “possible”. Completely excluding a mitochondrial component in a disease is very difficult; indeed mitochondrial contributions to a range of diseases, including cancer, Parkinson’s and Alzheimer’s diseases, are under intense investigation.

NIH is committed to understanding the causes of Autism Spectrum Disorders (ASDs), including possible contributions of mitochondrial disease and environmental factors, and will heed advice from its recent workshop in exploring research opportunities. NICHD supports research to determine how deficits in brain energy metabolism lead to cognitive and behavioral deficits in MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes). Studies will identify gene relationships in families with a MELAS mutation and look for early markers of brain dysfunction in carriers, possibly showing how such dysfunction could contribute to ASDs..

Item

Neurofibromatosis (NF) - The Committee encourages the NCI to substantially increase its NF research portfolio in pre-clinical and clinical trials. 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 disorders such as autism, spinal cord injury, learning disabilities and memory loss. In addition, the Committee continues to encourage the NICHD to expand funding for NF patients in the area of learning disabilities, including the creation of NF centers. NF2 accounts for approximately 5 percent of genetic forms of deafness; the Committee therefore encourages the NIDCD to expand its NF2 research portfolio. (p. 171)

Action taken or to be taken

The NCI supports comprehensive basic, translational, and clinical research programs directed at neurofibromatosis and its related diseases. NCI's basic research program includes 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 an example, 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. Clinical trials on NF are underway through the NCI Children's Oncology Group (COG) and in the NCI intramural Pediatric Oncology Branch (POB). The COG is specifically treating children with NF1-associated tumors, particularly low-grade gliomas. The study's primary objective is 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 National Institute of Neurological Disorders and Stroke (NINDS) support research to understand and develop treatments for NF tumors in the nervous system, as well as research on neurological complications of NF. Current funded projects include studying spatial learning deficits in a mouse model of NF1 to better understand how the NF1 mutation results in learning disabilities and studying behavioral and brain imaging methods to help determine the best interventions for reading disabilities in patients with NF. NINDS-funded researchers are also working to understand skeletal abnormalities associated with NF, including scoliosis and other spinal abnormalities.

The National Institute of Child Health and Development (NICHD) have funded multiple projects in recent years addressing the neurology, genetics, and the behavioral consequences of NF. Research in various developmental disorders, such as NF, which involve learning disabilities and specific profiles of cognitive/learning disabilities, create insights into gene-brain-behavior pathways associated with learning disability as well as provide a better understanding of what is required for normal (or typical) cognitive development. Likewise, with the development of mouse models of NF, there is an opportunity to study learning disabilities from embryonic molecular effects through young adult ages.

Mutation of the NF2 tumor-suppressor gene on chromosome 22 is strongly associated with bilateral nerve tumors called vestibular schwannomas, or acoustic neuromas. The National Institute on Deafness and Other Communication Disorders (NIDCD) supports research that focuses on multiple aspects of NF2 including studies on the molecular signals that lead to these schwannomas. The studies examine how gene transcription, specific biochemical signaling pathways, and growth factors are expressed and regulated in tumor formation in hopes that potential drug treatments can be developed. Typically, surgical removal of the NF2 tumors may sever the auditory nerve, causing hearing loss. These individuals cannot be helped by a cochlear implant (CI) in the inner ear because their auditory nerve is damaged. Since they do retain the central auditory circuits in the brain, researchers have developed surface auditory brainstem implants (ABIs).

Item

Neurofibromatosis (NF) - NF is an important research area for multiple NIH institutes. The Committee highlights NF research in the following specific areas and encourages further work by the institutes involved. The Committee encourages NINDS to continue its efforts to explore NF's implications with a growing number of disorders, including autism and spinal cord injury, in addition to the many other diseases and disorders with which NF has been directly connected, such as cancer, heart disease, learning disabilities and memory loss. (p. 171)

Action taken or to be taken

The NINDS has a broad research portfolio on NF and related complications. Research to understand and help treat learning disabilities in NF, the most common neurological complication, include a study of spatial learning deficits in a mouse model of NF to understand the mechanisms underlying learning disabilities in the human condition. Another project using brain imaging and behavioral methods will help identify the best interventions for improving reading ability in people with NF. NINDS also supports research on skeletal abnormalities seen in NF, including scoliosis and other spinal abnormalities.

NF manifests as tumors of the central and peripheral nervous systems. NINDS-funded research to understand tumorigenesis and develop treatments is carried out primarily through large-scale projects, including two NF Centers at the UT-Southwestern Medical Center and the Cincinnati Children’s Hospital Medical Center. Research at these two centers and a third project at Indiana University School of Medicine, focuses on genetic, molecular, and cellular approaches to understand NF tumor formation and progression and to determine how various cell types contribute to different kinds of NF tumors. These researchers are also working toward new NF tumor treatments and are pursuing both novel compounds that act on cell signaling pathways underlying tumor formation and compounds previously used for the treatment of more common cancers. Recent

findings from collaboration among these projects suggest that imatinib mesylate (known under the trade name Gleevec) may reduce the size of one type of tumor in a mouse model of NF as well as in a young patient with the disorder.

NF tumors can appear in many parts of the body, and several NIH Institutes support research related to NF in the context of their missions. NINDS continues to lead the Trans-NIH Neurofibromatosis Working Group, which also includes members from NHLBI, NIDCD, NHGRI, NEI, NICHD, NIMH, the ORD, as well as representatives from the Department of Defense Congressionally Directed Medical Research Program and patient organizations. The group meets to share information on NF research portfolios and recent advances, coordinate programmatic activities, and identify research opportunities. NINDS and NCI also co-lead a new Trans-NIH Brain Tumor Committee focused more broadly on conditions manifesting in brain tumors in adult and pediatric populations, including NF and tuberous sclerosis (TSC), a related tumor disorder.

NINDS also encourages research on NF and its associated complications through support for workshops and conferences. In 2007 and 2008, NINDS funded the Children's Tumor Foundation's annual International NF Conference, which has focused recently on moving from the bench to the bedside in NF. In January 2008, NINDS held the workshop "mTOR Signaling: From Cancer to CNS Function." Discussions centered on the role of the mTOR signaling pathway in various central nervous system tumors, including those in NF, with emphasis on potential therapies that target this pathway, since an mTOR inhibitor has been shown to reduce tumor size and ameliorate neurological symptoms in mouse models of NF and TSC.

Item

Neurofibromatosis (NF) - NF is an important research area for multiple NIH institutes. The Committee highlights NF research in the following specific areas and encourages further work by the institutes involved: The Committee continues to encourage NICHD to issue requests for application for NF research, to aggressively pursue clinical trials for NF patients in the area of learning disabilities, and support the creation of centers involved with treating and curing learning disabilities. (P. 171)

Action Taken or to be Taken

The National Institute of Child Health and Development (NICHD) have funded multiple projects in recent years addressing the neurology, genetics, and the behavioral consequences of NF. Research in various developmental disorders, such as NF, which involve learning disabilities and specific profiles of cognitive/learning disabilities, create insights into gene-brain-behavior pathways associated with learning disability as well as provide a better understanding of what is required for normal (or typical) cognitive development. Likewise, with the development of mouse models of NF, there is an opportunity to study learning disabilities from embryonic molecular effects through young adult ages.

Mutation of the NF2 tumor-suppressor gene on chromosome 22 is strongly associated with bilateral nerve tumors called vestibular schwannomas, or acoustic neuromas. The National Institute on Deafness and Other Communication Disorders (NIDCD) supports research that focuses on multiple aspects of NF2 including studies on the molecular signals that lead to these schwannomas. The studies examine how gene transcription, specific biochemical signaling pathways, and growth factors are expressed and regulated in tumor formation in hopes that potential drug treatments can be developed. Typically, surgical removal of the NF2 tumors may sever the auditory nerve, causing hearing loss. These individuals cannot be helped by a cochlear implant (CI) in the inner ear because their auditory nerve is damaged. Since they do retain the central auditory circuits in the brain, researchers have developed surface auditory brainstem implants (ABIs). The ABI technology is still relatively new and novel electrode arrays and sound-encoding strategies are being examined to improve sound perception in individuals with NF2. In addition, different auditory implant sites may affect sound perception.

Item

Neurofibromatosis (NF) - NF is an important research area for multiple NIH institutes. The Committee highlights NF research in the following specific areas and encourages further work by the institutes involved: NF accounts for approximately 5 percent of genetic forms of deafness. The Committee therefore encourages NIDCD to solidify its NF research portfolio. (p. 171)

Action taken or to be taken

The neurofibromatoses are genetic disorders of the nervous system that primarily affect the development and growth of neural (nerve) cell tissues. These disorders cause tumors to grow on nerves and produce other abnormalities such as skin changes and bone deformities. Several institutes at NIH are conducting research on the neurofibromatosis, and NIDCD is particularly interested on Neurofibromatosis type 2 (NF2), an autosomal dominant genetic disorder that affects hearing and balance and occurs in about one out of every 40,000 Americans. Mutation of the NF2 tumor-suppressor gene on chromosome 22 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 supports several research projects that focus on multiple aspects of NF2 including studies on the molecular signals that lead to these schwannomas. The studies examine how gene transcription, specific biochemical signaling pathways, and growth factors are expressed and regulated in tumor formation in hopes that potential drug treatments could be developed.

Several of NIDCD's NF2 research projects also involve auditory prostheses. Typically, surgical removal of the NF2 tumors may sever the auditory nerve,

causing hearing loss. These individuals cannot be helped by a cochlear implant (CI) in the inner ear because their auditory nerve is damaged. Since they do retain the central auditory circuits in the brain, researchers have developed surface auditory brainstem implants (ABIs). The ABI technology is still relatively new and novel electrode arrays and sound-encoding strategies are being examined to improve sound perception in individuals with NF2. In addition, different auditory implant sites may affect sound perception. Therefore NIDCD-supported researchers are trying to understand how different levels of auditory processing and different complexities of stimuli contribute to speech recognition. NIDCD also contributes support with other NIH institutes to the annual "Children's Tumor Foundation NF Conference" which is the premier gathering of researchers and clinicians working on neurofibromatosis. The conference has been expanded with two additional days of clinical data presentations. NIDCD is also participating with other NIH institutes on an NIH clinical trial to study the natural history of tumor formation and growth in individuals with NF2.

Item

Nontuberculous Mycobacteria (NTM) - The Committee commends NIH for its planning meetings regarding NTM outreach. The Committee recommends further NIH collaboration with CDC 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. The Committee encourages NIAID to issue program announcements or other appropriate mechanisms to spur grant proposals for pulmonary NTM disease. (p. 171)

Action taken or to be taken

NIH remains committed to basic and clinical research on nontuberculous mycobacteria (NTM) to improve the understanding, diagnosis and treatment of NTM infections. For example, NIAID researchers have just published a multi-year study of clinical, microbiologic, immune, and genetic aspects of NTM infection conducted in collaboration with NHLBI researchers, and are collaborating with health maintenance organization partners and the Agency for Healthcare Research and Quality to examine risk factors for NTM disease.

NIAID is currently supporting a clinical trial planning grant to create a NTM Research Consortium (NTMRC) and to design a Phase II trial to assess the safety, tolerability, and efficacy of the standard three-drug treatment regimen in previously untreated patients with pulmonary *Mycobacterium avium* complex (MAC) infection. MAC infections account for over 75 percent of pulmonary infections caused by NTM. The NTMRC will be coordinated by the National Jewish Medical and Research Center (NJC) and will include clinical sites that care for many NTM patients as well as microbiological reference laboratories highly experienced in NTM culture and identification. NIAID intramural scientists have been the key developers and remain central participants in this consortium.

In FY 2008, NIAID, NHLBI and NIDDK co-sponsored a scientific conference hosted by NJC and organized in close coordination with the NTM Information and Research, Inc. (NTMir), an advocacy organization. The conference addressed topics such as predisposing risk factors for NTM infection, immunologic aspects of NTM disease, current therapeutic modalities, and new directions for drug development. It is expected that novel research collaborations as well as grant applications to address specific topics in NTM research will be among the outcomes of the conference.

NHLBI also supports research focused on the association between NTM and the pathogenesis of bronchiectasis, a leading lung problem in cystic fibrosis and primary ciliary dyskinesia, two rare obstructive lung diseases. In addition, NHLBI is planning to release a new Funding Opportunity Announcement to promote research on the microbiome of the lung in HIV-infected and HIV-uninfected controls. The program is expected to stimulate research on the role of infectious agents in the development of lung diseases, including NTM–related disease.

NIAID will continue to support investigator-initiated research on NTM and to assess scientific opportunities in this field. In addition, to facilitate future research, NIAID is broadening its well established contract resources for tuberculosis to include NTM. Through these resources, genomic, biochemical, bacterial and other reagents will be available for researchers starting in 2010. The Institute hopes that these cumulative efforts will lead to more effective prophylactic and therapeutic approaches to the prevention and control of respiratory infections.

Item

Opsoclonus-Myoclonus Syndrome (OMS). - The Committee urges the Director to accelerate research on OMS and related paraneoplastic syndromes. Because the causes and symptoms of OMS cross scientific boundaries, research efforts should involve the Office of Rare Diseases (ORD), NINDS, NCI, NIAID and NEI, as well as private associations and nonprofit organizations. (p. 171/172)

Action taken or to be taken

The National Cancer Institute's Cancer Therapeutic Evaluation Program (CTEP) supports the Children's Oncology Group clinical trial entitled "Use of Intravenous Gammaglobulin Therapy for Patients with Neuroblastoma-Associated Opsoclonus-Myoclonus-Ataxia Syndrome Treated with Chemotherapy and Prednisone". This clinical trial investigates whether treatment with chemotherapy with or without gammaglobulin will improve the neurologic outcome in these children. Another project called "Protein-RNA Recognition in Neurodegenerative Syndromes" focuses on structural (x-ray and NMR) and functional (the impact of mutations) investigation of protein-RNA recognition in Fragile X retardation and paraneoplastic opsoclonus-myoclonus ataxia syndromes.

Another aspect of OMS is rapid, involuntary, horizontal and vertical, unpredictable, fast eye movements that threaten clear vision by causing image motion on the retina and may be caused by ion channel dysfunction in the burst cell membrane. This hypothesis has been tested by a neuromimetic computational model of the burst neurons. The simulations suggest that alterations in membrane properties can cause saccadic oscillations. This conceptualization of opsoclonus may lead to several novel therapies to suppress these abnormal eye movements and thereby restore normal vision. Furthermore, investigators are defining the role of neural circuits and neuronal membrane properties to understand what causes oscillations. By identifying which ligand-gated channels (i.e., receptor proteins) are involved in clinical deficits, we will be able to suggest drugs that may have therapeutic value. This research is currently undertaken by National Eye Institute researchers and researchers at Johns Hopkins University, and other medical schools in the country.

In paraneoplastic neurological disorders like OMS, the body's immune response to cancer triggers a secondary autoimmune response in the brain targeting proteins expressed in tumor tissue that normally appear only in certain types of neurons. National Institute of Neurological Disorders and Stroke supports two studies: "Hu Proteins as Novel Splicing Regulators in Neurons, and Neurology" and "The Molecular Role of N-RBPs in the Brain." The studies aim to understand the functions in the brain of proteins targeted in OMS and in a paraneoplastic disorder called Hu syndrome. This research may also lead to new insights into the pathogenesis of these disorders.

In addition, ORD has been invited together with other ICs to participate in an opsoclonus-myoclonus syndrome working group initiated by the Pediatric OMS Research Fund. The first working group meeting was held in fall 2008 and a scientific conference is planned for the summer of 2009. Objectives include developing research collaborations and identifying research opportunities for OMS and improving current treatment outcomes by determining diagnostic criteria and treatment options for healthcare providers. The OMS working group will involve research investigators from the academic community and the National Institutes of Health, patient organizations, medical specialty societies, industry, and others in the planning of the scientific conference.

Item

Pain Symptoms - Pain, shortness of breath, and nausea are common physical symptoms in serious illnesses. However, there is relatively little research addressing their impact. The Committee encourages NIH to strengthen its research portfolio on these three symptoms of serious illness. (p. 172)

Action taken or to be taken

One of the most common reasons for visits to a doctor is for treatment of pain. Most painful conditions are resolved with little to no treatment. However, in some patients, acute pain may become chronic. The NIH supports a wide variety of

multidisciplinary research on chronic pain conditions affecting a large portion of our population. This research is adding to our basic understanding of chronic pain conditions and providing opportunities for the development of novel therapeutic approaches to treat these disorders. The Pain Consortium, the Blueprint for Neuroscience Research, the Roadmap for Medical Research, and the individual Institutes are all working to develop new initiatives that will increase the scope of pain research at the NIH.

One of these new initiatives is that basic researchers are studying the molecules and neuronal circuits that make up the pathways of pain from the initial detection of a painful stimulus in the periphery to the recognition, in the brain, of the intensity and location of the pain. Additionally, basic and clinical studies are being conducted on the individual variation in sensitivity to a painful stimulus due to sex and gender differences. NIH is supporting research that may uncover mechanisms for the higher prevalence of these chronic pain conditions in females. Basic and clinical research is also being conducted on special populations of pain patients including the elderly, those with terminal disorders, pediatric pain patients, and those who abuse analgesic drugs. Research teams are uncovering biological and psychological risk factors that may cause increased sensitivity to a noxious stimulus and may predispose individuals to develop chronic pain conditions after an acute painful event. The NIH also supports a research network that will study chronic pelvic pain syndromes including interstitial cystitis, painful bladder syndrome, chronic prostatitis, and their major associated co-morbidities.

Pain and nausea are dominant symptoms of many types of gastrointestinal disease. The NIH supports research programs that address each of these disease features. For example, the NIH supports the Center for Neurovisceral Sciences & Women's Health at UCLA, with a research focus on women's health and functional pain disorders, including irritable bowel syndrome. The Center is investigating gender-related factors that contribute to these disorders, in terms of development, symptoms such as pain, and treatment response. The NIH also sponsors research efforts that address nausea. The Gastroparesis Clinical Research Consortium is conducting multicenter clinical research studies of gastroparesis, a clinical syndrome characterized by multiple symptoms, one of which is nausea. The purpose of this Consortium is to develop new approaches to diagnosis and treatment of this syndrome and its symptoms.

Shortness of breath or dyspnea is a symptom that results from a complex interaction of the central nervous system (brain) and the peripheral nervous system. Many things can trigger dyspnea. Dyspnea may occur in association with chest tightness, anxiety, worsening disease, or diminished quality of life. The NIH supports dyspnea-related research in three areas: (1) Pulmonary clinical trials; (2) Studies which address the factors that affect perception of symptoms; and (3) Basic researchers are studying respiratory drive, including the neurobiological basis for dyspnea in lung transplant patients.

Item

Primary Immunodeficiency Diseases - The Committee believes that useful research into primary immunodeficiency diseases could be jumpstarted by a public-private partnership among NICHD, NIAID, NHLBI, and NIDDK and extramural research centers. The Committee encourages the Director to ensure that this collaboration moves forward in a timely manner, responsive to recent progress in the field. (p. 172)

Action taken or to be taken

NIH remains committed to engaging in public-private partnerships to support basic and clinical research to improve the understanding and treatment of primary immunodeficiency (PI) diseases. For example, since FY 2003, NICHD and NIAID have collaborated to support the Primary Immunodeficiency Research Consortium (USIDNet), a public-private partnership that has supported research on the underlying causes of PI diseases. The Consortium funded 29 research proposals over a five-year period. The Consortium continues to maintain a registry that provides data to the research community about clinical characteristics, prevalence, and outcome of individuals with these diseases as well as a repository of specimens from patients with PI diseases. Clinicians and clinical support staff of the NIAID intramural program interact regularly with members of USIDNet to share new research findings and information about diagnostic tools and novel treatments for PI diseases. In addition, an NIAID physician-researcher is a member of the USIDNet steering committee. The Consortium also has an active education program.

NIH continues to support the research component of the USIDNet contract through a series of new funding opportunities. In September 2007, NIAID, NICHD, and NHLBI cosponsored two Program Announcements for exploratory/developmental investigations on PI diseases. These funding opportunities will support innovative exploratory and developmental research projects for the detection of PI diseases, identification of the molecular basis of PI diseases, and development of innovative therapies for these devastating conditions. In 2008, NIAID, NICHD, and NHLBI made a total of 21 awards through these initiatives. Additional applications under these funding opportunities will be received in 2008 and 2009.

In July 2008, NIAID, NICHD, NIDDK, and NINDS cosponsored the Investigations on Primary Immunodeficiency Diseases initiative, which involves a partnership with the Jeffrey Modell Foundation (JMF). The funding opportunity is soliciting applications that propose innovative investigations on PI disease with a focus on studies using human specimens as well as existing or new animal models. NIH anticipates issuing the first awards under this initiative in the summer of 2009, providing JMF with the opportunity to independently support additional applications submitted under this initiative. Additional applications will be received in 2009 and 2010. This public-private partnership between NIH and

the JMF promises to broaden opportunities for the support of innovative projects identifying the causes of PI diseases and developing innovative therapies for these devastating conditions.

Item

Psoriasis – The risk of mortality is 50 percent higher for people with severe psoriasis. The Committee encourages NIH to conduct research across the institutes and centers as described below with a particular focus on biomarkers for psoriasis and psoriatic arthritis and shared molecular pathways with co-morbid conditions. The Committee recognizes that research is beginning to identify the immune cells involved in psoriasis. The Committee encourages NIAMS to undertake and strengthen basic research related to advancing these findings by understanding the genetics and immunology of psoriasis, including how genetic variation gives rise to differences in treatment responses and mechanisms that link skin and joint inflammation. The Committee encourages NIAID to study the immune cells and inflammatory process as it relates to the pathogenesis of psoriasis. (p. 172)

Action taken or to be taken

NIH supports a wide range of research in psoriasis and psoriatic arthritis. In the area of genetics research, NIH researchers continue to use information from the Genetic Association Information Network (GAIN), a public-private partnership between the Foundation for the NIH and private industry, to identify genetic susceptibility factors for psoriasis. To date, twelve researchers have been approved to receive the data from the psoriasis-related project. Additionally, a recent genome-wide association study funded by NIAMS screened a large number of patient and control genomes. Links to genes for previously-identified immune system proteins were confirmed, and novel DNA variations were also linked to these diseases. Other projects funded by NIAMS are examining genetic susceptibility for psoriasis to better understand the interaction between genes and environmental factors.

NIEHS supports research on how environmental agents affect the immune system. Since the development of the antibody and T-cell repertoire occurs early in post-natal life, environmental exposures during this vulnerable period would be expected to have more of an influence. One project, co-funded by NIEHS and NIAID, attempts to define mechanisms controlling selective expression of specific cytokines (immune system regulatory molecules) and inflammatory pathologies associated with skin.

The NIAID supports a range of basic, translational, and clinical research to understand the roles of immune cells and the inflammatory response underlying the mechanisms of autoimmune diseases, including psoriasis. In addition, NIAID continues to support the development and implementation of clinical trials for autoimmune diseases through NIAID-sponsored clinical trial networks, including the Autoimmunity Centers of Excellence and the Immune Tolerance Network.

NIAID also supports studies to develop a test to characterize cytokines, as well as studies to understand how immune cells are recruited to inflamed and healthy skin. An additional project investigates the mechanism of action of a class of drugs known as LFA-1 inhibitors, which block immune cell interactions, to aid in the design of "second generation" therapies.

Numerous studies have indicated higher rates of comorbidities with psoriasis, including diabetes, cardiovascular disease, and obesity. The inflammatory pathways associated with psoriasis have also been linked to insulin resistance, which could mean that the pathophysiology of psoriasis itself may lead to diabetes. A NIAMS-supported study is investigating this association and the extent to which psoriasis severity and other factors such as obesity influence this risk. In addition, the NIMH encourages applications on the mental health aspects of other physical disorders through the Program Announcement "Research on Co-Morbid Mental and Other Physical Disorders." Applications proposing to investigate mental health aspects of psoriasis would be welcome under this funding opportunity.

Item

Psoriasis - The Committee encourages NIMH to conduct research to better understand the link between psoriasis and mental health, including identifying any underlying biologic reason for mental health issues associated with psoriasis. The Committee understands that as genetic determinants are better understood, it will be possible to study how environmental triggers interact with different genetic susceptibility factors. The Committee encourages NIEHS to study these associations to better understand psoriasis disease development and response to treatment to provide insight into psoriasis and prevention of psoriasis and psoriatic arthritis. (p.172/173)

Action taken or to be taken

NIMH supports a Program Announcement (PA), "Research on Co-Morbid Mental and Other Physical Disorders," that encourages applications on the risk for or treatment of mental illness in people with other physical disorders, such as psoriasis. One of the primary goals of this announcement is to identify potent, modifiable risk and protective factors amenable to intervention, and to translate the results of such studies into initial tests of prevention and intervention strategies. Risk and protective factors include biological, psychosocial, behavioral, and environmental contributors to co-morbid mental and physical disorders. This PA encourages research on the efficacy, effectiveness, long-term outcome, and safety of preventive, treatment, and rehabilitative interventions across the lifespan; clinical trials and intervention studies targeting functional and symptomatic outcomes; adapting pharmacological, psychosocial, behavioral, or environmental treatment approaches individually or in combination; studies to improve recruitment and retention of individuals with co-morbid disorders in practice settings; and research on the impact of separate organizational systems and different financing mechanisms for

mental and other physical disorders. At this time, there are no grants that involve psoriasis that are being funded.

NIEHS supports research on a key area related to psoriasis: how environmental agents affect the immune system. These environmental alterations might then influence the development of abnormal immune responses, such as psoriasis, by the affected individual. Since the development of the antibody and T-cell repertoire occurs early in post-natal life, environmental exposures during this vulnerable period would be expected to have more of an influence on the development of abnormal immune responses. NIEHS is supporting research on how early exposures to metals (most notably mercury), solvents (such as trichloroethylene), and indoor air contaminants can cause changes in immune function, such as shifts in the balance of Th1/Th2 (types of T-cells) and the development of tolerance. For instance, NIEHS supports gene-environment research on the mechanisms by which mercury increases the prevalence and severity of autoimmune disease in mice genetically predisposed to autoimmune disease. One example is a project co-funded by NIEHS and NIAID; the purpose of the project is to define mechanisms controlling selective expression of specific cytokines (immune system regulatory molecules) in skin and inflammatory pathologies associated with skin. A recent review by an NIEHS-funded scientist outlines the evidence for environmental and epigenetic factors (ways in which the environment influences gene expression) in the pathogenesis of this disease and cites several candidate genes for epigenetic regulation.[2]

Item

Research Centers in Minority Institutions (RCMI)- - The Committee continues to recognize the critical role of minority institutions in addressing the ongoing racial and ethnic health disparities in the United States. The Committee encourages NIH to expand its direct participation with minority institutions and increase the resources available to these institutions. The Committee also recognizes the importance of the RCMI program in building research capacity at minority institutions. The RCMI program assists minority institutions in competing for NIH grants and other funding by helping to recruit promising researchers, equip and modify existing laboratories, and fund core research facilities and other research support at minority institutions. The Committee further expresses support for the RCMI translational research network (RTRN) and its focus on strengthening ties between minority institutions, and encourages NIH to continue designating specific resources for the RTRN apart from the existing RCMI program. (p. 173)

Action taken or to be taken

The RCMI Program continues to develop the research infrastructure at predominantly underrepresented minority institutions that award doctorates in the health professions or a health-related science. The Program also continues to

[2] Strickland FM, Richardson BC. Epigenetics in human autoimmunity. Epigenetics in autoimmunity - DNA methylation in systemic lupus erythematosus and beyond. Autoimmunity. 2008 May;41(4):278-86.

expand the capacity for clinical and translational research by developing the appropriate infrastructure in minority institutions with affiliated medical schools through the RCMI Clinical Research Infrastructure Initiative and the RCMI Translational Research Network (RTRN). In addition, three of the RCMI institutions are serving as partners with Clinical and Translational Science Awards.

The 18 institutions currently funded via this program have an outstanding track record of producing minority scholars in science, medicine, and technology. Twenty-seven percent of the Ph.D.s earned by minorities in the biomedical and behavioral sciences were awarded by these institutions in FY 2005, according to the most recent available data, and the eight medical schools included in this group produced 18 percent of the minority M.D.s in the United States in FY 2007.

In FY 2008, NCRR continued to support the RTRN, a cooperative research network to facilitate clinical and translational research in health disparity areas. This Network consists of a consortium of researchers from the various RCMI programs; other academic health centers; community providers; community organizations; and a Data and Technology Coordinating Center. The goal is to facilitate development of multi-site clinical and translational research in health disparity areas. NCRR will continue to provide the resources necessary to support the RTRN.

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 of NINDS, NICHD, NIAMS and NIGMS, as well as other relevant institutes, to ensure ongoing support of SMA research and drug development, including the development of a clinical trials network. The NIH Director will ensure that trans-NIH cooperation on SMA continues, including the development of a clinical trials network. With respect to each institute's distinct work on SMA: The Committee encourages NINDS to plan for each of the successive stages of SMA research, including preclinical testing of multiple compounds and the necessary clinical trials infrastructure on a national and coordinated level; the Committee 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.

The Committee continues to support the development of a pan-ethnic carrier screening program for SMA. The Committee is pleased that NHGRI and NICHD held a conference in February 2008 exploring the complexities of carrier screening programs for diseases such as SMA and that the conference included scientific, medical, and advocacy perspectives.

The Committee encourages NHGRI, NICHD, and NINDS to collaborate in further exploration of pan-ethnic carrier screening for SMA and on the development of specific recommendations and guidelines for providers and patients, and to continue working cooperatively with professional societies and the advocacy community in these efforts; and The Committee also encourages NICHD to support large scale pilot studies that support the development of a national newborn screening program for SMA. (p. 174)

Action taken or to be taken

Scientific and clinical staff cooperates across the NIH Institutes on SMA whenever issues intersect their missions and expertise, such as clinical trials design issues and carrier screening. The NIH Director will establish a trans-NIH working group on SMA that includes NINDS, NICHD, NIAMS and NIGMS, as well as other relevant institutes to ensure that trans-NIH cooperation on drug development, clinical trials, and other aspects of SMA research continues.

NINDS continues to support the SMA Project and is planning for successive stages of preclinical drug development and clinical trials, as well as continuing to fund basic and translational research on SMA through investigator-initiated grant programs. The SMA Project Steering Committee includes experts from academia, the FDA, and industry who guide the project on pre-clinical drug development, clinical trials, and regulatory issues. In 2004, the NINDS convened an international scientific workshop on clinical trials for SMA, which has published recommendations on the challenges and opportunities, and a pilot NINDS clinical trial of phenylbutyrate for SMA is among the NIH supported projects that will provide information useful for future SMA clinical trials, including natural history data.

In August 2008, NINDS and NIAMS issued a translational research initiative for neuromuscular disease. This comprehensive preclinical therapy development program is designed to prepare novel therapeutics for clinical trials and complements the SMA Project by encouraging a broad spectrum of investigator-initiated preclinical therapy development strategies. Response has been encouraging, and NIH is working with SMA investigators to assist in the development of applications through this program and with non-governmental SMA groups to best coordinate the program with their efforts the overarching objective of the muscle biology and diseases program at the NIAMS is to advance the understanding of, and, ultimately, prevent and treat a wide range of diseases and conditions that directly affect skeletal muscle. Research supported in this area may help to identify new therapeutic approaches for preventing or reversing the loss of muscle mass, which could be applicable to SMA and other motor neuron disorders.

NICHD supports the development of both newborn and carrier screening tests for SMA, which will be critical for the success of clinical trials in infants, and supports research on testing muscle strength in SMA, a crucial outcome measure for

clinical trials of therapies. NICHD also organized a scientific meeting in 2008 on the development of new drugs for treatment of SMA, and is developing a translational research network intended to validate interventions for several conditions, including SMA.

Following the NIH-sponsored February 2008 discussion of population-based carrier screening, NHGRI continues its analysis of carrier screening, specifically including carrier screening for SMA. NHGRI is actively engaged with NICHD in the discussion of research concepts for SMA newborn screening programs.

Item

Tuberous Sclerosis Complex – The Committee encourages the Office of the Director to continue to support the Trans-NIH TSC Coordinating Committee, with particular emphasis on research on the link between TSC and autism spectrum disorder, as well as between common disorders (cancer, diabetes, aging, arthritis and obesity) and rare diseases (Peutz-Jegher Syndrome, Cowden's Disease, Proteus Syndrome, and Lymphangioleiomyomatosis) that share a link to signaling pathways in cells throughout the human body. (p. 174, 175)

Action taken or to be taken

Several NIH Institutes fund research on TSC and mTOR signaling (over-activated in TSC) to understand how TSC mutations affect multiple organ systems and to develop new treatments. To coordinate activities and implement the NIH Tuberous Sclerosis Research Plan, the NIH TSC Working Group meets regularly; members represent NINDS, NCI, ORD, NHLBI, NIDDK, NIAMS, NICHD, NIMH, NIGMS, NHGRI, the Tuberous Sclerosis Alliance and the Department of Defense Congressionally Directed Medical Research Program. A recent joint TS Alliance and NIH initiative led to new NCI, NINDS, and NIDDK grants, included among the NIH-funded research described below.

NINDS supports research on tumor growth in the brain and on neurological effects of TSC. Other projects may show how TSC mutations lead to autism, developmental disabilities, and epilepsy by studying TSC signaling in memory, brain development and connectivity, and seizure generation. NINDS-funded researchers recently reported that rapamycin (an FDA-approved mTOR inhibitor) reversed learning deficits and reduced seizures in TSC mouse models, suggesting the potential for similar treatment in people with TSC. NHLBI supports an international trial within the Rare Lung Diseases Consortium (supported by ORD and NCRR) of rapamycin for lymphangioleiomyomatosis (LAM), a TSC-related lung disease. The multisite trial builds on NHLBI-funded TSC and LAM research and a successful pilot trial. NHLBI intramural and extramural researchers are also working to improve LAM cell isolation from patients' pleural fluid for diagnosis and research. NCI supports a multicenter phase II clinical trial of rapamycin for kidney angiomyolipomas associated with TSC and LAM, with promising initial results. NCI-funded research also focuses on TSC protein and mTOR signaling in TSC pathogenesis and in the context of potential cancer

therapies, and recent advances include insights into TSC gene regulation of insulin signaling and apoptosis, a cell death mechanism. NIDDK supports research on molecular and cellular mechanisms in TSC and related diseases relevant to NIDDK, such as studies on genetic factors that lead to TSC; tumor growth inhibitors in mouse models; TSC signaling and nutrient sensing (related to obesity); TSC and insulin-signaling cross-talk (related to diabetes); and the role of TSC genes in kidney tumors in TSC and polycystic kidney disease. Finally, NIGMS supports basic science related to TSC and welcomes TSC research proposals through the RFA, "Collaborative Studies on Systems Biology of Complex Phenotypes," which encourages geneticists and computational and systems biologists to work together on models relating genomic information to complex human traits. The NIGMS Human Genetic Cell Repository holds 90 TSC cell lines for research use, including fibroblasts and lymphoblasts from TSC patients. Repository fibroblasts can be used to create pluripotent stem cell lines, which repository staff plans to produce and distribute on demand.

NIH also sponsors meetings where TSC researchers can discuss recent findings, identify priorities and form collaborations. Recently supported meetings include: "mTOR Signaling: From Cancer to CNS Function" (January 2008, held by NINDS); "Tuberous Sclerosis Complex: From Genes to New Therapeutics" (September 2007, organized by TS Alliance with a focus on diseases related to TSC, such as LAM and polycystic kidney disease); and "Shared Neurobiology of Autism and Related Disorders" (June 2007, sponsored by NINDS, NIMH, NICHD, NIEHS, and several private foundations).

Senate Significant Items

Item:

Data Security - The Committee was disappointed by the widely publicized reports this spring that a National Institutes of Health (NIH) employee had failed to encrypt sensitive patient data on a laptop computer which was stolen from his car, placing 2,500 people at risk of identity theft. While the incident served as an important reminder that all employees must comply with the Government's data-security policy, the handling of the incident by NIH officials, who delayed notification to the affected patients by almost a month, raised equally disturbing questions. The Committee expects to be updated on the NIH's efforts to institute stricter compliance of the security policy as well as clearer procedures for notifying patients immediately when their personal information is at risk of being compromised. (p. 120)

Action taken or to be taken:

Following the National Heart Lung and Blood Institute (NHLBI) laptop incident, which actually placed over 3,200 people at risk of identity theft, NIH conducted an immediate review and certification to ensure that all laptops that could be encrypted were in fact encrypted. On April 9, 2008, the NIH Director Dr.

Zerhouni sent a lengthy and detailed letter to all staff emphasizing the importance of compliance with privacy and information security measures and policy. Because encryption software for Apple Macintosh laptops was not immediately available, Dr. Zerhouni prohibited the storage of personally identifiable information (PII) and sensitive information on Apple laptops. Until encryption has been properly applied, Apple laptop users can only store sensitive data on encrypted removable devices. NIH has worked closely with its vendors and the Department of Health and Human Services (HHS) to facilitate the development of encryption for the 3,903 Apple laptop computers, and projects that testing and deployment will be complete by the second quarter of FY2009. NIH adheres to all policies issued by the Office of Management and Budget (OMB) and HHS regarding information security and privacy. After the issuance of OMB M-06-16, NIH developed and implemented *Incident Response Team (IRT) PII Breach Procedures* to define the steps required to report a suspected or confirmed PII breach. NIH also developed and implemented *Procedures for Lost or Stolen Computing Devices and Media* to provide for better reporting and accountability of equipment and data and reviewed and strengthened PII incident reporting policies that are used by NIH security officers, Help Desk staff, and the NIH IRT. NIH has also made strides in information security and privacy awareness. A new mandatory online *NIH Privacy Awareness Training* course was released and all NIH staff completed this training as of September 30, 2008. The NIH FY08 *Information Security Awareness Training* course was updated to emphasize the protection of PII and includes a requirement that staff electronically agree they will comply with the *NIH Information Technology (IT) General Rules of Behavior* (ROB). A November 2008 revision to the *NIH Lifecycle Account Policy* now mandates that staff must complete this training before activation of any logical access account for NIH computers or networks. Senior Executive Service and equivalent staff also take training which highlights executive responsibility for the protection of PII and staff agreement with the NIH ROB (including identification of risks and punishments associated with staff non-compliance). As a representative on the HHS Social Security Number (SSN) Reduction Team, NIH is actively involved with efforts to decrease the number of IT systems and paper forms which store the SSN and to ensure that entities with a legitimate need employ proper controls according to OMB, National Institute of Standards and Technology (NIST) and HHS policy. Recently, the Office of the NIH CIO (OCIO) was elevated organizationally into the Office of the NIH Director. To further strengthen their expertise, several OCIO staff has also achieved the *Certified Information Privacy Professional/Government Certification* in general and federal privacy protections and practices.

Item

New and Early-stage Investigators. - The Committee encourages the NIH to continue its commitment to maintaining the pipeline of new and early-stage investigators, who tend to fare more poorly during tight financial times than their veteran counterparts. Through programs such as the NIH Director's New Innovator Awards, the NIH Director's Bridge Awards, and the Pathway to

Independence Awards, as well as individual programs undertaken by the Institutes and Centers, the NIH has made significant investments to attract and support the researchers of the future. The Committee was pleased to note that in fiscal year 2007, the NIH set a policy to support its 5-year historical average of first-time and early-stage investigators at about 1,500, and that the NIH exceeded this target. The Committee encourages the NIH to continue these efforts, and to seek to support 1,750 new investigators in fiscal year 2009. (p. 120)

Action taken or to be taken

For more than three decades, the NIH has explicitly encouraged new investigators to apply for NIH research grant support. The vitality of the biomedical research enterprise and its capacity to address evolving health care challenges depends on a steady flow of new investigators, and their energy and ideas. In its ongoing efforts to encourage newly trained scientists and support their careers, the NIH is committed to funding at least 1,650 new investigators in FY 2009 an increase of 100 over the 2008 goal.

Along with this commitment to supporting substantial numbers of new scientists, the NIH has announced plans to ensure that at least 60 percent of the new researchers it supports in FY 2009 are also early-stage investigators, within ten years of completing their training. In order to achieve this goal, the NIH is adopting new procedures for identifying applications from early-stage investigators and considering the career stage of applicants during the course of review and in making funding decisions. By targeting early-stage investigators in this way, the NIH hopes to provide investigators and institutions with incentives to limit the duration of postdoctoral training and encourage earlier application for NIH research support.

Item

Basic Research - The Committee urges the OBSSR to continue to build collaborations with Institutes and Centers in support of basic behavioral and social science research, including Roadmap proposals and workshops. As the OBSSR has no grant-making authority, the Committee continues to urge focused scientific leadership for basic behavioral and social science research in an Institute that does have such authority. The Committee is pleased, meanwhile, that the OBSSR continues to provide leadership in support of this effort by coordinating targeted efforts among institutes. (p. 121)

Action taken or to be taken

As part of the ongoing effort to enhance our collaboration with ICs, OBSSR continues to be involved in several trans-NIH initiatives and programs in support of basic behavioral and social sciences research (bBSSR). In fiscal year (FY) 2009, the Office is participating in the NIH Roadmap's Science of Behavior Change initiative – a series of workshops designed to explore cutting-edge research on the mechanisms of behavioral change. In addition, one of the

identified areas of need in the new Roadmap Transformative R01 Program is "Understanding and Facilitating Human Behavior Change". Finally, in partnership with numerous Institutes and Centers (ICs), OBSSR released a number of Funding Opportunity Announcements (FOAs) which will support the development of research methodology and measurement techniques, new technology and databases for bBSSR.

The current NIH-wide approach of leadership for bBSSR within and across all the appropriate ICs with OBSSR and OPASI playing a coordinating role continues to provide an optimal way to support basic Behavioral and Social Sciences Research within and across the health and illness continuum.

Item
Health Disparities - The Committee encourages the OBSSR to maintain its important role in spurring new, innovative behavioral research on health disparities by coordinating work among several Institutes and Centers. (p. 121)

Action taken or to be taken
As outlined in OBSSR's strategic prospectus, health disparities and population health research is a priority area. OBSSR, in partnership with ICs, remains engaged in spurring new behavioral research on health disparities. In March 2008, the Office convened a health disparities summit at the Center for Advanced Study in the Behavioral Sciences at Stanford University to identify innovative research strategies that might lead to the elimination of health disparities. OBSSR will support a research network that was conceptualized as an outgrowth of this summit. The network will address the application of systems science approaches to health disparities and population health research. Systems science methodologies provide a way to address complex problems, while taking into account the "big picture" and context of such problems.

In partnership with NIH ICs, OBSSR developed and coordinated the release of two program announcements on health disparities research. OBSSR and several ICs are supporting the use of behavioral and social science theories and innovative methods to improve our understanding of the causes of health and disability among various populations.

Item
Chronic Fatigue Syndrome [CFS] - The Committee urges the ORWH to convene the annual meeting of investigators funded under the fiscal year 2007 CFS neuroimmune research initiative to stimulate new research initiatives and build 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 also continues to expect that the disease and research category reporting system being developed by the NIH will yield more accurate data on CFS funding. Finally, 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.121).

Action taken or to be taken
The Office of Research on Women's Health (ORWH), through the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG), sponsored the First Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome Principal Investigators on June 20, 2008. Principal Investigators presented their findings to date and participated in a team building exercise designed to encourage innovative collaborations. The CFSWG will address their needs and how best to assist them in these and future collaborative activities. In addition, ORWH and cosponsors from the CFSWG issued two new Program Announcements to encourage new research applications entitled, "CFS: Pathophysiology and Treatment" that were published on August 22, 2008. As the first step in establishing an intramural program, the ORWH has begun discussions with the Foundation for the NIH and the Intramural Psychoneuroimmunology Program through which possible sponsors are being sought to establish a three year intramural fellowship for CFS research. On June 6, 2008, the NIH announced the Peer Review Enhancement and Implementation Program that has four major priorities: Engage the Best Reviewers; Quality and Transparency of Review; Balanced and Fair Reviews Across Scientific Fields and Career Stages; and Continuous Review of Peer Review. The NIH Deputy Director, Raynard Kington, M.D, was named to chair the Peer Review Oversight Committee (PROC). The PROC's initial implementation plans were presented to the NIH Director in September, 2008. The Center for Scientific Review, NIH, has involved members of the CFSWG in this major revision in the Peer Review Process in an effort to correct many of the problems regarding qualified reviewers for CFS grants reported by researchers and constituents. Details may be accessed at http://enhancing-peer-review.nih.gov .

Item
Stroke in Women —The Committee continues to urge additional research in stroke among women of all ages, with specific attention to gender-related differences in stroke risk, and to prevention interventions, acute stroke management, post-stroke recovery, long-term outcomes, and quality of care. As an example, the Committee encourages research to determine the biologic basis, including studies of genetic susceptibility factors, as to why migraine with aura is a risk factor for stroke, particularly among young women. The Committee also supports the NIH's initiatives toward advancing the organization of stroke care in women, including post-stroke rehabilitation, and the identification of stroke treatment and research centers that would provide rapid, early continuous 24-hour treatment to stroke victims. (p. 121, 122)

Action taken or to be taken
The NINDS has invested heavily in genetic studies on stroke in women, and investigators involved in the NINDS-funded Ischemic Stroke Genetics Study

(ISGS) have recently demonstrated that no significant gender differences occurred in the diagnostic tests (e.g., brain and vascular imaging, heart tests) performed in the ISGS. Although this finding was not consistent with past epidemiological data, the team speculates that advanced stroke centers may be helping to prevent biases.

The Stroke Prevention in Young Women Study (SPYWS) is another large clinical research study supported by the NINDS, the ORWH, the NIA, NCRR, the VA and the CDC. Recently, SPYWS investigators have linked variations in two inflammatory genes to stroke risk in female smokers, and have demonstrated a strong dose-response relationship between smoking and ischemic stroke risk in young women. Both of these findings highlight the importance of educating young women about their risks.

Current areas of NINDS-funded basic science study include exploring the effects of anesthetics used in cardiovascular stroke procedures on perioperative stroke risk, and hormone-mediated neuroprotection. Both basic and clinical researchers are exploring the links between migraine and stroke, including clinical research exploring whether ischemic brain lesions observed in individuals with a history of migraine could be prevented with more aggressive migraine therapy. The association between migraine with aura and stroke has also been shown to vary according to a woman's overall risk of developing cardiovascular disease (CVD). In the large Women's Health Study, migraine with aura was associated with increased risk of ischemic stroke only among women with low levels of CVD risk factors such as high blood pressure and high cholesterol. Information on an individual's history of migraine and CVD risk status might help to identify women at increased risk for specific future CVD events.

As mentioned above, the NHLBI also supports research on stroke in women, including several large-scale population-based studies of CVD, all of which have found similar risks of stroke in women and men and similar risk factors for stroke such as high blood pressure. The NHLBI also supports five clinical trials that are testing approaches to improve control rates of hypertension in African American patients; about half of the study participants are women. The Institute is also undertaking a new multicenter randomized trial to determine whether treating systolic blood pressure to a lower goal than is currently recommended will reduce CVD mortality and morbidity, including stroke. Approximately half of the participants will be women.

The Women's Health Initiative (WHI) continues to follow women who participated in its clinical trials. This year a major report indicated that the women who had been assigned to receive estrogen/progestin therapy had an increased risk of stroke that persisted for at least 2.4 years after stopping the therapy. The WHI is planning a large-scale genetic study in a subset of participants and is also continuing an ambitious study of cognitive dysfunction, based on the hypothesis that vascular factors (the same as occur in stroke) may play a major role.

Item:
Vulvodynia **-** The Committee commends the ORWH for working with patient and professional groups, relevant ICs and women's health offices in HHS agencies to plan an educational outreach campaign on vulvodynia, launched in October 2007. The Committee calls upon the Director to allocate sufficient resources to this effort to ensure that the developed materials can be more widely disseminated to the public, patient and medical communities. Since, nearly 5 years have passed since the last NIH conference on vulvodynia, the Committee requests that ORWH convene, with the support of relevant ICs, a consensus conference on vulvodynia in fiscal year 2009, with specific emphasis on comorbidities. The Committee notes the lack of appropriate experts in vulvodynia and related chronic pain and female reproductive system conditions on peer-review panels and again encourages the Director to work with the Center for Scientific Review and ICs to ensure their adequate representation. The Committee ask NIH to include vulvodynia on its online ''Estimates of Funding for Various Diseases, Conditions, Research Areas'' table. (p 122)

Action taken or to be taken:
Please refer to page 200 of this document for the response to this significant item regarding Vulvodynia.

Item
Computer Science and Robotics Research **–** The Committee recognizes that research in the fields of computer science and robotics has demonstrated significant benefits in advancing the study and application of medicine and health care. The Committee urges the Director to investigate and broaden the currently defined categories of computer science and robotics research, and increase funding in this area. (p.122)

Action taken or to be taken
NIH institutes and centers participate in a trans-NIH coordination activity for bioinformatics and computational biology known as the Biomedical Information Science and Technology Initiative (BISTI). Several BISTI initiatives are currently active to promote research in a variety of computer science fields including neuroimaging informatics, data ontologies, multi scale modeling, and biomedical computational science (http://www.bisti.nih.gov/funding/index.asp). In addition, the NIH National Centers for Biomedical Computing include funding for significant research cores in algorithm creation and optimization, creation of appropriate languages, and creation of hardware architectures applicable to the solution of biomedical problems. NIH institutes support specific computer science focus areas both within NIH and across multiple federal agencies. For example, the NIBIB leads the Interagency Modeling Analysis Group of seven federal agencies in the promotion of multiscale modeling of biomedical, biological

and behavioral systems. Computer science at the NIH includes bioinformatics, defined as research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data as well as computational biology which is defined as the development and application of data-analytical and theoretical methods, mathematical modeling and computational simulation techniques to the study of biological, behavioral, and social systems.

The NIH currently supports research for the development and use of robotics in a variety of applications including minimally invasive robotic surgeries, robotics for rehabilitation therapy and prosthetic design, and the development of robotic simulation technology for training and education in clinical practice and biomedical research. For example, robotic systems to retrain motor circuits following stroke are being jointly developed in two NIH Institutes. Robotic simulators including systems with haptic feedback are being developed to facilitate training of surgeons.

Item

Duchenne and Becker Muscular Dystrophy - The Committee is encouraged by the progress made in the area of DBMD, particularly through support of the six Wellstone MD centers of excellence and advancement of a conference focusing on translational research opportunities. The Committee urges NIH to continue to provide sufficient funding through NINDS, NIAMS, and NICHD to advance the work of the centers, to encourage greater collaboration and resource sharing between centers, and to further additional DBMD research opportunities. The Committee is pleased that the Muscular Dystrophy Coordinating Committee (MDCC) now includes the Director of NHLBI, and supports the increased research emphasis on cardiopulmonary complications associated with muscular dystrophy and enhanced collaboration with other NIH institutes.

Action taken or to be taken

In August 2007, the NIH re-issued a Request for Applications (RFA) to solicit new proposals for Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (or Wellstone Centers), as well as competitive renewals for Centers nearing the end of their original award term. NHLBI participated with NINDS, NIAMS, and NICHD in the re-issue of this RFA. The NIH committed to fund three new or renewing Wellstone Centers at $1M in direct costs per year for five years. The University of Rochester, funded by NINDS, successfully renewed its award to identify new therapies and establish optimal efficacy assessments methods for myotonic dystrophy. In addition, NIAMS will fund a new Wellstone Center at the University of North Carolina, Chapel Hill, focusing on the development of gene-based therapies for Duchenne Muscular Dystrophy, and NICHD will fund another at Boston Biomedical Research Institute, concentrating on identifying biomarkers for the evaluation of facioscapulohumeral muscular

dystrophy (FSHD) clinical trial outcomes. The NINDS, NICHD, and NIAMS each will continue to fund Centers at the University of Iowa, Children's National Medical Center, and the University of Pennsylvania/Johns Hopkins University respectively.

To further encourage and enhance collaborative activities at the Wellstone Centers, NIH provides support for research conferences, research partnerships, and career development opportunities through administrative supplements outlined in two notices: "Support for Muscular Dystrophy Workshops and Research Conferences" and "NIH administrative Supplements for Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships at the Wellstone Muscular Dystrophy Cooperative Research Centers." Supplements have recently been used for two collaborative projects, one pursuing preclinical therapy development for myotonic dystrophy and another studying the cellular and molecular mechanisms involved in the development of FSHD.

The NIH actively collaborates and coordinates research efforts with other agencies and not-for-profit organizations through the Muscular Dystrophy Coordinating Committee (MDCC). NHLBI recently joined the MDCC and at the recent 7th Annual MDCC Meeting, held on June 23, 2008, Dr. Susan Shurin, Deputy Director of NHLBI, gave a thorough presentation on areas of research opportunity on cardiopulmonary complications of MD. The MDCC meeting also included presentations from individuals living with muscular dystrophy, Action Plan updates from members of the MDCC, and a session on partnering opportunities. Presenters discussed ways in which private organizations, the NIH, and Wellstone Centers may synergize support for the development of a muscular dystrophy research workforce. International collaborative research opportunities with organizations such as with TREAT-NMD or the MRC Centre for Neuromuscular Disease were highlighted, as was the recent establishment with philanthropic funds of the Fields Center for FSHD and Neuromuscular Research at the University of Rochester, which resulted in part from Wellstone Center-initiated collaborations with Leiden University and which will benefit from the infrastructure set up through the Wellstone program.

Item

Epilepsy - The Committee recognizes the NINDS as the primary Institute for epilepsy research and strongly encourages the coordination of research efforts with the NICHD, NIMH and NIA. Although epilepsy often begins in childhood, the number of affected senior citizens is growing at a rapid pace. This is partly due to the effects of age-related illness. As such, broad research in epilepsy must be made a priority, with special emphasis on the developmental effects of epilepsy, seizure prevention, improved therapies, and treatment. The Committee urges the Director of NIH to intensify coordination of cross-cutting research on epilepsy in all Institutes as appropriate and be prepared to provide a report during the fiscal year 2010 budget hearings. (p. 123)

Action taken or to be taken

The NINDS has continued to revise its Epilepsy Research Benchmarks, a series of goals designed to stimulate progress in very specific areas of epilepsy research. Both senior and junior researchers and clinicians contributed to the development of the most current set of Benchmarks, which now includes goals for understanding and treating co-morbidities of epilepsy such as cognitive problems and depression, which may facilitate collaborations with NIH Institutes/Centers (ICs) that share these research interests.

With respect to developmental forms of epilepsy, the NINDS supports research in many areas, including the development of biological markers that will predict progression, strategies to interrupt the development of epileptic activity, and screening methods to optimize therapeutics. Epilepsy prevention efforts will also be aided by new research funded on the genetics of epilepsy.

New treatment studies, while challenging, continue to advance. The Institute's Anticonvulsant Screening Program (ASP), in existence since 1975, plays a major role in the development/validation of new test models and the translation of new therapeutics. In the past year alone, the program has screened more than 700 potential therapeutics for activity against seizures. It has also developed an extensive database containing information critical for the development of new drugs and new screening tools for identifying new therapies to prevent status epilepticus (SE), a dangerous form of continuous seizures. Other NINDS-funded treatment research has shown that gene mutations that enhance seizures and those that inhibit seizures can in effect "cancel" each other out. In addition, the NICHD is also supporting an ongoing clinical trial to determine which of two commonly used drugs -- lorazepam and diazepam – is best for treating SE in children in the emergency room. This study should provide the critical information needed to help appropriately label the drugs for pediatric use.

The NINDS continues to promote collaboration with other NIH ICs through the Interagency Epilepsy Research Working Group. This group met in September 2008, and involved representatives from the NIMH, NICHD, NIA, and NIBIB, as well as the CDC and DoD. Current collaborations include co-funding of a workshop focused on the recently-identified links between amyloid beta, a protein implicated in Alzheimer's disease, and epilepsy. A second key collaboration involves the Congressionally-mandated Countermeasures Against Chemical Threats (CounterACT) Research Program, which is led by the NINDS and supported by six other NIH ICs. CounterACT supports studies of therapies that can be used in non-hospital settings to end seizures and SE induced by chemical threat agents. The NINDS is supporting the development of a clinical trial on treatments for SE in a non-hospital setting. Because midazolam (one of the drugs used in this trial) is of interest to CounterACT and is also in advanced development by the DoD for treating chemical exposures, these programs/agencies are collaborating with NINDS in this effort. The NICHD Pediatric Emergency Care Applied Research Network may provide an

opportunity for collaboration with the NINDS clinical trials group in the future. Lastly, areas of research such as prevention of posttraumatic epilepsy, neuroimaging, and epidemiology offer opportunities for collaboration between the NINDS and NIBIB and other agencies such as the DoD and CDC.

Item
Food Allergies- In addition to the recommendations under the NIAID section of this report, the Committee encourages the NIDDK to explore the linkage between digestion and severe food allergies. The Committee also encourages the NIEHS to continue funding research in conjunction with the NIAID on the relationship between environmental conditions and severe food allergies. (p. 123)

Action taken or to be taken
In addition to research led by the National Institute of Allergy and Infectious Diseases (NIAID) on food allergies, related efforts are also being pursued by other NIH Institutes. The NIDDK supports research relevant to digestion and food allergies, including research on eosinophilic esophagitis, a disease associated with food allergies and sensitivities to other allergens, and characterized by inflammation in the esophagus with high levels of cells called eosinophils. This disease is not well understood, and thus increased knowledge from this research will be important for the development of new therapeutic approaches. The NIDDK also participates on the NIAID-led Food Allergy Clinical Guidelines Coordinating Committee, which has nominated an Expert Panel to begin developing guidelines for the diagnosis and management of food allergies. The NIDDK additionally supports research on another disease induced by an adverse immune reaction to food, namely, celiac disease. Although celiac disease is an autoimmune disease, as opposed to a typical food allergy, it is triggered by gluten, a component of wheat, rye, and barley. NIDDK-funded research encompasses studies of the abnormal immune system reaction to gluten, which damages the small intestine and causes digestive problems, and other research. In a recent study of children at high genetic risk for celiac disease, NIDDK-supported scientists developed a new strategy that may facilitate early diagnosis and help patients and doctors monitor adherence to a gluten-free diet. The strategy uses a test to detect antibodies made by individuals with the disease against modified gluten proteins. Because celiac disease is common but often undiagnosed, the NIDDK also sponsors a Celiac Disease Awareness Campaign to provide informational resources and materials to healthcare professionals and the public.

The National Institute of Environmental Health Sciences (NIEHS) supports research to determine how environmental agents influence the development of abnormal immune responses, such as allergies. The development of various components of the immune system, including the antibody and T-cell repertoire occurs early in post-natal life, so environmental exposures during this vulnerable period would be expected to have a greater influence. NIEHS supports research to determine how early exposures to metals (most notably mercury), solvents

(such as trichloroethylene), and indoor air contaminants can cause changes in immune function, such as shifts in the balance of different types of T cells that would be relevant to the development of allergies.

Item

Fragile X - The Committee commends the Director for establishing the NIH Fragile X Research Coordinating Group and strongly urges his office to ensure that appropriate resources are provided to implement the objectives outlined in the Fragile X Research Plan that is being developed. As for individual Institutes, the Committee encourages the NIMH to enhance its critical Fragile X translational research efforts by joining with the NICHD and NINDS to develop cooperative research support mechanisms for controlled studies of existing and new pharmacological treatments for Fragile X and identification of the key molecular targets that are likely candidates for designing drug treatments for Fragile X and related disorders such as autism. (p. 123)

Action taken or to be taken

The NIH Fragile X Research Coordinating Group (comprising representatives from NICHD, NIMH, NINDS, NIA, NIDDK, NIGMS, NCI, and NIDCD) along with representatives from the scientific and clinical research communities, representatives for affected individuals and family members and other pertinent federal agencies formed three working groups in March of 2008 to provide input on proposed research objectives for Fragile X syndrome (FXS) and the associated disorders of Fragile X-associated Tremor/Ataxia (FXTAS) and Fragile X-associated Primary Ovarian Insufficiency (FXPOI). In addition, the NICHD, in collaboration with the Office of Rare Diseases (ORD), the NINDS, the NIMH, FRAXA, the National Fragile X Foundation (NFXF), and the Fragile X Clinics Consortium (FXCC), held a two-day scientific meeting on developing cognitive and behavioral outcome measures for clinical trials with children with FXS. The information gathered during these meetings was essential to the completion of the Research Plan for Fragile X, designed to be used by the NIH and the FXS, FXTAS, and FXPOI research communities, and to be shared with other federal agencies and outside organizations to facilitate coordinated research activities that will lead to timely detection, diagnosis, treatment, and prevention of disorders related to FXS.

Current NIH collaborative research activities relating to FXS and associated disorders include efforts aimed at developing treatments and novel interventions through an ongoing cooperative agreement for clinical trials of pharmaceuticals for FXS. This effort is led by NIMH in partnership with the NICHD, which is the NIH lead for research under the Best Pharmaceuticals for Children Act (BPCA), the NINDS, FRAXA Research Foundation (FRAXA), and Autism Speaks. The aim of the clinical trials is to develop therapeutics to treat FXS and autism. Compounds being developed through the NIH-supported cooperative agreement were shown to reverse many associated symptoms in mouse models of FXS. If further testing confirms the compounds' safety in animals, a Food and Drug

Administration (FDA) permit will be requested for research to determine dosage and safety in non-affected human volunteers before moving forward with clinical trials in people with FXS.

The NIH focus on efforts to understand the relationships between FXS and autism continues through the Program Announcement (PA) soliciting research to study the "Shared Neurobiology of FXS and Autism." Originally issued in 2005 and reissued in 2007, the PA established a public-private partnership led by the NIMH in collaboration with the NINDS and the NICHD. The partnership also includes the Canadian Institutes of Health, the Health Research Board of Ireland, FRAXA, and the National Alliance for Autism Research, and Autism Speaks. The grants awarded through this mechanism range from examining language in FXS children to studies in mouse models on structural abnormalities in neurons observed in FXS.

Item

Fragile X - Regarding other Institutes, the Committee urges the NIDDK to expand its research activities on Fragile X, given that Fragile X symptoms often include digestive difficulties, and some affected individuals also show hyperphagia and obesity. The NHGRI is urged to contribute to efforts to expand newborn screening to include Fragile X, and to understand the ethical and psychosocial implications of detection of children and young women who are found to be carriers of FMRP premutations and full mutations. The Committee urges the NICHD to include the collection of genetic and DNA data on women who are relatives of people living with Fragile X in the development of a National Fragile X Patient Registry, to ensure that a comprehensive research strategy on FXPOI as it relates to the FMR1 gene be included in the NIH's Fragile X Research Blueprint, and to continue to prioritize Fragile X as a key prototype in the development of cost-effective newborn screening programs. (pg. 123)

Action taken or to be taken

The NIH investigates fundamental questions related to Fragile X syndrome (FXS) and the other Fragile X related disorders. NIDDK researchers have recently identified a key enzyme responsible for switching the FMR1 gene off in Fragile X cells. They have also found a compound capable of inhibiting this enzyme thereby switching the gene back on. This discovery may mean that someday Fragile X symptoms could be prevented or even reversed, although much additional research is needed to determine whether that will become feasible. The NIDDK also supports robust research programs on obesity, hyperphagia, and digestive diseases, which may ultimately benefit people with FXS who have these conditions. The NIDDK actively participated in the NIH Fragile X Research Coordinating Group and contributed to the development of NICHD-led Fragile X Research Plan.

NHGRI supports research into the ethical and social aspects of Fragile X screening, including newborn screening and carrier screening across the

lifespan. NHGRI also continues to fund comprehensive research on the function of the human genome and the interplay between genetic variation and disease. To further expand our understanding of the genome, NHGRI has continued expansion of the ENCyclopedia Of DNA Elements (ENCODE) project that seeks to identify all functional elements of the human genome.

NICHD is the lead NIH institute for newborn screening research and in association with the Health Resources and Services Administration, Centers for Disease Control and Prevention, Agency for Healthcare Research and Quality, and other public and private partners, leads national efforts to enhance newborn screening programs. NICHD participates in the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children that provides guidance on criteria for the development and implementation of testing and treatment programs for a large number of conditions. NICHD supports research initiatives to develop new testing technologies and new treatments for screened conditions. Currently, the Institute is supporting the development of a screening tool for expanded FMR1 alleles (an alternative form of the gene). As envisioned, the method will be applicable for screening both males and females, and may be capable of using as little as 1 percent of the DNA from a single dried blood spot. The goal is to develop a methodology suitable for screening large populations of newborns or those at high risk (e.g., persons with autism, Fragile X-associated Premature Ovarian Insufficiency (POI), or ataxia). In addition, NICHD recently refunded three Fragile X Centers, which focus on newborn screening, and include studies that assess methods of testing immediate and extended family members and the impact of screening results.

Item

Gene Therapy- - The Committee is aware of the extensive and growing body of research indicating that gene therapy may be useful in developing treatments or cures for a wide range of problems, such as lung disease, retina-causing blindness, cancer, cystic fibrosis, and cardiovascular diseases. Nevertheless, clinical gene therapy protocols seem to be lagging in the United States, especially when compared to Europe. The Committee commends the NIDDK for its recent meeting aimed at delving into this issue and identifying challenges to gene therapy clinical trials and how these barriers could be overcome. The NIH is urged to address those challenges either through organizational improvements and inter-Institute collaboration, realigned funding streams, or other mechanisms aimed at unlocking the promise of gene therapy. (Senate Report No.110-410, p. 124)

Action taken or to be taken

In January 2008, the NIDDK hosted a meeting entitled, "Overcoming Barriers to Development of Gene Targeted Therapies for Hematologic Disease." Speakers and panelists included expert extramural investigators, as well as intramural and extramural scientists from the FDA and from several NIH ICs, including NIDDK, NHLBI, NIAID, NHGRI, NCI, and NCRR. An important opportunity for inter-

Institute communication intended to foster collaboration, the meeting included presentations on both specific gene therapy applications and general topics such as vector design and use, including a presentation on the FDA perspective.

The NIH also hopes to help unlock the promise of gene therapy through initiatives such as the Request for Applications on Molecular Therapy Core Centers. Through this initiative, the NIDDK is renewing its commitment to this centers program, which is intended to support molecular therapy research in order to develop treatments for cystic fibrosis and other genetic diseases within the Institute's mission. The purpose of the Core Centers is to provide shared resources to enhance the efficiency and foster collaborations within and among institutions with a strong existing base of funded research relevant to gene transfer and gene correction technologies.

Through these and other efforts, the NIH will continue to support research projects in the field of gene therapy.

Item
Human Tissue Supply - The Committee remains interested in matching the increased needs of NIH grantees that rely upon human tissues and organs to study human diseases and search for cures. The Committee encourages the Director to increase support for nonprofit organizations that supply human tissues to NIH-funded researchers. (p. 124)

Action taken or to be taken
The National Disease Research Interchange (NDRI) is one of many nonprofit organizations in the United States that provide human tissue and organ specimens to biomedical researchers for basic and clinical research. The National Center for Research Resources (NCRR) is the lead Institute/Center for the cooperative agreement that supports the Human Tissue and Organ Resource (HTOR), which is a division of NDRI. Since1995 to the latest statistics, over sixty four thousand 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. There were over 410 active biomedical researchers utilizing this program this past year including those that are NIH-funded.

NCRR maintains the core funding for Human Tissues and Organs Resource for Research cooperative agreement, now in its eighteenth year, with co-funding from NEI, NHLBI, NIAID, NIAMS, NIDDK and the Office of Rare Diseases. The 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 and the NIH is continually 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 supports for mission-specific resources. The NIH Office of Rare Disease provided additional funding this past year to support the National Disease Research Interchange (NDRI) Rare Disease Initiative for tissue distribution, research recruitment, source and database development, and outreach to rare diseases patient advocacy groups and their members.

Item
Hydrocephalus research - The Committee urges the Director to establish a working group to intensify research efforts into the epidemiology, pathophysiology, disease burden and treatment of hydrocephalus, and to ensure collaboration among relevant Institutes. The Committee requests an update on the progress of such collaborative efforts in the fiscal year 2010 budget justifications, as well as projected spending on hydrocephalus research. (p. 124)

Action taken or to be taken
Please refer to page 213 of this document for the response to this significant item regarding Hydrocephalus research.

Item
Inherited Diseases of Bone – The Committee urges the NIH to expand genetics research on diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, and Paget's disease. The Committee encourages the NIAMS, NIA and other Institutes to issue program announcements on the interaction of environmental and genetic factors in Paget's disease and for a study of the current prevalence of Paget's disease. Furthermore, the Committee urges the NIH to expand research on skeletal stem cell biology and the genetics and pathophysiology of rare bone disorders such as fibrous dysplasia, melhoreostosis, XLinked hypophosphatemic rickets and fibrodysplasia ossificans progressiva. (p. 124)

Action taken or to be taken
Please refer to pages 206 (Bone Diseases) of this document for the Office of the Director's response to the significant item on bone diseases.

Item
Limb-sparing Techniques – The Committee is aware that the wars in Iraq and Afghanistan are producing a new type of patient-a war fighter with multiple and severely mangled extremities. Therefore, there is a profound need for targeted medical research to help military surgeons find new limb-sparing techniques to save injured extremities, avoid amputations, and preserve and restore the function of injured extremities. The Committee urges the Director of NIH to make this issue a trans-NIH priority and to use the considerable expertise of all of the Institutes to fund research that will provide military surgeons with the tools to save severely injured limbs. (p. 124-125)

Action taken or to be taken

Please refer to page 214 of this document for the Office of the Director's response to the significant item on limb-sparing techniques.

Item

Lupus Research Plan. - In response to this Committee's request for a 5-year trans-Institute research plan on lupus, NIH last year developed and published ''The Future Directions of Lupus.'' The Committee requests an update in the FY 2010 congressional budget justifications. (p. 125)

Action taken or to be taken

An update on the plan is provided in the fiscal year 2010 congressional budget justification, within the NIAMS section, which is the lead Institute for lupus research.

Item

Metabolic Diseases and Bone – The Committee urges the NIH to support research in the emerging field of metabolic diseases and bone. The increase in childhood obesity and its negative consequences on bone represents a significant health threat. New research indicates connections between diabetes and neural diseases and bone that were previously not suspected and merit further research. Therapies are required for secondary osteoporosis in children such as calcium supplementation and physical activity. The Committee also encourages more research on the beneficial and/or adverse effects of bone therapies such as bisphosphonates in children and adults with many chronic diseases. (p. 125)

Action taken or to be taken

Metabolic diseases, such as diabetes, adversely affect the manner in which our bodies process food into growth and energy. Individuals suffering from these disorders tend to have an increase in osteoporotic bone fracture due to decreased bone density. In addition, since fat metabolism is an aspect of energy utilization where unused calories are stored as fat, diabetes is linked to obesity. The relationship between fat metabolism and bone growth is being investigated by researchers supported by NIAMS. Recently, a group of scientists identified the PPARG gene, which has long been known to be important for fat metabolism, as a key component of how a person's skeleton responds to dietary fat as measured by bone mineral density (BMD). Data in both mice and humans indicate that fat metabolism and BMD have much more to do with PPARG variation than diet. Therefore, it is reasoned that obesity and bone health are interrelated conditions that are at least partly dictated by the same gene.

NIAMS-supported researchers found that physical exercise, specifically jumping, by children results in increased skeletal growth. Since bone is responsive to mechanical loading, it has been assumed that physical activity and exercise contribute to achieving optimal bone mass during childhood and adolescence. It

was found that the bone gains in children that result from 7 months of jumping exercises during regular physical education classes can be maintained for up to 8 years. This build-up of healthy bone is one of the best ways to combat the bone loss that is commonly faced later in life.

Many characteristics of bone contribute to its strength and resistance to fracture. BMD is a quality that has a well-established measurement tool to assess an individual's risk of fracture. People who have low BMD can make lifestyle changes and take bone-active drugs, such as bisphosphonates, to protect their bone health. However, improvements in BMD do not completely explain the anti-fracture efficacy of different types of bone-active drugs on the market today. Bone mineral architecture, composition, distribution, and crystal structure are other properties affecting bone durability that may be influenced by these drugs. NIAMS-supported researchers have recently learned that bone mineralization is a strong predictor of bone strength and can be maintained through the use of biphosphonates. Experiments in an animal model of estrogen deficiency demonstrated that a single dose of bisphosphonates prevented loss of a type of bone that commonly deteriorates with age, and also preserved the bone density, mineral content, and ability to tolerate compression stress. These results will improve physicians' ability to effectively treat post-menopausal women and may help in targeting specific treatments to appropriate patients.

Item

Native Hawaiians - The Committee remains concerned about the high incidence of certain diseases among Native Hawaiians. In particular, it strongly urges additional research concerning these disparities in the areas of cancer, heart disease, cerebrovascular disease and diabetes. (p. 125)

Action taken or to be taken

The NCMHD has established a Center of Excellence in Hawaii as a regional focal point for research, research training and community engagement aimed at the health status of Native Hawaiians and other Pacific Islanders. Importantly, the University of Hawaii's Center for Native and Pacific Health Disparities Research has a particular emphasis on research aimed at the clustering of risk factors, such as dyslipidemia, hypertension, hyperglycemia, central adiposity and insulin resistance, which predisposes individuals to cardiovascular disease and diabetes.

In addition, grants through the NCMHD Endowment Program and the Research Infrastructure in Minority-Serving Institutions (RIMI) program have enhanced the research infrastructure and capacity at academic institutions in Hawaii which will allow them to seek additional resources and perform state-of-the-art health disparities research for Native Hawaiians and other Pacific Islanders. The purpose of the NCMHD Research Infrastructure in Minority Serving Institutions Program (RIMI) is to establish, strengthen and/or improve the scientific infrastructure and environment of academic institutions through grant support to

develop and/or expand existing capacities and programs for institutional and individual faculty initiated basic, biomedical, clinical and/or behavioral research and research training programs that contribute to building a cadre of research scientists in the elimination of health disparities.

Item

Neurofibromatosis (NF) - The Committee encourages the NCI to substantially increase its NF research portfolio in pre-clinical and clinical trials. 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 disorders such as autism, spinal cord injury, learning disabilities and memory loss. In addition, the Committee continues to encourage the NICHD to expand funding for NF patients in the area of learning disabilities, including the creation of NF centers. NF2 accounts for approximately 5 percent of genetic forms of deafness; the Committee therefore encourages the NIDCD to expand its NF2 research portfolio. (p. 125/126)

Action Taken or to be Taken

NCI's basic research program includes 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 an example, 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. Clinical trials on NF are underway through the NCI Children's Oncology Group (COG) and in the NCI intramural Pediatric Oncology Branch (POB). The COG is specifically treating children with NF1-associated tumors, particularly low-grade gliomas. The study's primary objective is 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 National Institute of Neurological Disorders and Stroke (NINDS) support research to understand and develop treatments for NF tumors in the nervous system, as well as research on neurological complications of NF. Current funded projects include studying spatial learning deficits in a mouse model of NF1 to better understand how the NF1 mutation results in learning disabilities and studying behavioral and brain imaging methods to help determine the best interventions for reading disabilities in patients with NF. NINDS-funded researchers are also working to understand skeletal abnormalities associated with NF, including scoliosis and other spinal abnormalities. In addition, NINDS organized a workshop in January 2008 entitled, "mTOR Signaling: From Cancer to CNS Function", which focused on the role of the mTOR signaling pathway in

the development of central nervous system tumors and on potential therapeutics that target this pathway.

The National Institute of Child Health and Development (NICHD) have funded multiple projects in recent years addressing the neurology, genetics, and the behavioral consequences of NF.

Mutation of the NF2 tumor-suppressor gene on chromosome 22 is strongly associated with bilateral nerve tumors called vestibular schwannomas, or acoustic neuromas. The National Institute on Deafness and Other Communication Disorders (NIDCD) supports research that focuses on multiple aspects of NF2 including studies on the molecular signals that lead to these schwannomas. The studies examine how gene transcription, specific biochemical signaling pathways, and growth factors are expressed and regulated in tumor formation in hopes that potential drug treatments can be developed. Typically, surgical removal of the NF2 tumors may sever the auditory nerve, causing hearing loss. These individuals cannot be helped by a cochlear implant (CI) in the inner ear because their auditory nerve is damaged. Since they do retain the central auditory circuits in the brain, researchers have developed surface auditory brainstem implants (ABIs). The ABI technology is still relatively new and novel electrode arrays and sound-encoding strategies are being examined to improve sound perception in individuals with NF2. In addition, different auditory implant sites may affect sound perception.

Item

Opsoclonus-Myoclonus Syndrome (OMS). - The Committee urges the Director to accelerate research on OMS and related paraneoplastic syndromes. Because the causes and symptoms of OMS cross scientific boundaries, research efforts should involve the Office of Rare Diseases (ORD), NINDS, NCI, NIAID and NEI, as well as private associations and nonprofit organizations. (p. 126)

Action taken or to be taken

The National Cancer Institute's Cancer Therapeutic Evaluation Program (CTEP) supports the Children's Oncology Group clinical trial entitled "Use of Intravenous Gammaglobulin Therapy for Patients with Neuroblastoma-Associated Opsoclonus-Myoclonus-Ataxia Syndrome Treated with Chemotherapy and Prednisone". This clinical trial investigates whether treatment with chemotherapy with or without gammaglobulin will improve the neurologic outcome in these children. Another project called "Protein-RNA Recognition in Neurodegenerative Syndromes" focuses on structural (x-ray and NMR) and functional (the impact of mutations) investigation of protein-RNA recognition in Fragile X retardation and paraneoplastic opsoclonus-myoclonus ataxia syndromes.

Another aspect of OMS is rapid, involuntary, horizontal and vertical, unpredictable, fast eye movements that threaten clear vision by causing image

motion on the retina and may be caused by ion channel dysfunction in the burst cell membrane. This hypothesis has been tested by a neuromimetic computational model of the burst neurons. The simulations suggest that alterations in membrane properties can cause saccadic oscillations. This conceptualization of opsoclonus may lead to several novel therapies to suppress these abnormal eye movements and thereby restore normal vision. Furthermore, investigators are defining the role of neural circuits and neuronal membrane properties to understand what causes oscillations. By identifying which ligand-gated channels (i.e., receptor proteins) are involved in clinical deficits, we will be able to suggest drugs that may have therapeutic value. This research is currently undertaken by National Eye Institute researchers and researchers at Johns Hopkins University, and other medical schools in the country.

In paraneoplastic neurological disorders like OMS, the body's immune response to cancer triggers a secondary autoimmune response in the brain targeting proteins expressed in tumor tissue that normally appear only in certain types of neurons. National Institute of Neurological Disorders and Stroke supports two studies: "Hu Proteins as Novel Splicing Regulators in Neurons, and Neurology" and "The Molecular Role of N-RBPs in the Brain." The studies aim to understand the functions in the brain of proteins targeted in OMS and in a paraneoplastic disorder called Hu syndrome. This research may also lead to new insights into the pathogenesis of these disorders.

In addition, ORD has been invited together with other ICs to participate in an opsoclonus-myoclonus syndrome working group initiated by the Pediatric OMS Research Fund. The first working group meeting took place in fall 2008 and a scientific conference is planned for the summer of 2009. Objectives include developing research collaborations and identifying research opportunities for OMS and improving current treatment outcomes by determining diagnostic criteria and treatment options for healthcare providers. The OMS working group will involve research investigators from the academic community and the National Institutes of Health, patient organizations, medical specialty societies, industry, and others in the planning of the scientific conference. The work of this broad-based group will significantly contribute to increased awareness of the need for accelerated research and collaborations towards better therapies for patients with OMS.

Item

Pain Research. - Pain, shortness of breath, and nausea are the most common physical symptoms in all serious illnesses. The Committee urges the NIH to devise a strategy that will increase the funding devoted to basic and clinical research in pain, shortness of breath, and nausea. In addition, the Committee requests an update on the Pain Progress Review Group in the fiscal year 2010 congressional budget justifications. (p. 126)

Action taken or to be taken

One of the most common reasons for visits to a doctor is for treatment of pain. Most painful conditions are resolved with little to no treatment. However, in some patients, acute pain may become chronic.

The NIH Pain Consortium serves as the focal point for collaborative pain research at the NIH. The goals of the Consortium are to develop a comprehensive and forward-thinking pain research agenda for the NIH, identify key opportunities in pain research, increase visibility for pain research, and pursue the pain research agenda through public-private partnerships. The Pain Consortium fosters these efforts through sponsorship of an annual symposium at the NIH. This day-long symposium highlights research by NIH supported pain researchers. Member Institutes co-sponsor initiatives on topics in pain research that span Institute-specific research missions.

Pain and nausea are dominant symptoms of many types of gastrointestinal disease. The NIH supports research programs that address each of these disease features. For example, the NIH supports the Center for Neurovisceral Sciences & Women's Health at UCLA, with a research focus on women's health and functional pain disorders, including irritable bowel syndrome (IBS). The Center is investigating sex-related factors that contribute to these disorders, in terms of development, symptoms such as pain, and treatment response. The NIH also sponsors research efforts that address nausea. The Gastroparesis Clinical Research Consortium is conducting multicenter clinical research studies of gastroparesis, a clinical syndrome characterized by multiple symptoms, one of which is nausea. The purpose of this Consortium is to develop new approaches to diagnosis and treatment of this syndrome and its symptoms.

Shortness of breath or dyspnea is a symptom that results from a complex interaction of the central nervous system (brain) and the peripheral nervous system. Many things can trigger dyspnea. Dyspnea may occur in association with chest tightness, anxiety, worsening disease, or diminished quality of life. The NIH supports dyspnea-related research in three areas: (1) Pulmonary clinical trials; (2) Studies which address the factors that affect perception of symptoms, an important issue in diseases such as asthma because patients with diminished symptom perception tend to reach care later and have more severe disease; and (3) Basic researchers are studying respiratory drive, including the neurobiological basis for dyspnea in lung transplant patients.

The Pain Consortium 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 current proposal includes three levels of planning meetings with different goals and scope to be held over the course of one year (by 2010), in order to develop a five-year plan for pain research support and evaluation. This planned process for the pain progress

review group is based on similar efforts executed by Institutes at NIH to examine important topics in health research.

Item
Psoriasis – The Committee strongly encourages the NIAMS and NIAID to undertake and expand basic research related to understanding the genetics and immunology of psoriasis, including how genetic variation gives rise to differences in treatment responses and mechanisms that link skin and joint inflammation. The Committee encourages the NIMH to conduct research to identify any underlying biologic reason for mental health issues associated with psoriasis and to understand how negative social and psychological effects impact psoriasis. The Committee encourages the NIEHS to study these associations to better understand psoriasis and psoriatic arthritis in order to treat and prevent these diseases. p. 126

Action taken or to be taken
Please refer to page 227 of this document for the Office of the Director's response to the significant item on psoriasis.

Item
Sex Differences - For many disorders, the sex of the patient influences disease etiology, natural history, diagnosis and treatment alternatives and outcomes. One of the fields where such differences are most pronounced is neuroscience. The Committee encourages each of the 15 institutes involved in the NIH Neuroscience Blueprint to carefully analyze their Blueprint research portfolio to ensure sex is included as a variable, when appropriate, and to require that all reported results include sex-specific analysis. (p. 126)

Action taken or to be taken
The 15 Institutes or Centers (ICs) of the NIH Blueprint for Neuroscience Research recognize that sex is an important variable that needs to be considered and analyzed in many studies of the nervous system. The NIH Blueprint aims to catalyze research progress by funding the development of tools and resources that transcend the mission of any single NIH Institute. These tools are available to be used in investigator-initiated projects across many fields of neuroscience. Several examples of how these tools are currently or could be used to study sex differences follow.

The NIH Neuroscience Microarray Consortium has proven invaluable to a number of researchers exploring the molecular basis of sex-based differences in nervous system development and dysfunction. The Microarray Consortium provides investigators with access to state-of-the-art technologies to identify gene activity levels and variations in DNA sequences.

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 of high interest to the neuroscience community 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 example of a study that has taken advantage of a marker mouse line from the GENSAT project mapped brain pathways that are involved in sex-specific reproductive and defensive behaviors in mice.

Several Blueprint clinical research tools may facilitate analysis according to sex. The NIH Pediatric MRI Study of Normal Brain Development, supported by the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Drug Abuse (NIDA), and the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) is collecting images of the brain throughout normal development. The Blueprint has supported the expansion of this study to include additional subjects and data collected using a state-of-the-art variation of MRI called Diffusion Tensor Imaging (DTI). The data collected from this project will enable the study of normal brain development, provide reliable control data for studies of childhood disorders and diseases that affect the brain, and may aid in the development of new diagnostic tools. The project includes both girls and boys and could therefore be a powerful tool for exploring sex differences in brain structures during development.

In addition to Blueprint-supported tools and resources, subsets of Blueprint ICs have participated in collaborative announcements to stimulate research that addresses sex differences in neuroscience. Several neuroscience research initiatives that aim to provide scientific knowledge related to sex differences on such chronic pain conditions as migraine; irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and interstitial cystitis are supported by Blueprint ICs, along with the Office of Research on Women's Health (ORWH).

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 prevention and treatment 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. 126)

Action taken or to be taken

NIDDK recognizes that the most common cause of pediatric neurogenic bladder is spina bifida, and that bladder research and bladder tissue regenerative research may lead to improvements in the quality of life for patients with this

condition. Recently, the NIDDK funded a study to explore the possibility of developing a neural prosthesis to restore bladder function in adults with neurological disorders. The NIDDK also is supporting developmental bladder studies, including use of the mouse model to understand how the components of the bladder are formed. Another study is determining the developmental progression involved in innervating the bladder.

The NICHD Birth Defects Initiative provides a venue for investigators interested in discovering the causes of structural birth defects, including spina bifida, to meet annually to discuss and share their knowledge. One of NICHD's currently funded projects focuses on the mechanisms of neural tube defects (NTDs), and the other is looking at prenatal factors that influence the nutritional/health status of pregnant women and its impact on the health of the developing fetus, particularly as it relates to NTDs. In addition, NICHD supports the maintenance and distribution of mouse models for NTDs and other conditions. The goal of another NICHD-funded project is to gather extensive information about the sensorimotor capacities of infants with spina bifida in their first year of life, which is critical for designing future interventions.

The NICHD is currently funding a multicenter network trial, the Management of Myelomeningocele study (MOMs) evaluating the safety and efficacy of fetal surgical repair compared to traditional postnatal repair of open NTDs. No other U.S. site is offering this procedure outside of the NICHD trial. Using a rigorous and common protocol, this study enrolls women with diagnosed isolated spina bifida in the midportion of their pregnancy. After consenting, they are randomized to receive either prenatal surgery on the mother and fetus or to return at the end of pregnancy to undergo standard closure by the same surgical teams. Study endpoints will include an evaluation of the effect on the mother's health during the index pregnancy and in future pregnancies; fetal outcome; and neonatal and infant need for shunting (treatment for orthopedic and urologic problems common to people with spina bifida); and an evaluation of early childhood neurologic and mental functioning. Information about the trial can be found at: www.spinabifidamoms.com.

NINDS supports research into the causes of spina bifida and other NTDs. Ongoing projects include a study of gene expression during neural tube closure in human fetuses, a prospective epidemiological study on the association of arsenic exposure with neural tube defects, and a collaborative study using large epidemiological datasets to examine the roles and interactions of genetic and nutritional factors. NINDS also supports research on other congenital brain malformations and has provided joint support with NICHD and NIH's Office of Rare Diseases for an upcoming scientific conference on Chiari Malformation, a cerebrellar malformation present in a majority of spina bifida cases.

Many children born with spina bifida develop hydrocephalus, and NINDS also supports research to better understand and treat this condition.

Item

Spinal Muscular Atrophy (SMA)) – Given the near-term scientific opportunity for an effective treatment, the Committee urges the Director to expeditiously establish a trans-NIH working group on SMA to include the NINDS, NICHD, NIAMS and NIGMS, as well. The Committee urges the NICHD to support large-scale pilot studies that support the development of a national newborn screening program for SMA. The NINDS is strongly encouraged to plan and budget for each of the successive stages of the SMA Project, including for preclinical testing of multiple compounds and the necessary clinical trials infrastructure on a national and coordinated level and to begin a multicenter trial with leading drug candidates. Finally, the Committee urges the 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. (p. 126, 127)

Action taken or to be taken

Please refer to page 230 of this document for the response to this significant item regarding Spinal Muscular Atrophy.

Item

Tuberous Sclerosis Complex – The Committee encourages the Office of the Director to continue to support the Trans-NIH TSC Coordinating Committee, with particular emphasis on research on the link between TSC and autism spectrum disorder, as well as between common disorders (cancer, diabetes, aging, arthritis and obesity) and rare diseases (Peutz-Jegher Syndrome, Cowden's Disease, Proteus Syndrome, and Lymphangioleiomyomatosis) that share a link to signaling pathways in cells throughout the human body. (p. 127)

Action taken or to be taken

Please refer to pages 232 of this document for the response to this significant item regarding Tuberous Sclerosis Complex.

Item

Renovation of Building 3. – The Committee strongly urges the NIH to use a portion of the recommended increase to renovate Building 3 on the Bethesda campus. The building has been decommissioned and is currently vacant. The renovation and restoration to productive use of this building will allow the NIH to provide space for administrative support of the scientific research portfolio. P. 128 (Senate Report 110-410)

Action taken or to be taken

The project, estimated at $20 million (in FY 2009 dollars) encompasses the renovation of 49,243 gross square feet of office space in presently vacant Building 3 on the NIH Bethesda campus. Funding would permit NIH to turn an underutilized, historic structure into a modern administrative facility by renovating the existing building rather than constructing new space, furthering NIH's

sustainability and environmental goals. Part of the historic core of the campus, the building has been vacant and underutilized since the early 2000's.

NIH is also in the process of implementing a cost effective, incremental plan to renovate the Warren G. Magnuson Clinical Center (Building 10). NIH plans to raise its Condition Index from 20 to an acceptable level, and convert unusable, vacant areas into viable biomedical laboratory and clinical research space. The renovation of Building 3 would facilitate this by liberating research space in Building 10 enabling needed renovations to occur, while at the same time not incurring the additional cost to house the affected staff in temporary leased space. The plan, as developed, calls for housing the Scientific Directors and their administrative staff in renovated Building 3. These groups do not have to be in Building 10 and can be located in other administrative space outside the building. Building 3 provides the best location given its close proximity to the clinical/research program which is largely located in Building 10, the CRC, and surrounding buildings.