

## SIGNIFICANT ITEMS (SIs)

### FY 2008 House Appropriations Committee Report 110-231 and FY 2008 Senate Appropriations Committee Report 110-107

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# National Cancer Institute

## House Significant Items

### Item

#### ***Cancer Metastasis to Bone***

A frequent complication of cancer is its spread to bone (bone metastasis) that occurs in up to 80 percent of patients with myeloma and 70 percent of patients with either breast or prostate cancer—causing severe bone pain and pathologic fractures. Only 20 percent of breast cancer patients and five percent of lung cancer patients survive more than five years after discovery of bone metastasis. The Committee understands that immune response plays a role in cancer metastasis and encourages NCI to focus research in the emerging area of osteoimmunology. The Committee encourages NCI, as well as NIAMS, NIA, and NIDDK, to support research to determine mechanisms to identify, block and treat cancer metastasis to bone. Furthermore, the Committee encourages NCI to expand research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma in children and teenagers who develop this cancer. In addition, NCI is encouraged to strengthen research on tumor dormancy as it relates to bone metastasis. (p. 127)

### Action taken or to be taken

NCI continues to support a diverse portfolio of research on bone metastasis, tumor dormancy and osteosarcoma. NCI convened a workshop related to understanding the field of tumor dormancy, the latency period that occurs in some patients between initial treatment and evidence of metastasis. The workshop addressed current barriers and research opportunities. The Workshop Report and recommendations were published in Cancer Biology and Therapy, Vol. 6: 1-9, September 2007.

NCI's cancer biology research portfolio includes support for four large program project grants that focus on bone metastasis with a special emphasis on tumor cell–bone interactions. Additionally, the NCI's Tumor Microenvironment Network initiative includes a research focus on the role of the microenvironment in bone metastasis. Several of the prostate cancer Special Programs of Research Excellence (SPOREs) are engaged in research on metastasis to bone as well, devoting research to the bone microenvironment as a target for multi-agent therapy and conducting studies focused on understanding the molecular mechanisms underlying prostate cancer angiogenesis (growth of blood vessels from surrounding tissue to the tumor) and bone metastasis.

Within the clinical research spectrum, NCI's Pediatric Pre-clinical Testing Program is now poised to assess 10 -12 new agents or combinations of agents for their activity against the osteosarcoma panel. The panel contains seven human xenograft (graft of tissue transplanted between animals of different

species) models of osteosarcoma, and these are used to evaluate the antitumor activity of novel anticancer agents for their potential utility against osteosarcoma in children and adults.

Pain can be a harsh reality when cancer metastasizes to the bone. Some studies show that 70 percent of patients with advanced stages of cancer experience significant levels of pain. NCI has several ongoing clinical trials to evaluate treatments for alleviating the pain associated with these conditions. These include: (a) evaluating the effectiveness of a single dose of radiation therapy compared to multiple smaller doses to see if the convenience of a single treatment can provide the same benefit as a more time-consuming multi-dose treatment; (b) comparing the effectiveness of radiopharmaceuticals (drugs that emit radioactivity at their site of action) and zoledronic acid, an agent that decreases the degree of bone loss; and (c) evaluating the effectiveness of using extremely cold temperature locally to freeze bone lesions and interfere with their growth.

Lastly, NCI continues to collaborate with other federal agencies and scientific societies and foundations to promote research related to bone metastasis and bone-related cancers such as osteosarcoma. NCI, along with a number of NIH Institutes, is an active participant in the Federal Working Group on Bone Diseases and participates in national and international conferences on bone metastasis, such as the one sponsored by the International Cancer Bone Society (2006, 2008) and the other on the skeletal complications of malignancy sponsored by the Paget Foundation, (October 2007).

#### Item

#### ***Gynecologic Cancers***

On average, in the United States, one woman is diagnosed with a gynecologic cancer every seven minutes. Thus, almost 200 women per day or 80,000 women per year are diagnosed with gynecologic cancers. Furthermore, almost 30,000 women die every year from a gynecologic cancer. Existing NCI funding for SPOREs, program projects, the Early Detection Network, and investigator initiated grants has accelerated basic, molecular-based research discoveries for gynecologic cancers. Recent progress combined with the need for further innovation makes this group of cancers an important focus under NCI's broader "roadmap" initiatives. The Committee encourages NCI to give priority to gynecologic cancers under its Nanotechnology Plan (CNPlan), its Oncology Biomarker Qualifications Initiative (QBQI), and its Cancer Genomics Atlas Project (TCGA), jointly conducted with the National Human Genome Research Institute. This inclusion will allow laboratory discoveries to be translated into clinical applications at the bedside causing a decrease in the mortality rates for women with gynecologic cancer. (p. 127/128)

### Action taken or to be taken

NCI's research on gynecologic cancers spans the continuum of cancer research with a focus on basic, clinical, translational, and prevention research. NCI is fostering translational research into biologic prognosticators and therapeutic effects of chemotherapy to speed the development of new gynecologic cancer treatments. Other recent activities include the establishment of a public-private partnership with the pharmaceutical/biotechnology industry, NCI-sponsored Cancer Centers and the cooperative groups to address these types of cancer, as described below.

Ovarian cancer is one of the cancers recently chosen as one of three tumors for study in the Cancer Genome Atlas (TCGA) Pilot Project. The (TCGA) Pilot Project is a three year, \$100 million collaboration to test the feasibility of using large-scale genome analysis technologies to identify important genetic changes involved in cancer. The project aims to identify all alterations in genes for selected tumors -- especially those that can serve to differentiate cancer subtypes. Processing of ovarian cancer samples under this pilot project is currently in progress.

NCI continues to support and advance ovarian cancer research through funding of Centers of Cancer Nanotechnology Excellence (CCNEs). Using mouse model systems, these centers have developed nanotechnology-based platforms for the successful delivery of therapeutic agents to ovarian cancers having resistance to multiple drugs. CCNEs have also developed new targeting methodologies for cervical cancer and have identified new biological markers for ovarian cancer using novel, nanotechnology-based screening platforms.

Two NCI-supported projects have found gene expression profiles that can distinguish chemo-sensitive from chemo-resistant ovarian cancer. These findings are critical because about two-thirds of advanced stage ovarian cancer patients will respond to standard chemotherapy with platinum-based drugs, but the rest are unresponsive or will relapse quickly. Determining a patient's chemo-resistance versus chemo-sensitivity will help clinicians offer experimental treatments to resistant women, rather than providing treatment likely to have little benefit. More work is required to refine these findings into reliable clinical tests. However, both studies suggest new targets for future drug development.

The NCI Specialized Programs of Research Excellence (SPORES) in Ovarian Cancer remains a key component of NCI's overall research portfolio for gynecologic cancers. Currently, a cervical SPORE is developing a single vaccine protective against all types of oncogenic Human Papilloma Virus (the main cause of cervical cancer). While the current vaccine protects against about 70% of cases, the new vaccine may protect nearly 100% of cervical cancer cases.

## Item

### ***Gynecologic Oncology Clinical Trials Cooperative***

The Committee recognizes NCI's longstanding commitment to improving the health of women through gynecologic oncology clinical trials. These trials have led to the identification of new therapeutic agents and techniques for treating gynecologic cancers. This effort has directly produced improved outcomes for ovarian cancer patients as a result of changes in the way ovarian cancer is treated and the development of a vaccine for preventing the virus that causes cervical cancer. The Committee encourages NCI to continue its support of gynecologic oncology clinical trials through public-private partnerships with the pharmaceutical and biotechnology industries and the NCI-sponsored cancer centers and cooperative groups. (p. 128)

### Action taken or to be taken

The Gynecologic Oncology Group (GOG) is one of the nine NCI-sponsored Clinical Trials Cooperative Groups (CTCG). Since, 1970 the NCI has worked closely with the GOG on the design and conduct of innovative phase II trials and definitive phase III trials, which have helped identify state-of-the-art care for women with gynecologic malignancies. More recently, the GOG has worked with NCI to expand its research portfolio into other critical areas of cancer research that includes prevention, epidemiology, quality of life, survivorship, prognostic markers, and translational science.

Through its public-private partnership with the pharmaceutical and biotechnology industries, NCI works to identify promising new anti-cancer agents and bring them to clinical evaluation quickly. For the evaluation of these novel agents in gynecologic cancers, the NCI relies heavily on the GOG, as well as NCI-designated Cancer Centers and other North American CTCGs. In addition, the NCI provides logistical support to the Gynecologic Cancer Intergroup, an umbrella organization which brings together 15 cooperative groups from around the world that conduct clinical trials for women with gynecologic malignancies. International collaboration permits trials to be completed faster, thus providing answers sooner on how best to treat cancer patients.

The GOG is also working with NCI researchers to study patterns, or profiles, of blood proteins among women with enlarged ovaries who 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 with surgery and chemotherapy. 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.

Scientists in NCI and NCI-sponsored SPORE are also searching for new therapies and biological markers that predict response to therapy or survival for ovarian cancer using powerful technologies to look at genes or proteins.

Building upon the success of the current vaccines to protect against cervical cancer, NCI continues to support development of the second generation HPV vaccines that can protect against an even higher proportion of serious HPV infections.

#### 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.128)

#### Action taken or to be taken

To date, prevention for cervical cancer has been achieved primarily through cervical examinations and screening tests and more recently with the introduction of HPV testing. This strategy has been successful, as evidenced by the 70% 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; however, vaccination could be redundant with current screening practices and therefore provide no net reduction in cervical cancer mortality. By implementing complementary vaccination and screening protocols, overall costs may be reduced, providing optimal protection and reducing consequences of unnecessary treatment of women. Determining the most cost-effective, evidence-based screening strategies among vaccinated populations will require studies to prospectively track Pap cytology and HPV typing results.

The two HPV types targeted by vaccines, HPV16 and HPV18, cause approximately 70% of all cervical cancer. However, the global impact of vaccinating adolescents and young adult women against a subset of HPV types linked to cervical cancer is not yet clearly understood. Since vaccination is not expected to protect against all types of HPV that can cause cancer and precancer, and since duration of protection is not fully understood, continued cervical cancer screening in vaccinated populations will remain a priority.

NCI is undertaking a community-based trial of an HPV-16/18 vaccine among nearly 7,500 women in Costa Rica, which will provide important information on the impact of HPV vaccination within a community undergoing a comprehensive

vaccination program 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.

#### Item

##### ***Liver Cancer***

The Committee notes that the incidence of primary liver cancer continues to increase. Liver cancer is one of the few cancers experiencing continuing increases in mortality, and treatment options remain very limited. The Committee encourages NCI to work closely with NIDDK to develop a basic, clinical and translational research program designed to reverse these trends and enhance survivability. (p. 128)

#### Action taken or to be taken

NCI continues to actively sponsor the clinical development of new, investigational agents in liver cancer. Over the past year, the NCI has sponsored development of 12 new agents in 17 phase I and phase II clinical trials for patients with liver and hepatobiliary cancer and has additional studies with new investigational agents under review in these diseases.

In FY 2007, the NCI contributed and assisted in supporting Biomarker Studies for Hepatocellular Carcinoma (HCC) for the NIDDK Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) Trial. The HALT-C Trial is a multi-center, randomized, controlled study that tested whether long-term pegylated interferon (i.e., interferon plus polyethylene glycol) treatment would prevent progression to liver failure, HCC, the need for liver transplantation, or death in persons with advanced chronic hepatitis C (significant fibrosis or cirrhosis).

NCI intramural investigators have used advanced genomic technologies to define subclasses of HCC with different gene expression patterns that are associated with length of survival. The “survival” genes provide a rich source of potential diagnostic markers and novel therapeutic targets for the development of new treatment modalities. The researchers have also identified a new class of liver tumors with a particularly bad prognosis, which appear to be derived from adult liver stem cells. A genetic signature has been identified that may be responsible for progression of these tumors and appears to be a likely target for chemotherapeutic intervention.

NCI along with NIDDK and the NIH Office of Medical Applications of Research are planning an NIH Consensus Development Conference on the Management of Hepatitis B. Hepatitis B and C infection appear to be significant causes of HCC or adult primary liver cancer. The NIH Consensus Development Conference, scheduled for October 20-22, 2008, will explore questions related to hepatitis B high risk groups and long term consequences of hepatitis B infection and liver cancer. Following the conference, an NIH consensus statement will be

disseminated widely to practitioners, health care policymakers, patients, the general public, and the media.

In addition, as part of the NCI's efforts to restructure the national clinical trials enterprise to ensure that it is founded on the best science, the NCI Gastrointestinal Steering Committee (GISC) and other stakeholders oversee major clinical trial development in GI cancers, including liver cancer. A major goal of the GISC and its associated task force is to increase the efficiency of clinical trial collaboration, reduce trial redundancies, and increase information exchange at an early stage of trial development in this disease area.

#### Item

##### ***Pancreatic Cancer***

The Committee recognizes that pancreatic cancer is the country's fourth leading cause of cancer death among men and women. While NCI support for pancreatic cancer research has increased during the past several years, unfunded opportunities remain. The Committee strongly encourages the Institute to continue to support the existing pancreatic cancer SPORES and to consider using separate pay lines for each cancer within the SPORE program. (p. 128)

#### Action taken or to be taken

NCI has three SPOREs that are exclusively devoted to research on pancreatic cancer. They are located at the Mayo Clinic, the M.D. Anderson Cancer Center, and the University of Alabama at Birmingham.

At Mayo, the rapid recruitment and follow-up of patients for the patient and tissue repository has significantly improved the quality and types of studies that can be done. Findings have included certain risk factors for developing pancreatic cancer at a young age and the characterization of a novel pathway for the regulation of migration and angiogenesis (development of the blood vessels) in pancreatic cancer cells.

Researchers at M.D. Anderson are conducting five translational projects ranging from the identification and development of a sophisticated pancreas-specific marker and exploration of the feasibility and therapeutic efficacy of gene therapy, to an investigation of the activity of a novel proteasome inhibitor, bortezomib, in pancreatic cancer cell lines and a Phase I clinical trial of bortezomib plus another agent, cisplatin, in patients with pancreatic cancer.

The Pancreatic Cancer SPORE at Birmingham has a tumor bank that houses specimens of pancreatic and other related cancers. It also tests tissue specimens using microarray real-time quantitative polymerase chain reaction (RT-PCR) assays in order to amplify DNA sequences and thereby distinguish potential long-term survivors from patients at high risk for recurrence. Among other results, they have made progress in the identification of markers for pancreatic cancer

progression and in the development of a genetic model for early detection.

In addition, there are pancreatic studies underway at the gastrointestinal SPOREs. The committee can be assured that NCI's review of pancreatic cancer grants, as are all applications submitted for NIH support, are reviewed by at least three experts in the areas proposed for study. The three assigned reviewers will include experts in both the organ site, in this instance, pancreatic cancer, as well as the other aspects of the application, such as drug development, genetics, biomarkers, or cell growth. The evaluations are done by experts in both the unique features of the specific cancer and the research areas of focus of the application.

The NCI is pleased to assure the Committee that R01 grant applications with 50 percent relevancy or greater to pancreatic cancer research have been given special funding consideration since FY2004. This policy will continue to be in place in the future.

#### Item

##### ***Non-Hodgkin lymphoma***

Although there are effective treatments for Hodgkin lymphoma, survivors of this form of lymphoma may have a wide range of side effects from the disease and will require long-term monitoring and follow-up care to address the long-term effects. The Committee encourages the NCI to dedicate some of its survivorship research to problems confronted by lymphoma survivors. (p.128/129)

#### Action taken or to be taken

Results from earlier epidemiologic studies have paved the way for genomic and molecular analyses that may be used to predict NHL survival and could ultimately lead to new prevention strategies. Leveraging the availability of several long-standing NCI resources, including population-based case-control and cohort studies, and linked registry databases, NCI investigators and their extramural colleagues are conducting critical evaluations of possible risks from environmental exposures together with genetic predisposition and identifying molecular markers of NHL, using new analytic tools. A recent NCI study was the first to show that common genetic variations in immune genes were associated with survival in patients with follicular lymphoma. Another study found that a gene expression signature of the tumor proliferation rate in mantle cell lymphoma (MCL) is effective in estimating the length of survival following diagnosis. Now, researchers are applying advanced microarray techniques to classify a number of molecular subtypes of NHL to evaluate potential etiologic differences and their prognostic significance.

Proteomic technology is another sophisticated molecular expression technique for identifying diagnostic markers for lymphoma diagnosis and survival. NCI researchers have performed a clinical trial showing that certain protein patterns

found in the blood of patients with cutaneous T cell lymphoma (CTCL) can distinguish this disease from a benign inflammatory disease (psoriasis) and from normal healthy individuals of similar age. They also found that selected markers found in blood are highly associated with mortality in the tumor phase of mycosis fungoides, the most common form of non-Hodgkin lymphoma in the skin. Using a proteomic technology to analyze blood samples, may make it possible for clinicians to recognize and predict how patients will fare with their disease.

Genotyping analyses currently confirmed suspected and identified new common genetic variants, along with gene-environment interactions that may indicate increased risk for developing different types of NHL. Because of the statistical power afforded by the intramural-extramural InterLymph international consortium (<http://epi.grants.cancer.gov/InterLymph>), a number of initial genetic findings implicating the role of immune response genes in the progression of NHL have been confirmed.

#### Item

#### ***Lymphatic Research and Lymphatic Diseases***

The Committee recommends that NCI support research on lymphedema, a chronic, progressive and historically neglected complication that must be endured by many cancer survivors. The Committee also encourages the Institute to support the study of lymphangiogenesis and lymphatic imaging, which are critical to a greater understanding of cancer metastasis and lymphedema. (p. 129)

#### Action taken or to be taken

Lymphedema, the condition of fluid retention due to problems with the lymphatic system, is a serious side effect of the spread of cancer and cancer treatment. This swelling is due to the disruption of the lymphatic system to drain off the normal flow of lymph from the vascular system's blood vessels into all tissues. It is especially clinically important in breast and gastrointestinal tract cancers, as well as a potential clinical problem in all metastatic cancers that involve the lymphatic system.

NCI supports research to measure the incidence, severity, and modulation of lymphedema, understand risk factors for its occurrence, and determine the impact on quality of life in the years after diagnosis and treatment of breast and other cancers. NCI is committed to funding research that improves technologies for measuring lymphedema as well as technologies for screening, diagnosis, and staging of cancers involving lymph nodes.

Recent research awards from NCI support development of improved ultrasound imaging systems to measure the flow of lymph fluids within tissues and the changes as a result of cancer and cancer treatment. This research may develop

into an ultrasound based clinical tool that can assess the impact of therapy and possibly distinguish reversible from irreversible lymphedema. Additional technologies recently funded include development of fluorescent probes for both lymphatic imaging and breast cancer imaging.

NCI researchers are exploring development of novel systemic imaging techniques that are minimally invasive and have the potential to provide both structural and functional information; this is a particular advantage for cancer imaging, where anatomical depiction alone often provides insufficient information.

Due to small size and poor access, lymphatic function has been difficult to study in the human body. Nanotechnology techniques can be used to produce multicolor images with high fluorescent intensity. Because they are extremely small, they can be directly injected interstitially and used for lymphatic imaging. NIH researchers have shown that two-color spectral fluorescence lymphangiography can provide insight into mechanisms of drainage from different lymphatic basins that may lead to detection of breast cancer in sentinel lymph nodes as well as prevention of complications such as lymphedema of the arm. Other research with quantum dots by NCI intramural investigators has produced noninvasive, simultaneous visualization of five separate lymphatic flows draining. This may have implications for predicting the route of cancer metastasis into the lymph nodes.

#### Item

#### ***Ovarian Cancer***

Today in the United States, there is no widely available screening test for ovarian cancer. More than 22,000 women will be diagnosed with ovarian cancer this year and 16,000 women are expected to die from it. Ovarian cancer has a high mortality rate, 55 percent over 5 years, mainly because there is no proven effective method for early detection. Research is being conducted on glycomic profiling that may identify unique patterns of glycosylation that may be more sensitive and specific than CA-125, an existing blood marker, in identification of early stage ovarian cancer. Circulating plasma proteins, another blood marker, could also possibly serve as biomarkers to differentiate women with ovarian cancer from healthy women.

The Committee encourages NCI to make randomized, prospective studies that would lead to the validation and acceptance of these and other biomarkers for the early detection of ovarian cancer a priority. (p. 129)

#### Action taken or to be taken

Due to the absence of a useful screening test for ovarian cancer and the lethality of the disease, NCI recognizes the need to fully explore biomarkers for early detection of ovarian cancer. NCI has been evaluating transvaginal ultrasound

(TVU) and CA-125 in the 155,000-person Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial since 1992. Screening in the first year of the PLCO Trial, CA-125 and TVU were able to identify both early- and late-stage ovarian cancers, but the ability of these tests to accurately predict the presence of the disease was relatively low. The effect that screening for ovarian cancer has on mortality in the PLCO population is still unclear and will require longer follow-up. Analysis of additional data from PLCO is under way.

In addition to answering critical questions about those two screening tests, blood samples collected from healthy individuals enrolled in PLCO who later developed ovarian cancer are being used in several early marker studies. Investigators are currently testing a number of potential serum biomarkers using PLCO samples. These studies include:

#### Validation of Serum Markers for Early Detection of Ovarian Cancer at Yale University

The PI of this study has identified 5 highly promising biomarkers from previous research. He will use pre-diagnostic samples from PLCO and serum samples from patients with early and late disease, with benign pelvic masses, and from healthy individuals to determine if these markers, together with CA-125, can detect cancers before symptoms develop.

#### Multiplexed Assay of Serum Biomarkers for Ovarian Cancer at the University of Pittsburgh

The PI of this study will test a previously published panel of 23 markers in pre-diagnostic samples from PLCO to determine if they can detect cancer before symptoms develop.

Early Detection of Ovarian Cancer Using Proteomic Analysis of Pre-diagnostic Serum Samples The PI will test a novel biomarker identified previously through proteomics technique. The goal is to confirm the performance of this marker in a larger, unbiased sample set from PLCO.

#### Collaborative EDRN/SPORE Validation of Serum Biomarkers for Early Detection of Ovarian Cancer

Early Detection Research Network (EDRN) investigators in collaboration with the Specialized Programs of Research Excellence (SPOREs) in ovarian cancer are performing a head-to-head comparison of several putative serum biomarkers that have demonstrated strong predictive value in early stage ovarian cancer.

NCI continues to seek new markers of ovarian cancer and ovarian cancer risk via funding to the SPORES, EDRN, NCI's Clinical Trials Cooperative Groups, the- NCI Tumor Glycome Laboratories of the NIH Alliance of Glycobiologists for Detection of Cancer and Cancer Risk, other grantees, as well as within NCI's

own Center for Cancer Research.

Item

***Clinical trial participation***

Despite efforts to improve participation in cancer clinical trials, only three percent of adult cancer patients participate in trials, and the participation by senior citizens is even more limited. The Committee strongly encourages NCI to support research to investigate decision-making by patients, particularly with respect to barriers to, and decisions on, participation in clinical trials. This research effort should be undertaken to inform strategies to enhance accrual in cancer clinical trials. Current low levels of accrual are often rate-limiting in the development of novel treatment approaches, and solving this problem would ultimately improve outcomes for cancer patients. (p. 129)

Action taken or to be taken

Decision making is fundamental to all aspects of cancer care, yet researchers and clinicians have limited knowledge of the ways in which patients and health care providers make critical health decisions. Individuals at risk, patients, and providers face a multitude of decisions across the cancer continuum that may profoundly affect outcomes in a number of domains: life expectancy, treatment outcomes, and overall quality of life. NCI supports research to enhance understanding of human decision-making processes so that individuals can make more informed and satisfying choices about their health. In order to achieve this aim, it is necessary to draw upon research in basic judgment and decision-making science, and applied behavioral science. For example, decision aids developed to assist patients to make complex health choices should be informed by sound basic science. In addition to evaluating the outcomes of decision aids, it is important to examine those processes that mediate the use of decision aids, such as risk perception and social influences.

The Funding Opportunity Announcement, Decision Making in Cancer: Single-Event Decisions invites research applications to elucidate single-event decision-making processes at the level of the individual patient or health care provider that are pertinent to cancer prevention, detection, treatment, survivorship, or end-of-life care. A single-event decision is a discrete decision made at a specific point in time. Examples of single-event decisions include selecting a cancer treatment, choosing to have mammography screening, or deciding to enroll in a clinical trial.

Factors affecting patient accrual are being examined by the operational efficiency initiatives recommended by the Clinical Trials Working Group.

The pilot NCI Community Cancer Centers Program (NCCCP), launched in 2007, a program to bring the latest scientific advances to patients in their home communities, will draw more patients into clinical trials in community-based settings.

To increase minority accrual, NCI provided supplemental funding to existing programs, including the Cancer Disparities Research Partnerships, the Minority-Based Community Clinical Oncology Program (MB-CCOP), and the Patient Navigator Research Programs. A specific goal of the NCCCP is to increase accrual for underrepresented and disadvantaged populations to clinical trials.

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. The Committee is pleased with NCI's attention to this important matter. (p. 129)

Action taken or to be taken

The NCI Comprehensive Minority Institution/Cancer Center Partnership Program links Minority-serving institutions (MSI) with NCI-designated Cancer Centers (or groups of centers) to develop comprehensive partnerships in cancer research, cancer training and cancer outreach programs in cancer education that will achieve the following goals: (1) build and stabilize independent competitive cancer research capacity at the MSI; (2) improve the effectiveness of the NCI-designated Cancer Center activities specifically designed to address cancer disparities in underserved racial and ethnic minorities and the socio-economically disadvantaged; and, (3) create stable, long-term collaborative relationships between the MSI and the Cancer Center in all areas of cancer research, training, education and outreach.

NCI is currently in the early phases of developing the "Geographic Management of Cancer Health Disparities Program". This initiative would create regional "synergistic hubs" to advance a transdisciplinary, multi-component network of NCI-supported cancer research institutions and programs, including minority-serving institutions, majority academic institutions, and NCI-designated cancer centers, and other health disparities programs (e.g., Community Networks Program, Patient Navigation Research Program), to strengthen collaborative efforts in biological science, clinical research, training and community-and population-based cancer health disparities programs. Many opportunities to advance the cancer research network and encourage translational efforts to impact the reduction of cancer in communities are expected to be developed through these "synergistic hubs", including creating new opportunities for minority-serving institutions to become competitive for NCI cancer center designation.

While the Cancer Centers Program makes significant contributions to advance cancer research, only 16% of cancer patients in the U.S. have access to these centers. The remaining 84% are cared for in community hospitals and physician offices. To bring the latest scientific advances and highest level of multi-specialty care to this larger population of cancer patients, NCI recently launched the NCI Community Cancer Centers Program as a 3-year pilot program. A specific goal of this program is to develop new or expand programs to increase outreach to the uninsured, underrepresented, and disadvantaged populations for prevention, screening, treatment, follow-up care, palliative care, survivorship plans and end-of-life-care. The success of the pilot will be determined by independent analysis of quantitative and qualitative data analysis.

Item

***Tissue repositories***

Cancer biorepositories, because they centralize and standardize molecular annotation of tissues, have the potential to accelerate the understanding of cancer and the discovery and development of new biomarkers, new diagnostics and new therapeutic approaches. The Committee encourages NCI to continue to support efforts to centralize the collection and distribution of tissue and pursue programs to make them available to researchers. (p. 129/130)

Action taken or to be taken

The shortage of high-quality, clinically annotated human tissues (or “biospecimens”) has been identified by the NCI as a major obstacle in cancer research. In June 2007, the NCI Office of Biorepositories and Biospecimen Research (OBBR) published NCI’s Best Practices for Biospecimen Resources to address this critical issue, which include recommendations for improving the standards of quality and annotation of biospecimens for research, as well as developing better access policies for biospecimens and associated data. The OBBR also initiated the Biospecimen Research Network (BRN) in 2006, to promote research which will contribute to the development of higher quality biospecimen resources, and inform future iterations of the NCI Best Practices.

In light of the recommendations made by the Best Practices, the NCI Clinical Cooperative Groups are improving standard operating procedures for the collection of specimens from patients entering clinical trials. Standardized and regulatory-compliant patient consent forms and new Group-wide bioinformatics systems will ensure that the consent forms are properly tracked, providing patients with greater confidence that their specimens are being used properly to accelerate the development of new diagnostics and treatments.

NCI extramural research programs that rely on networks for shared biospecimens, such as the Specialized Programs of Research Excellence and the Early Detection Research Network, are significantly affected by the

heterogeneity of human specimen quality. Large-scale genomic and proteomic studies such as The Cancer Genome Atlas and the Clinical Proteomic Technology Assessment for Cancer project require sufficient numbers of quality-controlled biospecimens to meet their research goals.

Other important initiatives include the Cooperative Breast Cancer Tissue Resource, which created tissue micro-arrays used to study the importance of the stem cell marker CD44+ as an indicator of therapeutic response in breast cancer. The Cooperative Human Tissue Network (CHTN) has provided specimens for basic cancer biology research as well as the early phases of development of new diagnostics, resulting in over 850 scientific publications from 2002 to 2006.

All of these efforts demonstrate NCI's commitment to establishing and maintaining resources to support the collection, annotation and broad dissemination of high-quality biospecimens for the research community.

#### Item

##### ***Radioisotope research***

The Committee encourages NCI to continue and enhance its support for radioisotope-targeted therapy and research. This research ultimately benefits cancer patients worldwide by developing new, productive avenues for the use of nuclear stockpile materials previously earmarked for weapons development. (p. 130)

#### Action taken or to be taken

NCI's Radiation Research Program (RRP) continues to support and encourage research and development into the use of radioactively labeled molecules and metals in targeted therapies for clinical application. The newest strategy in the fight against cancer involves the covalent linkage of monoclonal antibodies (mAbs), that target specific proteins found on cancer cells, with radioactive substances for radioimmunotherapy (RIT). This therapy selectively allows the concentration of radiation to multifocal tumor sites while minimizing exposure to healthy tissue.

Currently, the effectiveness of RIT has been primarily demonstrated in the treatment of hematological malignancies with the FDA approved use of Bexxar and Zevalin, for refractory/recurrent non-Hodgkin lymphoma. The research being funded in this area focuses on strategies to increase the dose of radiation to the tumor while decreasing the dose to normal tissues through: 1) the use of smaller antibody fragments/molecules with faster blood clearance rates; 2) use of pretargeting mAb approaches; 3) design of better tumor-targeting antibodies; and 4) design of more stable molecules linking the mAbs to the radioisotopes being investigated.

The recent preclinical research carried out at NCI's Center for Cancer Research

(CCR) has obtained very promising results using mAbs radiolabeled with alpha-emitting radioisotopes in the treatment of metastatic melanoma and disseminated colon and pancreatic cancers. This type of RIT is currently being validated in appropriate *in vivo* models for its efficacy as a new viable option for the treatment of metastatic melanoma, lung, liver and bone metastases.

Under SBIR and STTR Programs, companies have been funded to address the availability of various radioisotopes needed for future research and production of clinical radiopharmaceuticals. One company has been funded to isolate and purify Actinium-227 from the waste material from neutron generators in order to produce Radium-223 needed for the treatment of bone metastases. Additionally, this Radium-223 is a source for the production of Lead-212, a very promising high energy alpha-emitting radioisotope useful for treating small clusters of metastatic tumor cells.

Multiple clinical trials have evaluated the benefits of bone-targeted radiation therapy in advanced metastatic prostate cancer. In particular, beta-emitting radiopharmaceuticals have been developed that selectively irradiate bone metastases, with minimal or no effect on normal tissue, by binding to the bone mineral.

NCI-sponsored researchers, through the Radiation Therapy Oncology Group, are opening a novel trial to assess the toxicity and activity of a single dose of Samarium 153 administration in patients who are scheduled to receive prostatic fossa radiation for a rising PSA after prostatectomy. It is hypothesized that in such patients, the PSA elevation is driven predominantly by subclinical bony metastases which are not yet apparent on available imaging modalities, rather than remnant tissue at the surgical site, and that the administration of bone-targeted therapy with Samarium 153 could result in a measurable decline in the PSA. Effect on PSA will be evaluated over a 3 month period preceding radiotherapy, after which, long term toxicity and activity data will be assessed.

### **Senate Significant Items**

#### Item

#### ***Blood Cancers***

The incidence of lymphoma, multiple myeloma and acute leukemia/myelodysplasia increases dramatically with age, and chronic lymphocytic leukemia [CLL] is almost exclusively a disease of the aged. The Committee urges the NCI to place greater emphasis on translational and clinical research in blood cancers, with particular attention to blood cancers that affect the elderly. (p. 109)

#### Action taken or to be taken

Certain types of leukemia and lymphoma are more common in the older

population. Unfortunately, disease outcomes are worse in elderly individuals who may not tolerate therapy as well as their younger counterparts and because their cancers may be resistant to treatment. NCI-supported researchers are developing novel treatment strategies that are better tolerated and more effective in the elderly for many types of blood cancers.

Researchers in NCI's Center for Cancer Research (CCR) are engaged in nanobiology projects to develop human monoclonal antibodies to CLL, which primarily affects the elderly. A recently completed intergroup phase III trial showed significantly longer survival, without worsening of disease, in patients using such therapy as their first treatment for CLL.

Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (EPOCH) chemotherapy appears to be better tolerated in older persons, in part because the doses are adjusted according to individual patient tolerance. Another chemotherapy treatment, Rituximab, has been associated with significant additive effects when administered together with chemotherapy. NCI is conducting a randomized trial testing whether EPOCH, when combined with Rituximab, works better than standard chemotherapy in B-Cell Lymphoma, which is found in the elderly. This drug combination of Rituximab and EPOCH was shown in the NCI-sponsored AIDS-malignancy Consortium trial to be the new standard of care in AIDS-related lymphoma, and has transformed this disease from a median survival of 4-16 months to cure in the majority of patients.

Another example where lower doses of therapy are better tolerated include the treatment of dexamethasone for multiple myeloma, where not only is the lower dose better tolerated, longer survival is achieved when compared to the standard high dose dexamethasone therapy. This finding has resulted in improved treatment for elderly people with this relatively common blood cancer.

The Dana Farber/Harvard Cancer Center Myeloma Specialized Program of Research Excellence is testing novel myeloma therapies such as proteasome inhibiting agents, telomerase, and the MUC1 antigen. Researchers have found higher levels of a protein (CD 307) in the blood of patients with multiple myeloma, CLL, and mantle cell leukemia. This protein may be a useful marker for early detection and for monitoring recurrent disease. It may also serve as a target for immunotherapy. Another study has identified molecular changes in multiple myeloma cells that activate an important biological pathway associated with cell growth and survival, thereby revealing potential new drug targets.

These examples demonstrate advances in the screening and treatment for this disease in addition to ongoing efforts to improve transplantation options.

In certain patients with Acute Myeloid Leukemia (AML), allogeneic hematopoietic stem cell transplantation (HSCT) is one approach to extending relapse-free survival. However for the elderly, this may not be an option owing to their risk for transplant-related morbidity and mortality. Preliminary data from a recent study showed longer survival in elderly patients with high-risk Myelodysplastic Syndromes (MDS) or AML in their first clinical remission who had undergone reduced intensity conditioning (RIC) HSCT treatment rather than chemotherapy. NCI investigators have shown in other studies that JS-K, a prodrug designed to release nitric oxide, and analogues are active against AML and myeloma xenografts in mice. NCI researchers have also generated mice that develop MDS, a condition that often leads to AML. This animal model may advance our understanding of AML and provide opportunities to test promising treatment approaches for both the young and elderly.

#### Item

#### ***Brain Tumors***

The Committee strongly encourages the NCI to continue its support for clinical research consortia and SPOREs that focus on brain tumors. (p. 109)

#### Action taken or to be taken

NCI recognizes that brain tumors are a leading cause of cancer-related mortality in children and are the second leading cause of death in the 15-34 year age group, and that annually, 20,500 primary brain tumors are diagnosed in the U.S. leading to 12,740 deaths based on NCI's SEER (Surveillance Epidemiology and End Results) data. High grade, primary brain tumors in adults seldom respond to surgery, radiation, and systemic treatments, such as chemotherapy. Among children with brain tumors, many are not cured, and when long-term survival is achieved it often comes at the expense of significantly diminished quality of life. New treatment approaches are desperately needed for both adults and children with brain tumors. In recognition of this, NCI has supported over the past decade consortia composed of highly experienced and qualified investigators to conduct clinical trials for children and adults with brain tumors.

The two adult brain tumor consortia [North American Brain Tumor Coalition (NABTC) and the New Approaches to Brain Tumor Therapy (NABTT) consortia] have together enrolled over 2,000 patients into nearly 50 phase I/II trials in the past 10 years. NCI understands that an early clinical trials apparatus, focused on testing new agents rapidly and safely in this medically challenging group of patients, remains an essential interface between early discovery mechanisms and the late trials mechanisms typified by the NCI-supported Cooperative Groups. To improve the success rate of discovery of more effective treatments, the next generation of NABTC studies will require an increased emphasis on pre-

clinical correlations, pharmacokinetic-pharmacodynamic relationships, and evaluation of mechanistic endpoints based on tissue, imaging and biomarkers.

The Pediatric Brain Tumor Consortium (PBTC) was formed by NCI in 1999 to improve the treatment of primary brain tumors in children. The PBTC is responsible for rapidly conducting Phase I and Phase II clinical evaluations of new therapeutic drugs, injectable agents, delivery technologies, biological therapies, and radiation treatment strategies in children with central nervous system (CNS) tumors. The PBTC contains 10 member institutions selected based on their extensive experience with pediatric brain tumor clinical trials and the depth of their laboratory and imaging capabilities.

Brain cancer is one of the first of three types of cancer to be studied in The Cancer Genome Atlas pilot project, an NCI-National Human Genome Research Institute partnership program to assess the feasibility of systematically identifying the significant genomic changes involved in cancer.

The University of California, San Francisco, brain Specialized Programs of Research Excellence (SPORE) includes translational projects in population science, neuroimaging, molecular research of signaling pathways important in glioma, and developmental therapeutics with new delivery systems. The University of Alabama at Birmingham brain SPORE uses a multidisciplinary team focusing on pathogenesis, anti-invasion strategies, glioma-host interactions, virus gene therapy, and anti-angiogenesis strategies. The Duke University Medical Center brain SPORE works in many areas of translational research, with the main focus on anti-tumor therapeutics and risk factors.

NCI intramural investigators, in collaboration with the PBTC, are conducting a Phase I study of the immunomodulatory agent, lenalidomide, in children with recurrent, refractory and progressive CNS tumors. There is considerable interest in this agent because ten of 40 patients enrolled, primarily patients with low-grade gliomas, have had long term stable disease. The agent is well tolerated. Based on the results of this study, a Phase II study has been proposed within the Children's Oncology Group.

#### Item

#### ***Breast Cancer***

The Committee again strongly urges the NCI to give increased attention to breast cancer, particularly in the areas of lymphedema, stress, nutrition, exercise, weight, the environment, and ways to help women more fully restore and improve their quality of life after treatment. The Committee also urges the NCI to further accelerate advances in breast cancer screening technology and to capitalize on existing and create new technologies that improve early diagnosis, health outcomes, and survival. (p. 109)

### Action taken or to be taken

NCI is committed to funding research that improves methods for measuring and preventing lymphedema, advanced technologies for breast cancer screening, diagnosis and management, and promotes higher quality of life. Lymphedema is a common effect of breast cancer surgery, and the NCI has a clinical trial in progress that will determine if an exercise regimen can prevent this condition. NCI is also funding development of an ultrasound-based clinical tool that can assess the impact of therapy and possibly distinguish reversible from irreversible lymphedema. Other investigators are developing novel imaging methods for both lymphatic and breast cancer imaging.

The role of molecular imaging techniques in triaging of patients for appropriate therapy and for assessment of therapeutic response are being studied in Phase I and II clinical trials. Research to improve breast cancer screening, early diagnosis and health care outcomes is supported through the American College of Radiology Imaging Network (ACRIN). ACRIN trials include studies focused on the evaluation of contrast-enhanced breast MRI in patients undergoing drug treatment for locally advanced breast cancer; screening breast ultrasound in high-risk women; and MRI evaluation after focused ultrasound ablation of breast cancer.

Advances in breast cancer research have been provided by the revolution in genetic science and technology. The ability to interrogate the entire human genome for those genes important in cancer risks, led to NCI's efforts within the Cancer Genetic Markers of Susceptibility project which identified several areas of the human genome, previously unsuspected, that impact breast cancer risk. Efforts are underway to explore the effect of gene-environment interactions in groups with detailed anthropometric, physical activity, and dietary data, as well as data on unique environmental and occupational exposures. This improved understanding of susceptibility, along with emerging knowledge of which genes are altered in breast cancer, is opening new opportunities to develop molecular tools to screen for breast cancer susceptibility and for very early stage disease.

To study outcomes after treatment for breast cancer and to determine means for helping to improve QOL, NCI is supporting several studies in breast cancer with QOL objectives. NCI researchers are evaluating the effect of physical activity on QOL, including weight gain, and cancer recurrence in women undergoing chemotherapy, breast cancer survivors, and BRCA1/2 mutation carriers at high risk. Another study is evaluating the effects of age at diagnosis, type of treatment, and time since diagnosis on QOL of breast cancer patients several years after diagnosis. These research results should identify potential interventions for prevention or treatment of conditions affecting QOL.

Item

***Cancer Clinical Trials***

Only 3 percent of adult cancer patients participate in trials and the participation by senior citizens is even more limited. The Committee urges the NCI to support research to investigate decision-making by patients, particularly with respect to barriers to, and decisions on, participation in clinical trials. This research effort should be undertaken to inform strategies to enhance accrual in cancer clinical trials. Current low levels of accrual are often rate-limiting in the development of novel treatment approaches, and solving this problem would ultimately improve outcomes for cancer patients. (p. 109)

Action taken or to be taken

Please refer to page 12 of this document for NCI's response to this item.

Item

***Cancer in Native Hawaiians***

The Committee continues to be deeply concerned that mortality rates for all cancers are much higher for Native Hawaiian males and females compared to the other residents of the State. The Committee strongly urges the NCI to increase research that is focused towards understanding cancer among native Hawaiians. (p.109)

Action taken or to be taken

Significant progress toward understanding and addressing the needs of the Hawaiian and Pacific Islander populations is being achieved and monitored through an NCI-supported network of research in cancer and cancer health disparities. The key elements that comprise this network include surveillance to monitor the cancer burden and track progress, a strong clinical trials recruitment program, research training and education, and outreach initiatives and community-based efforts in primary and secondary prevention.

The *NCI Surveillance, Epidemiology and End Results Research (SEER)* Program uses special tracking of cancer incidence, mortality, and survival rates among Native Hawaiians and Pacific Islanders to uncover the serious extent to which cancer has impacted these populations. NCI's clinical trials network is growing and brings state-of-the-art treatments that have the potential to improve the prevention and treatment of cancer in Hawaii's native populations. The NCI-designated Cancer Research Center of Hawaii is participating in a growing number of clinical trials, is closely linked to eight major cancer cooperative groups, and participates in over 100 national research studies as a member of the NCI-funded Minority-Based Community Clinical Oncology Program.

Through NCI-supported research training programs, efforts are being made to improve participation of Native Hawaiian and Pacific Islanders in the fields of biomedical research and medical practice, another effective way to increase our

understanding of cancer among native Hawaiian and Pacific Island communities. Through the Community Networks Program `Imi Hale – Native Hawaiian Cancer Network initiative, NCI supports a variety of culturally competent cancer awareness, research, and training activities, and facilitates the application of evidence-based information in primary and secondary prevention to reduce the cancer burden in native Hawaiian and Pacific Island communities.

Item

***Cancer Metastasis to Bone***

A frequent complication of cancer is its spread to bone. The Committee understands that immune response plays a role in cancer metastasis and urges the NCI to focus research in the emerging area of osteoimmunology. The Committee encourages NCI, NIAMS, NIA, and NIDDK to support research to determine mechanisms to identify, block and treat cancer metastasis to bone. Furthermore, the Committee urges the NCI to expand research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma in children and teenagers who develop this cancer. In addition, the NCI is encouraged to expand research on tumor dormancy as it relates to bone metastasis. (p. 110)

Action taken or to be taken

Please refer to page 1 of this document for NCI's response to this item.

Item

***Gynecologic Oncology Clinical Trials Cooperative***

The Committee urges the NCI to provide additional resources to fund clinical trials through the Gynecologic Oncology Clinical Trials Cooperative Group. Priority should be given to translational research involving biologic prognosticators and therapeutic effects of chemotherapy to speed the development and delivery of new cancer treatments to women with gynecologic cancers. (p. 110)

Action taken or to be taken

The Gynecologic Oncology Group (GOG) is one of the nine NCI-sponsored Clinical Trials Cooperative Groups (CTCG). Since 1970, NCI has worked closely with the GOG on the design and conduct of innovative phase II trials and definitive phase III trials, which have helped identify state-of-the-art care for women with gynecologic malignancies. More recently, the GOG has worked with NCI to expand its research portfolio into other critical areas of cancer research that includes prevention, epidemiology, quality of life, survivorship, prognostic markers, and translational science.

Through its public-private partnership with the pharmaceutical and biotechnology industries, NCI works to identify promising new anti-cancer agents and bring them to clinical evaluation quickly. For the evaluation of these novel agents in

gynecologic cancers, the NCI relies heavily on the GOG, as well as NCI-designated Cancer Centers and other North American CTGs. In addition, NCI provides logistical support to the Gynecologic Cancer Intergroup, an umbrella organization which brings together 15 cooperative groups from around the world that conduct clinical trials for women with gynecologic malignancies. International collaboration permits trials to be completed faster, thus providing answers sooner on how best to treat cancer patients.

The GOG is also working with NCI researchers to study patterns, or profiles, of blood proteins among women with enlarged ovaries who 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 with surgery and chemotherapy. 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.

Scientists in NCI and NCI-sponsored SPORE are also searching for new therapies and biological markers that predict response to therapy or survival for ovarian cancer using powerful technologies to look at genes or proteins.

Building upon the success of the current vaccines to protect against cervical cancer, NCI continues to support development of the second generation HPV vaccines that can protect against an even higher proportion of serious HPV infections.

Item

***HPV Vaccine and Cervical Cancer***

The Committee urges the NCI to fund research that will allow for the identification of the most cost-effective management strategy for cervical cancer screening in the era of HPV L1 vaccines and to identify the circumstances where Pap test/HPV screening fails in vaccinated women. (p.110)

Action taken or to be taken

Please refer to page 5 of this document for NCI's response to this item.

Item

***Imaging Systems Technologies***

The Committee is aware of the potential for improved patient care and disease management represented by molecular imaging technologies, especially positron emission tomography [PET], through its ability to image the biology of many kinds of cancer and other diseases. The Committee continues to support the

NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee further encourages the testing of women for breast cancer and men for prostate cancer to demonstrate and quantify the increased diagnostic and staging capabilities of PET relative to conventional diagnostic and staging technologies, including mammography. (p. 110)

Action taken or to be taken

Molecular imaging is critical for fundamental improvements in the care of cancer patients. While we continue to discover new molecular signatures of cancer in our crusade to develop more effective therapies with lower morbidity, these efforts can be successful only through understanding how these targets integrate into the complex systems of tumor biology. *In vivo* molecular imaging is a unique method that allows us to acquire this knowledge. One of the most powerful molecular imaging techniques, now used routinely in patients, is PET. While the high sensitivity of PET has been known for decades, only recently has the power of the technique become apparent for pre-clinical development and discovery as well as clinical care.

The elucidation of tumor biology with PET imaging required the development of micro-PET systems engineered for use in animals. NCI funded the development of these devices and also funded national resource centers, Small Animal Imaging Resources. NCI has also funded *in vivo* Centers for Molecular and Cellular Imaging to study molecular targets of cancer and to develop new imaging technology and methods. A Cancer Research Imaging Camp designed to train basic researchers in molecular imaging methods is being expanded.

PET-labeled drugs can demonstrate whether a drug is reaching the tumor target or not. Imaging probes that report the metabolic status of a target can assess the potential efficacy of a therapy early on by reporting whether or not tumor growth is slowing down.

Imaging agents must follow the same drug development and approval process as therapeutic drugs, a significant barrier. NCI is trying to lower this barrier by supplying resources and expertise for early development of promising PET probes. So far, NCI has been involved in the filing of Investigational New Drug applications for 5 promising PET drugs. NCI is funding the development of approximately 120 probes, most of them for PET.

DCTD is also working in close collaboration with intramural NCI scientists on a trial combining PET imaging and MRI to determine the value of such combined imaging to improve the detection and staging of prostate cancer.

Item

***Liver Cancer***

The Committee notes that the incidence of primary liver cancer continues to increase, liver cancer is the only cancer experiencing continuing increases in mortality, and treatment options for physicians remain very limited. Therefore, the Committee urges the NCI to work closely with the NIDDK to develop a basic, clinical and translational research program designed to reverse these trends and enhance survivability. In addition, the Committee welcomes the conclusions of the October 2006 NCI-Hepatitis B Foundation workshop regarding the early detection of liver cancer, and it urges the NCI to support more work in this area. (p. 110)

Action taken or to be taken

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

Item

***Lung Cancer***

Lung cancer is the leading cause of cancer death among women and minority populations. The Committee encourages the NCI to work with the thoracic surgical community to initiate new clinical trials that involve patients at an early stage of the disease when surgery is a treatment option. (p. 110)

Action taken or to be taken

NCI has made lung cancer an Institute priority and is dedicating resources to support research into early detection and treatment – efforts most likely to provide more immediate benefit for lung cancer patients and those at-risk for the disease. Through increased understanding of the biology of lung cancer and the molecular aspects of this disease, NCI is working to better determine risk, develop targeted therapies, tailor treatment options, and better predict patient outcomes. Tobacco use remains the leading preventable cause of lung cancer and other diseases in the United States, and as such NCI continues to support tobacco control efforts in the behavioral, social, and population sciences.

Erlotinib (Tarceva<sup>®</sup>) and gefitinib (Iressa<sup>®</sup>) are agents that block tumor cell growth by targeting the Epidermal Growth Factor Receptor (EGFR). When a protein found on the surface of cells known as epidermal growth factor (EGF) attaches to EGFR, it activates specific enzymes, triggering reactions that cause the cells to grow and multiply. EGFR is found at abnormally high levels on the surface of many types of cancer cells, which may divide excessively in the presence of EGF. Initial efficacy and safety studies in non-small cell lung cancer (NSCLC) stimulated a remarkable degree of optimism based on prolonged remissions and improvements in the quality of life of a small number of patients whose disease was no longer responding to standard chemotherapy. A subsequent, randomized trial of erlotinib demonstrated a 2 month survival advantage for patients receiving erlotinib versus patients receiving a placebo, and suggested the possibility that certain molecular

targets might correlate with the effectiveness of erlotinib in NSCLC. NCI is working with FDA and CMS to develop a national level clinical trial to validate the predictive marker of EGFR for targeted therapy in non-small cell lung cancer using this new class of agents.

The Cancer Genome Atlas (TCGA) is a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing. One of the three cancers selected to be studied in the pilot study to identify all the important genes associated with cancer is lung (squamous carcinoma). The genomic information generated by TCGA could fuel rapid advances in cancer research and suggest new therapeutic targets. It could also suggest new ways to categorize tumors, which might allow clinical trials to focus on patients who are most likely to respond to specific treatments.

FDG-PET is an imaging test that uses a radioactive molecule to produce images that show increased metabolic activity of tissues, such as that seen in cancer cells, compared to the metabolic activity of normal tissue. NCI is leading an FDG-PET clinical trial in lung cancer that could have significant impact on patient management by validating a tool that could identify response to treatment and help facilitate new drug development.

NCI activated two definitive phase 3 studies involving early stage lung cancer in 2007 and is currently enrolling patients. One is an adjuvant trial for early stage non-small cell lung cancer testing if the addition of angiogenesis inhibition to standard chemotherapy will improve survival in patients undergoing surgery with curative intent. The other study compares two forms of surgery (standard lobectomy, which requires the removal of the whole lobe versus sublobar resection, in which only part of the lung is removed) for small peripheral tumors. The results of these studies may have an impact in the management and quality of life of patients with early stage lung cancer.

#### Item

##### ***Lymphatic Research and Lymphatic Diseases***

The Committee urges the NCI to support research on lymphedema and to devote increased resources toward the study of lymphangiogenesis and lymphatic imaging. (p. 110)

#### Action taken or to be taken

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

#### Item

##### ***Lymphoma Translational and Clinical Research***

The Committee urges the NCI to capitalize on the recent investment in basic research on lymphoma by aggressively funding translational and clinical research on this disease. The basic research program has resulted in significant

information about the biology of lymphoma and better strategies for identifying critical metabolic pathways and immune system functioning in lymphoma. The translational and clinical research effort should be strengthened to accelerate therapeutic development for lymphoma. (p. 110/111)

#### Action taken or to be taken

Recent discoveries on the genetic variations that influence risk of non-Hodgkin lymphoma (NHL) have informed NCI clinical follow-up projects. Microarray and genotyping technologies are now being used to classify distinct lymphoma subtypes and to better characterize treatment options. Multidisciplinary intramural-extramural collaborations are combining newly established molecular profiles of lymphoma subtypes and advances in the molecular pathology of lymphoma with data from population studies to identify clinically relevant genetic predictors of lymphoma survival.

NCI researchers have performed clinical trials identifying two different diagnostic markers for lymphoma. The first marker is present in the blood of patients with cutaneous T cell lymphoma (CTCL). Its presence distinguishes this cancer from a benign blood disease and from normal individuals. The second is a soluble protein, detectable in the blood of patients with B-cell malignancies that may be a useful target for immunotherapy. In addition, pathobiological markers of treatment failure in the incurable lymphomas are being targeted, and indications from early trials suggest these will likely be active therapies.

NCI-supported clinical trials have contributed to a doubling of the 5-year survival rates over the past 25 years in pediatric NHL. To extend this record of identifying more effective therapies, NCI is supporting clinical trials of novel approaches to the treatment of children with NHL through the NIH Clinical Center and nationally through the Children's Oncology Group.

Examples of improved outcomes that have resulted from NCI research within the past year includes transformation of AIDS-related lymphoma from a median survival of 6-18 months to a now highly curable condition, and has defined a new standard of care for this disease using a treatment regimen called EPOCH-R.

NCI investigators have also discovered several new therapeutic approaches for lymphomas and leukemias.

- Investigators are developing a human monoclonal antibody that could be therapeutic for blood cancers including chronic lymphocytic leukemia.
- Human monoclonal antibodies are being developed that bind to the receptors that trigger cell suicide, an approach that could be used to treat certain blood cancers.

- Researchers have identified molecular changes in multiple myeloma cells that activate an important biological pathway associated with cancer's growth and survival, thereby revealing potential new targets for new drug development.
- In addition, novel approach using radioactivity and immunotherapy (radioimmunotherapy) have been shown to provide effective therapy for patients with Hodgkin lymphoma that have relapsed.
- In an ongoing study, NCI investigators found that dose adjusted-EPOCH-R is highly effective while causing relatively low toxicity in untreated Burkitt lymphoma compared to the standard intensive high-dose regimens.
- The bcl-2 protein confers high-level resistance to chemotherapy in certain lymphomas, and targeting of this protein shows promise of potentially effective therapy in early clinical trials.

The University of Iowa-Mayo Clinic Lymphoma SPORE has four projects using advances in antibody-based therapies and other means to stimulate immune responses against malignant growth. Recent advances include the definition of new predictive and prognostic biomarkers for non-Hodgkin lymphoma. Investigators from the Johns Hopkins University Lymphoma SPORE are examining ways to achieve better outcomes using vaccination and adoptive immunotherapy.

#### Item

##### ***Mesothelioma Research***

The Committee is concerned with the pace of mesothelioma research. The NCI is encouraged to establish up to 10 mesothelioma centers and increase related research, including clinical trials, detection and prevention methods, palliation of disease symptoms and pain management. (p. 111)

#### Action taken or to be taken

Mesothelioma is a disease in which malignant cells are found in the sac lining of the chest, the abdominal cavity, or the heart. Most commonly linked to exposure to asbestos, this disease usually remains symptom-free for many years until detected at later stages that limit treatment options and result in poor rates of success. NCI is continuing to develop, test, and refine immunotherapeutic agents for treatment of patients with mesothelioma. Promising recent advances include:

- A Phase I clinical trial, established the safety, dosing regimen and anti-tumor activity of SS1P, a toxin coupled, anti-mesothelin antibody. A clinical trial using SS1P and chemotherapy agents together is being initiated based on promising laboratory data showing increased anti-tumor responses when they are combined.

- Recent laboratory studies show that the anti-tumor activity of SS1P when combined with gemcitabine, a chemotherapeutic agent, is markedly increased against mesothelin-expressing tumor xenografts in nude mice. These results suggest such a combination may be useful against mesothelin-expressing cancers including mesothelioma.
- A Phase I clinical trial of MORAb-009, a chimeric anti-mesothelin monoclonal antibody, is underway for patients with mesothelioma who have failed standard treatments.
- A phase I clinical trial is being initiated to examine a mesothelin-tumor vaccine for patients with mesothelioma.

The NCI continues to pursue detection and prevention methods through identification of potential biomarkers of early disease and better treatment options through the use of combinatorial therapies as indicated in the studies below:

- A prospective study designed to examine alterations in gene expression levels in tissues from patients with mesothelioma as well as non-small cell carcinoma and esophageal cancer.
- A trial studying combination therapy of two chemotherapy drugs, FR901228 and flavopiridol, in patients with advanced lung, esophageal, or pleural cancer.
- A trial studying combination therapy of two chemotherapy drugs, decitabine and FR901228, in patients with unresectable advanced lung cancer, esophageal cancer, pleural mesothelioma, or lung metastases.

#### Item

**Nanosystems Biology** - The Committee encourages NCI and the Office of the NIH Director to continue to support a collaborative effort to bring nanotechnology, systems biology and molecular imaging together to examine the molecular basis of cancer. Initial efforts have shown that cancers such as breast cancer are not a single disease, but may encompass many different diseases, when examined at the molecular level. Many clinical trials of new drugs are now considered to fail if only 10 percent of patients benefit, yet the 10 percent may represent a specific type of the disease for which the drug may be 100 percent effective. Bringing these three disciplines together may allow researchers to identify specific subtypes of cancer and to better target new interventions. Successful results of such an effort could lead to a molecular classification of many types of cancer and to targeted molecular treatments for molecular-specific diseases. (p. 111)

#### Action taken or to be taken

Nanotechnology, systems biology, and molecular imaging have all played significant roles in studying the molecular basis of cancer and identifying possible pathways and targets for treatment. Consistent with the relevant aims of the NIH Roadmap Initiative, the NCI continues to work to synergize the efforts in these disciplines to accelerate understanding and therapeutic applications. NCI's Alliance for Nanotechnology in Cancer, Integrative Cancer Biology Program, and Cancer Imaging Program are important parts of NIH's efforts to leverage the convergence of these disciplines to accelerate molecular-based research and development. Through the Alliance for Nanotechnology in Cancer (<http://nano.cancer.gov>), NCI has established eight centers of excellence, 12 technology platform developmental partnerships, and multidisciplinary career training and team development programs to integrate nanotechnology development and cancer research to accelerate molecular-level assessment and intervention based on nanotechnology and systems approaches. Resulting technologies being developed include platforms for detecting and quantifying biomarkers, and nanoelectronic sensors for simultaneously analyzing multiple parameters in blood, serum, or tissue. NCI's Nanotechnology Characterization Laboratory (NCL; <http://ncl.cancer.gov>), an on-going partnership with the National Institute of Standards and Technology and the Food and Drug Administration launched in 2005, continues to perform rigorous physical, in vitro, and in vivo characterization of nanomaterials to facilitate introduction of these materials and technology platforms into commercial use for research as well as clinical care.

Investigators within the NCI Integrative Cancer Biology Program (ICBP) <http://icbp.nci.nih.gov> are elucidating the complex networks within cancer cells, and between cancer cells and their environment to discover new leads for cancer prevention, detection, diagnosis, and treatment. The consortium of ICBP investigators connects research infrastructure to facilitate identification of molecular signatures of cancer cells and the tumor microenvironment and to develop targeted interventions based on the cellular interactions with the microenvironment. The ICBP has begun funding collaborations among various investigators and technologies. One of the goals is to help link the various system and computational approaches with nanotechnological approaches and to apply these integrated efforts to specific clinical concerns. The NCI has also formed a network of researchers examining the role of the microenvironment in cancer and those efforts will also be part of our larger effort in nanosystems biology.

NCI continues to support development of nanoprobes for imaging applications and is expanding trials in the detection and staging of various cancers including cervix, prostate and bladder. Exploratory trials have been undertaken in brain cancer extending beyond improved delineation of tumor margins to the study of tumor vasculature including altered physiology important to therapy delivery and effectiveness. During the last year, NCI implemented a multi-modality small animal imaging facility that will facilitate pre-clinical "in vivo" studies of novel

nanoplatfroms for both imaging and therapy. NCI's Cancer Imaging Program optical network, designed to enhance translation of optical methods, is working closely with leadership of the NCI Alliance for Nanotechnology in Cancer including exploring shared funding opportunities.

Item

***Non-Hodgkin lymphoma***

The incidence rates for non-Hodgkin lymphoma in the general population have doubled since the 1970s, for reasons that are not clear. The Committee strongly recommends an enhanced commitment to research focusing on the possible environmental links to lymphoma. The Committee suggests that the NCI direct funds to: (1) studies on the identification of environmental-genetic interactions that may influence the development of lymphoma; (2) studies of adequate scope to assure the identification of environmental risk factors for specific subtypes of lymphoma; (3) small studies designed to improve detection and quantification of historically difficult-to-measure environmental factors; (4) studies that are directed toward enhancing the understanding of the role of the immune system in the initiation and progression of lymphoma; and, (5) studies that examine the simultaneous presence of a wide profile of infectious agents among individuals with lymphoma. The Committee also notes that lymphoma is often diagnosed in young adulthood and middle age, and survivors may experience immediate, and also late and long-term effects of the disease and treatment. The Committee urges the NCI to dedicate some of its survivorship research funds on research issues related to problems confronted by lymphoma survivors. (p.111/112)

Action taken or to be taken

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

Item

***Ovarian Cancer***

The Committee urges the NCI to support randomized prospective studies that would lead to the validation and acceptance of biomarkers for the early detection of ovarian cancer. (p. 112)

Action taken or to be taken

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

Item

***Pancreatic Cancer***

Research on pancreatic cancer, the country's fourth leading cause of cancer death among men and women, remains underfunded as compared to the top five cancers based on mortality. The Committee notes that the NCI currently categorizes grants as falling under a specific cancer type if the grant is at least 25 percent relevant to that cancer. The Committee urges the NCI to increase this criterion to 50 percent relevancy for pancreatic cancer research and to fund

more pancreatic cancer grants at this higher level so that the minimal dollars being funded toward the disease are truly pushing the research forward. Further, the Committee requests that the Institute ensure that pancreatic cancer grants are reviewed by at least three reviewers who are experts in pancreatic cancer research. Finally, the Committee is disappointed that the three existing pancreatic cancer Specialized Projects of Research Excellence [SPORE] grants have never been fully funded, and it urges the Institute to fully fund no fewer than three pancreatic cancer SPOREs this year. (p. 112)

Action taken or to be taken

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

Item

***Prostate Cancer***

The Committee commends the NCI for its considerable investment in prostate cancer and encourages the Institute to continue to support research to improve the accuracy of screening and early detection of this disease. (p. 112)

Action taken or to be taken

NCI has been evaluating common prostate cancer detection tests in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial since 1992. In this trial, researchers are studying whether a digital rectum exam (DRE) and a blood test for prostate-specific antigen (PSA) will decrease deaths due to prostate cancer. Results of the initial screens showed that about 14 percent of men had either a positive PSA test or a positive DRE test. Of those men, about 12 percent were diagnosed with prostate cancer within 12 months, the majority with early stage disease.

The Prostate Cancer Prevention Trial (PCPT) established that it is possible to reduce prostate cancer prevalence by using a drug. The men randomized to receive finasteride had a 24.8% decrease in the relative risk of developing prostate cancer. During PCPT, blood and tissue were collected from study participants for the creation of a unique biospecimen resource. Investigators are using this resource to collaborate on a grant designed to better define the genetic, metabolic and environmental factors associated with prostate cancer risk, which may advance the field of prostate cancer prevention and improve the accuracy of prostate cancer screening.

The Early Detection Research Network (EDRN), a network of investigators nationwide working to identify and validate markers of early cancer and cancer risk, is examining the accuracy of prostate cancer detection in a number of projects. Additional information on EDRN can be found at <http://edrn.nci.nih.gov>.

The NCI has sponsored several studies to achieve improvement in prostate cancer diagnosis. Studies include combining ultrasound and magnetic resonance spectroscopy to obtain improved classification of prostate cancer risk and to guide needle biopsies. Studies are also comparing FDG-PET to bone scans to evaluate its improvement in detecting metastatic bone disease. Another trial is studying the effectiveness of new prostate cancer drugs in a neoadjuvant setting by contrast enhanced MRI. Additionally, novel PET tracers are being developed with support from NCI to assist in diagnosis and staging of prostate cancer.

#### Item

#### ***Tuberous Sclerosis Complex [TSC]***

The Committee applauds the NCI for supporting a multi-center clinical trial on TSC, and it urges the Institute to support additional clinical trials. The Committee also encourages the NCI to continue to support basic research on the mTOR signaling pathway and the role of the TSC1/2 genes in nutrient sensing, insulin signaling and cell growth and proliferation. (p. 112)

#### Action taken or to be taken

TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, lungs, liver, eyes or skin. The incidence of TSC has recently been estimated to be 1 in 6,000 live births. In light of its similarities to the uncontrolled growth of cancer cells, many scientists believe that determining the cause of tumor growth in TSC could open the way for treatments for TSC and for other cancers as well.

The NCI continues to support both intramural and extramural efforts directly investigating the molecular and cellular basis of TSC. To encourage basic and translational TSC research, the NCI is participating on the trans-NIH initiative, Understanding and Treating Tuberous Sclerosis Complex. This past year two new grants have been funded that were submitted in response to this initiative. The first supports studies on how mTOR molecule contributes to the development of TSC and lymphangioleiomyomatosis (LAM), a progressive lung disease. The other grant studies how dysregulation of specific stress response pathways affects cellular metabolism and contributes to TSC.

NCI is actively supporting efforts to understand and treat the symptoms of TSC. The first multi-center clinical trial for tuberous sclerosis, supported in part by NCI, has begun treating patients with rapamycin, an mTOR inhibitor, for renal angiomyolipomas (AML), a benign renal lesion common in TSC patients. The primary endpoints of this study will establish whether the kidney tumors shrink and whether rapamycin is a safe treatment for TSC patients. This year, the Trans-NIH Working Group on Tuberous Sclerosis established a committee to develop a plan of attack for treatment of brain tumors in TSC patients. NCI is working with the National Institute of Neurological Disorders and Stroke (NINDS)

and the Tuberous Sclerosis Alliance in this effort to design clinical trials that could also assess the cognitive effects of candidate cancer therapies.

NCI staff are participating with NINDS staff and the Trans-NIH Working Group on Tuberous Sclerosis in the organization of a symposium on "mTOR Signaling: From Cancer to CNS Function" to be held in January 2008 in Bethesda, MD. The meeting will compare and contrast the role of the PI3K/TSC/mTOR pathway in Tuberous Sclerosis, Neurofibromatosis, and Glioma with a focus on translational research and future clinical trial design.

Furthermore, NCI continues to support basic research on the mTOR-signaling pathway. Researchers are working to understand the mechanisms of activation in the Akt/mTOR pathway as well as interactions with a protein kinase, a key molecule for energy sensing which negatively regulates mTOR activity. In addition, researchers are exploring mTOR's role as tumor suppressor in plasma cell tumor development. NCI researchers are also focusing on the supply of oxygen and nutrients to the tumor which is critical to tumor invasion and metastasis. Characterization of this metabolic process may lead to novel approaches for cancer therapy.

## National Heart, Lung, and Blood Institute

### House Significant Items

#### Item

#### ***Congenital heart disease***

The Committee recognizes that congenital heart disease is a chronic disease affecting approximately 1.8 million Americans. It commends NHLBI for convening a working group to address this issue, and supports its recommendation that action be taken to prevent needless disability and premature mortality in this rapidly-growing population. The Committee urges NHLBI to work with patient associations and other appropriate public health organizations to develop education and research initiatives targeted to the life-long needs of congenital heart disease survivors. (p. 130)

#### 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. 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. A number of organizations representing patients with pediatric and adult congenital heart disease attend.

The NHLBI has taken a leadership role in research and education for congenital heart defect survivors and their families. The Pediatric Heart Network, established in 2001, conducts multi-center 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, [www.PediatricHeartNetwork.org](http://www.PediatricHeartNetwork.org), has a special section for patients and families that provides information about topics that affect their lives, including exercise and nutrition.

This year, the NHLBI and the National Center for Research Resources have embarked on a broader project to highlight the importance of including children in clinical research. An award-winning video production unit associated with the Pediatric Heart Network is producing a short documentary film about pediatric research that is accompanied by a series of educational segments to answer parents' questions. This DVD is designed to help patients and families from all walks of life, and will also be translated into Spanish.

The NHLBI and the CDC share many common interests pertaining to congenital heart disease. In recent years, the CDC has participated in an NHLBI 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 is

using natality data published by the CDC to update estimates of normal birth weight by gestational age. The NHLBI has identified CDC staff with whom to collaborate on further analysis of these data and other congenital heart disease issues.

#### Item

##### ***Cardiovascular disease and women***

The Committee remains concerned that as the population ages women will continue to be affected by cardiovascular disease at high rates. The Committee encourages the Institute to place a high priority on heart disease, stroke and other cardiovascular diseases in women by intensifying its investment in basic, clinical, translational, and trans-institute cardiovascular disease research. Despite new therapies, the Committee continues to believe that research is needed to better understand the causes of these diseases in women, develop more effective treatments and cures, and prevent cardiovascular diseases, which remain a major cause of permanent disability and the number one killer of women. Gender differences in health and disease are well established. For example, while cardiovascular disease is the number one killer of both women and men, women die of cardiovascular disease an average of ten to twenty years later than men. Numerous primary and secondary randomized controlled prevention trials have been conducted in men showing the benefit of lowering total and LDL cholesterol. Women have been included in many of these studies but not in sufficient numbers to permit a meaningful analysis of the benefits for women alone. As a result, women are currently treated according to the data from studies where there is a preponderance of men—the treatment is designed to lower total and LDL cholesterol. This is done on the assumption that this treatment regime is the best approach to primary prevention in women. However, there are some significant indications that high HDL-cholesterol and low triglycerides are more important for women’s cardiovascular health. The Women’s Health Initiative did not substantiate the expectations from observational studies that postmenopausal hormone therapy reduces the risk of coronary heart disease in spite of lowering total cholesterol and LDL-cholesterol. New research is needed to answer the question of the optimal lipid profile in primary prevention of cardiovascular morbidity and mortality in women and to define gender differences. The Committee encourages NHLBI to undertake this type of research. (p. 130/131)

#### Action taken or to be taken

For many years the NHLBI has been diligent in ensuring that its clinical research projects include adequate representation of women and that its overall research portfolio addresses gaps in our knowledge of how to diagnose, prevent, and treat disease in women. This effort has included not only careful monitoring of recruitment for clinical trials and other studies, but also support of certain studies conducted entirely in cohorts of women (e.g., the Women’s Health Initiative [WHI], the Women's Health Study, and the Women's Ischemia Syndrome

Evaluation). Throughout the history of the Institute, clinical trials of blood pressure lowering have been exceptionally strong in their inclusion of women—46% of participants in the Hypertension Detection and Follow-up Program (started in 1971) were women, 57% in the Systolic Hypertension in the Elderly Program (1984), and 47% in Antihypertensive and Lipid Lowering Treatments to Prevent Heart Attack Trial ALLHAT (1993)—and a projected 40-45% of participants in our new Systolic Blood Pressure Intervention Trial SPRINT trial will be women.

In the area of lipid-lowering, it is true that early trials focused on men. However, more recent years have produced an accumulation of robust evidence for use of statins in women. In that regard, NHLBI is pleased to highlight a recently published individual-patient meta-analysis of statin trials that included 21,575 women. There were 1,441 women who had major cardiovascular events. Women who were randomly assigned to statin treatment were significantly less likely to suffer events, and their reduction in risk was similar to that seen in men. NHLBI is looking more closely at the intriguing findings from the WHI hormone and diet trials. This work will include a large genotyping effort of African American and Hispanic women as well as a number of proteomic and biomarker investigations. Moreover, we are planning a major workshop involving nationally recognized experts to obtain advice about the future of research on cardiovascular health and disease in women.

NHLBI has a number of other ongoing or just-completed research programs that specifically focus on cardiovascular health in women, including the WHI Memory Study, an investigation of cognitive decline in elderly women; the Girls Health Enrichment Multi-Site Studies (GEMS), a group of studies to develop and test interventions to prevent obesity in high-risk African American preadolescent girls; and the Trial of Activity in Adolescent Girls (TAAG), a multi-center trial of a school- and community-based physical activity intervention to prevent the decline in physical activity that typically occurs in adolescent girls. Other ongoing trials involve large numbers of women, including the 10,000-patient Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, in which 35% of participants are women. We are supporting weight-loss trials in which the majority of subjects are women, including the Preventing Obesity Using Novel Dietary Strategies (POUNDS Lost) trial, which compares different types of diets in overweight adults.

Finally, NHLBI cohort studies are entering a new era of investigation because of the genetic revolution. The Institute has completed genotyping of nearly 10,000 subjects in the Framingham Heart Study and is about to genotype over 6,000 subjects in the Multi-Ethnic Study of Atherosclerosis; more than 50% of participants in both studies are women, enabling careful investigation of genetic and environmental risk factors for disease according to gender. The findings from these exciting genetic epidemiological studies hold promise for truly

effective, gender-specific personalized medicine.

Item

***Heart disease and diabetes***

Heart disease is the leading cause of death in diabetic patients, and individuals with type 1 diabetes have a 10-fold increased risk of heart disease compared to others of the same age. Research has shown that heart disease begins as early as childhood or adolescence in type 1 diabetes patients. NHLBI is encouraged to promote research to identify early biomarkers of cardiovascular disease in young diabetic patients to learn who might benefit from therapeutic agents that are currently used in adults. Delaying heart disease by even a few years could make a significant difference in the lives and health of young diabetic patients. (p. 131)

Action taken or to be taken

The NHLBI encourages and supports basic and clinical research to identify and validate early biomarkers of heart and vascular diseases in patients with type 1 diabetes. In August 2007, the NHLBI, in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), initiated a program titled “Biomarker Development for Diabetic Complications” to develop and validate biomarkers and surrogate end points for the complications of diabetes. The program seeks to establish multidisciplinary research teams that will merge innovative technologies, such as imaging, nanotechnology, molecular biology, proteomics, and metabolomics, with cutting edge-knowledge of the mechanisms of diabetic complications.

The NHLBI supports several clinical studies on patients with type 1 diabetes. To leverage its investment in these and other clinical research projects, the Institute is encouraging researchers to conduct ancillary studies. Special emphasis is being placed on studies addressing biomarker identification. The NHLBI is also supporting research to use imaging technology (such as electron-beam tomography and nuclear magnetic resonance) to predict cardiomyopathy and atherosclerosis in type 1 diabetes patients.

The NHLBI continues to work with the NIDDK to stimulate research on the cardiovascular complications of type 1 diabetes. In October 2007, the NHLBI convened a meeting of researchers funded by the “Progression of Cardiovascular Disease in Type 1 Diabetes” program to discuss scientific progress and recommend future research in this area. Representatives from the NHLBI, the NIDDK, and the Juvenile Diabetes Research Foundation were present.

Item

### ***Pulmonary hypertension (PH)***

The Committee commends NHLBI for its leadership in advancing research on PH, a rare, progressive, and fatal disease that predominantly affects women. The Committee continues to view research on pulmonary hypertension as a high priority. It encourages the Institute to consider expanding its specialized centers of clinically oriented research program in this area and to establish a PH research network to facilitate collaboration and data sharing among leading PH investigators. (p. 131)

#### Action taken or to be taken

Research on pulmonary hypertension (PH) continues to be a high priority for the NHLBI. The NHLBI Specialized Clinical Centers of Research SCCOR program in Pulmonary Vascular Disease funds new and innovative research to understand the molecular and genetic basis of PH, the complex lung vascular and right heart interactions and remodeling occurring in PH, and the effect of these interactions on PH morbidity and mortality. The SCCOR also supports research on the mechanisms leading to pulmonary vascular injury in the immature lung and the effects of lung injury on lung growth, development, and vascular disease in infants and children, including those with PH. The NHLBI will work with investigators funded by the SCCOR program to encourage collaborations among investigators studying PH in adult and pediatric patients. To facilitate the exchange of data and ideas, the NHLBI has organized the first meeting of the pulmonary vascular SCCOR investigators, in January 2008. At present, the NHLBI continues to encourage applications from PH researchers, including those focusing on translational research. The concept of a PH network was discussed with representatives of the pulmonary community at a recent NHLBI Workshop on "Clinical Research Networks for the 21st Century." The Institute will consider multiple approaches and its available resources in developing new programs to advance PH research.

#### Item

### ***Thalassemia***

The Committee remains strongly supportive of the focused research effort that is being undertaken by the thalassemia clinical research network, which is comprised of the leading research institutions in the field of thalassemia, or Cooley's anemia. In addition, the Committee commends NHLBI for its commitment to pursue gene therapy and urges the Institute to move aggressively in pursuing a research agenda that will lead to a cure. (p. 131)

#### Action taken or to be taken

The NHLBI is pleased to report that the Thalassemia Clinical Research Network was renewed for another 5 years, from 2005 to 2009. Currently, it has four active clinical studies: a test of a combination drug therapy to improve heart function in thalassemia major patients suffering from iron overload in the heart, an assessment of methods to measure iron burden in the body, a study of the

natural history of thalassemia in a cohort of patients in the network registry, and a test of decitabine to ameliorate symptoms in patients with thalassemia intermedia. Three new protocols are planned to begin in 2008.

During the past 5 years, much progress has been made in developing gene therapy for hemoglobinopathies, including Cooley's anemia (beta-thalassemia). Four U.S. laboratories have reported a gene therapy cure in mouse models, one using human thalassemic blood cells. The first human trial of gene therapy for hemoglobinopathies (funded by industry in France) enrolled two patients, one with Cooley's anemia. The patients were treated with lentiviral vectors developed by NHLBI-supported U.S. investigators. To assess when a similar trial might occur in the United States, the NHLBI convened a working group of leading investigators with representatives from the Cooley's Anemia Foundation, the Sickle Cell Disease Association of America, the FDA, and the extramural hematology and bioethics communities. Barriers to starting a U.S. trial included lentiviral vector production and preparation of applications to the FDA and the Recombinant DNA Advisory Committee (RAC).

The NHLBI funds several grants for research to develop safer, more effective viral vectors for gene therapy. In 2007, the NHLBI created a Gene Therapy Resource Program (GTRP) to facilitate translation of preclinical gene therapy research into clinical interventions. Its objective is to provide resources to produce preclinical and GMP (good manufacturing practices) vectors and to complete pharmacology and toxicology studies. The program also includes resources to assist investigators with the regulatory process. The GTRP also can support a maximum of two phase I/II gene transfer clinical trials per year that have successfully met all regulatory requirements and are ready to enroll patients within 12 months of application approval. Other ongoing NHLBI programs to facilitate trials in this area include the Production Assistance for Cellular Therapies (PACT), the Comprehensive Sickle Cell Centers, and the Center for Fetal Gene Transfer in non-human primates.

Through its programs, the NHLBI is establishing a foundation for U.S. human gene therapy trials for hemoglobinopathies. The NHLBI already has assembled experienced staff and a safety monitoring committee, and has developed standard operating procedures to monitor patient safety. Depending on the quality of proposals received, we anticipate that the first U.S. trial of human gene therapy for Cooley's anemia could start between 2008 and 2010.

#### Item

#### ***Lymphangioliomyomatosis (LAM)***

The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease of women with no effective treatment. The Committee supports both intramural and extramural means of expanding research on LAM and urges NHLBI to use all available mechanisms as

appropriate, including support of state-of-the science symposia, request for applications, and facilitating access to human tissues, to stimulate a broad range of clinical and basic LAM research. The Committee understands that recent scientific findings have presented new treatment approaches for clinical testing, and that experimental trials with the drug sirolimus have begun. The Committee commends NHLBI for supporting the multicenter international lymphangioleiomyomatosis efficacy of sirolimus trial (MILES) trial, and further encourages the support of other phase I and phase II clinical treatment trials to capitalize on the LAM patient population that NHLBI has assembled who do not qualify for the MILES trial. The Committee is also aware of the potential benefit of establishing LAM centers, and suggests NHLBI consider supporting these activities. (p. 131/132)

#### Action taken or to be taken

The NHLBI continues to use a variety of mechanisms to stimulate basic and clinical LAM research and facilitate access to LAM cells and tissues. The Institute supports grants for research on LAM, including grants for exploratory and developmental studies. NHLBI intramural investigators have fostered the collection and distribution of pleural fluid from LAM patients. This activity contributes to progress in the field by providing investigators studying Tuberous Sclerosis Complex TSC and LAM with a source of cells for laboratory investigations. The NHLBI recently transferred the collection, processing, and distribution of LAM specimens to the National Disease Research Interchange (NDRI), a not-for-profit corporation which uses a web-based inventory to provide easier access to specimens. The NDRI is supported through grant funds from the National Center for Research Resources (NCRR), the NIH Office of Rare Diseases (ORD), and multiple other components of the NIH, including the NHLBI. To stimulate clinical research and leverage its investment in clinical studies, the NHLBI recently released a new initiative to solicit ancillary studies to NHLBI clinical trials, including clinical trials of LAM. The NHLBI has discussed the possibility of establishing LAM centers, but believes that other mechanisms should be used fully prior to further consideration of this approach.

NHLBI-funded basic research on the cellular pathways affected by genetic abnormalities in TSC and LAM cells led to a successful pilot study, sponsored by the NCI through the Quick Trial Initiative, of sirolimus as a potential treatment for LAM and to the development of the larger, Multicenter International Lymphangioleiomyomatosis Efficacy of Sirolimus (MILES) trial. The MILES trial, which is being conducted within the Rare Lung Diseases Consortium supported by the ORD and the NCRR, is currently enrolling patients. The NHLBI will continue to consider support for additional LAM trials based on scientific advances and available resources.

#### Item

### ***Sleep disorders***

The Committee encourages the National Center on Sleep Disorders Research to partner with CDC to implement a sleep education and public awareness initiative using the roundtable model that has been successful for NIH institutes and public health service agencies. (p. 132)

#### Action taken or to be taken

An array of public awareness outreach initiatives and educational campaigns on sleep and sleep disorders have been under way since the National Center on Sleep Disorders Research (NCSDR) was established within the NHLBI by Congress in 1993. The NHLBI-initiated programs have engaged diverse public and professional audiences, using a rich variety of media to disseminate information about the importance of sleep.

The NCSDR participates with the CDC, other U.S. Public Health Service agencies, and voluntary health organizations in the National Sleep Awareness Roundtable (NSART), which is a recent initiative of the National Sleep Foundation. The roundtable has identified public health surveillance data and public awareness as primary areas of need, and the NCSDR is participating in the ongoing NSART discussion of potential initiatives to foster public awareness and education. The NCSDR has taken several steps to address the need for health surveillance data, including developing a list of selected federal and public-access sleep-related health surveillance data resources. In addition, the NHLBI and the CDC's National Health and Nutrition Examination Survey (NHANES) collaborated to produce the first national assessment of sleep quality, sleep disorders, and sleep-related quality of life in over 6,000 persons ages 16 and older. In order to further enable community-based sleep awareness initiatives that may arise from the NSART and other entities, the NHLBI intends to announce a funding opportunity in fiscal year 2008 encouraging academic, professional, and voluntary organizations to propose educational research projects aimed at increasing the awareness of researchers, health care providers, and the public about sleep disorders and the role of sleep, along with diet and exercise, as the basis for a healthy lifestyle. The NCSDR will continue to participate in the NSART process.

#### Item

##### ***Alpha-1 antitrypsin deficiency***

. . . . Alpha-1 is . . . a factor in the development of liver disease in children and adults. The Committee commends NHLBI for its plans to focus additional research efforts in the area of COPD. As there is a growing appreciation of the role of genetic influences on the development of COPD and as Alpha-1 is the major identified genetic risk factor in this condition, the additional focus on research leading to a better understanding of Alpha-1, including improved management and therapeutic approaches, is important. The Committee further recommends cooperation between NHLBI, NIDDK, NHGRI, and other institutes

to enhance the NIH research portfolio, and to provide appropriate information to health professionals. The Committee suggests achieving these goals through use of the NHLBI rare lung diseases consortium and the COPD clinical research network. (p. 132)

#### Action taken or to be taken

The NHLBI supports a broad portfolio of research related to Alpha-1, including studies of alpha-1 antitrypsin and the enzyme it inhibits, intracellular protein processing, human genetic factors that modify the severity of Alpha-1 lung disease, lung inflammation, and the pathogenesis and treatment of smoking-related COPD. Clinical studies are examining modifier genes, gene therapy, the use of stem cells to provide an endogenous source of alpha-1 antitrypsin, and various drugs of potential value for the treatment of emphysema. Recently, the NHLBI also funded a large study of the genetics of COPD to clarify the epidemiology of Alpha-1 and identify other genetic factors that contribute to the development of COPD in individuals with and without Alpha-1. The NIH Rare Disease Clinical Research Network, with support from the NHLBI, the NIDDK, and other institutes, recently initiated a clinical study to determine the ability of quantitative x-ray CT imaging of the lung to predict the course of disease in patients with Alpha-1.

Notable progress is being made in Alpha-1 research and education. Investigators are defining the molecular and cellular mechanisms that link alpha-1 antitrypsin to mucous production, inflammation, and cell death in the lungs of patients with COPD. State-of-the-art approaches are being used increasingly, and surprising discoveries have recently been made, including the discovery that alpha-1 antitrypsin can enter cells and protect them from death. To continue its emphasis on Alpha-1 research, the NHLBI will work with other NIH institutes, including the NIDDK and the NHGRI, and make use of existing programs such as the COPD Clinical Research Network, as appropriate. In 2007, the NHLBI, in cooperation with the NCI, convened a working group entitled "Lung Cancer and COPD," to consider possible mechanisms to explain the increased occurrence of lung cancer in patients with Alpha-1. The NHLBI's COPD awareness program, Learn More / Breathe Better, continues to raise awareness among health professionals and the public that Alpha-1 is a genetic risk factor for COPD.

#### Item

##### ***Nontuberculous mycobacteria (NTM)***

Mycobacteria are environmental organisms found in both water and soil that can cause significant respiratory damage. The Committee is aware of the increasing incidence of NTM pulmonary infections in women, particularly involving rapidly growing mycobacteria. The Committee commends NHLBI for its planning meetings regarding NTM; and recommends further collaboration with NIAID, the advocacy community, and other Federal agencies to provide a better understanding of NTM, enhance diagnostic and treatment options, and promote

education of health care providers. (p. 133)

Action taken or to be taken

Although the NIAID is the primary NIH component for NTM research, the NHLBI supports studies to address the role of NTM in obstructive lung disease. This work focuses on understanding the pathogenesis of bronchiectasis, a lung problem associated with NTM infection commonly seen in patients with cystic fibrosis or primary ciliary dyskinesia.

NHLBI staff members serve as liaisons to the Rare Diseases Clinical Research Network program (supported by NCRR and ORD). The main area of research of one of the Rare Lung Disease Consortia is ciliary dyskinesia. Progress is being made in identifying gene mutations associated with the disease.

NHLBI staff members communicate with NIAID staff on areas of mutual interest in NTM research. In 2006 the NHLBI held a workshop on “Research Needs in Bronchiectasis,” which was attended by NIAID intramural and extramural staff and representatives from patient interest organizations. The meeting brought together experts in the fields of pulmonology, infectious diseases (especially mycobacterial infections), immunology, and basic sciences to summarize the state of the field and identify research needs and priorities. The NIAID has been working with patient interest groups to follow up on recommendations from the meeting.

Item

***Bleeding and clotting disorders***

The Committee commends NHLBI for its commitment to research in bleeding and clotting disorders. The Committee encourages the Institute to continue these efforts focusing on improved and novel therapies for these disorders and maintaining its collaborative relationship with the scientific and medical research community and voluntary organizations. (p. 133)

Action taken or to be taken

The Institute continues to work with the American Society of Hematology (ASH), the National Hemophilia Foundation (NHF) and the Hemophilia and Thrombosis Research Society (HTRS) to identify and address the needs of people living with bleeding and clotting disorders.

The NHLBI and the NHF jointly developed the request for applications (RFA) “Improved Therapy for Hemophilia and Hereditary Bleeding Disorders.” Under this RFA, which offered 4 years of support, a total of eight grants were funded in 2005, five by the NHLBI and three by the NHF. The “Specialized Centers of Clinically Oriented Research in Hemostatic and Thrombotic Diseases” program was initiated in 2006 by the NHLBI. Awards were made to three centers for 5 years of support. Based on an ASH-sponsored workshop, the NHLBI, the National Institute on Aging, and the NIH Office of Dietary Supplements

developed the 2007 RFA, “Venous Thrombosis and Thromboembolism in the Elderly.” The NIA funded 5 grants and the NHLBI funded 3 grants via this solicitation.

Item

***Marfan syndrome***

The Committee commends NHLBI for its strong leadership on Marfan syndrome research, particularly its sponsorship of a landmark pediatric heart network clinical trial focused on the drug losartan. The Committee encourages NHLBI to continue to partner with the Marfan syndrome community on this research, and explore ways to support promising ancillary studies to the clinical trial. The Committee also applauds the Institute for establishing a working group on Marfan syndrome and looks forward to reviewing the group’s recommendations for future research. (p. 133)

Action taken or to be taken

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 NMF has been instrumental in getting out the key message to its membership that participation in the losartan clinical trial is necessary for providing a scientific basis to guide therapy. In addition, the NMF is supporting three ancillary studies that will leverage NHLBI’s investment in the main trial. 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.

Item

***Bone marrow failure diseases***

The Committee applauds NHLBI for funding research that has led to a greater understanding of bone marrow failure diseases. The Committee encourages NHLBI to collaborate with NCI to fund new research efforts that seek new treatments and cures for aplastic anemia, myelodysplastic syndromes (MDS), and paroxysmal nocturnal hemoglobinuria (PNH). (p. 133)

Action taken or to be taken

The NHLBI remains firmly committed to research on bone marrow failure diseases, including myelodysplastic syndromes (MDS) and other related disorders of hematopoietic stem cells, such as myeloproliferative diseases, aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH), and Diamond Blackfan anemia (DBA). The NHLBI collaborates with the NCI on many efforts in this area.

In FY 2005, the NHLBI and the NCI jointly issued two requests for applications (RFAs), “Myelodysplastic Syndrome (MDS): Seeking Cure through Discovery on Pathogenesis and Disease Progression” and “Cellular and Genetic Discovery

toward Curative Therapy in Myeloproliferative Disorders (MPD),” to stimulate research on bone marrow failure diseases. Research funded under the initiatives is expected to identify critical genetic, biochemical, and molecular pathways that affect the emergence and progression of the diseases and improve understanding of disease mutagenesis, evolution, and progression. The NHLBI continues to support 17 grants that were awarded in response to the RFAs.

The NHLBI and the NCI also co-sponsor the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), which is leading a national Phase I/II clinical trial using hematopoietic stem cell transplantation (HSCT) to treat patients with severe AA. The objective of the trial is to optimize HSCT conditioning regimens for high-risk patients with severe AA. The treatment offers a potential cure for these patients, who often fail conventional treatments and die from infection or bleeding.

The NHLBI also continues to support 16 research grants that were awarded in FY 2004 in response to the RFA “Molecular Mechanisms Underlying Diamond-Blackfan Anemia and Other Congenital Bone Marrow Failure Syndromes.” The research funded by these awards focuses on rare bone marrow deficiency disorders such as DBA, dyskeratosis congenita, severe congenital neutropenia, Shwachman-Diamond syndrome, and congenital amegakaryocytic thrombocytopenia. The program has led to the creation of a DBA registry, to advances in areas such as gene discovery, and to a report that DBA is the first human disorder ever to be linked to a ribosomal protein deficiency. To promote the exchange of new scientific information among the RFA investigators, the NHLBI hosts annual scientific grantee meetings. Recent progress in understanding DBA and related disorders is expected to stimulate new research on blood cell formation, recovery from cancer chemotherapy, cancer predisposition, and the effectiveness of steroids and blood transfusions as treatments for bone marrow failure syndromes and to thereby create new opportunities for collaboration with other NIH components.

#### Item

##### ***Lymphatic research and lymphatic diseases***

The Committee recognizes the leadership role NHLBI has played in advancing lymphatic research within its Institute and strongly encourages continuation of these efforts in concert with NSE /ORWH AND OTHER RELEVANT/CI, NIAID, NIDDK, NIAMS, and other relevant Ics. The Committee urges NHLBI’s lung division to engage in lymphatic research initiatives, with particular attention to congenital lymphatic malformation-induced pulmonary dysfunction. (p. 133)

#### Action taken or to be taken

The NHLBI and the Trans-NIH Coordinating Committee for Lymphatic Research, which includes representatives from the NCI, NIAID, NIDDK, NIAMS, NEI, NINR and other NIH components, continue to develop research programs in lymphatic

biology. The NIH has renewed the program announcement “Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases” with continued participation of the NHLBI, NCI, NICHD, NIAMS, NCCAM, NIBIB, and NINR.

In 2007, the NHLBI, NCI, NICHD, NIDDK, and NINR issued a new program announcement on “Lymphatic Biology in Health and Disease.” This solicitation will be amended by issuing a notice in the NIH Guide for Grants and Contracts encouraging grant applications that address congenital lymphatic malformation-induced pulmonary dysfunction, pulmonary lymphatic biology, and pulmonary lymphatic development in the hope of generating new research in these areas.

To stimulate additional research, the Trans-NIH Coordinating Committee for Lymphatic Research, with NHLBI leadership, convened a working group of experts representing a variety of disciplines to discuss future research directions.

The NHLBI continues to support a research program in lymphatic biology, including studies of mechanisms that control lymphatic development, defects in lymphatic growth, and lymphatic regeneration after injury in the lung.

### **Senate Significant Items**

#### Item

#### ***ACCORD Trial***

The Committee commends the NHLBI on the ACCORD trial, which should definitively address the relationship between glucose levels, blood pressure and lipids in the formation of macrovascular disease. The NHLBI is urged to consider utilization of new therapeutic options, particularly continuous glucose sensors, to assist those patients in the study for whom current treatments are not allowing target glycemic control levels to be achieved. (p. 113)

#### Action taken or to be taken

ACCORD is examining the effects of three separate interventions—one on blood sugar (glycemia), one on blood pressure, and one on blood lipids. The glycemia trial tests whether intensive lowering of blood sugar, as measured by glycated hemoglobin (HbA1c; an indicator of average blood sugar levels over 2-3 months), will reduce risk of subsequent cardiovascular events compared with standard treatment. It is designed to evaluate intervention strategies that could be applied in clinical practice and, therefore, uses routinely available technology and FDA-approved medications that are currently being prescribed. The intensive glycemia intervention does not test any particular drug or approach but, rather, combines approaches tailored to the individual patient to reach an HbA1c goal of less than 6%. Thus, the treatment strategy used in one person may differ from that used in another, depending on issues such as lifestyle adherence, medication tolerance, medication adherence, and side effects.

ACCORD is co-sponsored by the National Institute of Diabetes and Digestive and

Kidney Diseases, which is ultimately involved in all discussions and oversight of the trial. Continuous glucose monitoring was not part of routine diabetes care at the initiation of the ACCORD trial, and so is not part of the ACCORD treatment strategy. However, the ACCORD protocol does allow for adding treatments, strategies, or medications as they become available for use in clinical practice. ACCORD will continue treating patients for two more years. Continuous glucose monitoring is currently being considered by the study investigators, the data and safety monitoring board, and the two NIH sponsors.

#### Item

##### ***Advanced Imaging Technology***

The Committee is aware that heart perfusion PET scans using Rubidium-82 are considered the 'gold standard' for determining the extent of muscle damage to the heart following a heart attack. The Committee encourages the NHLBI to expand its research efforts into the role of biological imaging and PET in delivering more accurate information to determine appropriate treatment for heart disease patients. (p. 113)

#### Action taken or to be taken

The NHLBI is funding research on many imaging techniques for rapid, accurate diagnosis and treatment of heart disease and stroke, both noninvasive (e.g., positron emission tomography—PET, magnetic resonance imaging—MRI, ultrasound, computer-assisted tomography—CT) and invasive (e.g., optical coherence tomography, near-infrared spectroscopy). A growing body of clinical and experimental evidence suggests that cardiac MRI may prove to be more beneficial than PET because MRI can detect the delivery of blood to the heart with better spatial resolution than PET, and MRI used with contrast agents to determine myocardial viability is nearly as accurate as observations made directly at autopsy. Thus, contrast-enhanced MRI is quickly being adopted as the gold standard for determining the extent of irreversible damage in the heart. Ultra-fast CT methods for imaging coronary vessels and observing calcified regions therein have been rapidly improving over the last year. The recent commercial release of a 256 sensor system essentially provides a real-time view of the heart and coronaries using CT technology which may have a very significant impact on the early detection of heart disease.

PET remains one of the most important tools in the molecular imaging of the body because of its superior sensitivity and specificity with appropriate biomarker probes. The NHLBI is actively supporting research into the analysis of biomarkers that might be coupled to PET detection schemes to give the clinician a new, early view of vascular diseases. These include markers of inflammation, enzymes involved in the degradation of macromolecules, and clot formation. The recent coupling of PET and xray-CT instruments may provide a new cardiovascular imaging platform that combines the high resolution of the xray-CT with the molecular imaging capabilities of PET. Clearly, many of these exciting

imaging applications will rely on the development of appropriate biomarkers/imaging probes of cardiovascular disease, a major current effort of the NHLBI.

Item

***Bone Marrow Failure Diseases***

The Committee applauds the NHLBI for funding research that has led to a greater understanding of bone marrow failure diseases. The Committee encourages the NHLBI to collaborate with the NCI to fund new research efforts that seek new treatments and cures for aplastic anemia, myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria. (p. 113)

Action taken or to be taken

Please refer to page 45 of this document for NHLBI's response to this item on Bone Marrow Failure Diseases.

Item

***Congenital Heart Disease***

The Committee commends the NHLBI for convening a working group to address congenital heart diseases, and supports its recommendation that action be taken to prevent needless disability and premature mortality. The Committee urges 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. 114)

Action taken or to be taken

Please refer to page 35 of this document for NHLBI's response to this item on Congenital Heart Disease.

***Cooley's Anemia [Thalassemia]***

The Committee remains supportive of the effort being undertaken by the Thalassemia Clinical Research Network. In addition, the Committee commends the NHLBI for its commitment to pursue gene therapy and urges the Institute to move more aggressively in pursuing a research agenda that will lead to a cure. (p. 114)

Action taken or to be taken

Please refer to page 39 of this document for NHLBI's response to this item on Thalassemia.

Item

***Depression and Heart Disease***

The NHLBI is encouraged to work closely with the NIMH to ensure that projects examining depression in heart disease patients, or how treatment of depression may improve adherence to cardiovascular health regimens, are routed to the

appropriate Institute and review groups so that this type of research may be supported. (p. 114)

Action taken or to be taken

Because depression is a serious mental health condition that also increases cardiovascular risk, the NIMH and the NHLBI have supported research on its etiology, mechanisms of action, and treatment. Staff of both Institutes meet to discuss research on depression and cardiovascular disease and to consider investigator- and Institute-initiated studies. In addition, NHLBI and NIMH staff closely monitor research applications submitted in this area to ensure that those focused on depression in cardiovascular disease patients are routed to the appropriate Institute and review groups. This process often entails discussions between Institute staff in what has been a collegial and effective process to enhance the likelihood that meritorious applications will be supported.

Item

***Diabetic Cardiovascular Disease***

Research has shown that heart disease begins as early as childhood or adolescence in type 1 diabetes patients. The NHLBI is encouraged to promote research to identify early biomarkers of cardiovascular disease in young diabetic patients to learn who might benefit from therapeutic agents that are currently used in adults. (p. 114)

Action taken or to be taken

Please refer to page 36 of this document for NHLBI's response to this item on Heart Disease and Diabetes.

Item

***Heart Disease in Native Hawaiians***

The Committee continues to be concerned that Native Hawaiians have a higher rate of mortality from heart disease and cerebrovascular disease compared to other residents of the State. The Committee strongly urges the NHLBI to increase research that is focused towards understanding heart disease and cerebrovascular disease among Native Hawaiians. (p. 114)

Action taken or to be taken

The NHLBI supports research in heart failure disparities at the University of Hawaii at Manoa and at the Queen's Medical Center in Hawaii. This work is intended to improve understanding of the impact of heart failure on Native Hawaiians and to identify the most appropriate treatments for this population. The Institute also supports a research scientist award in molecular cardiology at the University of Hawaii to enhance the research capacity in cardiovascular disease.

Native Hawaiians have high rates of obesity and diabetes, both significant risk

factors for cardiovascular disease. The NHLBI's major ongoing commitments to research on these conditions are expected to yield improved strategies to prevent cardiovascular diseases in vulnerable populations.

Item

***Hematology***

The Committee commends the NHLBI for developing a strategic plan based on input from its broad constituency and for committing 70 percent of its budget to the funding of investigator-initiated research. The Committee encourages the NHLBI, in conjunction with the NIDDK, NCI and NIA and experts in hematology research, to identify hematology research priorities that can impact chronic malignant and non-malignant bleeding disorders. (p. 114)

Action taken or to be taken

The NHLBI has worked closely with the NCI to foster inter-institute priority setting and collaboration to pursue therapies for malignant blood disorders. Through the joint NHLBI/NCI-supported Blood and Marrow Transplant Clinical Trials Network, 10 trials have been launched to improve outcomes of blood and marrow transplants, particularly for patients with malignant blood disorders. In the FY 2008 renewal process we anticipate a joint NCI-NHLBI-NIAID collaboration for the Center on International Blood and Marrow Transplantation Research (CIBMTR), which coordinates an international effort to collect and analyze data on outcomes of blood, bone marrow, and umbilical cord blood transplantation. The key objective of this collaboration is to support the continued availability of the CIBMTR to investigators and health policy makers, and help to define the usefulness of transplants in various clinical situations, the vast majority of which are for hematologic malignancies.

Where the missions of various Institutes intersect, NHLBI cooperates with sister components such as the NIA and NIDDK in the area of non-malignant hematology, for example, in the areas of anemia or thrombosis in the elderly. While there are currently no inter-Institute collaborations on specific bleeding disorders such as thrombocytopenia, hemophilia, or von Willebrand disease, the NHLBI supports a rich portfolio of research in these disorders and collaborates broadly with outside organizations such as the American Society of Hematology (ASH) and the National Hemophilia Foundation (NHF). NHLBI has worked with ASH on establishing guidelines for the diagnosis, evaluation, and treatment of von Willebrand disease and is jointly sponsoring an RFA program on Improved Therapy for Hemophilia and Hereditary Bleeding Disorders with the NHF.

Item

***Kidney Disease***

The Committee notes that chronic kidney dysfunction is a unique and important risk factor for the development of cardiovascular disease. Additionally, hypertension, or high blood pressure, is the second-leading cause of end-stage

renal disease [ESRD]. Given the significant morbidity and mortality associated with cardiovascular disease among patients with kidney disease, the Committee recognizes the importance of the urgency to examine the relationship between cardiovascular disease and kidney disease. The Committee encourages the NHLBI and NIDDK to work together to develop appropriate basic and clinical research initiatives addressing the pathogenesis of cardiovascular events in patients with kidney disease and exploring therapeutic and preventive interventions. The Committee also encourages the NHLBI to work with the renal community to support ongoing educational programs directed to health professionals, patients and the public to raise the awareness of the relationship between cardiovascular disease, hypertension and kidney disease. (p. 115)

#### Action taken or to be taken

On January 16, 2007, the NHLBI and the NIDDK convened an expert panel to make recommendations on a planned Hypertension Treatment Trial initiative. The main recommendation was to undertake a large randomized clinical trial to test whether treating systolic blood pressure to a lower goal than is currently recommended would reduce cardiovascular and kidney morbidity and mortality. The panel recommended including a substantial number of patients with chronic stage 3 kidney disease in the trial and incorporating both kidney events and changes in renal function as measures of the intervention's effect. The NHLBI and NIDDK are currently planning this trial for 2009.

The two institutes also support a large number of investigator-initiated studies on pathophysiologic mechanisms relating renal disease to hypertension and cardiovascular disease. In 2005 and 2006 the NHLBI cosponsored NIDDK program announcement "Pilot and Feasibility Program Related to the Kidney" to foster the development of innovative early-stage investigations addressing basic problems relevant to the study of acute and chronic kidney diseases and their complications. The NHLBI currently funds several projects that resulted from this solicitation.

The NHLBI continues to support the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study, a randomized clinical trial to evaluate the effectiveness of renal artery stenting in patients with renal artery stenosis and either hypertension or chronic kidney disease. In addition, the NHLBI continues to support three large epidemiological cohort studies, the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and the Coronary Artery Risk Development in Young Adults study, to enable further investigation of the relationship between kidney function and cardiovascular disease.

The NHLBI is a member of the NIDDK's National Kidney Disease Education Program Coordinating Committee, which meets periodically to develop and coordinate messages and approaches to educating clinicians, patients, and the public about kidney disease. Through the Committee, the NHLBI has shared

information on its Mission Possible program, which focuses on prevention and control of high blood pressure. New high blood pressure guidelines are being developed, the NHLBI looks forward to opportunities for further collaboration with NIDDK to ensure that the guidelines reflect the latest science on the relationship between CVD risk factors and chronic kidney disease and possibly to develop joint prevention and education outreach efforts.

Item

***Lupus***

The Committee strongly encourages the NHLBI to expand and intensify research on lupus, with a special focus on its links to early-onset cardiovascular disease. (p. 115)

Action taken or to be taken

The NHLBI supports a growing research portfolio on premature cardiovascular disease in patients with lupus, including studies of the role of immune cells, such as T lymphocytes, in the development of atherosclerosis in lupus. An NHLBI-sponsored program is conducting comprehensive genetic studies to investigate the influence of genetic variation on cardiovascular disease risk in people with lupus. The NHLBI also is supporting a case-control study to quantify differences in underlying cardiovascular disease risk factors in lupus patients compared with controls.

Representatives from the NHLBI and many other NIH components continue to participate in the Lupus Federal Working Group, which is developing a detailed lupus research agenda, and in the Autoimmune Disease Coordinating Committee, which facilitates collaboration among NIH components, other federal agencies, and private organizations that have an interest in autoimmune diseases.

Item

***Lymphatic Research and Lymphatic Diseases***

The Committee commends the NHLBI for its leadership role in lymphatic research and strongly encourages amplified continuation of these efforts in concert with the NCI, NIAID, NIDDK, NIAMS, and other relevant ICs. In addition, the Committee urges the NHLBI's Lung Division to engage in lymphatic research initiatives, with particular attention to congenital lymphatic malformation-induced pulmonary dysfunction. (p. 115)

Action taken or to be taken

Please refer to page 44 of this document for NHLBI's response to this item on Lymphatic Research and Lymphatic Diseases.

Item

### ***Marfan Syndrome***

The Committee commends the NHLBI for its strong leadership on Marfan syndrome research, particularly its sponsorship of a landmark “Pediatric Heart Network” clinical trial focused on the drug losartan. The Committee encourages the NHLBI to continue to partner with the Marfan syndrome community and explore ways to support promising ancillary studies to the clinical trial. The Committee also applauds the Institute for establishing a Working Group on Marfan Syndrome. (p. 115)

#### Action taken or to be taken

Please refer to page 45 of this document for NHLBI’s response to this item on Marfan.

#### Item

### ***Neurofibromatosis [NF]***

The Committee applauds the NHLBI for its involvement with NF research and with NF patient advocacy groups, and it encourages the Institute to continue to expand its NF research portfolio. (p. 115)

#### Action taken or to be taken

The NHLBI supports research on neurofibromatosis-related diseases of the heart (congenital heart disease), lung (interstitial lung disease), and blood (myeloproliferative disease). In the past year, the NHLBI has supported one research grant and one Mentored Clinical Scientist Development Award to investigate neurofibromatosis-related congenital heart disease. A third investigator has been supported as part of a Specialized Center of Clinically-Oriented Research to address congenital heart disease associated with Noonan syndrome, which is known to occur in some neurofibromatosis patients. The NHLBI also supports a program project grant that includes a project investigating the switch from fetal to adult hemoglobin. High fetal hemoglobin levels are associated with juvenile myeloid leukemia, which is also known to occur in neurofibromatosis patients. The NHLBI also funds an Exploratory/Developmental Research Grant investigating potential inhibitors of juvenile myelomonocytic leukemia, another blood disorder associated with neurofibromatosis, and Noonan syndrome. A common thread in all these disorders is altered Ras signaling. The NHLBI supports numerous grants investigating the role of Ras signaling in heart, lung, and blood disorders, which may facilitate the development of therapies for neurofibromatosis and its complications.

#### Item

### ***Nontuberculous Mycobacteria [NTM]***

The Committee commends the NIH for its planning meetings regarding NTM and recommends further collaboration with the NIAID, the advocacy community, and other Federal agencies to provide a better understanding of NTM, enhance diagnostic and treatment options and outcomes, and promote education of health

care providers. The Committee also encourages the NHLBI to issue a program announcement or other appropriate mechanism to ensure the initiation of grant proposals.

Action taken or to be taken

Please refer to page 41 of this document for NHLBI's response to this item on Nontuberculous Mycobacteria [NTM].

Item

***Pulmonary Hypertension [PH]***

The Committee continues to view research on PH as a high priority. It encourages the NHLBI to expand its successful SCCOR program in this area and establish a PH Research Network to facilitate collaboration and data sharing among leading PH investigators. (p. 115/116)

Action taken or to be taken

Please refer to page 39 of this document for NHLBI's response to this item on Pulmonary Hypertension [PH].

Item

***Sickle Cell Disease [SCD]***

The Committee encourages the Institute to continue to strengthen its efforts related to the funding of the Comprehensive Sickle Cell Centers, the SCD Comprehensive Clinical Network centers, and related activities. Specifically, the Committee encourages the expansion of opportunities available for patients to participate in large, multi-center clinical trials to support the development of more treatment options and the establishment of a central prospective registry of several thousand well-characterized individuals with SCD. Additionally, the Institute is encouraged to bring new health and medical professionals and researchers into the field to support the next generation of researchers equipped to integrate genomics, proteomics and high-throughput screening expertise into the SCD research field. The Committee also encourages the Institute to expand the use of transgenic mice and a tissue bank facility, and to encourage collaboration between the NHLBI, HRSA, CDC, and national and local organizations. The Committee requests an update on these efforts in the fiscal year 2009 congressional budget justifications. (p. 116)

Action taken or to be taken

The NHLBI currently funds several programs, including 10 Comprehensive Sickle Cell Centers, a Sickle Cell Disease Clinical Research Network, and three multi-center clinical trials, to support the development of treatment options for sickle cell disease (SCD). The SWITCH clinical trial will compare hydroxyurea therapy to transfusion in children with SCD who have had a stroke. The Baby HUG trial is evaluating the use of early hydroxyurea treatment for prevention of spleen and kidney damage in infants. The PhASST study is testing whether sildenafil

ameliorates pulmonary hypertension in SCD patients. The NHLBI has awarded grants to study pulmonary complications of SCD. Excellent transgenic mouse models, which are widely used in basic and translational projects, exist for SCD. To expand resources for sharing with the research community, blood and DNA samples are being collected and processed from the Comprehensive Sickle Cell Centers and from the PhASST study for storage in the NHLBI Biological Specimen Repository.

From November 2006 to June 2007, the NHLBI consulted with the Sickle Cell Disease Association of America, the CDC, HRSA, professional organizations, and consumers, to discuss a national patient registry, including its potential purpose, utility, and feasibility. In consultation with the NHLBI's Sickle Cell Disease Advisory Committee, stakeholders and DHHS agencies concluded that a surveillance system, rather than a registry, should be developed to characterize the U.S. sickle cell population's clinical features, epidemiology, health care and provider practice patterns, and community organization involvement. The NHLBI is continuing discussions with the CDC, other DHHS agencies, and stakeholders to determine which type of data system would best describe the epidemiology, health status, and effect of sickle cell disease. The surveillance system concept was discussed further at the NHLBI Sickle Cell Disease Advisory Committee meeting on October 29, 2007.

The NHLBI is funding the new "Clinical Hematology Research Career Development Program" at six medical schools to develop and evaluate multidisciplinary training in non-malignant hematology to equip new investigators with the knowledge and skills to address complex problems in blood diseases. The program is expected to encourage new health and medical professionals and researchers to specialize in the treatment of non-malignant conditions such as SCD.

The NHLBI continues to work with HRSA and other national partners on issues related to SCD. The NHLBI has begun discussions with HRSA about a proposed initiative to compile and evaluate clinical practice guidelines for the management of SCD. The NICHD has invited the NHLBI and HRSA to participate in organizing a translational Newborn Screening Coordinating Center to provide the research community with improved diagnostics, treatments, and preventive strategies for genetic diseases identified by HRSA-funded newborn screening programs. The NHLBI also is leading an NIH consensus development conference on the use of hydroxyurea in SCD. Multiple NIH components and DHHS agencies are co-sponsors.

Item

***Sleep Disorders***

The Committee continues to urge the National Center on Sleep Disorders Research to partner with other Federal agencies and voluntary health organizations to implement a sleep education and public awareness initiative using the roundtable model. (p. 116)

Action taken or to be taken

Please refer to page 42 of this document for NHLBI's response to this item on Sleep.

Item

***Tuberous Sclerosis Complex***

The Committee urges the NHLBI to support basic research on the mTOR signaling pathway and the role of the TSC1/2 genes in cell growth and proliferation in the heart and lungs. The Committee also urges the NHLBI to continue and expand intramural and extramural programs on lymphangioleiomyomatosis [LAM], a lung disorder that primarily affects women. In particular, research should focus on the natural history of LAM in TSC and sporadic LAM, as well as support for clinical trials. (p. 116)

Action taken or to be taken

Please refer to page 40 of this document for NHLBI's response to this item on Lymphangioleiomyomatosis (LAM).

# National Institute of Dental and Craniofacial Research

## House Significant Items

### Item

#### ***Dental disease***

Dental disease is the most common chronic childhood illness and one of the most prevalent unmet needs in poor children. Research indicates that dental disease has a serious impact on learning and overall health of children, and recent data indicates an increase in early childhood cases. The Committee commends NIDCR for its current efforts in this area and encourages NIDCR to support additional research to determine the most effective methods for preventing, controlling, and treating early childhood caries. (p. 133)

### Action or to be taken

The NIDCR is funding numerous studies that will contribute to our understanding of the complex interplay of factors that contribute to dental caries. Better understanding these factors will lead to the development of more targeted preventive and therapeutic approaches. These studies explore a wide range of factors that include genetics, family contextual factors, psychosocial determinants, diet, neighborhood settings and environmental factors, and their interactions. New conceptual models that take a holistic, systems approach are emerging. These conceptual models will guide the work of future researchers and decision makers.

The NIDCR is making substantial contributions in developing effective, practical approaches to prevent and treat this common childhood disease. Four NIDCR-supported *Centers for Research to Reduce Oral Health Disparities* focus on identifying and modifying the complex range of factors underlying the high rates of early childhood caries (ECC) in minority and underserved populations. The Oral Health Disparities Centers are conducting numerous intervention studies to prevent this devastating form of caries in very young children. These studies involve children and their caregivers from a variety of vulnerable populations (inner city African Americans, Latinos, rural and urban dwelling poor, Asian and Pacific Islanders and families receiving health care in Community Health Centers). For example, a clinical trial assesses fluoride varnish use in infants combined with chlorhexidine use by their mothers at Federally Qualified Health Centers to prevent the disease at the earliest age possible. Another clinical trial focuses on effectiveness of multiple applications of fluoride varnish with children attending Head Start centers in rural, agricultural areas. Other studies focus on behavioral interventions specifically tailored to inner city individuals and neighborhoods, and others on practice-based and hospital-based approaches to influence the oral health status of vulnerable populations. In FY08 the

competitive renewal of the *Centers for Research to Reduce Disparities in Oral Health* is occurring with funding commitments through 2015. These new Centers will continue to support dental caries intervention research.

NIDCR is also encouraging studies to establish the foundation for conducting large multi-center trials for the prevention and control of ECC. One such planned trial would determine if applying fluoride varnish to the teeth of toddlers during well-child visits to pediatric clinics reduces ECC. The rationale for developing a pediatric clinic-based intervention is that children from poor families often have limited access to dental providers, while they are seen more frequently for well-child visits in medical clinics. Unfortunately, ECC is so severe that approximately 40% of children receiving dental treatment for the disease do so under general anesthesia. NIDCR is supporting the planning phase of a multi-center trial that would determine if the application of a povidone iodine solution, applied in an operating room setting, can decrease the rate of recurrent decay amongst children with ECC.

In addition, NIDCR is funding research to promote the oral health status of women and their infants before, during and after pregnancy. Since ECC is an infectious disease that is influenced by the mother's or caretaker's oral health and knowledge about ECC prevention, this research is expected to yield innovative, practical approaches. The projects include those that assess the feasibility of using public health nurses to incorporate oral health promotion activities into an ongoing pre- and post- natal home visiting program and that apply behavioral and organizational theory to assess barriers to oral health care among pregnant women that will contribute to intervention strategies.

### **Senate Significant Items**

#### Item

#### ***Temporomandibular Joint and Muscle Disorders [TMJDs]***

The Committee commends the NIDCR for its efforts to increase funding for TMJDs research and stimulate interest in young investigators in TMJD research.

The Committee urges the NIDCR to give priority to the recommendations of the Fourth Scientific Meeting of The TMJ Association, especially those calling for the establishment of Regional TMJD Centers of Excellence. Because the multifaceted nature of TMJDs requires an approach that coordinates the work of many interested parties at the NIH, the Committee expects the NIDCR to continue to collaborate and coordinate research and awareness activities with the NIBIB, NINDS, NIAMS, ORWH and all other relevant ICs as well as the trans-NIH Pain Consortium and the NIH Blueprint for Neuroscience Research. The Committee also urges the NIDCR to consult regularly with patient advocacy groups in the planning of research initiatives. (p. 116-117)

Action or to be taken

Based on the recommendations of the Fourth Scientific Meeting of the TMJ Association, the NIDCR organized a meeting of leaders in the field of systems biology and interdisciplinary research, held on September 16-18, 2007 as a working group of the National Advisory Dental and Craniofacial Research Committee (NADCRC). The purpose of the meeting was to make recommendations to the NADCRC regarding the best research model that is justified by the current state of the science and which is most likely to lead to significant treatment advances for TMJD patients. A report from the working group will be reviewed at the January 25, 2008 meeting of the NADCRC by the full Council. Based on the outcome of that meeting, the Institute will develop an implementation plan.

The NIDCR, as the lead of the TMJD Interagency Working Group, one of the leads for the NIH Pain Consortium and a participant in the NIH Blueprint for Neuroscience Research, continues its history of collaboration with other ICs at NIH in all areas related to TMJDs.

Finally, the NIDCR continues to actively seek input from patients and their advocates in several ways including: (a) hosting an annual meeting of patient advocates; (b) soliciting input for comments during the early stages of scientific program initiatives; (c) providing membership of a patient advocate on the National Advisory Dental and Craniofacial Research Council; and (d) holding regular private meetings between the Director, NIDCR or other senior members of the Institute and representatives of TMJD patient advocacy groups.

# National Institute of Diabetes and Digestive and Kidney Diseases

## House Significant Items

### Item

#### ***Cooley's anemia***

The Committee continues to support the high quality research being conducted by NIDDK on such issues as iron chelation and non-invasive iron measurement. The development of a less burdensome means of iron chelation is urgently needed. In addition, the Committee encourages NIDDK to continue to work closely with NIBIB to develop and perfect non-invasive means of measuring iron that accumulates in the heart and liver. (p.134)

### 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 anemias, 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 "smart" combinations of chelators that may enhance the effectiveness of iron removal, while decreasing the doses of drugs needed for effective treatment. The NIDDK currently funds a study of the preclinical toxicity of iron chelators for potential use in the safe and effective removal of iron deposits in patients with iron overload conditions. Another high priority of iron metabolism research is to develop better methods to detect and measure iron overload 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. Research sponsored by the NIDDK has shown that magnetic resonance imaging (MRI) can serve as a potentially useful and widely available technique for monitoring excess iron in individuals with iron overload. Ongoing refinements in MRI technology promise further advances in the non-invasive measurement of body iron that will allow chelation treatment to be tailored to the needs of individual patients.

In 2003, NIDDK collaborated with NIBIB to sponsor an RFA on "Noninvasive Measurement of Iron by Magnetic Resonance Imaging" (DK-03-007), from which a total of seven grants were funded, six by NIDDK and one by NIBIB. These projects are now in their final years of funding. The NIDDK is currently organizing a follow-up workshop to be held in May 2008, on "Iron overload: Mechanisms, Measurement, and Therapy." NIDDK plans to collaborate with NIBIB in developing this workshop to address the current state-of-the-art in the use of MRI to measure tissue iron burden and the efficacy of iron chelation therapy. This workshop will inform continuing collaborations between NIDDK and

NIBIB to address future research priorities in this important area, focusing on the standardization of MRI techniques to detect and measure iron overload and on the full translation of these techniques to clinical practice.

#### Item

##### ***Drug-induced Liver Injury***

The Committee is aware of the good work of the five centers which comprise the drug-induced liver injury network (DILIN). This network represents an important database to record, examine, and research the liver toxicity of various pharmaceutical and over the counter products. In view of the increasing incidence of liver injury from prescription and nonprescription drugs, the Committee encourages NIDDK to strengthen the DILIN network and requests a review of progress made in the use of the DILIN network data in developing findings or recommendations to reverse the incidence of liver injury.

#### Action taken or to be taken

The NIDDK-sponsored Drug-Induced Liver Injury Network (DILIN) is engaged in vigorous research efforts to address the problem of drug-induced liver injury, including: (1) expansion and extension of the Network to include a total of up to eight clinical centers and a data coordinating center to be funded for an additional 5 years; (2) planning for an international workshop on drug-induced liver injury for December 2008; and (3) development of a website with the National Library of Medicine to provide comprehensive, up-to-date information for health care providers as well as researchers.

The Network currently represents a consortium of the five NIDDK clinical centers, and a data coordinating center. The Institute plans to expand this Network to include as many as eight clinical centers and a data coordinating center, in order to strengthen its studies of liver injury due to drugs or complementary and alternative medicines (CAM) by enrolling more cases from a larger, more diverse demographic area. Clinical information and samples collected from patients who participate in the Network will enable studies that aim to provide the improved diagnostic tools needed for assessment of the causes and, ultimately means of prevention of drug- or CAM-induced liver injury. Studies are also planned on such topics as the role of genetic factors in susceptibility to this injury, which could enhance understanding of the disease processes involved and form the basis for developing specific treatments. The Network is also pursuing the development of partnerships with the pharmaceutical industry to collaborate on identifying cases of drug-induced liver injury and applying genome-screening techniques.

The NIDDK is also planning an international workshop on drug-induced liver injury for December, 2008. This meeting will bring together world experts in this field of study to work toward improving standardization of the processes used to determine whether a drug or CAM causes liver injury in individual cases.

Additionally, the NIDDK, in conjunction with the National Library of Medicine, is developing a website on the topic of drug-induced liver injury. The website will feature examples of cases of drug-induced liver injury based on DILIN, as well as a database summarizing reports of liver injury for a given drug. The website will aid health care providers in diagnosing, and investigators in studying, this form of injury.

Item

***Polycystic kidney disease (PKD)***

The Committee is pleased that NIH-supported PKD research has rapidly led to the development of multiple human clinical trials and interdisciplinary studies focused on slowing PKD disease progression or even reversing the progression of PKD. Given the momentum in PKD research, the Committee encourages NIDDK to promote additional PKD clinical trials and multidisciplinary research, and expand knowledge-based studies of pathophysiology and molecular biology. The Committee encourages NIDDK to conduct a comprehensive review of its structure to ensure that funding is directed to areas of research (such as PKD) that show the best return on investment in terms of ameliorating and/or curing diseases. (p. 134)

Action taken or to be taken

The NIDDK is investing in major clinical research efforts to combat Polycystic Kidney Disease (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. The CRISP study demonstrated that magnetic resonance imaging could accurately track structural changes in the kidneys, and may be able to predict functional changes earlier than standard blood and urine tests in these individuals. The NIDDK has funded an extension of this study, CRISP II, to continue to monitor this important cohort of patients and to determine the extent to which changes in kidney volume predict changes in kidney function.

The NIDDK, with co-funding from the PKD Foundation, is also conducting two clinical trials of people with Autosomal Dominant Polycystic Kidney Disease (ADPKD)—one in patients with early kidney disease and another in patients with more advanced disease. These two trials are the largest multi-center studies of PKD conducted to date, and are collectively termed HALT-PKD. The studies are testing whether optimum blood pressure management, in combination with drugs—either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers—will slow the progression of this more common form of PKD.

In FY07, the NIDDK expanded its support of the HALT-PKD studies, allowing investigators to undertake genetic screening of all enrolled subjects for mutations

in the PKD genes, *PKD1* and *PKD2*. This effort will be the largest PKD genetic sequencing project undertaken to date, and should provide important information on whether specific genetic mutations and clinical factors are predictive of disease activity in PKD. Although several clinical studies have suggested that *PKD2* genes are associated with a less severe disease course, presentation of kidney disease in PKD is highly variable, even within families that express the same mutation.

The NIDDK has also expanded support for data analysis in the CRISP clinical cohort study. The CRISP study has accumulated a rich clinical data set on a cohort of over 220 patients with PKD, which has suggested a new kidney imaging endpoint for clinical studies of PKD. The CRISP investigators are continuing to follow the cohort to further verify that this imaging endpoint, and perhaps other clinical parameters, can reliably predict disease progression. The identification of potential new endpoints in this disease has already increased industry interest in testing new therapeutics for PKD.

#### Item

##### ***Management of pediatric kidney disease***

The complexity and variety of causes unique to childhood kidney diseases require multiple detailed treatment regimens for chronic kidney disease, dialysis and kidney transplantation. When these life-saving medication and treatment plans are not followed, patients experience life-threatening complications and costly hospitalizations. The Committee urges NIDDK to conduct trans-institute trials to study methods to improve adherence with treatment regimens for children and adolescents throughout the spectrum of chronic kidney disease, particularly in the areas of dialysis and post-kidney transplantation. Additionally, the Committee urges NIDDK to support collaborating networks of health care providers to collect data and plan trials to improve therapy for the spectrum childhood kidney diseases and the transition of children with kidney disease into adulthood. (p.134)

#### Action taken or to be taken

Chronic kidney disease (CKD) and its accompanying metabolic complications substantially affect the well-being of children. Adherence to therapy is particularly important in the pediatric population, because significant problems may occur with neurocognitive development when CKD develops during the neonatal period or in early infancy.

The NIDDK plans to hold a meeting in mid-2008 to discuss the issue of non-adherence to treatment in patients with chronic kidney disease. The meeting will address possible trials regarding improving adherence to therapy and will be relevant to all patients on dialysis. Additionally, in January 2008 the American Society of Transplant Physicians held a Consensus Conference on non-adherence with treatment regimens for children and adults. Representatives

from the NIDDK attended the meeting, which focused on the scope of the problem of non-adherence, risk factors, the impact of non-adherence on function of transplanted kidneys, and possible new approaches to the problem in the subpopulation of transplant patients.

To bolster our understanding of chronic kidney disease in the pediatric population, the NIDDK has launched The Prospective Study of Chronic Kidney Disease in Children (C-KiD), a longitudinal, observational study of 540 children, ages 1-16, who have mildly to moderately impaired kidney function. By studying this new, important cohort of children with chronic kidney disease, researchers will be able to explore the associated cardiovascular morbidity and mortality, and a number of risk factors for worsening kidney disease, including obesity, type 2 diabetes, and hypertension. The information obtained from this study will establish natural history and outcome measures for future intervention and prevention trials.

Item

***Bowel incontinence***

This condition affects people of all ages and is associated with a wide variety of causes. The Committee is pleased that NIDDK is collaborating with NICHD on an incontinence state-of-the-science conference and encourages the Institute to prioritize implementation of this conference. (p. 135)

Action taken or to be taken

An NIH Consensus Development Conference on the “Prevention and Treatment of Fecal and Urinary Incontinence” was held at the NIH on December 10-12, 2007 (<http://consensus.nih.gov/2007/2007IncontinenceSOS030main.htm>). The conference, which was co-sponsored by the NIDDK and the National Institute of Child Health and Human Development (NICHD), brought together experts in urology, gastroenterology, and geriatrics to evaluate the state-of-the-science in fecal and urinary incontinence and to address future challenges brought on by the aging U.S. population—a population that will be at increased risk for these conditions. Topics discussed included the burden of illness on society, the impact of these conditions on individuals, risk factors for incontinence, prevention strategies, and research priorities. Recommendations from the conference will set the stage for future NIH initiatives to increase the public’s knowledge of these conditions, and reduce their burden on society and affected individuals.

Item

***Inflammatory bowel disease***

The Committee has been encouraged in recent years by discoveries related to Crohn’s disease and ulcerative colitis, collectively known as inflammatory bowel disease (IBD). These extremely complex disorders represent a major cause of morbidity from intestinal illness. The Committee commends NIDDK for its strong leadership in this area and continues to encourage the Institute to strengthen

research focused on: (1) the cellular, molecular and genetic structure of IBD, (2) identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and (3) translation of basic research findings into patient clinical trials as outlined in the research agenda developed by the scientific community entitled, "Challenges in Inflammatory Bowel Disease." (p.135)

#### Action taken or to be taken

During the past year, genetics has taken the lead in advancing understanding of inflammatory bowel disease (IBD). Based on the accomplishments of the International Genome and International HapMap Projects, new technologies have been developed that allow scientists to perform genome-wide association (GWA) scans that screen entire genomes for small DNA mutations that contribute to a specific disease. The NIDDK IBD Genetics Research Consortium has been at the forefront in supporting research using this state-of-the-art technology to uncover genes associated with IBD. For example, the IBD *IL-23* receptor gene was recently discovered using a GWA screen. Notably, one of the variants of the *IL-23R* gene was found to protect against Crohn's disease (CD). Scientists have since learned that CD cannot develop without a functioning IL-23 receptor. Another significant genetic finding emerged with the discovery of an autophagy gene, *ATG16L1*, which plays a role in Crohn's disease. Until recently, the autophagy process, which allows the capture and degrading of unwanted material within a cell, had not been associated with IBD. In addition to these high-profile genes, several other genes and chromosomal regions have been identified that have strong associations with CD. This advance may lead to approaches to prevent or treat IBD.

In addition, the results of a significant NIDDK-supported clinical trial demonstrating the efficacy of the drug rosiglitazone for the treatment of ulcerative colitis (UC) were presented in May 2007 at the Digestive Disease Week meeting. This is the first approved drug shown to be effective in the treatment of UC.

Finally, the NIDDK is committed to continuing its valuable partnership with the IBD community and to supporting research goals outlined in the Crohn's and Colitis Foundation of America's (CCFA) research plan, "Challenges in Inflammatory Disease."

#### Item

##### ***Hepatitis B***

The Committee is pleased with the NIH commitment to conduct a consensus conference in 2008 on best treatment practices for individuals with hepatitis B, especially with the growing number of treatment options. As most people who are infected with hepatitis B are unaware of their infection, the Committee encourages NIDDK to continue to collaborate with CDC in the development of a public health strategy to expand the screening of individuals at risk for chronic

hepatitis B. (p.136)

Action taken or to be taken

The NIDDK continues to collaborate with the Centers for Disease Control and Prevention (CDC) on research efforts related to improving screening of individuals at risk for chronic hepatitis B. For example, the NIDDK is collaborating with the CDC, as well as other NIH Institutes (National Institute of Allergy and Infectious Diseases and National Cancer Institute) and Federal health agencies to plan the Consensus Development Conference on Management of Chronic Hepatitis B to be held October 20-22, 2008. The Conference will focus on building consensus in the research community to address current issues surrounding management of chronic hepatitis B. The Conference will consider issues such as the disease's current burden in the U.S., natural history, benefits and risks of current therapies, and the most important future directions for hepatitis B research. At the Conference, representatives from the CDC will present an overview of the current recommendations for screening for the hepatitis B virus. The CDC is co-sponsoring the Consensus Conference and participated actively in the planning and organizational meetings.

Additionally, a one-and-a-half day advisory meeting to develop United States Public Health Service recommendations on screening for hepatitis B was held on February 7-8, 2007 in Atlanta, Georgia. The NIDDK participated in this meeting and is working with the CDC to develop formal recommendations that will be published in the CDC's Morbidity and Mortality Weekly Report.

The NIDDK also recently sponsored an initiative to establish a Hepatitis B Clinical Research Network. This Network aims to promote translational research on hepatitis B by elucidating the pathogenesis and natural history and developing means of treatment and control. Research conducted by the Network will address hepatitis B research goals identified through the 2006 NIH workshop on hepatitis B management, as well as the trans-NIH *Action Plan for Liver Disease Research*.

Item

**Hepatitis C**

The Committee notes that several new antiviral agents are in development against hepatitis C. However the problem of antiviral drug resistance has emerged as a stumbling block. The Committee encourages implementation of clinical studies aimed at overcoming antiviral drug resistance, possibly by utilizing novel agents in combination. (p.136)

Action taken or to be taken

The NIDDK and other NIH Institutes support robust clinical research on hepatitis

C, including studies investigating causes of and approaches to overcoming antiviral drug resistance. For example, the NIDDK supports, with co-sponsorship by the National Institute of Allergy and Infectious Diseases and the National Cancer Institute, 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 trial is studying the efficacy of long-term combination treatment with peginterferon and ribavirin for chronic hepatitis C in patients who did not respond to previous therapy with interferon alone. The steering committee for this trial has met with scientific representatives of pharmaceutical companies that have developed new antiviral agents targeting hepatitis C virus, in order to consider proposals for combination studies. At the present time, combination studies with the new agents have not been initiated, as the safety and efficacy of the individual agents have yet to be clearly defined. Provided the safety of these agents is established and there is some evidence for efficacy, combination studies could then commence.

Additionally, the trans-NIH *Action Plan for Liver Disease Research* (<http://liverplan.niddk.nih.gov>) features research goals relevant to therapy of chronic hepatitis C and new approaches to overcoming antiviral drug resistance. These research goals include: (1) to evaluate new approaches to therapy in all forms of viral hepatitis; (2) to achieve a sustained response rate of over 90 percent in chronic hepatitis C; (3) to define the basis for interferon resistance of hepatitis C virus infection in humans; (4) to define whether long-term interferon therapy is beneficial in nonresponders with hepatitis C; and (5) to define the efficacy of interferon and ribavirin in subgroups of patients with hepatitis C. A recent *Action Plan* progress review, revealed considerable advances made toward achieving these goals. For example, NIH-funded research focusing on the biologic basis for non-response to treatment for hepatitis C has pinpointed several possible factors. The HALT-C trial is addressing whether long-term interferon therapy benefits those with chronic hepatitis C who were not responsive to previous treatment. Another ongoing NIDDK-sponsored clinical trial, called the Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (“Virahep-C”) is investigating differences in response rates and predictors of response to combination therapy of hepatitis C in African Americans compared to Caucasian Americans.

#### Item

##### ***Obesity-related liver disease***

The Committee notes that there is an emerging obesity-related chronic liver disease, which may affect as many as one in four adults and a significant number of obese children. The Committee encourages NIDDK to continue to support fatty liver disease clinical trials that includes both adult and pediatric populations. (p.136)

#### Action taken or to be taken

The NIDDK's vigorous support for research on fatty liver disease includes funding for the multi-center non-alcoholic steatohepatitis (NASH) Clinical Research Network, which conducts research focused on this serious form of fatty liver disease, which is often associated with obesity, as well as with type 2 diabetes and resistance to the hormone insulin. The Network is investigating the nature and causes of NASH and is conducting two clinical trials of potential therapies. One of the clinical trials is to evaluate in adults the safety and efficacy of potential treatments for NASH, the drug pioglitazone or vitamin E, as compared to a placebo. The other clinical trial is in children and will compare the drug metformin, vitamin E, and placebo in treating non-alcoholic fatty liver disease. Metformin is one of the most commonly used medications for the treatment of type 2 diabetes. Additionally, through an ancillary study to this Network, the NIDDK is funding research toward the development of imaging technology for non-invasive diagnosis and monitoring of non-alcoholic fatty liver disease. Complementing this extramural research is an NIDDK-supported study conducted by intramural scientists to determine whether the medical problems of adult NASH patients, specifically liver damage, improve with the drug metformin. To build knowledge that may help inform the design of future clinical trials, the NIDDK is also co-sponsoring a research solicitation, with other NIH components, to foster research on molecular and biochemical mechanisms underlying both alcoholic and non-alcoholic fatty liver. These efforts are consistent with the goals of the trans-NIH *Action Plan for Liver Disease Research*.

#### Item

##### ***Beta cell research***

The Committee commends NIDDK for its support of the beta cell biology consortium (BCBC) which has developed excellent resources, research reagents, and databases that add value to the entire beta cell biology research community. NIDDK is encouraged to support research focused on translating the fundamental discoveries made by the BCBC into clinical applications that may directly benefit type 1 diabetes patients. (p.136)

#### Action Taken or To Be Taken

The NIDDK supports research that is translating the discoveries made by the Beta Cell Biology Consortium (BCBC) into clinical applications. For example, researchers supported by the BCBC recently developed a genetically-engineered mouse model that is useful for studying beta cell regeneration. Using this mouse model, the scientists found that insulin-producing beta cells of the pancreas have a significant capacity for spontaneous regeneration. These results suggest that beta cell regeneration can potentially be therapeutically useful in type 1 diabetes patients. Importantly, the mouse model also provides a system for testing the effects of drugs on beta cell regeneration. Researchers have shown that drugs commonly used to suppress the immune system after islet transplantation have an adverse affect on beta cell regeneration. This result may help explain why transplanted islets lose function in human patients over time. The mouse model

may also be useful for identifying other drugs that do not have this negative affect on beta cell regeneration. In addition, the BCBC is planning to support a new project using this mouse model to examine the effect on beta cell regeneration of several commonly-used diabetes drugs.

One of the major, long-term goals of the BCBC is to develop a cell-based therapy for insulin delivery. Achieving this goal could help overcome the shortage of islets, which is a major barrier limiting the use of islet transplantation as a therapy for type 1 diabetes. Another major barrier is the requirement for lifelong drug intervention to prevent rejection of transplanted islets and to prevent recurrence of the underlying autoimmunity that initiated type 1 diabetes. Because of the necessity to overcome both of these barriers to effectively treat the disease and obviate the need for insulin administration, the NIDDK plans to foster collaborations among immunologists and BCBC researchers. Bringing together these different groups of scientists could propel research progress toward clinical goals that can benefit type 1 diabetes patients.

Scientists in the BCBC are also studying the steps needed to turn embryonic stem/progenitor cells into insulin-producing beta cells. This knowledge can help to achieve the Consortium's long-term scientific goal of developing a cell-based therapy for diabetes. Scientists in the BCBC have made progress in this regard using mouse embryonic stem cells. They are now trying to recapitulate their findings in federally-approved human embryonic stem cell lines.

Using new tools and resources, researchers are already making key discoveries about underlying molecular mechanisms of type 1 diabetes. For example, using a protein array, researchers identified a new protein that is a target of the immune system's attack in type 1 diabetes. The discovery of this new protein may inform the development of novel strategies to preempt the disease. Therefore, fundamental discoveries about disease processes set the stage for the development of new interventions or therapeutic approaches that can ultimately improve the health and well being of type 1 diabetes patients.

#### Item

#### ***Digestive diseases***

Diseases of the digestive system may affect up to one-half of all Americans at some time in their lives. Serious disorders such as colorectal cancer, inflammatory bowel disease, irritable bowel syndrome, hemochromatosis, celiac disease, and hepatitis take a tremendous toll in terms of human suffering, mortality, and economic burden. The Committee commends NIDDK on the success of its digestive disease centers program in addressing a wide range of disorders that result in tremendous human suffering and economic cost. The Committee encourages NIDDK to strengthen this important program with an increased emphasis on irritable bowel syndrome. (p. 136)

#### Action taken or to be taken

The NIDDK remains committed to its substantial digestive diseases centers program and to maintaining its vigorous irritable bowel syndrome (IBS) research portfolio. For example, NIDDK recently renewed its support for the Center for Neurovisceral Sciences and Women's Health at the University of California, Los Angeles. This Center is part of the Office of Research on Women's Health (ORWH) Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) initiative. The SCORs initiative promotes transfer of women's health research advances from the laboratory to clinical practice by supporting centers which house both basic science and clinical studies.

The Center for Neurovisceral Sciences and Women's Health research focuses on the identification of sex-related factors that play a role in the development, clinical manifestation, and treatment response of IBS and interstitial cystitis (IC). Both of these visceral pain syndromes occur more frequently in women than in men, show differences in treatment responses for women and men, and cause significant reductions in the quality of life of those affected. The Center features an optimal environment for collaboration and cooperation among basic scientists and clinicians. Contributions by investigators and consultants from several universities and institutions enhance the Center's interdisciplinary approach to conquering IBS and IC.

#### Item

##### ***Acute liver failure***

The Committee is concerned that over one-third of acute liver failure cases, resulting from over the counter drug interactions and other causes, are fatal due largely to the continuing shortage of livers available for transplantation. The Committee is aware that there is no effective and approved medical procedure such as dialysis, cellular transplants, or other techniques to maintain liver function after acute failure for a period of time until a liver becomes available for transplantation or the liver repairs itself naturally. The Committee encourages research in this area, consistent with the liver disease research action plan, to reduce the mortality rate for those who suffer from acute liver failure. (p. 136)

#### Action taken or to be taken

The NIDDK is actively pursuing research on ways to reduce mortality from acute liver failure through efforts that are responsive to research goals for this area outlined in the trans-NIH *Action Plan for Liver Disease Research*. The *Action Plan* includes specific research goals addressing acute liver failure, such as: (1) to determine whether the drug N-acetylcysteine is beneficial in acute liver failure; (2) to develop an artificial or bioartificial liver support system and demonstrate that it prolongs survival in acute liver failure; and (3) to develop a noninvasive means to assess regeneration and reserve in liver failure. A recent annual review of progress on the *Action Plan* highlighted examples of research advances made toward achieving these goals.

Relevant to the first goal, two major clinical trials sponsored by the NIDDK through the Acute Liver Failure Study Groups are evaluating the compound N-acetylcysteine as a potential therapy for acute liver failure in adults and children. Recent advances made by this group include identifying biomarkers that might be used in patients with acute liver failure, for such purposes as determining the specific cause (e.g., drug-induced liver injury) or predicting a patient's outcome. Additionally, the NIDDK-funded Drug-Induced Liver Injury Network is studying drug-induced cases of acute liver failure. The Network aims to develop tools needed to identify causes and, ultimately, prevent drug-induced liver injury resulting in acute liver failure.

Regarding the goal to develop a liver support system, the research community considered the current status of these devices at an NIH-sponsored meeting on "Acute Liver Failure" held in December, 2006. Although these devices have shown limited clinical success to date, vigorous research continues in pursuit of an effective liver support device for those with acute liver failure.

Efforts to address the research goal to develop noninvasive means to assess regeneration and reserve function in liver failure are being encouraged by an NIDDK-cosponsored initiative on "Development of Disease Biomarkers." NIDDK-sponsored investigators are also conducting basic research to identify the cellular and molecular pathways involved in injury to donor livers during storage prior to transplantation. Identifying these pathways can help to uncover ways to better preserve the donor liver to ensure a successful transplantation for patients with acute liver failure.

#### Item

##### ***Glucose monitoring***

Recent advances in continuous glucose monitoring technology have the potential to revolutionize the way diabetes is managed on a daily basis, but more research is needed to validate this technology in a variety of patient populations under "real world" conditions. Moreover, biomedical research progress is enabling increasing numbers of type 1 diabetes patients to live with this disease for more than fifty years. The NIDDK is urged to support clinical research on the potential benefits of continuous glucose monitoring in type 1 diabetes patients over the age of 65 to assess the potential of this technology to produce better health outcomes in these individuals and to obtain evidence to support healthcare coverage for continuous monitoring devices in elderly diabetic patients. (p.136)

#### Action taken or to be taken

The NIDDK vigorously supports research aimed at examining how continuous glucose monitoring technology may improve the health of patients with diabetes across the lifespan. This research and other efforts are proceeding in tandem

with the Institute's continuing efforts to develop new and improved basic technologies for continuously monitoring blood glucose levels. Clinical research efforts the NIDDK supports to assess the impact of continuous glucose monitors include the National Institute of Child Health and Human Development-led DirecNet study. DirecNet has conducted several independent and scientifically rigorous studies to determine the benefit of new continuous glucose monitoring technologies. For example, DirecNet studies using the new technologies have revealed that exercise much earlier in the day increases the risk of nocturnal drops in blood glucose. This finding resulted in the practical suggestion of increased bedtime snacks on days when children with type 1 diabetes are particularly physically active. The NIDDK-led TrialNet clinical trials network is also examining how continuous glucose monitors (CGMs) may improve health outcomes. TrialNet is focused on testing promising new strategies to prevent, delay, or reverse progression of type 1 diabetes. TrialNet is developing an inpatient study to see if use of CGMs in newly-diagnosed type 1 diabetes patients will help preserve function of the insulin-producing beta cells, thereby reducing treatment burden for patients. Other potential uses of these technologies are also being explored.

CGMs are a key component of "artificial pancreas" systems currently under development. As envisioned, these artificial systems would "close the loop" between blood glucose monitoring and insulin delivery to substitute for the pancreatic functions lost in diabetes—greatly reducing patient treatment burden and improving patient health outcomes. The NIDDK is participating in a Food and Drug Administration-led interagency "Artificial Pancreas Working Group," whose goal is to promote cross-fertilization of knowledge, resources, and ideas that will lead to safe and effective closed-loop systems being available to the public in a timely manner. The Working Group is planning to hold a public workshop on the closed-loop system in July 2008. A key topic of discussion will be the design of clinical trials to test these new systems, including the study of different patient groups.

#### Item

##### ***Prostatitis***

The Committee supports the efforts of the NIDDK chronic prostatitis collaborative research network (CPCRN) to find the cause and a cure for prostatitis. The past ten years of research by the CPCRN have produced important progress. The Committee encourages NIDDK to maintain the momentum of this research to prevent the loss of previous work, which would have to be duplicated at a later date if this silent epidemic is to be controlled. (p.137)

#### Action taken or to be taken

Established in 1997, the Chronic Prostatitis Collaboration Research Network (CPCRN) has made significant contributions to the field of chronic prostatitis, including the development of the NIH-Chronic Prostatitis Symptoms Index to

assess the severity of symptoms and their change with treatment. The CPCRNI is currently recruiting patients for two parallel randomized, placebo-controlled, multicenter clinical trials to evaluate the efficacy and safety of Alfuzosin in the treatment of chronic prostatitis, and Pregablin for the treatment of refractory chronic prostatitis. An alpha blocker used primarily to treat symptoms associated with prostate enlargement in older men, the effectiveness of 12 weeks of alfuzosin therapy will be evaluated in a trial consisting of 280 participants. The effectiveness of 6 weeks of Pregablin therapy will be evaluated in a trial consisting of 318 men. Pregablin is an anti-epileptic medication that also affects chronic pain and is used to treat post-herpetic neuralgia and diabetic neuropathy. The NIDDK will continue to investigate chronic prostatitis as part of the new initiative, "Multidisciplinary Approach to Pelvic Pain" (MAPP). This research initiative seeks to establish a collaborative network of investigators conducting basic, clinical, and translational research on chronic prostatitis/chronic pelvic pain syndrome (CPPS) and on another urologic pain syndrome (interstitial cystitis/painful bladder syndrome). The ultimate aim of the initiative is to provide findings useful for development of future prevention or treatment strategies.

#### Item

#### ***Hemophilia and hepatitis C***

The Committee understands that hepatitis C continues to have a devastating impact on the hemophilia population, with as many as 75 percent of all persons with hemophilia having contracted HCV and many of these individuals co-infected with HIV. The Committee encourages NIDDK to pursue research initiatives on co-infection and the progression of liver disease in this population. (p.137)

#### Action taken or to be taken

Consistent with the research goals of the trans-NIH *Action Plan for Liver Disease Research*, the NIDDK and other NIH Institutes will 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 those with hemophilia who were infected by contaminated blood transfusions prior to a screening program for these pathogens in donor blood.

The *Action Plan* goals are responsive to the Committee's request to pursue research efforts that address issues of co-infection with HCV and HIV, and the progression of liver disease in patients with hemophilia. For example, the *Action Plan* includes research goals to determine: (1) the prevalence, etiology, and severity of liver diseases in different groups of HIV-infected patients; (2) the effectiveness and safety of treatments such as interferon and ribavirin in subgroups of patients with hepatitis C, such as those with hemophilia and/or HIV co-infection; (3) whether long-term treatment with peginterferon slows progression of chronic hepatitis C in those co-infected with HIV; and (4) the

safety and efficacy of new agents for therapy of hepatitis C in HIV co-infected individuals.

In a recent review of progress made toward achieving the goals of the *Action Plan*, advances were noted in these areas. For example, the AIDS Clinical Trials Group (ACTG) funded by the National Institute of Allergy and Infectious Diseases (NIAID) is conducting 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 this long-term antiviral treatment in co-infected individuals. The NIAID is also supporting a study of HCV viral kinetics, viral load, and associated liver injury in co-infected subjects treated with antiretroviral therapy. 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 National Cancer Institute and the National Heart, Lung, and Blood Institute.

#### Item

##### ***Interstitial cystitis/painful bladder syndrome IC/PBS***

The Committee is concerned about the lack of clarity surrounding the definition of IC and suggests that NIDDK host a meeting of international IC experts that specifically addresses these issues to update its research criteria and clarify its investigative questions on IC. The Committee encourages NIDDK to support research in areas that examine predisposition/risk factors, underlying cellular and molecular pathology of IC/PBS and the association/cross-sensitization of IC/PBS with other disorders/diseases. The Committee also suggests that NIDDK fund translational research in IC/PBS that would include pilot therapy testing and early intervention of lifestyle/behavioral changes to prevent/lessen symptoms. The Committee encourages NIDDK to take an active role in ongoing studies of the epidemiology of IC in order to address design issues and to ensure the consultation of outside experts. (p.137)

#### Action taken or to be taken

The NIDDK is taking significant steps to improve the understanding of interstitial cystitis/painful bladder syndrome (IC/PBS). A new Request for Applications (RFA), “Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network,” has been issued, with funding anticipated in FY 2008. This program initiative seeks to establish a collaborative network of investigators conducting basic, clinical, and translational research on IC/PBS and on another urologic pain syndrome (chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)). The ultimate aim of the initiative is to provide findings that will be useful in the development of future prevention or treatment strategies. It is anticipated that the initiative will help us obtain a greater understanding of the pathophysiology, biologic and behavioral risk factors, natural history, and genetics of IC/PBS. The Network researchers will also be charged with

investigating why many patients with IC/PBS also have other painful, symptom-based conditions, such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome—knowledge which could aid development of prevention and treatment strategies.

The NIDDK is also in an ongoing process of re-visiting the NIDDK research definitions for both IC/PBS and CP/PPS, addressing new research evidence. A multidisciplinary Chronic Pelvic Pain Working Group established by the Institute in December 2007 considered this issue; a plenary meeting with a larger group of representatives working in this field is planned for June 2008, at which time the definition(s) will be finalized for use in NIH-funded studies.

Regarding the epidemiology of IC, the NIDDK is continuing to take an active role in ongoing studies. In one major study, the RAND IC Epidemiology study, many of the study issues that initially delayed progress have been resolved with the assistance of the External Advisory Committee (EAC) and through the use of consultants to the study. Study investigators are currently collecting data using a questionnaire reviewed and approved by outside experts in the field of IC/PBS and other pelvic pain conditions. The NIDDK will continue to encourage the use of expert consultants as appropriate when data collection draws to a close. The NIDDK also continues to confer regularly with the RAND investigators and the EAC to monitor progress and provide feedback.

#### Item

##### ***Cellular therapies***

The committee is encouraged by recent clinical trial results, in which 14 patients recently diagnosed with type 1 diabetes remained insulin-free for up to 34 months, post treatment with an immunosuppressive regimen followed by the infusion of autologous hematopoietic stem cells. Given these positive results, the Committee recommends NIH continue to support clinical trials in the U.S. using cellular therapies to treat type 1 diabetes, including therapies such as the lymphoablative hematopoietic stem cell treatment used in this trial as well as alternative therapies using cell sources such as dendritic cells, T-regulatory cells, or umbilical cord blood cells. (p. 137)

#### Action taken or to be taken

The NIH supports several lines of clinical research testing cellular therapies to treat type 1 diabetes. In response to a solicitation for bench to bedside research to develop new therapies for type 1 diabetes, scientists were invited to propose projects in two phases: a preclinical phase to test the potential therapy in animal models followed by a clinical study. Of note two projects to develop dendritic cells as therapies for type 1 diabetes met the milestones established in the preclinical phase, showing that modified dendritic cells could prevent or delay type 1 diabetes in a mouse model of the disease. The NIDDK recently provided the second phase of support to allow the scientists to translate these results from

mice to people. The clinical phase of these studies will examine the use of modified dendritic cells as a treatment for type 1 diabetes. One of the studies has received Food and Drug Administration (FDA) approval to go forward in human trials and the other study is under FDA review. These studies will use cellular therapy to modify the immune response but do not involve destruction of the patient's own bone marrow, as was done in the lymphoablative procedure.

Because of the considerable risks associated with lymphoablative hematopoietic stem cell treatment, the NIH does not currently support clinical trials on this approach as a treatment strategy for type 1 diabetes. The participants in the recently-reported clinical trial had significant side effects; the drugs administered in the treatment could also increase risk of future problems (e.g., long-term reproductive side effects). Recent data indicate that people with type 1 diabetes are living longer, healthier lives than ever before. Therefore, the benefits of a treatment strategy would have to outweigh the risks, particularly because the outcomes for type 1 diabetes patients continue to improve. The NIH is committed to ensuring the safety of participants in its clinical trials.

The safety issues associated with lymphoablative hematopoietic stem cell therapy underscore the need for more tolerable methods for suppressing or modulating the immune system in type 1 diabetes. The NIH vigorously supports research in this area. For example, studies testing less toxic drugs are being performed by NIDDK's Type 1 Diabetes TrialNet and NIAID's Immune Tolerance Network. In addition, researchers in NIAID's Cooperative Study Group for Autoimmune Disease Prevention are creating improved animal models of disease pathogenesis and therapy to better understand immune mechanisms. Thus, the NIH supports "bench-to-bedside" research to identify improved methods to intervene in the immune system's attack in type 1 diabetes.

### **Senate Significant Items**

#### Item

#### ***Acute Liver Failure***

The Committee is aware that there is no effective and approved medical procedure to maintain liver function after acute failure for a period of time until a liver becomes available for transplantation or the liver repairs itself naturally. The Committee urges research in this area, consistent with the Liver Disease Research Action Plan, to reduce the mortality rate for those who suffer from acute liver failure. (p.117)

#### Action taken or to be taken

Please refer to page 71 of this document for the NIDDK's response to this significant item regarding acute liver failure.

#### Item

### ***Animal Models of Diabetes***

The Committee applauds the NIDDK, in partnership with the NHLBI, for its renewal of the Animal Models of Diabetic Complications Consortium [AMDCC]. While the AMDCC focuses on rodent models, the NIDDK is also encouraged to support the development and use of larger animal models that more closely mimic diabetes in humans and that can be used for preclinical testing of new therapeutic agents to treat complications. (p.117)

#### Action taken or to be taken

The NIDDK appreciates the Committee's commendation of the interdisciplinary Animal Models of Diabetic Complications Consortium (AMDCC) and the desire to extend this type of work to larger animal models. New validated animal models of human diabetic complications remain a high priority for NIDDK. Such models are critical for identifying and testing diagnostic, preventive, or therapeutic interventions for these devastating conditions—including kidney, eye, nerve, heart, and vascular disease. The NIDDK is currently supporting several research studies utilizing larger animal models to investigate diabetes and diabetes complications, and encouraging other research and development in this area. For example, one research team is using a cat model to examine diabetic nerve disease. Maternal diabetes can cause complications during pregnancy and is associated with long-term effects on the child, including metabolic abnormalities. NIDDK-supported researchers are using non-human primates to examine the effects of maternal hyperglycemia and obesity on the fetus, which will improve understanding of perinatal complications of diabetes. A current Program Announcement, "Animal Models of NIDDK Relevant Diseases," encourages support for the development and validation of new animal models of NIDDK-relevant diseases, including diabetic complications. The NIDDK also encourages research on these models for use in testing new therapies through the NIH Small Business Innovation Research solicitation. Finally, the AMDCC is also contributing to study of larger animal models of diabetes complications. Since its inception, the AMDCC has made great strides in the development of rodent models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention and treatment. Among its accomplishments, the AMDCC has established "validation criteria" for what defines a good mouse model of diabetic kidney, heart and vascular disease. Although these criteria have been developed for mice, they generally apply to any animal, and thus could contribute to the development of larger animal models of diabetic complications.

To foster discussion and trans-NIH coordination on diabetes complications, the NIDDK leads a working group on this topic. Scientific program staff from participating NIH ICs, including the National Heart, Lung, and Blood Institute (NHLBI), meets regularly to discuss research and new initiatives related to diabetes complications. A recent meeting focused on large animal models of

diabetes complications. The meeting included a presentation by an NIH-supported academic researcher who is examining the development of diabetes complications in a large monkey colony. Such discussions engender new ideas for animal models, illuminate challenges and possibilities, and can help to advance this research field.

Item

***Beta Cell Biology***

The Committee urges the NIDDK to support research focused on translating the fundamental discoveries made by the Beta Cell Biology Consortium into clinical applications that may directly benefit type 1 diabetes patients. (p.117)

Action taken or to be taken

Please refer to page 67 of this document for the NIDDK's response to this significant item regarding beta cell research.

Item

***Clinical Trials for Type 1 Diabetes***

The Committee urges the NIDDK to continue to expand the pipeline of new therapies being tested by the Type 1 Diabetes TrialNet to accelerate the rate of drug discovery and development to combat type 1 diabetes. For example, anti-CD3 monoclonal antibodies represent a breakthrough in the treatment of type 1 diabetes and, for the first time, provide a way to intervene in the natural history of the disease. The Committee urges the NIDDK and the NIAID to foster mechanistic and clinical research aimed at understanding how anti-CD3 works so that drug design can be optimized to reduce side effects and define all patient populations who might benefit from anti-CD3 therapy. (p.117)

Action taken or to be taken

The NIH supports clinical research to test the anti-CD3 monoclonal antibody. An NIDDK-supported clinical trial demonstrated that treatment with anti-CD3 could arrest the loss of insulin production for at least 2 years after diagnosis of type 1 diabetes. The NIDDK is supporting a new clinical trial to examine whether anti-CD3 will arrest the loss of insulin production when the agent is administered to patients who have a longer duration of disease. The National Institute of Allergy and Infectious Diseases Immune Tolerance Network (ITN), in collaboration with NIDDK's Type 1 Diabetes TrialNet, is conducting a clinical trial in newly-diagnosed patients to test whether a second course of anti-CD3 can prolong or improve the drug's effects. Associated mechanistic studies, to examine how anti-CD3 exerts its effects are ongoing and are an important component of clinical trials conducted by the TrialNet and the ITN. Type 1 Diabetes TrialNet is exploring the possibility of conducting additional clinical trials to test anti-CD3, such as whether anti-CD3 can prevent or delay type 1 diabetes in people at very high risk of disease development. In addition, the NIDDK supports a study on the use of anti-CD3 in islet transplantation. Industry is supporting an

international licensure trial of anti-CD3 in newly-diagnosed type 1 diabetes patients.

TrialNet and ITN are performing mechanistic studies to understand the underlying type 1 diabetes disease processes and learn how best to assess disease progression or reversal. For example, TrialNet researchers are trying to improve assays to measure T cells associated with type 1 diabetes in the blood. T cells are immune system cells that play a key role in destroying insulin-producing beta cells. These assays could serve as markers of disease progression and of effectiveness of interventions tested in TrialNet. TrialNet is also saving samples collected from patients participating in its studies. These samples can be studied as new technologies and assays are developed. In addition, the ITN is examining immunologic measurements that can differentiate responses in subjects with type 1 diabetes from those of healthy controls and their potential utility in immune intervention studies.

There is a robust pipeline of potential new therapies to be tested for type 1 diabetes. Researchers participating in TrialNet launched a clinical trial to test whether oral insulin could prevent type 1 diabetes in people with a certain predictive disease marker, and a pilot study of a nutritional supplement to prevent the disease in newborns at high genetic risk. They also completed recruitment for trials to test whether various agents (i.e., rituximab, MMF/DZB) could preserve insulin production in new onset patients. A TrialNet study of another agent (GAD) is scheduled for launch in late 2008 and studies of additional agents are under development for testing through TrialNet. The TrialNet infrastructure is also facilitating the conduct of several ITN trials in new onset type 1 diabetes, including two new ITN studies evaluating the potential of thymoglobulin and the combination of IL-2/rapamycin as interventions. Furthermore, the Rapid Access to Intervention Development Program provides resources to make and test potential new therapeutics, expanding the pipeline of therapies to be tested. Thus, in addition to the studies currently underway or in development, TrialNet is considering and prioritizing other therapies that are in the pipeline for future study.

#### Item

#### ***Continuous Glucose Monitoring***

Recent advances in continuous glucose monitoring technology have the potential to revolutionize the way diabetes is managed on a daily basis, but more research is needed to validate this technology in a variety of patient populations under "real world" conditions. Moreover, biomedical research progress is enabling increasing numbers of type 1 diabetes patients to live with this disease for more than 50 years. The NIDDK is urged to support clinical research on the potential benefits of continuous glucose monitoring in type 1 diabetes patients over the age of 65. (p.118)

Action taken or to be taken

Please refer to page 72 of this document for the NIDDK's response to this significant item regarding glucose monitoring.

Item

***Cooley's Anemia***

The Committee continues to support NIDDK research on iron chelation and non-invasive iron measurement, and to encourage the NIDDK to work closely with the NIBIB to develop and perfect non-invasive means of measuring iron that accumulates in the heart and liver. (p.118)

Action taken or to be taken

Please refer to page 61 of this document for the NIDDK's response to this significant item regarding Cooley's anemia.

Item

***Diabetes in Native Hawaiians***

The Committee is concerned about the high prevalence of diabetes among Native Hawaiians, and it urges the NIDDK to continue research in this area. (p.118)

Action taken or to be taken

The NIDDK is continuing its support of diabetes research and education efforts for Native Hawaiians and other Pacific Islanders disproportionately burdened by type 2 diabetes. The NIDDK is supporting the Diabetes Prevention Program (DPP) Outcomes Study, which is following the Native Hawaiian and other participants in the original DPP clinical trial to assess the long-term effects of the interventions that were used to prevent type 2 diabetes. The Diabetes Prevention Program Outcomes Study (DPPOS) has a site in Hawaii, and a recent DPPOS newsletter focused on Hawaiian DPPOS participants and the healthful use of local foods. The landmark DPP multicenter clinical trial demonstrated that people at increased risk for type 2 diabetes can prevent or delay disease onset through relatively modest changes in diet and moderate physical activity.

The NIDDK is also supporting a study that, building on data from the Hawaii component of the NIH-supported Multiethnic Cohort Study, is expected to provide a better understanding of dietary and behavioral factors related to excess body weight and diabetes in Native Hawaiians. This information can help identify preventive strategies to modify lifestyle factors. The Institute is also intensifying research on type 2 diabetes in children, which is an emerging public health issue that predominantly affects minorities. To determine the prevalence and incidence of both type 1 and type 2 diabetes in children, the NIDDK is supporting the Centers for Disease Control and Prevention (CDC)-led SEARCH for Diabetes in Youth epidemiological study. One of the six nationwide SEARCH centers is in

Hawaii. SEARCH is providing important information on how to characterize childhood diabetes.

To disseminate the positive results of the DPP, the NIDDK and CDC co-sponsored National Diabetes Education Program (NDEP) developed the “Small Steps. Big Rewards. Prevent Type 2 Diabetes” educational campaign, which includes materials specifically developed for Pacific Islanders. The NDEP has a new brochure on diabetes control targeted to Hawaiians. The NIDDK also supports research efforts to translate advances in the prevention and treatment of diabetes and obesity into clinical practice for individuals and communities at risk.

Item

***Digestive Diseases***

The Committee continues to encourage the NIDDK to expand its Digestive Disease Centers program, with an increased emphasis on irritable bowel syndrome. (p. 118)

Action taken or to be taken

Please refer to page 70 of this document for the NIDDK’s response to this significant item regarding digestive diseases.

Item

***Drug-induced Liver Injury***

In view of the increasing incidence of liver injury from prescription and nonprescription drugs, the Committee urges an expansion of the Drug-Induced Liver Injury Network. (p.118)

Action taken or to be taken

Please refer to page 62 of this document for the NIDDK’s response to this significant item regarding drug-induced liver injury.

Item

***Environmental Triggers of Type 1 Diabetes***

The Committee encourages the NIDDK to ensure that resources are made available to maximize the knowledge about type 1 diabetes that can be gained from The Environmental Determinants of Diabetes in the Young Study [TEDDY], including the support of innovative ancillary studies using biosamples and data collected from TEDDY participants. (p.118)

Action taken or to be taken

The Environmental Determinants of Diabetes in the Young study is a long term study designed to provide samples and data to explore hypotheses about type 1 diabetes pathogenesis. The data and biosamples collected through the study are unique and vital resources in the effort to stop the disease. Because of the

enormous value of all of the samples and non-renewable nature of many of them, they are being repositied so that the NIDDK can ensure they are used for studies of the highest priority as assessed by peer review. Careful attention is given to what samples to collect and how best to collect and store them to ensure that they can be used for state-of-the-art studies, such as genomic investigations to identify pathogens in stool or to detect key differences in gene expression in blood samples. While the study is ongoing and expected to run through 2023, three ancillary studies involving stool samples have already been approved to go forward.

Item

***Fragile X***

The symptoms of Fragile X syndrome include digestive difficulties. The Committee urges the NIDDK to expand its research activities on Fragile X and to coordinate these efforts with other Institutes working on related activities, including the NIMH, NINDS, NICHD, NHGRI and the Fogarty International Center. (p.118)

Action taken or to be taken

The NIDDK investigates fundamental questions associated with the cause of fragile X syndrome, and the genetic mutations that lead up to the disease. The Institute also supports work on gene therapy which could one day help lead to treatment for the disease. The Office of Rare Diseases has the primary role in coordinating research on genetic disorders such as fragile X. Because this developmental disorder has its most devastating effects on the central nervous system, other Institutes and Centers—most notably National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, and National Institute of Child Health and Human Development—have primary responsibility for fragile X research.

Item

***Genetics of Type 1 Diabetes***

The Committee commends the NIDDK for its oversight of the International Type 1 Diabetes Genetics Consortium, which is in the final stages of recruiting 2,800 families with two or more children with type 1 diabetes. As the sample collection phase nears completion, the NIDDK is encouraged to support researchers who plan to use the genetic collection to fully understand the genetic causes of type 1 diabetes. (p.118)

### Action taken or to be taken

The NIDDK is seeking to maximize the research return on the investment in the Type 1 Diabetes Genetics Consortium (T1DGC). To that end, a great deal of vital data generated by the Consortium has already been shared with the scientific community. These data includes the identification of 6,000 genetic differences in siblings with and without the disease, and fine mapping data of the major histocompatibility complex, the area of the genome with the greatest genetic influence on whether a person will develop type 1 diabetes. The information is available on T1DBase, a public web site and database that supports the type 1 diabetes research community and contains analysis tools and data pertinent to type 1 diabetes research. T1DBase includes annotated genome sequences, type 1 diabetes susceptibility regions defined from linkage and association studies, descriptions of type 1 diabetes mouse model strains, expression data in the Beta Cell Gene Expression Bank, annotations of gene function in beta cells, and other valuable data. The initial release of T1DBase for T1DGC is now “live” at <http://t1dbase.org/page/Welcome/display>

To further accelerate progress toward understanding the genetic underpinnings of type 1 diabetes, the T1DGC Steering Committee approved two lists of genes to be more deeply and rapidly investigated as part of a “Rapid Response project.”

The lists are grouped on the basis of the strength of their apparent association with the disease. The T1DGC then issued an announcement inviting participation in the Rapid Response Working Group by interested parties in the scientific community.

### Item

#### ***Hematology***

Research into basic mechanisms of blood cell formation and function is intimately linked to determining the health risks of different diseases and in developing novel therapies for treatment. An example is the study of anemias of inflammation and chronic disease, which would greatly improve the understanding of chronic infection and immune activation, severe trauma, heart disease, arthritis, and diabetes. The Committee urges the NIDDK, using the findings of the 2006 workshop on this topic, to work with the NHLBI, NCI, NIA, NIAID and NIAMS to develop a research agenda on anemias of inflammation and chronic disease. The Committee requests an update in the fiscal year 2009 congressional budget justification on the research opportunities identified and the next steps to be taken. (p.119)

### Action taken or to be taken

Research on the anemia of inflammation and of chronic disease is an important component of NIDDK’s hematology research program. This type of anemia is very common and is a major cause of reduced red blood cell mass that often accompanies aging. It is characterized by a decreased availability of iron for

support of red blood cell production, caused largely by acquired abnormalities in both iron absorption and release of iron from tissue stores.

To spur new ideas and research progress in this field, the NIDDK convened a two-day workshop in May 2006 that focused on this common form of anemia. The workshop highlighted current insights into the clinical presentation and underlying causes of these anemias. It also highlighted unanswered questions and promising new opportunities for basic and translational research. Experts from within and outside the NIH discussed 1) Clinical features, diagnosis, epidemiology, and impact of these anemias; 2) Disease mechanisms relating to disordered iron metabolism, disturbances in erythropoietin production and response, the action of inflammatory cytokines, and age-related changes in red blood cell development; and 3) New directions and opportunities for molecular diagnosis, clinical stratification, and treatment of people with this condition. Based on scientific recommendations from this workshop, the NIDDK, in collaboration with the National Institute on Aging (NIA), the National Cancer Institute (NCI), and the National Heart, Lung, and Blood Institute (NHLBI) issued a Program Announcement in 2007 to encourage and promote research that will lead to advances in the detection, prevention, and treatment of the anemia of inflammation and of chronic disease.

To identify opportunities and help formulate a research agenda for the broader hematology community, the NIDDK convened a Hematology Strategic Planning Workshop in October 2007. This workshop focused on enhancing trans-NIH coordination, research priorities, and improving dialog within the hematology research community. Additionally, a meeting of the Interagency Coordinating Committee for Hematology Research has been planned to focus on “Overcoming Barriers to the Clinical Development of Gene Targeting Therapies for Hematologic Diseases.” This meeting will take place on January 14, 2008, and is being organized in collaboration with staff representatives from NHLBI and NCI. Representatives of NCCR, NIA, NIAID, and the Food and Drug Administration (FDA) are also expected to attend, together with representatives of a number of patient and professional organizations.

#### Item

#### **Hepatitis B**

The Committee is pleased with the NIH commitment to conduct a consensus conference in 2008 on best treatment practices for individuals with hepatitis B. The Committee is aware that there are six hepatitis B pharmaceutical products on the market and that three of them have become available in the last two years. The growing number of treatment options is encouraging and suggests a strong rationale for conducting a consensus conference to provide state of the art treatment guidelines for the practicing physician community. As only approximately one-third of individuals with hepatitis B are aware of their condition, the Committee urges the NIDDK to continue to collaborate with the

CDC in the development of a public health strategy to expand the screening of individuals at risk for chronic hepatitis B. (p.119)

Action taken or to be taken

Please refer to page 66 of this document for the NIDDK's response to this significant item regarding hepatitis B.

Item

***Hepatitis C***

The Committee encourages implementation of clinical studies aimed at overcoming antiviral drug resistance to hepatitis C, possibly by utilizing novel agents in combination. (p.119)

Action taken or to be taken

Please refer to page 67 of this document for the NIDDK's response to this significant item regarding hepatitis C.

Item

***Inflammatory Bowel Disease [IBD]***

The Committee has been encouraged in recent years by discoveries related to Crohn's disease and ulcerative colitis, collectively known as IBD. The Committee commends the NIDDK for its strong leadership in this area and continues to encourage the Institute to increase funding for research, particularly pediatric research, focused on; (1) the cellular, molecular and genetic structure of IBD, (2) identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups, and (3) translation of basic research findings into patient clinical trials as outlined in the research agenda developed by the scientific community titled, "Challenges in Inflammatory Bowel Disease." The Committee also encourages the NIDDK to continue to strengthen its partnership with the IBD community and increase support for its successful Digestive Disease Centers program with an emphasis on IBD. (p.119)

Action taken or to be taken

Please refer to page 65 of this document for the NIDDK's response to this significant item regarding inflammatory bowel disease.

Item

***Interstitial Cystitis [IC] and Painful Bladder Syndrome [PBS]-***

The Committee is concerned by a pattern of inconsistent funding at the NIDDK on IC/PBS-specific research, and it urges the Institute to make a sustained investment in this area. The Committee urges the NIDDK to issue a request for applications for IC/PBS specific research in areas that examine predisposition/risk factors, underlying cellular and molecular pathology of IC/PBS and the association/cross-sensitization of IC/PBS with other disorders/diseases. The Committee also encourages translational research in IC/PBS that includes

pilot therapy testing and early intervention of lifestyle/behavioral changes to prevent or lessen symptoms. The Committee remains concerned about the lack of clarity surrounding the nomenclature and definition of IC, and it urges the NIDDK to host a meeting of international IC experts that specifically addresses these issues not only to update its own research criteria and clarify its investigative questions on IC but also to ensure that the United States continues to be at the forefront of all IC research activities. In addition, the Committee is discouraged by the lack of progress in the NIDDK-funded RAND study on the epidemiology of IC. The NIDDK is urged to take an active role in the last two years of this study to ensure that any design flaws are addressed, outside experts are consulted and it is well executed. (p.119)

Action taken or to be taken

Please refer to page 73 of this document for the NIDDK's response to this significant item regarding interstitial cystitis/painful bladder syndrome.

Item

***Irritable Bowel Syndrome (IBS)***

The Committee is pleased that the NIDDK is formulating an action plan for digestive diseases through the National Commission on Digestive Diseases and that IBS will be included. The Committee continues to urge the NIDDK to expedite this plan and ensure that IBS be given sufficient attention. (p.120)

Action taken or to be taken

The National Commission on Digestive Diseases (NCDD), chaired by NIDDK's Director of the Division of Digestive Diseases and Nutrition, is progressing expeditiously in its mission to develop a 10-year plan for improving the health of the nation through research on digestive diseases such as irritable bowel syndrome (IBS). The Commission is composed of leading experts in digestive diseases who have come together to review the state-of-the-science of these diseases and to determine the goals and challenges to be met in the quest to prevent, treat, and cure them. The Commission has formed 12 working groups to address major topics pertaining to digestive diseases research and to develop the topical chapters for the research plan. The challenges and goals that apply to IBS research will be addressed extensively in the chapter on Functional Gastrointestinal Disorders and Motility Disorders in the research plan which will be released in fall 2008. At the Commission's third meeting, held in June 2007, the Chairs of the 12 working groups presented recommendations for the research goals in their chapters. To insure that the entire scientific community and the public are part of the planning process, the revised presentations have been posted on the NCDD website for public review and comment. Following the June meeting, the working groups prepared draft chapters for the long-range research plan, which were considered at the Commission's meeting held in November 2007, and then revised to reflect the input of the Commission. Prior to the research plan's release, the chapters will be posted on the Commission's

website for public comment : <http://www2.niddk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/>). The Commission's plan is scheduled for release in 2008.

#### Item

##### ***Islet Transplantation***

The Committee acknowledges the productive collaboration of the NIDDK and NIAID in overseeing the Clinical Islet Transplantation Consortium. The development of seven clinical trial protocols of islet transplantation marks a significant step toward validating this procedure as a viable treatment for type 1 diabetes patients suffering from extremely "brittle" or difficult-to-control blood sugar levels. The NIDDK and NIAID are urged to take steps to ensure the efficient launch of these trials and to expedite patient recruitment and enrollment. (p.120)

#### Action taken or to be taken

Six trials to be conducted in North America have undergone review by a Data and Safety Monitoring Board, Institutional Review Boards and the Food and Drug Administration (FDA). A detailed uniform islet manufacturing process has been developed and agreed upon by the participating centers. Subjects are being recruited into these trials. To help expedite patient recruitment and enrollment, the Clinical Islet Transplantation (CIT) Consortium developed a website with information for patients regarding eligibility for clinical trials ([www.citiletstudy.org/](http://www.citiletstudy.org/)). Information on CIT trials can also be obtained through the NIDDK patient recruitment website ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)), and/or through the National Institutes of Health clinical trials website ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

The North American trials include two multicenter clinical trials that could lead to licensure of islets as a biological product by the FDA. The first trial is enrolling individuals with type 1 diabetes, severe hypoglycemic (low blood sugar) events, and normal kidney function. The effectiveness of islet transplantation will be measured by the number of people who achieve good diabetes control, as measured by their hemoglobin A1c level, and freedom from severe hypoglycemic events at 1 year after the first islet transplant. The second trial is enrolling individuals with type 1 diabetes who previously received a kidney transplant and are therefore already receiving immunosuppressive therapy to prevent rejection of the transplanted kidney. This trial will compare outcomes of islet transplant recipients to those of comparable patients treated medically with an intensive insulin regimen. Designing these trials has required extensive discussion and collaboration not only among the investigators and NIH staff but also with other Health and Human Services agencies such as the FDA and the Centers for Medicare & Medicaid Services. In Europe, CIT investigators have completed a phase 1 human trial of an investigational agent that will be tested in a

randomized trial of islet transplantation. The protocol for the randomized trial is ready for is expected to be submitted to the local European regulatory agency by the end of calendar 2007.

Item

***Kidney Disease***

The Committee encourages the NIDDK to expand the kidney disease research infrastructure through an increased number of kidney research core centers to promulgate collaborative research on a local, regional and national level. In addition, the Committee recommends expanded support for investigator-initiated research projects in five priority areas of greatest importance clinically: acute renal failure, diabetic nephropathy, hypertension, transplantation, and uremic cardiovascular toxicity. The Committee commends the NIDDK for moving forward with the Clinical Trials Cooperative Group and supports collaboration with the renal community to seek new strategies and energize clinical investigation in the above-mentioned areas. (p.120)

Action taken or to be taken

Maintaining and expanding the kidney disease research infrastructure is a high priority within the NIDDK. In April 2007, the NIDDK issued a new Request for Applications (RFA) for its George M. O'Brien Kidney Research Core Centers. The emphases for this program are fourfold: 1) to attract new scientific expertise into the study of the basic mechanisms of kidney diseases and disorders; 2) to encourage multidisciplinary research focused on the causes of these diseases; 3) to explore new basic areas with translational potential; and 4) to generate Developmental Research/Pilot and Feasibility studies which should lead to new and innovative approaches to study kidney disease. Three Centers were funded from the initial solicitation, and much progress has been made since the initial solicitation of the O'Brien Kidney Research Centers in 1987. The NIDDK is further enhancing this program to promote regional, national, and international collaboration to expand the kidney disease research infrastructure.

The NIDDK recognizes that investigator-initiated research is an essential part of the research enterprise, and encourages applications that address both basic and clinical aspects of kidney disease. In January 2007, the Institute convened a two-day meeting to discuss key clinical research opportunities in kidney disease.

Meeting participants met in three groups to identify clinical research opportunities in key areas: acute kidney injury, chronic kidney disease, and end-stage renal disease. The NIDDK also continues to foster clinical research in kidney disease through a research solicitation that supports a number of investigator-initiated clinical studies each year.

Item

***Lupus***

The Committee encourages the NIDDK to expand and intensify research on lupus, which can damage virtually any organ system in the body, including the kidneys, stomach and intestinal tract. (p.120)

Action taken or to be taken

To address the difficult issue of lupus, NIDDK is currently funding several studies to gain new insight into this complex disease. Using animal models of systemic lupus erythematosus, one study seeks to understand how genetics influences disease progression, while another is assessing the role of the blood complement system in lupus. The NIDDK is also supporting a study investigating the various forms of colony stimulating factor, and their potential role in the pathogenesis of human lupus nephritis, as well as a study evaluating the contribution of renal parenchymal cells and antigen-presenting cells in the regulation of lupus nephritis. Furthermore, NIDDK is funding a project to develop and characterize an animal lupus model of hepatitis, which will provide an invaluable resource for the study of mechanisms of autoimmune liver damage.

To promote additional research, NIDDK released a Program Announcement entitled “Grants for Basic Research in Glomerular Disease,” in April 2007 to encourage research on glomerular diseases, including lupus nephritis.

Item

***Lymphatic Research and Lymphatic Diseases***

The NIDDK is urged to study the metabolic link between lymphatic function and obesity, dyslipidemia and diabetes. In addition, the Committee strongly urges the NIDDK to study protein-losing enteropathy, a life-threatening complication associated with numerous syndromes involving congenital lymphatic malformations. (p.120)

Action taken or to be taken

Because of the importance of accelerating research on the lymphatic system, the NIDDK is partnering with the National Heart, Lung and Blood Institute and other NIH Institutes and Centers in co-sponsoring a research solicitation on lymphatic biology in health and disease. Released in 2007, this solicitation is intended to encourage new research in areas which may include: the developmental biology of the lymphatic system; lymphatic biology at the molecular, cellular, tissue, organ, and whole body levels; lymphatic function as related to diseases of the intestine; the role of the lymphatic system in specific organ systems including lacteals for absorption of dietary lipids from the gut; investigations in the area of lymphatic functions and their link to development of metabolic problems, including diabetes or obesity; and other topics. The specific research areas for which grants would be funded will depend on the nature of the applications received and their scientific merit, as assessed by the peer review system.

The NIDDK participates in the Trans-NIH Working Group for Lymphatic Research, which held a meeting in September 2007. This meeting was a forum for discussion of major areas of current and future research in lymphatics. Presentations and discussions included information on connections between lymphatic system function and development of fat cells, diseases and syndromes involving lymphatic system malformations, and lymphatic repair.

In other efforts, NIDDK is supporting research on cholesterol uptake, lymphatic transport, and on the development of intestinal lymphatic tissue. With respect to protein-losing enteropathy, this condition is a manifestation of many inflammatory diseases including inflammatory bowel disease, on which the NIDDK supports vigorous research. Other inflammatory disorders associated with protein-losing enteropathy, such as disorders affecting the immune system as well as cancer of the lymphoid system, are within the missions of other NIH ICs.

Item

***Management of Pediatric Kidney Disease***

The complexity and variety of causes unique to childhood kidney diseases requires multiple detailed treatment regimens for chronic kidney disease, dialysis and kidney transplantation. When these medication and treatment plans are not followed, patients experience life-threatening complications and costly hospitalizations. The Committee urges the NIDDK to conduct trans-institute trials to study methods to improve adherence with treatment regimens for children and adolescents, particularly in the areas of dialysis and post kidney transplantation. Additionally, the Committee urges NIDDK to support collaborating networks of health care providers to collect data and plan trials to improve therapy for the spectrum of childhood kidney diseases and the transition of children with kidney disease into adulthood. (p.120)

Action taken or to be taken

Please refer to page 64 of this document for the NIDDK's response to this significant item regarding management of pediatric kidney disease.

Item

***National Commission of Digestive Diseases***

The Committee applauds the continuing work of the National Commission of Digestive Diseases to develop a 10-year plan and urges that the chapter on liver disease encompass the findings and recommendations of the recently updated Liver Disease Research Action Plan. (p.121)

Action taken or to be taken

The Commission is working closely with those individuals involved in the development and implementation of the trans-NIH *Action Plan for Liver Disease Research* to ensure that the Commission's digestive diseases research plan

reflects the *Action Plan's* updated research recommendations within its chapter on "Diseases of the Liver and Biliary System." For example, the Chair and most members of the Working Group responsible for providing input for this chapter also participated in the development of the *Action Plan* and have expressed their support for including the *Action Plan's* updated research goals in the Commission's research plan. Additionally, Dr. Jay Hoofnagle, Chief of the NIDDK Liver Disease Research Branch who provided leadership for the development and implementation of the *Action Plan*, is an *ex officio* member of the Commission who was consulted on liver disease research-related content for inclusion in the Commission's research plan. Commission leaders have also attended annual meetings that are held on the *Action Plan* to discuss progress on implementation of its research goals relevant to liver and biliary diseases.

The Commission members are currently on schedule to fulfill their charge to develop a long-range plan for digestive diseases research. Through public meetings and conference calls, the members and their Working Groups have developed recommendations for specific digestive diseases research goals to include in the research plan. The Commission is developing content for the research plan based on these recommendations.

#### Item

#### ***Obesity and Translational Research***

The Committee urges the NIDDK to address the growing obesity crisis by investigating the role of the gastrointestinal tract in regulating food intake, how obesity causes liver disease and colon cancer, and the best treatment options and novel therapeutic approaches for preventing and treating obesity, including novel endoscopic therapies and other approaches that extend beyond existing treatment modalities. (p.121)

#### Action taken or to be taken

The NIDDK's strong support for obesity research includes a broad spectrum of basic, clinical, and translational studies. For example, NIDDK funds research to elucidate the role of the gastrointestinal tract in appetite control, including studies of signaling molecules produced in the gut, such as ghrelin and glucagon-like peptide-1; these molecules are potential drug targets. In research on surgical and related approaches to obesity, NIDDK-supported Longitudinal Assessment of Bariatric Surgery (LABS) consortium has been analyzing the risks and benefits of bariatric surgery as a treatment for extreme obesity. Although not yet common in adolescents, bariatric surgery is increasingly being used in clinical practice in this age group, and thus NIDDK supports the observational Teen-LABS study to collect data on health outcomes. The NIDDK is also pursuing an effort to build on observations that certain bariatric surgical procedures are associated with amelioration of obesity-related type 2 diabetes and insulin resistance even before substantial weight loss has occurred. Because greater knowledge of the mechanisms underlying this phenomenon may help improve both surgical and

non-surgical therapies, a solicitation was issued to foster research in this area. The solicitation also encourages studies of other technologies, procedures, or devices that may have a similar effect to the surgery.

Examples of other efforts relevant to obesity and its associated diseases include the following. The NIDDK supports a multi-center clinical research network focused on non-alcoholic steatohepatitis (NASH), a serious form of fatty liver disease. This network is investigating the nature and causes of NASH and conducting clinical trials of potential therapies in adults and children. Although research on colon cancer is primarily under the mission of the National Cancer Institute, studies supported by the NIDDK on fatty acid and cholesterol metabolism will help augment understanding of the link between obesity and colon cancer. In other efforts, NIDDK is funding translational research to bring knowledge from clinical research into medical practice and community settings, including, for example, studies of interventions to improve diet and activity and reduce excess body weight in different populations. In a different research avenue, NIDDK is supporting novel studies of the role of gut bacteria in obesity, which may lead to new prevention or treatment approaches. Finally, to encourage further novel research, NIDDK is sponsoring a solicitation for exploratory and developmental clinical research in obesity. The solicitation encompasses studies of behavioral, environmental, pharmacological, surgical, and other approaches; the specific research areas to be funded will depend on the nature and scientific merit of the applications received.

#### Item

##### ***Obesity-related Liver Disease***

There has been a dramatic increase in obesity-related chronic liver disease, which may affect as many as one in four adults and a significant number of obese children. This diagnosis encompasses a spectrum of severity with many cases evolving into non-alcoholic steatohepatitis (NASH) and, ultimately, cirrhosis. NASH-related liver disease has already become an important indicator for liver transplantation, and in the absence of better treatments, the need for NASH-related liver transplantation will increase significantly over time. The Committee urges the NIDDK to continue to support fatty liver disease clinical trials that includes both adult and pediatric populations. (p.121)

#### Action taken or to be taken

Please refer to page 66 of this document for the NIDDK's response to this significant item regarding obesity-related liver disease.

Item

***Polycystic Kidney Disease [PKD]***

The Committee is pleased that NIH-supported research has rapidly led to the development of multiple human clinical trials and interdisciplinary studies focused on slowing or even reversing the progression of PKD. However, the Committee is deeply concerned by recent cuts in NIH funding for PKD research, combined with coding errors that made it appear as if NIDDK funding for PKD were higher than the actual figures. Therefore, the Committee strongly urges the NIDDK to increase its investment in PKD research by promoting additional PKD clinical trials and multidisciplinary research, and expanding studies of pathophysiology and molecular biology. (p.121)

Action taken or to be taken

Please refer to page 68 of this document for the NIDDK's response to this significant item regarding polycystic kidney disease.

Item

***Prostatitis***

The Committee supports the efforts of the Chronic Prostatitis Collaborative Research Network [CPCRN] to find the cause and a cure for prostatitis. The past 10 years of research by the CPCRN have produced important progress, and the Committee urges the NIDDK to fund the research to completion. (p.121)

Action taken or to be taken

Please refer to page 73 of this document for the NIDDK's response to this significant item regarding prostatitis.

Item

***Spina Bifida***

The Committee encourages the Institute to undertake research efforts to study the causes and care of the neurogenic bladder to improve the quality of life of children and adults with spina bifida. (p. 121)

Action taken or to be taken

The NIDDK recognizes that spina bifida is the most common cause of pediatric neurogenic bladder. The association between neural tube defects and bladder dysfunction, as well as the neural crest origin of sympathetic and parasympathetic inputs that innervate the bladder, implies that neural crest derived cells are essential components in normal bladder development. In follow-up to issuing a Program Announcement to encourage research grant applications on "Basic Research in the Bladder and Lower Urinary Tract," the NIDDK has funded a project to begin to assess the relative contribution of bladder cell types that derive from neural crest. The identification of neural crest cell types and the genes that control their differentiation within the bladder is

significant in understanding the cause and potential treatments for neurogenic bladder.

#### Item

##### ***Tuberous Sclerosis Complex***

TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body including the kidneys, where patients are at risk for polycystic kidney disease (PKD), cancer or, most commonly, benign growths known as angiomyolipoma that can result in kidney failure. The Committee urges the NIDDK to continue to support basic research on the mTOR signaling pathway and the role of the TSC1/2 genes in nutrient sensing, insulin signaling and cell growth and proliferation. The Committee also urges the NIDDK to support research on the link between TSC and PKD. (p.122)

#### Action taken or to be taken

Not only has the study of Tuberous Sclerosis Complex (TSC) greatly expanded our knowledge of this serious disease, it has also provided a dramatic scientific windfall through the valuable insights it has afforded into general issues of metabolism and the control of cell division. These key insights have improved understanding in other disease areas including cancer, diabetes, and polycystic kidney disease (PKD). Because of the value and fruitfulness of this area of research, the NIDDK participates with other Institute and Centers (ICs) in the TSC Research Coordination Committee, which works to implement the NIH Tuberous Sclerosis Research Agenda. As part of that effort, NIDDK is one of several ICs sponsoring an initiative entitled “Understanding and Treating Tuberous Sclerosis Complex.”

The NIDDK supports a wide array of research grants exploring the role of mTOR and the *TSC1* and *TSC2* genes in nutrient sensing, insulin-signaling, and the regulation of cell growth and proliferation. Among the recent advances made in this area are: the recognition that platelet derived growth factor receptors are major targets of negative feedback regulation in cells with activated mTOR, which limits the growth potential of TSC tumors; and the discovery of a protein with a key role in mediating signal transduction from insulin to mTOR. NIDDK-supported research with a bearing on TSC and PKD include grants to study: the process of somatic mutation in the neighboring *TSC2* and autosomal dominant *PKD1* genes that leads to cyst formation; and regulation of mTOR by the *PKD1* gene product. Together with the rest of NIDDK’s broad portfolio of research in this area, these grants are shedding important light on this physiologically critical regulatory pathway.

# National Institute of Neurological Disorders and Stroke

## House Significant Items

### Item

#### ***Charcot-Marie-Tooth (CMT)***

CMT is one of the most common inherited neurological disorders. It is characterized by a slowly progressive degeneration of the peripheral muscles in the foot, lower leg, hand, and forearm. In severe forms it debilitates children so that they require wheelchairs and may even result in premature death. The Committee recognizes the NINDS workshop on peripheral neuropathies held in the fall of 2006 that focused on developing research opportunities to address CMT. The workshop concluded that there were a number of specific research directions that were particularly relevant including (1) the development of high throughput screening to identify candidate treatments that may be currently available for patients, (2) research into novel mechanisms to repair genetic abnormalities in patients with CMT, (3) research into interactions between neurons and glial cells that are disrupted and cause disability in many CMT patients, and (4) research into the biological role of inflammatory cells that may exacerbate disability in CMT patients. The Committee encourages NINDS to capitalize on these recommendations through mechanisms such as a relevant program announcement or request for applications. (p.138-139)

### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) recognizes the significant disease burden of Charcot-Marie-Tooth (CMT) syndrome and other peripheral neuropathies, and is working to promote advances in basic, clinical, and translational research, with the goal of developing therapies for this disorder. The NINDS supports a broad portfolio of investigator-initiated grants that focus on several aspects of basic CMT research, including identifying and characterizing the genetic mutations leading to CMT, understanding how these mutations affect various neuronal processes (e.g. transmission of electrical nerve impulses, transport of proteins within a cell), and understanding how these mutations that often result in the disrupted formation of myelin (the insulating cover of nerves) affect neuronal communication with other cells.

The NINDS-supported workshop on peripheral neuropathies held in October 2006 brought these and other basic research topics to the forefront of discussion. With the input of scientific researchers and representatives from patient voluntary groups, the workshop helped to identify several research areas as potential targets for therapeutic intervention. Discussions also focused on understanding and treating the pain associated with neuropathy, and improving diagnostic and research tools used for these disorders. A summary of the workshop is available at

[http://www.ninds.nih.gov/news\\_and\\_events/proceedings/10\\_2006\\_NIH\\_Peripher](http://www.ninds.nih.gov/news_and_events/proceedings/10_2006_NIH_Peripher)

[al Neuropathy Conference.htm](#). The NINDS is working to capitalize on the workshop recommendations as well as recent advances in the field, and is planning to issue a program announcement to solicit grant applications with the goal of identifying and validating therapeutic targets for use in CMT and other peripheral neuropathies.

#### Item

##### ***Dandy-Walker/Hydrocephalus***

The Committee encourages NINDS to establish a coordinating committee for Dandy-Walker and hydrocephalus research. This coordinating committee is encouraged to report its findings to the public on the progress in the epidemiology, pathophysiology, disease burden, treatment improvements, diagnoses and awareness for Dandy-Walker and hydrocephalus. (p.140)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in basic, translational and clinical research to understand and treat Dandy-Walker and other congenital brain malformations and their associated secondary conditions.

Dandy-Walker malformation (DWM) is a congenital malformation of the cerebellum that disrupts the normal flow of cerebrospinal fluid (CSF) in the brain, resulting in excessive fluid accumulation and pressure in the skull (hydrocephalus). NINDS-supported research to determine the causes of DWM includes an ongoing clinical study to identify genes associated with DWM and similar congenital malformations. In addition, studies in experimental animal models are examining the role of DWM candidate genes in brain development, molecular mechanisms underlying cerebellar malformations, and processes guiding the development of the nervous system's basic structural organization. Such studies may provide insights into new strategies for early detection and treatment.

Cerebrospinal shunting to remove excess CSF is the principal treatment available for hydrocephalus due to DWM or other causes. NINDS supports research on improvements to shunts, including the development of non-invasive and ambulatory devices to monitor shunt function and an effort to engineer a new type of catheter that uses a microelectro-mechanical system to resist blockage, a major cause of shunt malfunction. In addition, the NINDS funds basic research on CSF flow and production, which may lead to alternative approaches to preventing CSF accumulation in disorders such as DWM that are accompanied by hydrocephalus.

The NINDS held a workshop in 2005 entitled "Hydrocephalus: Myths, New Facts, Clear Directions," and a summary of the proceedings is available through the NINDS website

([http://www.ninds.nih.gov/news\\_and\\_events/proceedings/Hydrocephalus\\_2005.htm](http://www.ninds.nih.gov/news_and_events/proceedings/Hydrocephalus_2005.htm)). During fiscal year 2008, the NINDS will work with other NIH Institutes to establish a committee of program staff to coordinate research on hydrocephalus and conditions whose neurological sequelae include hydrocephalus, such as Dandy-Walker, spina bifida, and other congenital malformations. The committee will consider the recommendations of the 2005 workshop and, as a first step, will discuss how best to advance research in this field, including whether a second workshop would be beneficial at this time.

#### Item

##### ***Down Syndrome***

The Committee notes the recent publication of a number of breakthrough studies concerning the structure and function of synapses in cognitive circuits in mouse models of Down syndrome. These findings suggest that important advances are possible that could enhance cognitive function in both children and adults with this disorder. The Committee notes that these advances were suggested by the Down syndrome workshop sponsored by NINDS, the goal of which was to address research priorities for optimizing the structure and function in neuronal circuits important for cognition. The Committee commends NINDS for its leadership in organizing the workshop and encourages it to build upon the important findings from the meeting. In particular, the Committee encourages NINDS to identify opportunities for investigating the genetic and cellular basis for abnormalities in the structure and function of cognitive circuits in both the developing and mature nervous systems of people with Down syndrome. NINDS is also encouraged to work with NIA to develop strategies to investigate the biology of age-related disorders, such as Alzheimer's disease and Parkinson's disease, in people with Down syndrome. (p.139)

#### Action taken or to be taken

The NIH Down Syndrome Working Group, led by NICHD, and consisting of representatives from the Office of the Director and nine additional NIH Institutes (including NINDS, NIA, and others) has recently developed the NIH Research Plan on Down Syndrome with input from the scientific research community and national organizations that focus on Down syndrome. The Plan was developed at the request of Congress in the Labor-HHS-Education Appropriations legislation for fiscal year 2007, which asked that the Plan include a focus on genetic and neurobiological research relating to the cognitive dysfunction in Down syndrome.

Recommendations from the February 2005 NIH-sponsored workshop, "Down Syndrome: Toward Optimal Synaptic Function and Cognition," were considered during the development of the research objectives in the Plan, which also built on recent scientific advances in these areas. Relevant research objectives in the Plan include studying structure and function of synapses and understanding how synaptic dysfunction correlates with abnormal cognition in mouse models of Down syndrome. Other research objectives include identifying the cognitive phenotype of Down syndrome in a patient cohort, linking human and mouse

cognitive studies, and exploring the genetic and environmental determinants of cognitive function in Down syndrome. The Plan was published in October 2007.

NINDS currently supports research to understand why many individuals with Down syndrome exhibit early-onset Alzheimer's disease and other age-related disorders. One project aims to clarify the role of amyloid precursor protein (APP) – a protein involved in the pathogenesis of Alzheimer's disease - in neuronal degeneration in a mouse model of Down syndrome. NINDS also funds a number of studies focused on understanding how abnormal processing of APP and the resulting beta-amyloid protein leads to neuronal degeneration. Objectives in the NIH Research Plan on Down Syndrome include studying the aging process in Down syndrome, investigating further the contribution of APP in Down syndrome, and applying relevant knowledge from Alzheimer's disease research to help alleviate cognitive dysfunction in Down syndrome individuals. As implementation of these objectives begins, NINDS will partner with NIA on these and other objectives as appropriate.

In addition to the research plan, NIH continues to sponsor meetings and workshops to discuss future research directions for Down syndrome. For example, a September 2007 meeting co-sponsored by NIH entitled, "Expert Workshop on the Biology of Chromosome 21 Genes: Toward Gene-Phenotype Correlations in Down Syndrome," made recommendations regarding future research on the genetics of trisomy 21. Genes involved in the pathogenesis of both Alzheimer's disease and Down syndrome, as well as genetic pathways relevant to cognitive dysfunction were discussed.

#### Item

#### ***Dystonia***

The Committee continues to support research regarding the neurological movement disorder dystonia. The Committee is pleased with progress made in broadening the dystonia research portfolio resulting from the joint dystonia research program announcement and understands that eleven new grants have been funded as a result of this initiative. The Committee commends NINDS on its sponsorship of the June 2006 scientific workshop on dystonia and looks forward to initiatives based on this activity. The Committee is very pleased with progress demonstrated by the NIH intramural research program in the treatment and understanding of dystonia. NIH intramural researchers have successfully utilized injections of botox to treat many patients who otherwise would be severely debilitated by dystonia. The Committee urges continued work in this important area of study and treatment. (p.138)

#### Action taken or to be taken

NINDS continues its strong commitment to dystonia research in both its intramural and extramural programs. Among the new extramural grants in dystonia are an epidemiological study in an ethnically diverse population that

reflects well the diversity of the U.S. population, brain imaging studies that are mapping the roles of the sensory and motor systems of the brain in focal hand dystonia, generation of genetic mouse models of dystonia, and the use of genetically engineered simple organisms for screening drugs for dystonia, with three classes of drugs now moving from these studies to testing in mice.

To follow up the June 2006 scientific workshop, the NINDS issued a program announcement in July 2007, together with the 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 invites research grant applications aimed at understanding or treating generalized and focal dystonias and encourages basic, translational and clinical studies. The goals are to determine the underlying causes of dystonia, to develop resources to further dystonia research, to accelerate research into therapies, and to stimulate progress through interdisciplinary interactions. The program announcement is scheduled to be active through July 2010.

The intramural program is also continuing its strong program of research to understand the underlying brain mechanisms that cause dystonia and to develop better treatments, including those that use botulinum toxin and other approaches. Intramural investigators have found a number of changes in how the brain controls movement in dystonia, including abnormal plasticity and defective sensory function, and are now working to identify structural pathology in dystonia using magnetic resonance imaging and to identify genetic mutations that cause focal dystonia. As research continues on the mechanisms of the abnormal movement in dystonia, investigators are developing novel treatments informed by insights about how the normal brain controls movement and what goes wrong in dystonia.

#### Item

#### ***Epilepsy***

Epilepsy remains a major, unsolved public health problem affecting the lives of millions of Americans and their families. The Committee seeks intensified efforts by the Institute to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds NINDS for hosting the second “Curing Epilepsy 2007” Conference in March 2007 and encourages NINDS to issue a report and develop plans and goals based on the latest research developments—as highlighted at the conference. Additionally, the Committee recognizes that trials and longitudinal studies are needed to test findings and further develop exciting research directions in epilepsy. (p.141)

### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is extremely pleased with the success of its March 2007 Conference; it was well-attended and highlighted several very exciting trends in epilepsy research. First, the ideal way to treat (and cure) epilepsy would be to prevent the development of seizures in the brain, not just to stop them from progressing or diminish their behavioral effects (e.g., seizures). Second, advances in imaging are also making a dramatic impact on a number of disciplines in epilepsy research, including the development of potential biomarkers of seizure-prone brain regions, the characterization of the effects of epilepsy on brain development, and the cognitive impact of the disorder. Third, completely new therapeutic approaches are emerging in epilepsy research, including the possibility that cell-based therapies may be able to restore normal patterns of activity in seizure-prone brain circuits and advancements in nanotechnology may improve devices that sense impending seizures with greater accuracy than ever before. Of note, the 2007 conference placed special emphasis on the psychiatric, behavioral and cognitive effects of epilepsy, and highlighted the importance of recognizing these often under-reported disorders as having a significant impact on the quality of life of individuals with epilepsy.

The NINDS and the epilepsy community view planning as a community effort. Since the 2000 Curing Epilepsy Conference, researchers and representatives from the voluntary organizations have worked with the NINDS to develop and implement a series of planning goals called "Benchmarks." Members of the research community volunteered to serve as Steward of specific Benchmarks and have met regularly to gauge progress and discuss future directions. This effort is continuing following a planning session at the March 2007 Conference. In October, the Institute met with the Stewards to revise the Benchmarks to reflect advances in the field highlighted at the March 2007 meeting, and to identify junior investigators to participate as Stewards. The NINDS released the revised Benchmarks at the American Epilepsy Society meeting in December 2007; the Benchmarks have been posted on the NINDS website at <http://www.ninds.nih.gov>.

The NINDS has invested considerable funds to identifying and testing potential therapies for epilepsy. Currently, the NINDS is anticipating or currently funding nine clinical trials in epilepsy, including a planned trial of midazolam for the pre-hospital treatment of continuous seizures (including those that might result from a biohazard exposure) and an ongoing trial of levetiracetam to prevent post-traumatic epilepsy. The Institute also supports a pilot study of gamma knife radiosurgery in patients with temporal lobe epilepsy and a large trial to evaluate progesterone therapy for decreasing the frequency of seizures in women with epilepsy.

The NINDS also funds a number of longitudinal studies, including the Epilepsy Phenome/Genome Project Consortium, which will explore the influence of genetic variation and brain abnormalities in the development of epilepsy and contribute to an understanding of the causes of the disorder and potential therapies. Another longitudinal study is exploring the neurobehavioral outcomes in children exposed in utero to four commonly-used anti-epileptic drugs.

#### Item

##### ***Hereditary Hemorrhagic Telangiectasia***

HHT is a multi-system vascular genetic disorder that affects 75,000 Americans, producing arteriovenous malformations in the brain and lung. The Committee recognizes that while HHT is largely preventable with proper intervention, twenty percent of children and adults with HHT die or become disabled due to lack of recognition by the medical community. The Committee encourages NINDS to support research that would improve the quality of life for people living with HHT.(p. 141)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) recognizes the significant burden of hereditary hemorrhagic telangiectasia (HHT) through its manifestations in brain. The NINDS has supported critical basic science research focused on the genetic, molecular, and cellular causes of brain arteriovenous malformations (BAVMs) -- one of the most serious health problems associated with HHT -- and clinical research to optimize therapies.

For example, NINDS-funded researchers have found that tissue from BAVMs produces higher levels of a growth factor called VEGF and an enzyme linked to brain bleeding called MMP-9. In a recent study, these investigators have linked the bleeding caused by VEGF to increased production of MMP-9 and have shown that blocking this enzyme with drug therapy can reduce the amount of bleeding. These findings offer a potential therapeutic strategy for further preclinical and clinical studies.

NINDS-supported investigators have also conducted extensive work exploring the links between risk factors and the clinical features of BAVMs and later outcomes. For example, researchers have recently shown that factors such as active bleeding at clinical presentation, increasing age, and specific features of the affected blood vessels influence the likelihood of later AVM bleeding. Other investigators have compared outcomes of patients who have bleeding from their AVMs with individuals who have experienced brain bleeding from other causes and have found that bleeding appears to be less severe and disabling in the BAVM cases. While the latter findings are encouraging, the body of research in this field strongly suggests that clinicians should consider multiple factors when treatment decisions are made, that broad treatment recommendations (across multiple age groups) will probably not be possible for BAVMs, and that the risks

and benefits of every treatment strategy should be weighed carefully on a patient-by-patient basis.

To try to address the need for tailored treatment protocols, the Institute is supporting the continuation of a 12-year clinical study of BAVMs which is tracking the natural history of affected individuals. Goals of this study include an exploration of the connections between initial clinical presentation and later complications; the categorization of risk factors that are predictive of spontaneous BAVM bleeding and specific treatment outcomes; and the development of a basis for future clinical trials in individuals with BAVMs, in order to optimize treatment options based on each patient's individual risk profile. The Institute is also planning a workshop in April 2008 that will focus on blood vessel growth, including abnormalities of blood vessels like AVMs.

#### Item

#### ***Hydrocephalus***

Hydrocephalus is a serious neurological condition, characterized by the abnormal buildup of cerebrospinal fluids in the ventricles of the brain. It is a condition, not a disease, which affects an estimated one million Americans. It can be congenital, or acquired for no known cause or secondary to many conditions, illnesses, or injuries. Normal pressure hydrocephalus (NPH) is an acquired condition that generally affects people over the age of 50 and often goes undetected or misdiagnosed for many years as dementia, Alzheimer's disease, or Parkinson's disease. Some estimates suggest that over 375,000 older Americans have NPH. There is no known cure for hydrocephalus. The standard treatment was developed in 1952, and carries multiple risks including shunt failure, infection and over-drainage. The Committee commends NINDS for taking lead sponsorship of the 2005 workshop to set national research priorities for hydrocephalus. The Committee encourages the institute to significantly strengthen funding for hydrocephalus research along with actively soliciting grant applications based on the findings from the workshop. The Committee also encourages NINDS to seek opportunities to collaborate with other institutes and offices at NIH, including NIA, NICHD, NEI, NIBIB and ORD, to support research collaboratively in epidemiology, pathophysiology, disease burden and improved treatment for hydrocephalus. (p.139)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in basic, translational and clinical research to understand the causes of hydrocephalus and to advance methods for its diagnosis and treatment.

Current diagnostic procedures for hydrocephalus include invasive measurements of intracranial pressure, and NINDS supports the development of new non-invasive technologies that may allow easier and more rapid diagnosis. NINDS

also funds several efforts to enhance the effectiveness of shunting to remove excess CSF, the principal treatment available to hydrocephalus patients. These include the development of non-invasive and ambulatory devices to monitor shunt function and a project to engineer a new type of catheter that uses a microelectro-mechanical system to resist blockage, a major cause of shunt malfunction. NINDS also supports a prospective clinical trial to compare two shunt valve types for the treatment of NPH, as well as a training grant to a clinical scientist to determine how different treatment parameters affect cognitive recovery in NPH patients treated with adjustable pressure shunts. The results of these studies may inform the development of evidence-based care guidelines for NPH. In addition to efforts to improve shunts, the NINDS funds basic research on CSF flow and production, which may lead to new alternative strategies for preventing CSF accumulation in disorders accompanied by hydrocephalus.

The NINDS held a workshop in 2005 entitled “Hydrocephalus: Myths, New Facts, Clear Directions,” and a summary is available through the NINDS website [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/Hydrocephalus\\_2005.htm](http://www.ninds.nih.gov/news_and_events/proceedings/Hydrocephalus_2005.htm). During fiscal year 2008, the NINDS will work with other NIH Institutes to establish a committee of program staff to coordinate research on hydrocephalus and conditions whose neurological sequelae include hydrocephalus, such as Dandy-Walker, spina bifida, and other congenital malformations. The committee will consider the recommendations of the 2005 workshop in its discussions of how best to advance research in this field.

#### Item

#### ***Mucopolidosis Type IV (ML4)***

Now that NIMH has created and can make available to researchers a strain of mice that replicates the genetic mutation which causes ML4 in humans, the Committee encourages NINDS to sponsor targeted research to develop therapies which might alleviate some of the effects of ML4 and similar genetic disorders, or even lead to their cure. (p.140)

#### Action taken or to be taken

The NINDS encourages scientists to take advantage of the new mouse model of ML4 for therapy development research. A description of the mouse model will be published shortly, and the mice are now available to interested investigators. There are also many funding opportunities for research utilizing the ML4 mouse model. The NINDS welcomes investigator-initiated grant applications. Researchers can also take advantage of several active NINDS solicitations for preclinical therapy development projects. One current program announcement invites applications for pilot projects to generate research tools or conduct “proof-of-principle” experiments on potential new therapies. Under this program, researchers could test new therapeutic strategies in the ML4 animal model or design screens for compounds that could be developed into ML4 drugs. The NINDS also solicits applications for cooperative agreements for full-scale therapy

development projects and research centers. The cooperative agreements are milestone-driven awards, and the applications undergo special review. The NINDS recently funded a cooperative agreement for a preclinical gene therapy study on Batten disease, a lysosomal storage disorder like ML4. The results were promising, and preparations are underway for a clinical trial.

From FY 2004 through FY 2007, the NINDS funded a program announcement with set-aside funds to develop new treatments for the central nervous system effects of lysosomal storage disorders. Researchers funded under this program announcement are testing new gene therapy approaches, small molecule drugs, enzyme replacement strategies, and cell-based therapies in animal models of various lysosomal storage disorders. The results of these projects could suggest promising avenues for ML4 therapy development.

#### Item

#### ***Opsoclonus-Myoclonus (OMS)***

OMS is a rare, auto-immune, disorder that targets the brain. In childhood, it is associated with neuroblastoma of the chest, abdomen, or pelvis. Besides the hallmark features of involuntary eye movements, muscle jerks, and gait disorder, the children have rages, inability to sleep, and may become mute and unable to sit or stand. Permanent problems in motor control, language development, behavior and cognition, even mental retardation, are common. The available treatment options for OMS are extremely limited. The Committee encourages the Institute to accelerate research efforts to identify OMS susceptibility genes and biomarkers, and to develop innovative immunotherapeutic strategies. (p.140)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in research to understand and treat OMS and related paraneoplastic neurological disorders.

Paraneoplastic neurological disorders arise when the body mounts an immune response to tumors that express proteins normally restricted to certain types of neurons, which then become targets of an autoimmune attack. Ongoing research supported by the NINDS includes studies on neuronal proteins targeted by such attacks in OMS and other paraneoplastic disorders. Further understanding of these proteins and their functions in neurons may provide new insights into how to treat and prevent paraneoplastic neurological disorders such as OMS. The NINDS also supports basic research on other autoimmune diseases that affect the nervous system, as well as translational and clinical research toward the development of strategies to prevent and repair immune-mediated damage to nervous system tissues.

The NINDS participates with several other NIH Institutes in a Program

Announcement (PA) on “Functional Links between the Immune System, Brain, and Behavior.” This PA solicits research on immune molecules, cells, and mechanisms involved in regulating normal and pathological central nervous system (CNS) function. Grant applications to study or develop treatments for OMS would be viewed as highly responsive to this PA. In addition, the NINDS is actively working to develop plans for a workshop on the role of B cells in autoimmune and paraneoplastic neurological disorders, including OMS. The goal of this workshop, to be held in 2008, would be to encourage additional research and collaboration in this field.

#### Item

#### ***Spinal Muscular Atrophy***

The Committee commends NINDS for the advancement of the SMA therapeutics development program and encourages NINDS to continue to commit the full range of resources to identifying and completing preclinical research and development (R&D) of SMA drug candidates. The Committee urges NINDS to plan clinical trials and infrastructure including site support, patient registries, biomarker development and natural history studies. (p.140)

#### Action taken or to be taken

The SMA therapeutics development program, also known as the SMA Project, is making encouraging progress toward its goal of bringing a drug to readiness for clinical testing. This year the project selected a promising candidate drug from its development pipeline and is beginning the preclinical safety studies that could lead, if successful, to an IND (Investigational New Drug) application for beginning human testing in 2008. NINDS is strongly committed to this program and will provide the necessary resources to sustain its momentum.

For several years, the NINDS and other components of the NIH have invested in preparing for SMA clinical trials through investigator-initiated research and targeted programs. The NINDS Therapeutics Advancement Program for SMA (TAP-SMA) systematically examined whether any currently available drugs might warrant clinical trials for SMA. TAP-SMA solicited recommendations of drug candidates from clinicians, researchers, and voluntary health organizations and rigorously evaluated these drugs against a standard set of criteria. In 2004, the NINDS convened an international scientific workshop on the development of clinical trials for SMA that discussed the TAP-SMA data and broader issues relating to developing SMA trials. Informed by these discussions, NINDS is developing a pilot clinical trial of phenylbutyrate for SMA that will provide valuable information on future SMA clinical trials, including biomarker and natural history data. The institute has also recently funded research to improve animal models and better define the “therapeutic window” when intervention can be effective. The National Institute of Child Health and Human Development (NICHD) supports natural history studies of SMA and research on quantitative testing of muscle strength in SMA, which will be a crucial outcome measure for clinical trials of

therapies for adults and children. NICHD also 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, ultimately, ensuring that interventions can be administered as soon after diagnosis as possible.

Between FY 1998 and FY 2003, NINDS' research investment in SMA increased by more than 10 fold, compared to the approximately 2 fold growth in NINDS as a whole. This reflected the responsiveness of the investigator-initiated research system to new opportunities in SMA research. The NINDS will continue to encourage and support high quality research on SMA through all appropriate mechanisms via its basic, translational, and clinical research programs.

#### Item

##### ***Tarlov cysts***

The Committee encourages NINDS to collect and analyze data on tarval cysts, their causes, their diagnosis, and their treatment.(p. 140)

#### Action taken or to be taken

Tarlov cysts are fluid-filled sacs that can compress nerves, most often as they enter the lower spinal cord. These cysts can cause lower back pain, sciatica, urinary incontinence, sexual dysfunction, and some loss of feeling or control in the leg or foot. Although most Tarlov cysts do not cause these problems, those that do can cause permanent damage if untreated. Treatment may include removal by a neurosurgeon. NINDS supports research on treatments to reduce and prevent nerve damage and pain from many causes, including compression. In October 2006 NINDS convened a major workshop on the peripheral neuropathies, that is, disorders that affect the nerves of the body. The workshop brought together researchers from across the different types of neuropathy to share information and identify cross-cutting research objectives for the field as a whole. Progress on each disorder that affects peripheral nerves may have benefit for many other disorders, including compression injury due to Tarlov cysts.

#### Item

##### ***Traumatic brain injury***

The Committee is pleased with the work being done at NINDS on TBI translational basic science research and rehabilitation and encourages the Institute to continue such work, specifically bench science research into the cellular and molecular mechanisms of TBI and into neuroprotection/regeneration and repair of the injured brain. (p. 140-141)

#### Action taken or to be taken

The NINDS continues to fund a wide spectrum of research on traumatic brain injury, from molecular and cellular mechanisms, through studies of biomarkers and preclinical therapy development, to clinical trials, as well as supplements to

encourage interdisciplinary research on TBI. The institute's cross-cutting programs in stem cells, brain plasticity, brain imaging, clinical trials for neurological emergencies, deep brain stimulation, neuroprotectants, neural prostheses, and other areas may also have an important bearing on TBI.

The NINDS has always worked closely with other parts of the NIH, including NICHD's National Center for Medical Rehabilitation Research, on TBI. More recently, the NINDS has enhanced its coordination of research with other agencies that conduct TBI research, including the Departments of Defense and Veterans Affairs. In October 2007, NINDS convened a scientific workshop to identify strategies to develop a TBI classification system for targeted therapies. The Defense and Veterans Brain Injury Center (DVBIC) and the Department of Education's National Institute of Disability and Rehabilitation Research (NIDRR) and the Brain Injury Association of America co-sponsored the workshop. NINDS also assisted the Department of Defense with planning a Federal Interagency Meeting on TBI that was held in January, 2008 to promote a coordinated and collaborative research program. A February 2008 scientific meeting will develop a rational strategy for selecting and testing combination therapies for TBI, which is a critical issue because no single intervention is likely to address the multiple mechanisms that damage the brain.

#### Item

##### ***Tuberous Sclerosis***

TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, lungs, liver, eyes, or skin. The Committee applauds the leadership undertaken at NINDS to coordinate research through the trans-NIH tuberous sclerosis coordinating committee. The Committee recommends that the scope of the coordinating committee be broadened to include planning of international conferences and annual targeted workshops on specific areas of TSC research as identified by the coordinating committee and the TSC research community. The Committee also suggests that NINDS human genetics resource center develop a TSC DNA Repository that would serve as a research resource for the TSC research community. Finally, the Committee encourages NINDS to stimulate and support research on the role of early onset seizures in TSC and subsequent cognitive development. (p.141)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) leads the Trans-NIH Tuberous Sclerosis Working Group, composed of representatives from nine other NIH Institutes and Centers, the Department of Defense (DoD), and a representative from the TS Alliance patient voluntary organization. At the most recent meeting in August 2007, members gave updates on their activities, including recent NIH-funded research and a DoD effort to compile and publicize DoD-funded TSC research resources and research highlights. Two meetings organized by members of the working group were also discussed. The first,

“Tuberous Sclerosis Complex: From Genes to New Therapeutics,” held in September 2007, was supported in large part by an NIH conference grant together with the TS Alliance. The workshop brought together prominent researchers to discuss recent advances in understanding the molecular basis of TSC and opportunities for therapy development. The second, “mTOR Signaling: From Cancer to CNS Function,” sponsored by NINDS and planned for January 2008, will focus on a specific molecular pathway - the mTOR pathway – which has been implicated in TSC as well as other cancers and disorders of the nervous system.

NINDS has recently funded a number of grants focused on understanding the mTOR signaling pathway, its interactions with other molecular pathways, and the role of these molecules in the growth and modulation of connections between nerve cells. The role of the mTOR pathway in spatial memory and in the process of neuronal cell death is also being pursued by recently-funded NINDS investigators. A number of these scientists are new or junior investigators. A program announcement with set-aside (PAS) issued by NINDS along other NIH Institutes and the TS Alliance in 2005 has been instrumental in stimulating the field and helping to increase the NINDS portfolio in this area. The PAS is active until March 2008.

NINDS recognizes the potentially severe cognitive consequences of early onset seizures resulting from TSC, and the Institute included several presentations relevant to this issue at its March 2007 Curing Epilepsy conference. These included a talk from a parent of twins with TSC and an entire scientific session focused on the cognitive and psychological issues associated with seizures, from the scope of the problem to underlying mechanisms and potential cures. The September 2007 TSC workshop mentioned above also included both epileptogenesis and cognitive effects of TSC as areas of focus. A number of epilepsy researchers, including a recent NIH Pioneer Awardee, are beginning to focus their research on questions related to epileptogenesis in the context of TSC.

The NINDS Human Genetics Resource Center is a repository for human cells, DNA samples, clinical data, and information sources, to help accelerate research on genetics of disorders of the nervous system. While only a small number of diseases are currently included in the repository, additional diseases may be added in the future.

#### Item

#### ***Vulvodynia***

NIH-supported research indicates that millions of women suffer from chronic pelvic and genitourinary pain conditions such as vulvodynia. The Committee encourages NINDS, in coordination with the NICHD, Office of Research on Women’s Health (ORWH), the NIH pain consortium and other institutes, to

strengthen its support of research in this area, with a focus on etiology and multi-center therapeutic trials. The Committee also encourages NINDS to work with ORWH and other relevant institutes and government agencies, as well as patients and professional organizations, to implement an education outreach campaign on vulvodynia. (p.140)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research to understand and treat chronic pain, including pelvic and gynecological pain conditions. Studies funded by NINDS are characterizing pain originating from the uterine cervix, studying the neural mechanisms of pelvic pain using an animal model of endometriosis, and examining how neurotransmitters (substances released by neurons), their receptors, and hormones contribute to pelvic pain. NINDS also supports a number of studies on the mechanisms and modulation of visceral pain, including understanding the pain pathways between the brain and internal organs, and the mechanisms underlying painful conditions such as irritable bowel syndrome. These studies, as well as NINDS's larger portfolio on understanding pain pathways, may help to shed light on conditions such as vulvodynia. In addition, NINDS funds studies on understanding mechanisms underlying recently discovered sex-related differences in pain and analgesic response. These studies may be of particular importance to chronic pain conditions specific to women. NINDS continues to welcome applications for clinical trials aimed at treating chronic pain conditions.

On October 24, 2007, NIH's Office of Research on Women's Health (ORWH), in partnership with NIH components, the National Vulvodynia Association, the National Women's Health Resource Center, and the American College of Obstetricians and Gynecologists, launched a Vulvodynia Awareness Campaign to bring more attention about vulvodynia to health care professionals and consumers. NINDS, NICHD, and the NIH Pain Consortium are the other NIH partners in this campaign. The Pain Consortium will provide a website link to the ORWH vulvodynia webpage and will utilize the Pain Consortium's existing distribution networks for dissemination of information about this program. NINDS will also contribute to the campaign by providing links to the ORWH website.

NINDS will continue to support research on pain mechanisms to help advance our understanding and treatment of vulvodynia and related genitourinary pain conditions, and to partner with other organizations and NIH components as appropriate.

**Senate Significant Items**

Item

***Alzheimer's Disease***

The Committee recognizes that the NINDS has funded several new areas of research on Alzheimer's that may ultimately contribute to the development of therapeutics, as well as a translational project involving the screening of small molecules that may prevent mutant proteins linked to inherited forms of the disease from contributing to detrimental cellular changes. The Committee encourages the NINDS to continue to assign a high priority to its Alzheimer research portfolio; expand its research into early diagnosis of Alzheimer's using PET imaging of the brain and to share its results with the Centers for Medicare and Medicaid Services; and to continue to work in collaboration with the NIA, NIMH and other Institutes. (p.122).

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in basic and translational research aimed at designing new tools for the early diagnosis of Alzheimer's Disease (AD), understanding the complex biological mechanisms leading to disease onset and progression, and developing novel therapeutic interventions to mitigate or reverse the course of this disease. NINDS also maintains research support for other neurodegenerative disorders that share features in common with AD. An NINDS-funded, high-throughput screen for small molecules that inhibit the buildup of mutant AD-related proteins may also provide critical insights into Parkinson's, Huntington's and Lou Gehrig's disease, as protein accumulation is thought to be a common feature of these conditions.

NINDS continues to fund projects focused on the development of superior diagnostic tools using advanced imaging technologies (e.g. positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) to visualize cellular features of AD, including plaques and tangles. Furthermore, NINDS is committed to the design of innovative tools for earlier clinical diagnosis and enhanced monitoring of disease progression, and has funded a study to correlate over time, AD-associated brain atrophy with changes in blood-derived lipids in an effort to identify more sensitive predictors of disease progression.

NINDS maintains strong collaborations with the National Institute on Aging (NIA), the National Institute of Mental Health (NIMH), and with other NIH Institutes and Centers to advance AD research. These partnerships led to a joint solicitation for proposals that use large-scale analyses to identify and characterize cellular metabolites to better diagnose and monitor AD. Additionally, NINDS has joined with NIA and NIMH in the solicitation of preclinical research proposals aimed at identifying novel therapeutic agents for the treatment of AD. One such study is designed to identify therapeutic strategies to structurally modify proteins in a way that will enhance their ability to remove amyloid-beta (A $\beta$ ), a known precursor of

AD-associated plaques, from the brain. NINDS-supported researchers regularly communicate their findings in peer-reviewed journals that are available to the Centers for Medicare and Medicaid Services and the public.

Item

***Charcot-Marie-Tooth (CMT)***

The Committee commends the NINDS for holding a workshop on peripheral neuropathies that focused on developing research opportunities to address CMT. The workshop concluded that a number of specific research directions are relevant to developing treatments for CMT and related disorders, including: (1) the development of high-throughput screening to identify candidate treatments that may currently be available for patients; (2) research into novel mechanisms to repair genetic abnormalities in patients with CMT; (3) research into interactions between neurons and glial cells that are disrupted and cause disability in many CMT patients; and (4) research into the biological role of inflammatory cells that may exacerbate disability in CMT patients. The Committee strongly urges the NINDS to capitalize on these recommendations and follow up with a relevant program announcement or request for applications. The Committee also requests an update on these activities in the fiscal year 2009 congressional budget justifications. (p.123)

Action taken or to be taken

Please refer to page 96 of this document for the NINDS response to this significant item regarding CMT.

Item

***Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)***

The Committee urges the NINDS to support research to assist in the diagnosis and treatment of CIDP, a rare disorder of the peripheral nerves characterized by gradually increasing weakness of the legs and arms. (p.123)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports basic, clinical, and translational research aimed at understanding, treating and preventing CIDP and other related peripheral neuropathies. CIDP stems from an attack of the immune system that leads to the breakdown of myelin, the insulating cover of peripheral nerves, resulting in the diminished ability of affected nerves to conduct electrical signals. One currently funded study is investigating ways to sequester the cells responsible for such an attack, thereby restricting their ability to participate in the processes leading to myelin destruction.

Peripheral neuropathies share many biological and pathological features in common, and thus research into these disorders may provide critical insight into the underlying events leading to CIDP and represent viable targets for therapy development. Several NINDS-funded researchers are working to understand the

cellular and molecular mechanisms involved in myelin formation and maintenance, while another group of NINDS-funded researchers is investigating the mechanisms responsible for the failure of nerves to transmit electrical impulses, a common clinical feature of CIDP. Understanding these principles may result in the identification of novel therapeutic targets for CIDP and other similar diseases. In addition, investigators funded by NINDS are working to identify genetic mutations responsible for other forms of peripheral neuropathy, leading to the improved ability of clinicians to accurately diagnose and treat this complex class of diseases.

In October 2006, NINDS hosted a workshop that brought together researchers studying many types of peripheral neuropathies, as well as representatives from several patient voluntary groups, including the Charcot-Marie-Tooth Association, the Juvenile Diabetes Research Foundation, the Neuropathy Research Foundation and the Muscular Dystrophy Association. This workshop was designed to evaluate the status of peripheral neuropathy research with the ultimate goal of identifying ways to effectively develop new strategies for therapeutic intervention. Several specific research areas were identified as being critical to this goal, including understanding the interaction between neurons and myelin-forming glial cells, identifying the mechanisms leading to neuropathic pain, and developing better animal models to study peripheral neuropathies, including CIDP. A summary of this workshop is available at [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/10\\_2006\\_NIH\\_Peripheral\\_Neuropathy\\_Conference.htm](http://www.ninds.nih.gov/news_and_events/proceedings/10_2006_NIH_Peripheral_Neuropathy_Conference.htm). To begin to address some of the research questions highlighted during the workshop, NINDS is planning program announcements to advance preclinical and translational research in the field of peripheral neuropathies.

Item

***Dandy-Walker/Hydrocephalus***

The Committee urges the NINDS to form a coordinating committee for Dandy-Walker and hydrocephalus research, and to sponsor a workshop to increase awareness and set national research priorities for these diseases. (p.123)

Action taken or to be taken

Please refer to pages 97 of this document for the NINDS response to this significant item regarding Dandy-Walker/Hydrocephalus.

Item

***Down Syndrome***

The Committee notes the recent publication of a number of breakthrough studies concerning the structure and function of synapses in cognitive circuits in mouse models of Down Syndrome. These findings suggest that important advances are possible in the near future that could enhance cognitive function in both children and adults with this disorder. The Committee notes that these advances were, in

part, forecast by the Down syndrome workshop sponsored by the NINDS. The Committee commends the NINDS for its leadership in organizing the workshop and urges it to build upon the important findings that came out of the meeting. In particular, the Committee encourages the NINDS to identify opportunities for investigating the genetic and cellular basis for abnormalities in the structure and function of cognitive circuits in both the developing and mature nervous systems of people with Down syndrome. The NINDS is also encouraged to work with the NIA to develop strategies to investigate the biology of age-related disorders, such as Alzheimer's disease and Parkinson's disease, in people with Down syndrome. (p.123)

Action taken or to be taken

Please refer to pages 98 of this document for the NINDS response to this significant item regarding Down syndrome.

Item

***Duchenne Muscular Dystrophy***

The Committee is pleased that the Muscular-Dystrophy Coordinating Committee (MDCC) has approved the Action Plan for the Muscular Dystrophies. However, the plan does not make clear the agency or agencies tasked with primary and secondary responsibilities for achieving each of the 76 research objectives. The Committee requests the MDCC to designate those agencies by February 1, 2007. The Committee also encourages the NINDS, NIAMS, and NHLBI to provide the funding needed to support the research agenda at each of the six Paul Wellstone Muscular Dystrophy Cooperative Research Centers. (p.124)

Action taken or to be taken

In its report on the fiscal year 2007 budget for the Department of Health and Human Services, the House and Senate Committees on Appropriations requested that the Muscular Dystrophy Coordinating Committee (MDCC) designate the agencies and organizations with responsibility for the goals in the Action Plan. To address the Committees' requests, NIH asked the MDCC members to identify those components of the Plan that their agency or organization is contributing toward or can contribute toward in the future. Compiled responses, organized by thematic groupings of the Plan, were included in a February 2007 report to Congress, and were discussed further at the most recent MDCC meeting in June 2007. An "Implementation Grid" listing the thematic groupings and the responses from MDCC member organizations and agencies can be found in conjunction with the minutes from the June 2007 MDCC meeting at:

[http://www.ninds.nih.gov/find\\_people/groups/mdcc/MDCC\\_Action\\_Plan\\_Implementation\\_Grid.pdf](http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan_Implementation_Grid.pdf). The Plan will be updated with recent accomplishments related to the five broad categories of the Plan within the next fiscal year.

NIH currently funds six Wellstone Centers, with two Centers each funded by the

National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Child Health and Human Development (NICHD). The Wellstone Centers program has built-in set-aside funds to promote new collaborations, and a total of 14 projects - 10 in 2007 - have been approved for funding using these collaborative funds. To further enhance ongoing and collaborative activities, the Wellstone Centers may apply for supplemental funds to support senior postdoctoral fellows or non-tenure track investigators affiliated with the Centers or to support small workshops or conferences focused on specific topics in muscular dystrophy research. To date, four fellowships and two workshops have been funded through this supplement program.

NIH recently reissued the Request for Applications for Wellstone Centers. The existing Wellstone Centers will be competing with new applications for selection during the next funding period. NIH anticipates awarding these Wellstone Center grants in 2008. The National Heart, Lung, and Blood Institute (NHLBI) will support meritorious research projects or cores associated with these Centers that are relevant to NHLBI's mission to support research on the cardiopulmonary effects of these disorders.

#### Item

#### ***Epilepsy***

The Committee applauds the Institute on the second "Curing Epilepsy" conference, held in March 2007, and it encourages the NINDS, along with the epilepsy community, to update the Epilepsy Research Benchmarks to reflect promising future directions for research toward a cure. The Committee requests an update in the fiscal year 2009 congressional budget justifications on the state of the science in epilepsy research and critical areas for future study, which should include collaborative initiatives with the NIMH, NIA, NICHD and patient and scientific organizations. (p.124)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is extremely pleased with the success of its March 2007 Conference; it was well-attended and highlighted several very exciting trends in epilepsy research. First, the ideal way to treat (and cure) epilepsy would be to prevent the development of seizures in the brain, not just to stop them from progressing or diminish their behavioral effects (e.g., seizures). Second, advances in imaging are also making a dramatic impact on a number of disciplines in epilepsy research, including the development of potential biomarkers of seizure-prone brain regions, the characterization of the effects of epilepsy on brain development, and the cognitive impact of the disorder. Third, completely new therapeutic approaches are emerging in epilepsy research, including the possibility that cell-based therapies may be able to restore normal patterns of activity in seizure-prone brain circuits and advancements in nanotechnology may improve devices that sense

impending seizures with greater accuracy than ever before. Of note, the 2007 conference placed special emphasis on the psychiatric, behavioral and cognitive effects of epilepsy, and highlighted the importance of recognizing these often under-reported disorders as having a significant impact on the quality of life of individuals with epilepsy.

The NINDS and the epilepsy community view planning as a community effort. Since the 2000 Curing Epilepsy Conference, researchers and representatives from the voluntary organizations have worked with the NINDS to develop and implement a series of planning goals called "Benchmarks." Members of the research community volunteered to serve as Steward of specific Benchmarks and have met regularly to gauge progress and discuss future directions. This effort is continuing following a planning session at the March 2007 Conference. In October, the Institute met with the Stewards to revise the Benchmarks to reflect advances in the field highlighted at the March 2007 meeting, and to identify junior investigators to participate as Stewards. The NINDS released the revised Benchmarks at the American Epilepsy Society (AES) meeting in December 2007; the Benchmarks have been posted on the NINDS website. The Institute also works with a number of voluntary organizations on a regular basis and met with these groups during the final stages of development of Epilepsy Research Benchmarks, to collect feedback and make additional refinements to these goals. These nongovernmental organizations, collectively known as "Vision 2020," have also assisted in additional efforts with the NINDS, including organizing the Hoyer Lecture on Epilepsy that is held in conjunction with the annual AES Meeting and planning the 2007 Curing Epilepsy Conference in March.

The NINDS has also worked with the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Child Health and Human Development (NICHD) and the Centers for Disease Control and Prevention (CDC) for several years as part of an Interagency Epilepsy Working Group. The purpose of this group is to increase communication among institutes and agencies sponsoring epilepsy-related research and explore opportunities for increased coordination. For example, both NIA and NINDS representatives assisted in the organization and proceedings of a workshop held on "Models of Geriatric Epilepsy" in November 2006.

#### Item

#### ***Fragile X***

The Committee strongly endorses accelerated funding for basic and translational Fragile X research, especially efforts to analyze the linkages among Fragile X syndrome, autism, and autism spectrum disorders. The Committee urges the NINDS to participate in the scientific session described under the section on the NICHD and to collaborate with the Fragile X Centers of Excellence as well as the Fragile X Clinics Consortium. (p. 124)

### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in basic and translational research to understand and treat Fragile X Syndrome (FXS) and related disorders.

FXS results from a mutation in a single gene (FMR1) on the X chromosome that causes a small region of DNA to be expanded, or repeated many times, preventing expression of the Fragile X Mental Retardation Protein (FMRP). NINDS supports basic science research to study the normal function of FMRP and the consequences of its absence in mouse and fruit fly models of FXS. These studies in animal models are providing insights into the mechanisms leading to FXS symptoms, which may inform the development of treatment strategies. An NINDS-funded translational research project has developed a cell culture assay from fly neurons that can be used to characterize the effects of genetic mutations implicated in FXS and other forms of mental retardation, and to screen for potentially therapeutic compounds.

Between 2.5% and 6% of individuals with autistic symptoms have FXS, and approximately 15% to 25% of individuals with FXS have autism, suggesting shared underlying mechanisms. Along with other NIH Institutes and several private foundations, NINDS supported a workshop in June 2007 on “Shared Neurobiology of Autism and Related Disorders,” which brought together researchers in FXS, Rett syndrome, Angelman syndrome, tuberous sclerosis, Joubert syndrome and other disorders to encourage collaborative and multidisciplinary approaches. In addition, NINDS has partnered for the last two years with NIMH, NICHD, the Canadian Institutes of Health Research, Ireland’s Health Research Board, Cure Autism Now, the National Alliance for Autism Research, Autism Speaks, and the FRAXA Research Foundation to issue a Program Announcement (PA) entitled “Shared Neurobiology of Fragile X and Autism.” The goal of this PA is to solicit grant applications for research to characterize, understand and treat mechanisms common to FXS and autism spectrum disorders. One project currently funded by NINDS in response to this PA focuses on a signaling pathway in neurons that is involved in some forms of learning and memory, and that is altered in a mouse model of FXS. Also in response to this PA is a project to advance a compound targeting the same signaling pathway to clinical trials for the treatment of symptoms associated with FXS and possibly other developmental disorders, such as autism. This translational research project receives joint funding from NIMH, NINDS, and NICHD, and it is administered as a cooperative agreement that allows NIH to monitor its progress and provide advisory support.

NINDS is participating in plans for a scientific session on FXS as part of the NIH Fragile X Research Coordinating Group established by NICHD during fiscal year 2007. This group will seek input from NICHD's Fragile X Research Centers and from the Fragile X Clinics Consortium as it considers ways to move FXS research forward. NINDS currently funds a project on Rett Syndrome, an autism spectrum disorder, by a leading investigator at one of the Fragile X Research Centers, as well as a training program associated with this center that aims to promote careers in research on developmental brain disorders.

Item

***Hydrocephalus***

The NINDS is commended for taking lead sponsorship of the 2005 workshop "Myths, New Facts, Clear Directions" to set national research priorities for hydrocephalus. The Committee urges the Institute to significantly increase funding for hydrocephalus research and awareness along with actively soliciting grant applications based on the findings from the workshop. The Committee also encourages the NINDS to seek opportunities to collaborate with other Institutes, including the NIA, NICHD, NEI, NIBIB and ORD, in developing a coordinating committee to support research collaboratively in epidemiology. (p.124)

Action taken or to be taken

Please refer to pages 103 of this document for the NINDS response to this significant item regarding hydrocephalus.

Item

***Lupus***

The Committee encourages the NINDS to expand and intensify research on lupus, which can attack the blood vessels in the brain, causing seizures, psychosis, and stroke. (p. 124)

Action taken or to be taken

Lupus can cause neurological symptoms when the immune system attacks the brain and nerves of the body. These symptoms include fever, seizures, psychosis, stroke, headaches, cognitive problems, movement problems, and sensory dysfunction. NINDS supports grants directly focused on understanding the neurological consequences of lupus and their mechanisms, including, for example, ongoing research to define more precisely how lupus affects cognitive function and what mechanism might underlie those effects. In addition to grants directly focused on how lupus affects the nervous system, NINDS supports research on the interaction of the immune system with the nervous system in health and disease and on the development of generally effective interventions for stroke, seizures, headache, and other symptoms that lupus can cause. In

2009, NINDS plans to issue a program announcement focused on how immune cells contribute, in beneficial and detrimental ways, to lupus and other neurological disorders.

Item

***Neurofibromatosis***

The Committee encourages the NINDS to continue its efforts in the creation, implementation and funding of NF pre-clinical and clinical trials infrastructures, including NF Centers, translational research, genetic and drug screening, training of new NF researchers, and clinical trials using existing and new drugs on NF patients. The Committee applauds the ongoing work of analyzing DNA of NF tumor samples, which not only will help find a treatment for NF but also connect it to other forms of cancers and other diseases. (p.124-125)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research to better understand and treat neurofibromatosis (NF). In fiscal year 2004, NINDS issued a program announcement (PA) for National Centers for NF Research to accelerate basic, translational, and clinical research on NF. NINDS has funded one center, which is developing mouse models to better understand the molecular signals and the different cell types that contribute to tumor formation in neurofibromatosis-type 1 (NF1). Although the PA is no longer active, investigators who have already submitted an application may continue to submit revised applications for NF Centers. NINDS will also soon fund a translational project to identify efficacious therapies for NF1. The researchers have previously identified a number of molecular pathways involved in NF1, which represent drug targets for treating this disease. Since many of these molecular targets have already been identified for the treatment of some more common forms of cancer, the researchers are testing the efficacy of existing pre-clinical compounds and drugs in their NF1 models.

NINDS also funds research aimed at more effective diagnosis of NF, including a project to develop a cost-effective test to screen for the wide variety of mutations in the NF1 gene, which cause NF1. The small business funded through this grant has already developed alternative testing methods for certain types of mutations, and plans to further improve the tests to allow scanning of larger portions of the NF1 gene. The company will then collaborate with an academic investigator who has collected a repository of DNA and mRNA (genetic material) samples from NF1 patients to validate these tests. If successful, the test will enable more effective diagnosis and therefore better treatment management of NF1. In addition, the technology developed may be applicable to testing for other genetic conditions as well. Other grants in the NINDS portfolio are focused on understanding the mechanisms underlying learning deficits in NF using

animal models and characterizing reading disabilities in children with NF. The latter grant is also testing interventions to treat these reading deficits as well as underlying cognitive disabilities.

NINDS continues to lead the trans-NIH NF Working Group, which includes representatives from other NIH Institutes as well as the Department of Defense (DoD). At its last meeting in February 2007, the group discussed ongoing and future clinical trials for NF, including the DoD's NF Consortium Award, a recently funded program to support clinical trials networks in NF. There were also updates on two NINDS-supported workshops. The first, the "2007 NF Conference," sponsored by NIH and the Children's Tumor Foundation, took place in June 2007 and brought together leaders in the NF field. The second, "mTOR Signaling: From Cancer to CNS Function," sponsored by NINDS and planned for January 2008, will focus on a specific molecular pathway - the mTOR pathway - which has been implicated not only in NF but also in other cancers and disorders of the nervous system.

Item

***Opsoclonus-Myoclonus Syndrome (OMS)***

The Committee continues to urge the Institute to accelerate research efforts to identify OMS susceptibility genes and biomarkers and to develop innovative immunotherapeutic strategies. (p.125)

Action taken or to be taken

Please refer to pages 105 of this document for the NINDS response to this significant item regarding Opsoclonus-Myoclonus Syndrome (OMS).

Item

***Parkinson's Disease Research Centers***

The Committee continues to support the Morris K. Udall Parkinson's Disease Research Centers of Excellence and applauds the creation of an additional center to further focus and manage their interdisciplinary efforts. The Committee further encourages NIH to require that the centers include a significant clinical component, in addition to their ongoing basic and translational research. (p.125)

Action taken or to be taken

The NINDS periodically revisits the Morris K. Udall Parkinson's Disease Research Centers of Excellence program requirements to enable its researchers to take advantage of the latest scientific opportunities and address the key roadblocks that stand between current knowledge and a cure. In 2003, the NINDS increased the annual funding limits for Udall centers conducting clinical research from \$1 million to \$1.5 million to ensure that patient-oriented projects proceed with adequate resources. More than half of the Udall centers now have a significant clinical component in order to take advantage of the higher funding level. Current clinical projects include longitudinal studies to better understand

Parkinson's disease progression; research to untangle the genetic and environmental risk factors for Parkinson's disease; studies of the non-motor aspects of the Parkinson's disease, including depression and dementia; and searches for biological markers of Parkinson's disease that precede the classic clinical signs, allowing for earlier intervention.

In 2007, the NINDS completed its first formal evaluation of the Udall program. The NINDS convened a Working Group of its National Advisory Neurological Disorders and Stroke Council comprised of expert scientists, clinicians, and representation from the Parkinson's patient community. This Working Group reviewed the activities and outcomes of the first eleven Udall centers. In its final report (available at <http://www.ninds.nih.gov/funding/research/parkinsonsweb/index.htm>), the Working Group recognized the importance of clinical research but emphasized that the main barrier to developing clinical treatments at this time is a lack of knowledge about the causes of the disease. While some basic research investigations require analysis of patients, others are best done in animal and cell models of the disease.

The NINDS is currently reviewing the specific recommendations that emerged from the Udall evaluation and determining the best course for implementation. Some of the recommendations may be incorporated into future solicitations for Udall center applications. The NINDS will continue to review the structure of the Udall centers program as new scientific opportunities and challenges emerge.

#### Item

##### ***Peripheral Neuropathy***

More than 60 percent of diabetic patients experience some degree of nerve damage that can lead to skin ulceration on the feet, poor wound healing, and, in extreme cases, lower limb amputation. The NINDS is recognized for organizing a workshop of leading experts in diabetic nerve damage who defined challenges and barriers to the successful implementation of clinical trials to combat this long-term complication. The NINDS is urged to consider establishing a clinical trial network to design and conduct clinical research protocols of new agents to prevent or treat diabetic nerve damage. (p.125)

#### Action taken or to be taken

The National Institute of Neurological Disease and Stroke (NINDS) is investing in research strategies designed to understand, treat and prevent peripheral neuropathies associated with diabetes and other diseases. NINDS is funding a large-scale epidemiological study designed to investigate the heterogeneity of diabetic neuropathies by variety, characteristic features, and course in a diverse population-based study. The findings of these and other similar studies may be

used to improve disease classification, diagnosis and treatment. Other NINDS-funded studies are focused on understanding the cellular, molecular, and pain mechanisms associated with diabetic neuropathy.

In October 2006, NINDS hosted a workshop to evaluate the state of peripheral neuropathy research and to identify areas for potential therapeutic development, the findings of which are available at [http://www.ninds.nih.gov/news\\_and\\_events/proceedings/10\\_2006\\_NIH\\_Peripheral\\_Neuropathy\\_Conference.htm](http://www.ninds.nih.gov/news_and_events/proceedings/10_2006_NIH_Peripheral_Neuropathy_Conference.htm). Although the workshop aimed to integrate concepts and research strategies from different areas in the peripheral neuropathies field to facilitate a more holistic approach to disease treatment and therapy design, several concepts particular to diabetic neuropathy emerged during this meeting. Specifically addressed was a need for improved animal models of painful diabetic neuropathy, a need to understand the relationship between glucose intolerance and diabetic neuropathy, and a need for more sensitive early diagnostic measures and biomarkers. Research areas common to other peripheral neuropathies, (e.g. nerve degeneration and regeneration, neuropathic pain, and the cause and process of the destruction of the insulating cover of peripheral nerves (myelin)) were also significant points of discussion and represent potential target areas for therapeutic development. Although there was considerable discussion of approaches to improve future clinical trials, it is not clear that there are sufficient preclinical drug candidates to warrant investment in a clinical trials network at this time. It is for this reason that NINDS is focusing its future efforts towards the development of preclinical therapeutic candidates. To stimulate this effort, NINDS is planning a program announcement to solicit applications with the goal of identifying and validating therapeutic targets for peripheral neuropathy.

#### Item

##### ***Spina bifida***

The Committee encourages the Institute to continue and expand research to address issues related to the prevention and treatment of spina bifida and associated secondary conditions such as hydrocephalus. (p.125)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to investing in basic and clinical research to understand, treat and prevent spina bifida and other neural tube defects and their associated conditions.

The NINDS supports an ongoing study to identify genes that may contribute to neural tube defects in humans by analyzing gene expression during critical periods of human embryonic development. Adequate dietary intake of folate is associated with a decreased risk of neural tube defects, and another project funded by NINDS is studying the mechanisms underlying this association. This

collaborative project is looking for genetic pathways that may interact with folate or other nutritional factors in four large epidemiological datasets and in mouse models with impaired folate transport. These studies may inform the development of improved strategies to detect and prevent spina bifida and other neural tube defects.

The NINDS provided support to the 5<sup>th</sup> International Neural Tube Defects Conference held in September 2007. This biennial meeting has received NINDS support since 2001 and brings together researchers from many disciplines to promote collaborative research on the causes, treatment and prevention of neural tube defects such as spina bifida. Scientific sessions cover topics such as clinical aspects of neural tube defects, genetic and nutritional factors contributing to their occurrence, population differences in frequency, mouse models, and many others.

NINDS also supports research on the treatment and prevention of secondary conditions, such as hydrocephalus, associated with spina bifida and other congenital malformations. Cerebrospinal shunting to remove excess CSF is the principal treatment available for hydrocephalus. NINDS supports research on improvements to shunts, including the development of non-invasive and ambulatory devices to monitor shunt function and an effort to engineer a new type of catheter that uses a microelectro-mechanical system to resist blockage, a major cause of shunt malfunction. In addition, the NINDS funds basic research on CSF flow and production, which may lead to new strategies for preventing CSF accumulation in disorders accompanied by hydrocephalus.

Item

***Spinal Muscular Atrophy***

The Committee commends the NINDS for the advancement of the SMA Therapeutics Development program and strongly urges the Institute to continue identifying and completing preclinical research and development of SMA drug candidates. The Committee urges the NINDS to plan and budget for the successive stages of the project, including, most importantly, funding for clinical trials and infrastructure (e.g., site support, patient registries, biomarker development and natural history studies). Lastly, the Committee notes the need to expand basic research funding on SMA and requests that a request for applications be issued. (p.125)

Action taken or to be taken

Please refer to pages 104 of this document for the NINDS response to this significant item regarding spinal muscular atrophy.

Item

***Stroke Rehabilitation***

The Committee notes the growing body of evidence that stroke victims do not

achieve the fullest possible recovery from rehabilitation because of limited awareness of appropriate rehabilitation protocols. The Committee therefore urges the convening of an expert's panel to examine this issue with the goal of developing consensus treatment protocols. Finally, the Committee urges implementation of the Stroke Progress Review Report's recommendations on recovery and rehabilitation. (p.126)

#### Action taken or to be taken

The National Institutes of Health considers rehabilitation a critical component of relieving the public health burden of stroke, and believes that it is critical to promote evidence-based practice in rehabilitation intervention. Extraordinary advances have been made in stroke rehabilitation research in recent years. These include promising results from studies on robotic-assisted or constraint-induced therapies, non-invasive brain stimulation, as well as on the biological processes underlying the plasticity of the nervous system. The research community, nevertheless, has not yet gathered sufficient information about different treatment approaches to develop rational, evidence-based rehabilitation protocols. Thus, the lack of an evidence base on effective practices is the issue, not a lack of consensus. For example, while the results of a major clinical trial of constraint-induced therapy funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS) indicated that this therapy is more effective than usual care for rehabilitation of arm paralysis in stroke, a report presented at the American Society of Rehabilitation meeting in Washington in October 2007 demonstrated that when the time of therapy was controlled for, constraint therapy was no more effective than conventional methods. Moreover, and contrary to expectation, patients who received more intensive constraint therapy in the acute period after stroke were found to recover more slowly than those receiving less intense therapies.

The use of advanced imaging methods to predict outcomes and guide therapies for stroke rehabilitation is also promising, but still requires much research. Investigators are exploring new approaches such as bilateral arm training, but these strategies are not always effective. Other new techniques, including the use of medications to promote recovery, the use of electrical or magnetic stimulation in conjunction with training, and the use of robotic training, are also under study, but need careful evaluation by multiple groups of investigators to establish their safety and efficacy.

The NINDS has included Rehabilitation Research as a focus in every phase of its stroke research planning, guided by the recommendations of the Stroke Progress Review Group (see: [http://www.ninds.nih.gov/find\\_people/groups/stroke\\_prg/04\\_2002\\_stroke\\_prg\\_report.htm](http://www.ninds.nih.gov/find_people/groups/stroke_prg/04_2002_stroke_prg_report.htm) for more information). In addition, the National Center for Medical Rehabilitation Research (NCMRR) has held several workshops to develop

research agendas around critical issues regarding rehabilitation including: timing intensity and duration of therapies (2003), determining appropriate settings for rehabilitation (2005), examining the basis of the rehabilitation "plateau" of recovery after stroke (2007). All of the recommendations from these workshops highlighted the need for further research. While it is clear that patients with stroke benefit from rehabilitation, the actual content of the optimal therapy program remains to be established. The NIH is committed to working with the stroke research community to provide the data needed to establish this content and to support the development of consensus treatment protocols as rapidly as possible.

Item

***Tuberous Sclerosis***

The Committee applauds the leadership undertaken at the NINDS to coordinate research on TSC through the Trans-NIH Tuberous Sclerosis Coordinating Committee. The Committee believes the scope of the committee should be broadened to include planning of international conferences and annual targeted workshops on specific areas of TSC research. The Committee also urges the NINDS Human Genetics Resource Center to develop a TSC DNA Repository that would serve as a research resource for the TSC research community. Finally, the Committee urges the NINDS to stimulate and support research on the role of early-onset seizures in TSC and subsequent cognitive development. (p.126)

Action taken or to be taken

Please refer to pages 108 of this document for the NINDS response to this significant item regarding tuberous sclerosis.

Item

***Vulvodynia***

The Committee urges the NINDS, in coordination with the NICHD, ORWH, NIH Pain Consortium and other ICs, to expand its support of research in vulvodynia, with a focus on etiology and multi-center therapeutic trials. The Committee also calls on the NINDS to work with the ORWH and other relevant ICs and government agencies, as well as patient and professional organizations, to implement an educational outreach campaign on vulvodynia. (p.126)

Action taken or to be taken

Please refer to pages 109 of this document for the NINDS response to this significant item regarding vulvodynia.

# National Institute of Allergy and Infectious Diseases

## House Significant Items

### Item

#### ***Antiviral Drug Resistance***

The committee recognizes that several new drugs to treat hepatitis B have become available recently and several more are being developed, both against hepatitis B and hepatitis C. One of the major challenges in implementing these therapies is the development of antiviral drug resistance. The Committee encourages the development of standardized terminology to describe this resistance and studies of the mechanism of resistance and methods to overcome resistance. (p.142)

### Action taken or to be taken

NIAID acknowledges the need for harmonization of nomenclature and standardization of assays relating to hepatitis B antiviral resistance; for example, standard definitions of genotypic, phenotypic, and clinical resistance are not recognized. To this end, NIAID convened an international Working Group for Hepatitis B Virus Drug Resistance. The Working Group recommendations on standardization of nomenclature and assays were published in July 2007 in the journal *Hepatology*. The issues identified by the Working Group were discussed at the annual meeting of the American Association of Liver Diseases (AASLD) in Boston in November 2007. This session, jointly organized by NIAID and the AASLD, provided an opportunity for wider consultation in this area. Additionally, NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases, is planning to cosponsor the *Management of Hepatitis B Consensus Development Conference* in October 2008.

Research to develop new classes of drugs that are safe and effective in treating hepatitis B (HBV) and hepatitis C virus (HCV) infections remains a priority for NIAID. It is critical that HBV and HCV are not readily able to develop resistance to these new classes of drugs. For example, in studies conducted in non-human primates, 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.

Currently licensed antiviral drugs for HBV target a single step in the viral replication cycle. As resistance with this class of drugs seems inevitable, NIAID-supported investigators, through partnership initiatives, are redirecting their research to novel targets in the replication cycle and are pursuing the

development of different classes of drugs. Researchers are currently developing synthetic derivatives of helioxanthin, a natural product that exhibits antiviral activity against HBV. As this class of drugs works via a different mechanism than licensed HBV polymerase inhibitors, it does exhibit activity against drug-resistant HBV strains.

In addition, NIAID supports contracts to test therapeutics for HBV and HCV in animal models. A broad range of novel antiviral therapeutics are undergoing testing in animal models for HBV, including small interfering RNA, therapeutic vaccines, toll-like receptor agonists, immunomodulators, and interferon inducers.

NIAID supports a contract for testing therapeutic drugs and vaccines against HCV in a novel transgenic mouse model. Through an investigator-initiated award, researchers created a simple fluorescent-based screen that allows investigators to look at the mechanism of hepatitis B viral capsid assembly and identify novel agents that affect it.

#### 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.142)

#### Action taken or to be taken

NIAID remains committed to research to improve prevention and management of asthma, particularly in pediatric populations. For example, NIAID continues to support the Inner-City Asthma Consortium (ICAC) to evaluate 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 these immune-based therapies, develop and validate biomarkers of disease progression, and investigate the immunopathogenesis of asthma. The ICAC Asthma Control Evaluation (ACE) trial of exhaled nitric oxide as a biomarker to guide asthma management in inner-city children is complete. The results are being prepared for publication.

NIAID continues to actively engage with voluntary health organizations. For example, NIAID shares information on its current programs and future direction with organizations such as the Asthma and Allergy Foundation of America, the American Lung Association, the Sandler Program for Asthma Research, and the American Asthma Foundation.

In FY 2007, NIAID established the "Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases" program to identify novel allergens and reagents

to facilitate research on the immunological mechanisms of asthma and allergic diseases and the development of therapeutic strategies to treat and prevent asthma and allergy. In addition, NIAID re-competed the Immune Tolerance Network (ITN) contract, which is conducting two clinical trials and mechanistic studies in asthma.

NIAID supports fifteen Asthma and Allergic Diseases Research Centers and Asthma and Allergic Diseases Cooperative Research Centers to conduct basic and clinical research on the mechanisms, diagnosis, treatment and prevention of asthma and allergic diseases. Currently, two clinical studies are being conducted and eight additional studies are in development at four sites.

The NIAID Pediatric Allergy Clinic at the NIH Clinical Center provides opportunities for translational research, physician training, and clinical trials of novel therapies in the management of asthma and allergies. The clinic uses and evaluates child-friendly, non-invasive clinical tests to evaluate asthma and allergy symptoms. In FY 2007, allergen immunotherapy was added to the services offered by the clinic; this contributed to the doubling of patient visits to over 500 compared to FY 2006.

NIAID collaborates with other Institutes on studies related to pediatric asthma. For example, a recent study conducted in collaboration with the National Institute of Environmental Health Sciences demonstrated the link between allergies and the development of asthma. More than 50 percent of the current asthma cases in the country can be attributed to allergies, with approximately 30 percent of those cases attributed to cat allergy.

#### Item

##### ***Drug-resistant Tuberculosis (TB)***

The Committee understands that NIAID is working on a response plan to drug resistant tuberculosis, including extremely drug resistant TB (XDR-TB), and applauds these efforts. The Committee encourages the appropriate allocation of resources to effectively address this global health emergency. (p.142)

#### Action Taken or to be taken

NIAID remains firmly committed to leading and supporting a robust program of tuberculosis (TB) research, including multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB. To this end, it supports more than 300 TB-related research projects around the world, many in collaboration with government and private sector partners. For the first time in the history of TB research, a robust pipeline of promising TB products is available. More than a dozen drug and vaccine candidates and approaches are being tested in clinical trials and dozens of new candidates are being evaluated in early development and preclinical studies. Five new diagnostics tools are being validated in clinical trials and

existing diagnostic platforms are being adapted for use in TB applications, including the detection of XDR-TB.

NIAID is committed to rapidly responding to the growing concerns about drug resistant TB, and, thus, recently developed a research agenda for MDR and XDR-TB that is designed to complement NIAID's ongoing TB research activities.

NIAID is leveraging resources to give priority to drug resistance research in TB, including supporting studies to maximize the effectiveness of currently available antimicrobial drugs; accelerating preclinical and clinical development of new TB drugs and combinations; facilitating feasibility testing of new diagnostics, therapeutics, and vaccines; characterizing the pathogenicity of MDR- and XDR-TB strains; encouraging and supporting research on the management of TB/HIV co-infections; and strengthening international TB research capacity.

An example of an existing program that can be leveraged to respond to the threat of drug-resistant TB is the TB Research Unit (TBRU) consortium, renewed in fiscal year 2007. The TBRU addresses critical questions in TB clinical research and develops surrogate markers of disease and human protective immunity. These studies are essential to inform clinical trials of new drugs, vaccines, and diagnostics and are coordinated with other government and non-government organizations involved in TB research, including the Centers for Disease Control and Prevention, the U. S. Agency for International Development, the Food and Drug Administration, the World Health Organization, the Global Alliance for TB Drug Development, the AERAS Global TB Vaccine Foundation, the Foundation for Innovative Diagnostics, professional organizations involved in TB research and care, and interested industrial partners.

NIAID scientists collaborate with international partners on MDR-TB, expanding this collaboration to include investigations of XDR-TB. For example, working with researchers in South Korea, NIAID scientists initiated a research protocol at the Masan National Tuberculosis Hospital in South Korea to study the natural history of MDR-TB. Masan Hospital has the largest population of inpatient MDR-TB patients in the world. Several hundred volunteers have enrolled to date. In addition, this cohort has allowed an examination of the occurrence of XDR-TB in patients that have failed chemotherapy completely. The results of initial epidemiological studies of 26 patients with XDR-TB, a subset of this cohort, are completed and were submitted for publication.

#### Item

#### ***Liver Transplantation***

The Committee encourages additional research focused on these long-term quality of life issues, as well as research to improve patient and graft survival, pre-transplant graft evaluation and preservation, with a particular focus on research to reduce and eventually eliminate a transplant recipient's dependence on immunosuppressive drugs. (p.142)

### Action taken or to be taken

NIAID supports a broad portfolio of basic and clinical research in the immunology and outcomes of transplantation. The goals of these studies 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.

NIAID, with the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute for Diabetes and Digestive and Kidney Diseases, supports 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.

In early fiscal year (FY) 2008, liver transplant recipients will start enrolling in a new CTOT study to correlate the inflammatory state of the donor with early outcomes of transplantation.

In FY 2007, NIAID and NHLBI solicited applications for the Clinical Trials in Organ Transplantation in Children (CTOT-C) consortium. CTOT-C will support clinical, mechanistic and epidemiological studies in children who have undergone heart, lung, small intestine, liver, and/or kidney transplantation. Awards for this consortium are anticipated in FY 2008.

The Immune Tolerance Network (ITN), supported by NIAID and renewed in FY 2007, solicits, develops, implements, and evaluates clinical strategies and biologic assays for the induction, maintenance, and monitoring of immune tolerance in humans. It currently supports three drug withdrawal trials in liver transplantation, including a pediatric study in which six of eleven children have had all immunosuppressive medications withdrawn.

NIAID sponsors a multicenter study of kidney and liver transplantation in individuals with Human Immunodeficiency Virus (HIV) infection. This study, ongoing since FY 2003, is investigating the clinical outcomes and immunologic responses of these individuals.

### Item

#### ***Malaria Vaccine***

The Committee commends NIAID for its malaria research and, specifically, its effort to create a malaria vaccine. The Committee encourages NIAID to target

resources to support malaria vaccine development, drug development, diagnostics, vector control, infrastructure and research capability, and to strengthen components of the implementation plan for global research on malaria. The Committee encourages NIAID to strengthen its efforts related to developing improved diagnostic tools which will help in the early identification of malaria and support the provision of rapid treatment. The Committee is concerned that drug-resistant malaria increasingly is being reported around the world, making the development of new drugs to treat malaria essential. Of further concern is that reports of insecticide-resistant mosquitoes are on the rise. To that end, the Committee encourages NIAID to undertake additional research on the basic biology and ecology of mosquitoes, as well as work in genomics to develop new insecticides or render mosquitoes incapable of transmitting malaria. (p.142-143)

#### Action taken or to be taken

NIAID remains committed to conducting and supporting research on malaria, including the development of vaccines, drugs, and diagnostics. For example, at the NIAID Malaria Research and Training Center (MRTC) in Bamako, Mali, scientists are developing diagnostics that can detect parasite resistance to several first-line malaria drugs, which may help researchers track patterns of emerging resistance in the field and help healthcare workers target appropriate interventions to patients. Other NIAID-supported investigators developed methods for rapid detection of malaria and assays capable of distinguishing among the four most common malaria parasites in a laboratory sample.

In 2007, NIAID launched an innovative new program, *NIAID Partnerships with Public-Private Partnerships*, to support Public Private Partnerships (PPPs) in the development of new drugs, vaccines, and diagnostics for high-priority neglected infectious tropical diseases of global importance, such as malaria. Under this program, NIAID awarded a cooperative agreement to the Medicines for Malaria Venture (MMV) to support early drug discovery research on inhibitors of an enzyme that is essential for malaria parasite survival, with the goal of developing a new antimalarial drug. NIAID also made an award to St. Jude Children's Research Hospital to support a newly established antimalarial drug discovery consortium.

NIAID-supported investigators are developing a wide variety of vaccines against different life cycle stages of the malaria parasite. These candidate vaccines include vaccines that target the stages of the parasite that first infect the bloodstream and liver, vaccines that target later stages of the life cycle when the parasite is infecting the red blood cells, and vaccines that block the ability of the sexual stages of the parasite to infect mosquitoes, thus breaking the cycle of transmission.

NIAID's vector biology program supports basic research in areas such as mosquito development, metabolic pathways, and host-seeking behavior; all of which can serve as sources of new concepts for potential translation into vector management strategies. In addition, data available from NIAID's mosquito genome sequencing efforts provide a rich source of new targets for potential vector management tools. Further, NIAID scientists collaborate with Malian colleagues at the MRTC on field studies of mosquito biology and ecology, including the development of a two-camera video system to record behavior of mosquitoes in swarms. These studies may have practical implications on strategies to render mosquitoes incapable of transmitting malaria.

In addition to these research programs, NIAID continues to support special programs focused on building international research capacity, including the Tropical Medicine Research Centers Program, the International Collaboration in Infectious Disease Research Program, the International Research in Infectious Diseases Program, and the MRTC in Bamako, Mali.

#### Item

##### ***Antibiotic Resistance***

The Committee is concerned about the alarming rates of antibiotic resistance and the related increase in morbidity, mortality and health care costs. Little research has been devoted to defining optimal dosing regimens, particularly in defining the minimal duration of therapy necessary to cure many types of infections. The Committee recognizes that studies of this type require a long-term commitment and are not likely to be funded by pharmaceutical manufacturers since the products are already approved by the FDA. The consensus of many experts is that infections may be treated for longer periods of time than are necessary, needlessly increasing the antimicrobial resistance. Therefore, the Committee encourages NIAID to support randomized controlled trials to define the necessary length of therapy. (p. 143)

#### Action Taken or to be taken

Research to better characterize the public health threat posed by antimicrobial-resistant infections and to develop therapeutics that minimize the emergence of drug resistance in pathogens remains a priority for NIH and NIAID.

NIAID supports basic research that includes the study of mechanisms of resistance and the identification of new therapeutic targets. This fundamental work continues to direct translational and clinical research activities. For example, in fiscal year (FY) 2007, NIAID awarded two five-year contracts through the "Clinical Trial for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA)" initiative to study whether selected oral, off-patent antibiotics can effectively treat uncomplicated cases of skin and soft tissue infections caused by CA-MRSA bacteria. Because CA-MRSA bacteria may be more susceptible to a greater number of antibiotics than healthcare-associated MRSA

strains, the overarching goal of this study is to determine the optimal treatment, including duration of therapy, for CA-MRSA infections. Should the data from these studies demonstrate that off-patent antibiotics are effective, final-option drugs such as vancomycin and linezolid could be preserved for treating healthcare-associated MRSA. These contracts were awarded to two groups of researchers qualified to address the questions within this specific disease area. These researchers, and the multiple sites associated with them for these studies, form a “functional network”, an approach that provides NIAID with a flexible structure in which to address specific scientific questions of highest priority.

NIAID supports clinical trials that examine the necessity of antimicrobial therapy for certain illnesses in order to alleviate non-essential antimicrobial use. A clinical study, which began in October 2006 and is expected to be completed in May 2008, is evaluating the efficacy of antimicrobials in young children with acute ear infections. The study will compare the resolution of symptoms in children receiving antimicrobial therapy versus placebo. An additional clinical study, currently enrolling, will evaluate the infection status of children requiring mechanical ventilation and will form the basis for future management of antimicrobial use in these patients.

Rapid diagnostic tests are not currently available for many infections. In lieu of these tests, healthcare providers commonly prescribe broad-spectrum antimicrobial drugs, the overuse of which has been attributed to the accelerated development of resistance. Research initiatives such as “Sepsis and CAP: Partnerships for Diagnostics Development” and “Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections” support the development of new diagnostics that may facilitate the optimization of antimicrobial therapy.

In FY 2008, NIAID anticipates making awards through the “Pharmacological Approaches to Combating Antimicrobial Resistance” initiative to support research to apply pharmacokinetic and pharmacodynamic principles to studies on the prevention of emergence of antimicrobial 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.

#### Item

#### ***Primary Immunodeficiency Diseases***

NIAID is the lead agency for research into bone marrow transplantation (BMT), which can cure some primary immunodeficiencies. The Institute has made significant progress in reducing graft versus host disease (GVHD) and improving therapies when GVHD develops. With newborn screening of certain PI diseases being piloted in the States, the Committee urges the Institute to redouble its

efforts to assure that identified patients have the best possible chance for survival. (p. 143)

#### Action taken or to be taken

NIAID continues its commitment to research on the natural history, genetics, pathogenesis, and mechanisms of primary immunodeficiency diseases (PID). For example, NIAID, with the National Institute for Child Health and Human Development, continues to support the Primary Immunodeficiency Diseases Research Consortium (USIDNet). In addition to fostering research in PID, the Consortium maintains a PID registry that provides data to the research community about the clinical characteristics, prevalence, and outcome of individuals with these diseases. The consortium also has an active education program. In addition, NIAID, with the National Heart, Lung, and Blood Institute and the National Cancer Institute (NCI), supports the Center for International Blood & Marrow Transplant Research, which provides a mechanism for collecting outcome data on hematopoietic stem cell transplantation, including for PID.

Gene therapy has the potential to correct the molecular defects responsible for a variety of inherited immune deficiencies. Basic research by NIAID scientists is focused on developing gene therapy methods to correct three specific primary immunodeficiencies: X-linked chronic granulomatous disease (X-CGD), X-linked severe combined immune deficiency (X-SCID), and leukocyte adhesion deficiency. Two clinical protocols are enrolling patients for treatment with genetically modified cells: one is a gene therapy clinical trial for X-CGD; the other is a gene therapy clinical trial for X-SCID. These trials are conducted in collaboration with the NIH Clinical Center, NCI, and the National Human Genome Research Institute. NIAID also supports a research portfolio on the development of gene therapy, as well as thymic transplantation, for PID.

In addition NIAID supports a portfolio of investigator-initiated projects aimed at improving identification, understanding, and outcome of PID. These include long-term follow-up of a cohort of patients with severe combined immunodeficiency who have received bone marrow transplantation. NIAID supports research in large animal models of PID as well as clinical trials to determine the most efficacious bone marrow transplantation regimens in patients with these diseases.

Transplant protocols developed to make use of stem cells from tissue-matched donors (referred to as allogeneic donors) hold great potential to cure many types of severe primary immune deficiencies. These protocols include the use of donated bone marrow, hematopoietic stem cells (stem cells that form blood and immune cells) mobilized into the circulating (peripheral) blood of a donor with drug therapy, or the use of stem cells derived from donated umbilical cord blood. One of the main barriers to more extensive use of these allogeneic transplant

techniques, however, is acute and chronic graft versus host disease (GVHD). A clinical protocol conducted by NIAID investigators is currently enrolling patients with inherited immune deficiencies for treatment with allogeneic bone marrow, peripheral blood stem cells or cord blood from either matched sibling donors or unrelated donors. The protocol employs a regimen which suppresses the patient's immune system sufficiently to allow engraftment of the donor cells but uses a less aggressive approach than conventional pre-transplant conditioning. This allows the treatment of PIDD patients with untreatable infections. The protocol utilizes the immunosuppressive drug, Sirolimus, as the basis of its post transplant regimen for prevention of GVHD and tolerance induction. NIAID scientists are working to improve GVHD therapies in other ways. These researchers and their colleagues from the NIH Clinical Center and NCI are collaborating to test therapeutic options to treat GVHD. They are also studying the patterns of immune system proteins (or cytokines) in the blood and tissues of patients with chronic GVHD to determine what types of treatments may be helpful.

#### Item

##### ***Clinical Islet Transplantation***

The Committee acknowledges the productive collaboration of the NIDDK and NIAID in overseeing the Clinical Islet Transplantation Consortium (CIT). The development of seven clinical trial protocols of islet transplantation marks a significant step toward validating this procedure as a viable treatment for type 1 diabetes patients suffering from extremely “brittle” or difficult-to-control blood sugar levels. NIDDK and NIAID are urged to take steps to ensure the efficient launch of these trials and to expedite patient recruitment and enrollment. (p. 143)

#### Action taken or to be taken

All six of the trials to be conducted in North America have undergone review by a Data and Safety Monitoring Board, Institutional Review Boards and the Food and Drug Administration (FDA). A detailed uniform islet manufacturing process has been developed and agreed upon by the participating centers. Individuals are being recruited into these trials. To help expedite patient recruitment and enrollment, the CIT developed a website with information for patients regarding eligibility for clinical trials ([www.citisletstudy.org/](http://www.citisletstudy.org/)). The NIDDK also posted information on CIT trials on its patient recruitment website ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)). The trials are also listed on the NIH's clinical trials website ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

The North American trials include two multicenter clinical trials that could lead to licensure of islets as a biological product by the FDA. The first trial is enrolling individuals with type 1 diabetes, severe hypoglycemic (low blood sugar) events, and normal kidney function. The effectiveness of islet transplantation will be measured by the number of people who achieve good diabetes control, as

measured by their hemoglobin A1c level, and freedom from severe hypoglycemic events at 1 year after the first islet transplant. The second trial is enrolling individuals with type 1 diabetes who previously received a kidney transplant and are therefore already receiving immunosuppressive therapy to prevent rejection of the transplanted kidney. This trial will compare outcomes of islet transplant recipients to those of comparable patients treated medically with an intensive insulin regimen. Designing these trials has required extensive discussion and collaboration not only among the investigators and NIH staff but also with other HHS agencies such as the FDA and the Centers for Medicare & Medicaid Services.

In Europe, CIT investigators have completed a phase 1 human trial of an investigational agent that will be tested in a randomized trial of islet transplantation. The protocol for the randomized trial is ready for Health Authority submission.

#### Item

##### ***Anaphylaxis***

The issue of food allergies is an area of particular concern to this Committee. As many as 30,000 individuals, many of whom are children, require emergency room admission for food allergies every year, and several hundred die. The Committee supports intensive NIAID research in anaphylaxis and food allergy research to develop a cure for anaphylaxis, or severe allergic reactions to food or medications. (p. 143)

#### Action taken or to be taken

NIAID remains committed to basic research to advance the understanding of food allergy and food allergy-associated anaphylaxis. To promote the development of new methods for diagnosing, treating, and preventing these diseases, NIAID is expanding support for research on the causes, treatment, and prevention of allergic diseases; supporting national and international conferences to disseminate new knowledge; and fostering the development of clinical guidelines to promote a more cohesive approach to the diagnosis, prevention, and clinical management of anaphylaxis.

In August 2007, NIAID announced a new initiative “Exploratory Investigations in Food Allergy.” Co-sponsored with the Environmental Protection Agency, the Food Allergy and Anaphylaxis Network, and the Food Allergy Project, this initiative will support high impact, innovative research to identify the mechanisms underlying food allergy using human specimens or animal models of human food allergy. Research objectives in this initiative respond to several recommendations identified by the NIH Expert Panel on Food Allergy Research convened in March 2006. NIAID anticipates making awards in late fiscal year 2008.

The NIAID Laboratory of Allergic Diseases (LAD) supports basic, translational, and clinical research on anaphylaxis. Researchers in the LAD seek to better understand the various immune system components, such as mast cells, histamine, and immune cell receptors, that are involved in anaphylaxis; identify molecular-level events that precipitate and characterize anaphylactic reactions in order to understand their triggers; and discover diagnostic markers, or reveal targets for new chemotherapies.

In 2007, LAD investigators reported results from a study of patients with idiopathic anaphylaxis (IA), or anaphylaxis with unknown cause. These researchers, collaborating with the NIAID Biostatistics Research Branch and the NIH Clinical Center, found that a subset of patients with idiopathic anaphylaxis had a mutation in a molecule called KIT that is associated with mast cell activation. This mutation is commonly found in patients with mastocytosis, although the IA patients did not fit the major criteria for a diagnosis of mastocytosis. These findings provide a basis for the etiology of anaphylactic episodes in a significant subset of patients with idiopathic anaphylaxis and suggest that they may respond to inhibitors targeting mutated KIT.

The NIAID-supported Consortium of Food Allergy Research is conducting an observational study of the natural history of food allergy. When complete, this study is expected to provide new information about severe allergic reactions and anaphylaxis. In addition, the Consortium is conducting a clinical trial focused on severe food allergy in which increasing oral doses of egg are used to treat patients with severe egg allergies. The Immune Tolerance Network (ITN), is conducting a clinical trial related to severe allergic reactions and anaphylaxis. This study seeks to determine whether high doses of peanut early in life will prevent the development of peanut allergy in high-risk infants.

### **Senate Significant Items**

#### **Item**

#### ***Antiviral Drug Resistance***

One of the major challenges in implementing therapies for hepatitis B and hepatitis C is antiviral drug resistance. The Committee encourages the development of standardized terminology to describe this resistance, as well as studies of the mechanism of resistance and methods to overcome it. (p.127)

#### **Action taken or to be taken**

Please refer to page 125 of this document for the NIAID's response to this significant item regarding antiviral drug resistance.

Item

***Asthma***

The Committee urges the NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. (p.127)

Action taken or to be taken

Please refer to page 127 of this document for the NIAID's response to this significant item regarding asthma.

Item

***Atopic Dermatitis and Asthma/Allergic Diseases***

The Committee applauds the NIAID for focusing on atopic dermatitis [AD] as a risk factor for adverse reactions to the smallpox vaccine. However, the Committee believes that the NIAID should focus additional attention on the relationship between AD and asthma and other allergic diseases. Studies have confirmed that individuals with severe AD are more likely to develop particularly severe asthma and allergies. The Committee encourages the NIAID to coordinate with other Institutes on a multidisciplinary initiative to encourage investigator-initiated research projects on AD as it relates to the progression to asthma and other allergic diseases as well as changes in immune responses to allergen exposure in sensitized patients. (p.127)

Action taken or to be taken

NIAID remains committed to supporting research to better understand the relationship of atopic dermatitis (AD) to asthma and other allergic diseases, particularly food allergy. NIAID currently collaborates with other Institutes, agencies and organizations on research in this area. For example, NIAID collaborates with the National Heart, Lung and Blood Institute on the "Immune System Development and the Genesis of Asthma" initiative, which supports a grant to study the relationship of AD to asthma.

The Immune Tolerance Network, co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, is conducting two clinical trials related to food allergy and AD. These trials include studies of the immune mechanisms that may contribute to the progression of AD to asthma and other allergic diseases. The first clinical trial seeks to determine whether feeding a peanut-containing snack to young children at risk of developing peanut allergy will prevent development of this allergy. The study participants are children between 4 and 10 months of age with AD and/or allergy to egg. They will be followed until they reach 5 years of age. The second clinical trial is enrolling children between the ages of 18 and 30 months who have AD and who are at high risk for developing allergies. The aim of this study is to determine whether oral

administration of cat, grass, and house dust mite allergens will prevent the development of allergy to these and other allergens as well as the development of asthma.

In August 2007, NIAID announced a new initiative “Exploratory Investigations in Food Allergy.” One of the aims of this initiative is to encourage research proposals on the relationship of food allergy to AD and asthma. Co-sponsored with the Environmental Protection Agency, the Food Allergy Project, and the Food Allergy and Anaphylaxis Network, this initiative will support novel mechanistic studies in food allergy using human specimens or animal models of human food allergy. NIAID anticipates making awards through this initiative in fiscal year 2008.

The NIAID Inner-City Asthma Consortium is conducting the Urban Environment and Childhood Asthma (URECA) observational study, which will assess antibodies to milk, egg white, and peanut in infants at risk for developing allergic diseases, including asthma, allergic rhinitis, and AD. The study will determine if there is a correlation in these children between food allergies and the onset of asthma later in life.

A second NIAID-supported consortium, the Consortium of Food Allergy Research, is conducting an observational study of the development and loss of tolerance to foods in a cohort of 400 children, aged three to twelve months, at a high-risk of developing food allergies, including children with AD. The study will correlate biological markers and immunologic changes associated with the development of peanut allergy and the resolution of allergies to egg and cow’s milk, and evaluate genetic and environmental influences on these food allergies.

#### Item

##### ***Biocontainment Labs***

In 2003, the NIH awarded contracts for construction of two extramural National Biocontainment Laboratories for research on infectious agents and related countermeasures. These facilities are to open in 2008. The Committee encourages NIH to provide the Committee with its strategic plan for the continued operations of these facilities and for protection of the substantial Federal investment in them. (p.127)

#### Action taken or to be taken

NIH and NIAID are committed to an agenda of basic and translational research for biodefense. NIAID is the primary Institute at the NIH for emerging infectious disease research, including research aimed at developing new and improved medical tools against potential bioterrorism agents. Through the execution of its *Strategic Plan for Biodefense Research and Biodefense Research Agenda*,

NIAID continues to focus on basic research and its application to development of medical countermeasures. Biocontainment facilities are essential to achieving the goals outlined in these documents.

In FY 2003, NIAID awarded grants for the construction of two National Biocontainment Laboratories (NBLs) and nine Regional Biocontainment Laboratories (RBLs). The Institute awarded four additional grants for RBLs in FY 2005. While these laboratories are still in various phases of design and construction, NIAID has taken steps to protect this substantial Federal investment. Planning for the use and operation of these RBLs and NBLs was included as a term and condition for each of these construction awards. By accepting a facility construction award, each institution agreed that the facilities created with the Federal grant funds and required matching funds, must be used in support of the *NIAID Biodefense Research Agendas* or other NIAID-approved biomedical research activities for twenty years after initial occupancy unless prior written approval is obtained from NIAID. During that twenty-year period, the grantee must provide to NIAID program staff annual progress reports on the research conducted in these laboratories. These reports will be evaluated to ensure that the facility is being used for designated purposes. In addition, NIAID staff will conduct site visits to monitor facility operations and the scientific research operations. Further, the facility is required to be available and prepared to assist with national, state, and local public health efforts in the event of a bioterrorism or infectious disease emergency.

A critical component in ensuring the continued operation of these biocontainment facilities as they are completed is the development of a cadre of highly trained personnel both to conduct research and to operate these facilities. To this end, NIAID support for biosafety and biocontainment training has expanded as the NIH biodefense research program has grown. The National Biosafety and Biocontainment Training Program (NBBTP) is a partnership between NIAID and the NIH Division of Occupational Health and Safety and is managed by a not-for-profit education and research foundation. The program offers two-year post-baccalaureate and postdoctoral fellowships at NIH's campus in Bethesda, Maryland, comprised of both academic and hands-on training. The NBBTP also provides training for biocontainment laboratory operation and maintenance personnel across the country. In addition to this program, NIAID funds 28 Institutional Training Grants in Biodefense, and the Regional Centers of Excellence (RCEs) conduct extensive training in biosafety and biocontainment. For example, the RCE at Emory University in Atlanta constructed mock BSL-3 and BSL-4 laboratory suites specifically for training purposes.

#### Item

#### ***Drug Development for Type 1 Diabetes***

The NIAID, in collaboration with the NIDDK, is recognized for its successful renewal of the Immune Tolerance Network [ITN], which designs and conducts

clinical trials of new immune modulating therapies for type 1 diabetes and other diseases. The Committees encourages the NIAID to continue to explore opportunities for testing drugs that are already approved by the FDA for other indications for use as therapies for Type 1 diabetes. (p. 127)

#### Action taken or to be taken

NIAID remains deeply committed to supporting research to improve the treatment of type 1 diabetes. In fiscal year (FY) 2007, NIAID, along with the National Institute of Diabetes and Digestive and Kidney Diseases, renewed support for the Immune Tolerance Network (ITN) to evaluate novel, tolerance-induction strategies and their mechanisms of action in asthma and allergic diseases; prevention of rejection of transplanted organs, tissues, and cells; and autoimmune diseases such as type 1 diabetes.

Examples of recently completed ITN clinical studies on type 1 diabetes include two Phase I/II studies. The first is determining the safety and efficacy of anti-CD3 in new onset type 1 diabetes patients; the second is a pilot study to examine the safety of human insulin B-chain peptide immunotherapy. The ITN is currently enrolling patients in several clinical trials: a Phase II study of anti-CD3 antibody in new onset type 1 diabetes patients to assess the safety and effectiveness of two different dosing cycles; a Phase II study to assess thymoglobulin, a molecule that modulates the immune response, for safety and its effect on preserving islet beta-cell function in new onset type 1 diabetes patients; and a Phase I study of two drugs that modulate the immune response, interleukin-2 and rapamycin, in order to assess their safety and impact on islet beta-cells and immune function. Further, the ITN has a Phase II clinical trial in development that will analyze the safety and preliminary efficacy of human insulin B-chain peptide in subjects with type 1 diabetes; additional novel interventions are in earlier stages of development.

The Cooperative Study Group for Autoimmune Disease Prevention, in an effort to support a robust development pipeline, supports novel preclinical animal studies of immune-modulating therapies, such as anti-CD3 in combination with mucosal administration of insulin peptides. To support drug development that is further along the pipeline, the ITN, in partnership with the Juvenile Diabetes Research Foundation International, has developed a program to encourage academic and industry collaborations with the ITN to bridge early preclinical development to critical safety studies needed to sustain clinical development of immune tolerance-inducing treatments for Type 1 Diabetes.

#### Item

##### ***Food Allergy and Anaphylaxis***

The Committee is pleased that the NIAID plans to solicit grant applications for research on food allergy, and it urges the highest possible level of funding for this

initiative. The Committee believes that a similar, complementary effort should be undertaken with respect to anaphylaxis. A report of a second symposium on anaphylaxis co-sponsored by the NIAID highlighted a number of areas requiring additional research, including the identification of relevant biomarkers; improved understanding of the basic immunology and pathophysiology of anaphylaxis; and studies of the mechanisms that determine the severity of allergic reactions and the variability of organ system responses. The report also noted that the three-step treatment follow-up recommended for anaphylaxis is 'infrequently performed in North American emergency departments.' The Committee urges the NIAID to stimulate investigator-initiated research on anaphylaxis including clinical studies of ways to improve its diagnosis and prevention as well as emergency treatment. The Committee requests a report outlining these efforts in the fiscal year 2009 congressional budget justifications. (p.127-128)

#### Action taken or to be taken

NIAID is committed to reducing the burden of food allergy and food-allergy-induced anaphylaxis through the support of research in allergy and immunology.

For example, in fiscal year (FY) 2007, NIAID renewed support for the Immune Tolerance Network (ITN), which is conducting a clinical trial to determine whether high doses of peanut early in life will prevent the development of peanut allergy in high-risk infants.

NIAID also supports the Consortium of Food Allergy Research (CoFAR), which is conducting an observational study of the natural history of food allergy; this study is expected to provide new information about severe allergic reactions and anaphylaxis. In addition, the Consortium is conducting a clinical trial focused on severe food allergy, in which increasing oral doses of egg are used to treat patients with severe egg allergies.

The NIH Expert Panel on Food Allergy Research identified important areas for future research in this area, including research on severe food allergic reactions and food-induced anaphylaxis. In response to the panel's recommendations, NIAID recently announced a new initiative, "Exploratory Investigations in Food Allergy." This initiative, co-sponsored with the Environmental Protection Agency, the Food Allergy and Anaphylaxis Network, and the Food Allergy Project, will support high impact, innovative research to identify the mechanisms underlying food allergy using human specimens or animal models of human food allergy. It encourages studies of severe, life-threatening food allergy that leads to anaphylaxis. NIAID anticipates making awards in FY 2008.

Investigator-initiated research in allergic diseases, which includes activities ranging from basic research to clinical trials in food allergy, continues to be a priority for NIAID. For example, in FY 2007, NIAID, in collaboration with The Food Allergy Project, a patient advocacy and research funding organization, supported a new investigator-initiated research project. This project will evaluate

desensitizing regimens that use oral egg or oral peanut in young children with egg or peanut allergies.

A major goal of the recent expansion of NIAID-supported food allergy research, including the initiative “Exploratory Investigations in Food Allergy” and programs such as CoFAR, is to generate important new publications relevant to anaphylaxis. These publications will benefit the field in manifold ways, including providing investigators not currently in the field with the knowledge needed to design innovative programs to address basic and clinical anaphylaxis research from novel perspectives.

In addition to supporting research, NIAID has initiated efforts to coordinate development of *Guidelines for Diagnosis and Treatment of Food Allergy*, which will address the practice needs of multiple specialties including food allergy and food allergy-associated anaphylaxis. This effort will involve more than 20 professional societies, advocacy groups and NIH Institutes. Once the Guidelines are completed, NIAID will facilitate their dissemination through meetings and symposia.

#### Item

#### ***Hepatitis B***

The Committee encourages the NIAID to continue work in the area of therapeutic drug discovery for hepatitis B. (p. 128)

#### Action taken or to be taken

NIAID remains committed to therapeutic drug discovery for hepatitis B virus (HBV) infection. Through multiple public-private partnerships, NIAID maintains a drug development program that supports drug discovery and preclinical evaluation of therapies for HBV infection.

NIAID continues support of two in vitro screening contracts to evaluate preclinical candidate drugs for HBV and hepatitis C virus (HCV). Both contracts support studies that use human liver cancer cells to test HBV drugs. NIAID also supports contracts that utilize HBV animal models for the evaluation of therapeutic candidates. These contracts are working at full capacity on screening a variety of novel antiviral candidates, including small interfering RNA, therapeutic vaccines, toll-like receptor agonists, immunomodulators, and interferon inducers.

In addition to these drug development activities, in fiscal year (FY) 2009, NIAID plans to cosponsor, with the National Institute of Diabetes and Digestive and Kidney Diseases, the Management of Hepatitis B Consensus Development Conference. This conference aims to review the most recent developments regarding management and treatment options for hepatitis B and may inform future plans with regard to the evaluation of potential candidates for treatment.

Item

***Inflammatory Bowel Disease***

The Committee continues to encourage the NIAID to expand its research partnerships with the IBD community and increase funding for research focused on the immunology of IBD and the interaction of genetics and environmental factors in the development of the disease, particularly in pediatric populations. (p. 128)

Action taken or to be taken

NIAID is committed to research to understand and reduce the burden of inflammatory bowel disease (IBD). The Institute continues to initiate and support cross-disciplinary research, including studies that investigate the immunological, genetic, and environmental factors that contribute to IBD. Using basic research methods to define the immune and genetic mechanisms underlying IBD, NIAID seeks to translate this basic research into clinical trials of novel therapies for IBD.

In FY 2007, NIAID researchers received encouraging preliminary safety and efficacy results of an open-label trial of type 1 interferon for treatment of ulcerative colitis (UC). Based on these results, NIAID is collaborating with Biogen-Idec on a multicenter Phase II study using Avonex (interferon beta 1a) in UC. This study will provide an opportunity to conduct immune monitoring during therapy to identify factors predicting or underlying clinical response. Several studies are underway at the NIH Clinical Center that engage the IBD community. These include natural history studies of the immune regulation of Crohn's disease, UC, and undefined inflammatory conditions of the gut; and a pilot study of an oral interleukin-12/23 inhibitor to investigate immune responses in patients with Crohn's disease.

NIAID investigators have shown that patients with the same clinical disease presentation of IBD can have distinctly different responses to the same therapy, as reflected by measurement of the levels of various inflammatory proteins produced by cells in the gut mucosa. In order to discover novel susceptibility genes for IBD, these researchers are now testing IBD patients to determine whether genetic differences may be associated with particular immunologic presentations and responses to treatment. Such susceptibility genes could explain aberrant responses to environmental factors in IBD patients. In addition, NIAID researchers conducted experiments in mice with a gene mutation seen in Crohn's disease patients. They found that the presence of this mutation in mice can lead to disease susceptibility, thus advancing the understanding of the underlying genetic susceptibility to Crohn's disease.

NIAID supports the Cooperative Study Group for Autoimmune Disease Prevention, which conducts research on the development of new therapeutic

targets and approaches to prevent autoimmune diseases, including IBD, and co-sponsors the Autoimmunity Centers of Excellence to conduct collaborative basic and clinical research on multiple autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies.

NIAID will continue to support research on IBD through sponsorship of the Immune Tolerance Network, the Multiple Autoimmune Diseases Genetics Consortium, 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.

Item

***Liver Transplantation***

The Committee applauds the significant progress in developing successful techniques for liver transplantation, but notes that more work remains on improving the long-term quality of life of individuals who receive such transplants. The Committee urges additional research in this area, as well as research to improve patient and graft survival, and pre-transplant graft evaluation and preservation, with a particular focus on research to reduce and eventually eliminate a transplant recipient's dependence on immunosuppressive drugs. (p.128)

Action taken or to be taken

Please refer to page 129 of this document for the NIAID’s response to this significant item regarding liver transplantation.

Item

***Lupus***

The Committee urges the NIAID to expand and intensify genetic, clinical, and basic research on lupus, with particularly strong focus on gene-gene and gene-environmental interactions, epidemiological research, biomarkers, pediatric research, environmental factors, and factors related to the health disparities and co-morbidities associated with this disease. (p. 128)

Action taken or to be taken

NIAID maintains its commitment to supporting basic research on autoimmune diseases such as lupus. For example, NIAID scientists have developed a mouse model in which certain strains of these mice spontaneously develop a disease resembling lupus. Researchers are studying genetic factors that augment the susceptibility and severity of lupus in this mouse model to understand cellular mechanisms that cause autoimmune disease and identify new genes that can be used as therapeutic targets. Using this mouse model, NIAID scientists, in collaboration with the National Cancer Institute and the University of Texas Southwestern, sought to determine how a known genetic modifier increases

severity of systemic lupus erythematosus. The findings from this study demonstrated that minor genetic mutations, which commonly occur in both mice and humans, are important. This research provides new insight into the genetic basis of lupus and highlights an additional potential target for lupus therapies.

NIAID supports the Autoimmunity Centers of Excellence (ACEs), which conduct collaborative basic and clinical research on autoimmune diseases such as lupus. Currently, the ACEs support clinical trials and mechanistic studies of immunomodulatory therapies for lupus, including a completed Phase I/II clinical trial of anti-CD20 for treatment for lupus nephritis, the analysis of which is currently in progress; the development of a Phase I clinical trial of anti-TNF for treatment of lupus nephritis; and a preclinical study of DNase treatment that is currently in progress. NIAID anticipates the renewal of the ACEs in fiscal year (FY) 2009. In addition, NIAID supports the Autoimmune Disease Prevention Centers to conduct research on the development of new targets and approaches to prevent autoimmune diseases, including lupus. In FY 2007, NIAID renewed support for the Immune Tolerance Network (ITN), which is developing a Phase II trial of a treatment of lupus nephritis.

#### Item

#### ***Lymphatic Research and Lymphatic Diseases***

With a portfolio that includes chronic infections, immune-mediated diseases, transplantation, allergy, asthma and airway infections, the NIAID has a significant stake in advancing lymphatic research. The Committee urges the NIAID to work closely with the NHLBI to support research that addresses the immune functions of the lymphatic system and the role of immune mechanisms and inflammation in lymphatic diseases, with particular attention to the immunodeficient complications associated with congenital lymphatic malformations and lymphedema. (p. 128)

#### Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to supporting research on the lymphatic system and lymphatic diseases. Congenital lymphatic malformations can disrupt the normal functioning of the lymphatic system. NIAID's U.S. Immunodeficiency Network (USIDnet), a research consortium established to advance scientific research in the primary immunodeficiency diseases, is currently funding two studies of genetic conditions affecting the lymphatic system. These studies seek to elucidate molecular mechanisms underlying these diseases as well as to improve treatment for their consequences. NIAID is also supporting projects using animal models as tools to understand the causes of lymphoproliferative and other immune-mediated diseases.

Because of its role in immunity, the lymphatic system is sometimes vulnerable to infectious diseases. NIAID scientists are studying lymphatic filariasis, a parasitic disease which may provide insights that are relevant to lymphatic diseases in

general. This disease is caused by parasitic worms; a small percentage of infected persons progress to lymphedema and elephantiasis. NIAID scientists have developed a model to examine the interaction of the parasite with the body's lymphatic cells. Ongoing studies will characterize the mechanisms by which infection with the filarial parasites leads to lymphatic malformations.

The lymphatic system is also vulnerable to HIV infection. In individuals infected with HIV, the virus becomes latent in the lymphoid tissue, which serves as a persistent reservoir for the virus even in those who are on highly active antiretroviral therapy (HAART) and have no detectable virus in their blood. The NIAID research portfolio covers all aspects of this lymphoid infection, from the basic biology of the cells in the lymphoid tissue and their interaction with HIV, to explorations of the inflammatory response to HIV in lymphoid tissue, to examinations of whole sections of lymphoid tissue to explore HIV infection and latency in the tissue microenvironment.

NIAID is a member of the Trans-NIH Coordinating Committee for Lymphatic Research, which is led by NHLBI and includes representatives from NCI, NIDDK, NIAMS, NEI, and NINR. The Committee continues to develop research programs in lymphatic biology. In September 2007, the Committee convened a working group of experts representing a variety of disciplines to discuss future directions in lymphatic research. NIAID will continue to conduct and support lymphatic research and, where appropriate, will collaborate with other NIH Institutes and Centers in this important research area.

#### Item

##### ***Malaria***

The Committee urges the NIAID to allocate additional resources to support malaria vaccine development, drug development, diagnostics, vector control, infrastructure and research capability, and to strengthen components of the Implementation Plan for Global Research on Malaria. The Committee is concerned that reports of drug-resistant malaria and insecticide-resistant mosquitoes are on the rise. To that end, the Committee urges the NIAID to undertake additional research on the basic biology and ecology of mosquitoes, as well as work in genomics to develop new insecticides or render mosquitoes incapable of transmitting malaria. (p. 128-129)

#### Action taken or to be taken

Please refer to page 131 of this document for the NIAID's response to this significant item regarding malaria.

#### Item

##### ***Nontuberculous Mycobacteria (NTM)***

The Committee commends the NIH for its planning meetings regarding NTM and recommends further collaboration with the NIAID, the advocacy community, and

other Federal agencies to provide a better understanding of NTM, enhance diagnostic and treatment options and outcomes, and promote education of health care providers. The Committee also encourages the NHLBI to issue a program announcement or other appropriate mechanism to ensure the initiation of grant proposals. (p.129)

Action taken or to be taken

NIAID remains committed to supporting research collaborations that may lead to more effective, standardized approaches for preventing, treating, and controlling the respiratory infections that are caused by the group of microorganisms known as mycobacteria other than tuberculosis, including non-tuberculous mycobacteria (NTM), atypical mycobacteria, and environmental mycobacteria. For example, an intramural NIAID multi-year study to identify and characterize the clinical, microbiologic, immune, and genetic aspects of NTM infection is in final analysis, and a comprehensive epidemiological study of NTM disease is planned.

Currently, through an NIH inter-Institute collaboration between NIAID, the National Heart, Lung, and Blood Institute (NHLBI), and the NIH Critical Care Medicine Department, NIH researchers are conducting an investigation which examines the site of most NTM infections, the airway, including examination of ciliary function and nitric oxide generation, as well as the genetics of these conditions. This basic study of the mechanisms by which the airway defends itself against infection by NTM has been expanded by the creation and initiation of a large protocol to obtain bronchoscopic material from healthy and NTM-infected individuals. This work has been further enhanced by collaboration with and outreach to the local and national cystic fibrosis communities at both clinical and scientific levels.

In FY 2008, NIAID anticipates co-funding, with NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases, a scientific conference held in coordination with the National Jewish Medical and Research Center and the NTM Information and Research, Inc., a NTM advocacy group. The conference is expected to include discussions of predisposing risk factors and immunologic aspects of NTM disease, current therapeutic modalities, and new directions for drug development.

NIAID is currently funding a clinical trial planning grant to create an NTM Research Consortium (NTMRC) and to design a Phase II trial to re-assess the safety, tolerability, and efficacy of the standard three-drug treatment regimen for previously untreated patients with pulmonary *Mycobacterium avium* Complex (MAC) infection. The NTMRC will include clinical sites that currently care for many NTM patients, as well as microbiological reference laboratories

experienced in NTM culture and identification. The planning grant should allow researchers to finalize a clinical trial protocol and necessary study materials for the Phase II study.

#### Item

##### ***Parasitic Tropical Diseases***

The Committee urges the NIAID to continue research on the development of new vaccines, diagnostics, and safe, effective treatments for cholera, African trypanosomiasis (African Sleeping Sickness), American trypanosomiasis (Chagas disease), visceral leishmaniasis, Buruli ulcer, and other debilitating parasitic infections. (p. 129)

#### Action taken or to be taken

NIAID continues its commitment to conduct and support basic and translational research on tropical parasitic diseases such as African trypanosomiasis, Chagas diseases, leishmaniasis, and schistosomiasis, as well as other tropical diseases such as cholera and Buruli ulcer, with an important goal of developing vaccines, therapeutics, and diagnostics for these diseases. For example, in fiscal year 2007, NIAID-supported research generated genome sequences for several parasitic tropical diseases. This genomic information may help researchers identify new targets for development of vaccines and therapeutics.

In 2007, NIAID launched an innovative new program, *NIAID Partnerships with Public-Private Partnerships*, to support Public-Private Partnerships (PPPs) in the development of new drugs, vaccines, and diagnostics for high-priority neglected infectious tropical diseases of global importance. Through this initiative, NIAID awarded two cooperative agreements that focus specifically on the development of new drugs for leishmaniasis and African trypanosomiasis, respectively.

NIAID continues to support the Tropical Diseases Research Units program (TRDU). Initiated in 1980, the TRDU supports multi-project, multi-disciplinary research programs that support translational research, which may lead to the discovery and pre-clinical development of new drugs or vector control methods with the potential to reduce or eliminate morbidity and mortality associated with parasitic infections. For example, the research supported by this program has led to the preclinical development of the compound K777, a cysteine protease inhibitor, as a possible oral treatment for Chagas disease.

The Institute also continues its commitment to the Tropical Medicine Research Centers program, which supports international centers located in disease endemic areas to conduct research on major tropical diseases. In 2007, awards were made to centers in Brazil, Tunisia and India to study mucocutaneous, cutaneous and visceral leishmaniasis, respectively, and a center in Peru to study Chagas disease.

The NIAID intramural Laboratory of Parasitic Diseases (LPD) includes a clinical group that conducts patient-centered research at the NIH Clinical Center as well as international field studies in India, Latin America and Africa. Ongoing clinical studies led by LPD investigators include a study of the natural history of leishmanial infection and its treatments; a study to evaluate, treat and follow patients with Chagas disease, malaria, trypanosomiasis, and other parasitic infections; and an evaluation of a new drug treatment regimen of albendazole and diethylcarbamazine for lymphatic filariasis.

Item

***Primary Immunodeficiency Diseases***

NIAID is the lead agency for research into bone marrow transplantation [BMT], which can cure some primary immunodeficiencies. The Institute has made significant progress in reducing graft versus host disease (GVHD) and improving therapies when GVHD develops. With newborn screening of certain PI diseases being piloted in the States, the Committee urges the Institute to redouble its efforts to assure that identified patients have the best possible chance for survival. (p. 129)

Action taken or to be taken

Please refer to page 134 of this document for the NIAID's response to this significant item regarding primary immunodeficiency diseases.

Item

***Tuberculosis***

The Committee is extremely concerned about the spread of tuberculosis in the United States and around the world, and urges the NIAID to continue supporting research toward the development of improved medications; an effective, safe vaccine; and diagnostics. P.129

Action taken or to be taken

Please refer to page 128 of this document for the NIAID's response to this significant item regarding tuberculosis.

Item

***U.S. Immunodeficiency Network (USIDNet)***

The Committee recognizes the importance of the USIDNET research and training portfolio and urges the NIAID to increase support for the consortium. This unique program provides a mechanism to foster progress in this important and under-supported group of primary immunodeficiency diseases [PIDD] that historically have impacted clinical medicine far beyond their proportional representation in the population. The program supports research in this area by both new and established investigators with a goal of training the next generation of clinicians and scientists to take on the questions that can continue to benefit the greater population with suppressed immune systems. A DNA and cell repository and an

immunodeficiency patient registry have been established to further facilitate research in this area. The registry can provide a mechanism of improved communication with patients to assist recognition of new patterns of disease and long-term surveillance of the effect of therapeutics and live-agent vaccines in this patient group. (p. 129)

Action taken or to be taken

NIAID established the Primary Immunodeficiency Disease Research Consortium (USIDnet) in fiscal year (FY) 2003. Through this contract, a consortium of investigators from the primary immunodeficiency disease field was formed in order to: (1) solicit, evaluate, and fund innovative projects in primary immunodeficiency disease (PIDD) research; (2) educate, mentor and foster interest in PIDD research, especially among investigators starting their professional careers; (3) maintain, modify and improve the existing PIDD registry; and (4) develop a repository of cell lines from individuals with PIDD. Since its inception, USIDnet has awarded 29 research subcontracts; many of these projects are ongoing. A mark of the success of this program in fostering interest in this area of research is that several early subcontract holders have successfully obtained independent NIH funding for their work.

To build on the success of the USIDnet in developing a cadre of researchers in PIDD, NIAID, with the National Institute of Child Health and Human Development (NICHD) and the National Heart, Lung, and Blood Institute, is soliciting proposals for PIDD research through two funding opportunity announcements for Exploratory/Developmental Investigations on Primary Immunodeficiency Diseases. The projects supported through these announcements will supplement the portfolio of NIAID investigator-initiated research in PIDD, which includes two program projects, a demonstration project grant, and individual projects focused on resources, clinical protocol development, and innovative treatments. In addition to providing support for educational activities through USIDnet, NIAID, with co-sponsorship from NICHD and the NIH Office of Rare Diseases, supports conferences on PIDD through investigator-initiated grants.

In FY 2009, NIAID will re-compete the PIDD registry, repository, and educational components of the current USIDnet contract. To inform this re-competition, in FY 2008, NIAID is soliciting public comment on the USIDnet PIDD registry and repository.

# National Institute of General Medical Sciences

## House Significant Items

### Item

#### ***Training Programs***

The Committee continues to be pleased with the quality of NIGMS's 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. The Committee urges continued, long-term support of this program.

### Action taken or to be taken

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

In order to increase the enrollment of competitively trained underrepresented students in Ph.D. or MD/Ph.D. programs and prepare for research careers in the biomedical sciences, the MARC Branch focuses on undergraduate research training by supporting both institutional research training grants and grants for ancillary training activities. In FY 2007, the MARC institutional 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 that supports meetings, conferences, technical workshops and other training activities, the MARC Branch supports partnerships with professional societies, and other scientific and educational organizations. For example, MARC partners with such organizations as FASEB, SACNAS, ASM, ASCB, APS 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 the Ph.D. degree. In FY 2007, the RISE program supports the research development of

over 1055 underrepresented minority students, most of whom are undergraduates. 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.

In FY 2006, a working group of the National Advisory General Medical Sciences Council advised the Institute to rebalance its MORE portfolio to place greater emphasis on student development and training. In response, MORE program staff has begun to reorganize existing programs to comply with this recommendation. For example, the MBRS RISE program, the MARC U\*STAR program, the PREP program, and the two Bridges to the Future programs have been refocused to better achieve the anticipated outcomes and ensure that students at minority/minority serving institutions develop the knowledge and skills needed to move to the next stage of their academic path in pursuit of a research career.

### **Senate Significant Items**

#### Item

#### ***Behavioral Research***

The Committee continues to be concerned that the NIGMS does not support basic behavioral research. The Institute's statutory mandate includes basic behavioral research and training, and the Committee believes that the NIGMS has a scientific mandate in this area because of the clear relevance of fundamental behavioral factors to a variety of diseases and health conditions. To date, the NIGMS has not responded to this concern despite the recommendation of an NIH working group that called for the establishment of such a program, and similar recommendations from the National Academy of Sciences, the Institute of Medicine, and others. The Committee expects the NIGMS to support basic behavioral research and training.

#### Action taken or to be taken

NIGMS has initiated two behavioral programs recently. The first, "Collaborative Research for Molecular and Genetic Studies of Basic Behavior in Animal Models," is intended to facilitate research involving basic behavioral scientists and investigators with expertise in modern molecular biology and/or genomics. This new program supplements existing NIGMS support of behavioral research in the area of behavioral genetics.

The second, a new training program "Predoctoral Training at the Interface of the

Behavioral and Biomedical Sciences,” will support institutional training grants that provide new scientists with rigorous and broad training in behavioral, biological, and biomedical sciences. These new programs reflect the importance of integrating behavioral and biological approaches to advance fundamental understanding and yield new approaches to promoting human health and treating disease.

Basic behavioral research, like basic biomedical research, is supported throughout the NIH, both in disease- and stage-of-life-specific institutes and in the institutes and centers with more general missions. An analysis performed by the working group of the Advisory Committee to the Director, NIH, indicated that nearly \$1 billion in basic behavioral research is supported across NIH, including support within NIGMS. There is, and should be, basic behavioral research supported by each of the Institutes that relates to its mission. The NIH Office of Behavioral and Social Sciences Research (OBSSR) was established by Congress to stimulate research in behavioral and social sciences research throughout NIH and to integrate these areas of research across the NIH institutes and centers. Coordination across NIH is also enhanced by the establishment of the Division of Coordination, Portfolio Analysis, and Strategic Initiatives by the NIH Reform Act of 2006. NIGMS and the other institutes and centers are working with OBSSR and the new division to ensure that NIH supports a broad portfolio of basic behavioral research to further the broad NIH mission. This broad base of support provides a wide range of opportunities for behavioral scientists to find support for their research that is relevant to the NIH mission. In addition, basic behavioral research, just like basic biological and chemical research, that underpins the NIH mission at a deeper level, can find support at the National Science Foundation.}

#### Item

##### ***Training Programs***

The Committee continues to be pleased with the quality of NIGMS's 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. The Committee urges continued, long-term support of this program.

#### Action taken or to be taken

Please refer to page 152 of this document for the NIGMS response to this significant item.

# National Institute of Child Health and Human Development

## House Significant Items

### Item

#### ***Demographic research***

The Committee applauds NICHD for supporting demographic research. As a result of this support, important strides have been made in our understanding of family dynamics—especially how these factors influence marriage and the health and development of children. In addition, interdisciplinary demographic research has uncovered clues regarding the causes of health disparities across racial, ethnic, educational, and income groups. The Committee encourages NICHD to maintain its levels of investment in demographic training and infrastructure support and to support opportunities for interdisciplinary research into the complex environmental and biological mechanisms that produce health disparities. (p. 144)

### Action taken or to be taken

NICHD continues to provide support for critically important studies that provide information on the nation's families, including the Fragile Families Study, the Three-City study, the National Longitudinal Study of Adolescent Health, the National Longitudinal Surveys, and the National Survey of Family Growth. These studies, all of which represent partnerships with other NIH Institutes or federal agencies, are used extensively by scientists throughout the United States 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 National Longitudinal Study of Adolescent Health, funded by NICHD and 14 federal partners, combines biomedical with social science to investigate the processes through which health disparities emerge during the transition to adulthood.

During the past year, the NICHD undertook a review of its program of demographic research under the auspices of the National Advisory Child Health and Human Development Council. The review identified several areas of research that merited expanded attention in the future, including family formation and family processes; immigration and population movement within the United States, and various aspects of health, including population health monitoring, interdisciplinary studies that trace the biological pathways along with social and economic influences that affect health, and the consequences of health and disease for individual and societal productivity. NICHD is currently engaging in several activities that begin this process. A new study will examine health disparities in pregnancy outcomes and child health in partnership with five U.S. communities; another will examine the impact of employer workplace policy

interventions on improving the health of families and children. A collaborative effort within the Institute is exploring the complex environmental and family influences that have contributed to the epidemic of childhood obesity, and the potential for new methods of modeling these influences to cultivate intervention strategies.

NICHD recognizes the need to continue to support infrastructure and training in support of demographic research. In the recent review, the Institute's Population Research Infrastructure Program was found to be highly successful in stimulating interdisciplinary and innovative research. Investments are leveraged to multiply the impact of the resources invested by the Institute in the program. These investments are critically important given the increased need for interdisciplinary teams to tackle complex problems in population health. Similarly, interdisciplinary training remains an urgent need and NICHD has developed innovative and cost-effective mechanisms, including short-term training courses to address expanded training needs.

Item

***Pulmonary rehabilitation***

Pulmonary rehabilitation has been increasingly recognized as an important treatment option for the many patients with disabling chronic lung diseases, like chronic obstructive pulmonary disease (COPD). The Committee encourages the National Center for Medical Rehabilitation Research (NCMRR) to expand research opportunities in this area. (p. 144)

Action taken or to be taken

The NCMRR, a center within the NICHD, supports a broad range of basic and applied research to improve the daily functioning of people with disabilities. NCMRR encourages investigators who are submitting applications seeking funding for research in this area to also designate the NICHD along with NHLBI on the application. NICHD actively seeks out opportunities to co-fund such applications.

Item

***Newborn screening***

Screening is used for early identification of infants affected by certain genetic, metabolic, hormonal or functional conditions for which there are effective treatment or intervention. Screening detects disorders in newborns which, if left untreated, can cause death, disability, mental retardation and other serious illnesses. The Committee encourages NICHD to continue to prioritize fragile X as a key prototype in the development of cost effective newborn screening programs. (p. 144)

Action taken or to be taken

The NICHD is the lead NIH institute in funding of research in the area Fragile X

syndrome (FX) and its portfolio has grown to include the associated disorders of Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) and Premature Ovarian Failure (POF) related to Fragile X permutation (explain permutation). Development of effective, affordable newborn and carrier screening tests for Fragile X is a high priority for the NICHD Newborn Screening Initiative. Grants are presently being funded to develop the needed screening test and to pilot test its application before universal implementation begins.

The NICHD Newborn Screening Research Initiative is an effort that seeks to apply, through newborn screening, the rapidly accumulating information about the genetic basis of disease to the prevention of the serious effects these diseases create. Such an effort requires tests be developed for a vast array of abnormalities on small and easily collected samples. The ability to identify large numbers of conditions in the newborn period has the potential to significantly reduce the burden of the increasing numbers of treatable diseases, as well as to inform families of the nature of the conditions identified. Currently, there is no technology available for clinical use that permits such screening. Therefore, the primary goal of NICHD's research program is to identify and test suitable new technologies that will permit such a considerable expansion in the number of diseases for which screening is routinely done. NICHD is currently supporting several grants and contracts whose focus is the development and pilot testing of new newborn screening technologies.

Recognizing that screening for potential carriers of genetic diseases is complementary to the development of improved newborn screening, NICHD is organizing and co-sponsoring a conference entitled "Carrier Screening: Lessons learned, advancing technologies, and new opportunities," in cooperation with the National Human Genome Research Institute. This February 2008 conference's intent is to engender discussion of the potential opportunities to improve health through carrier screening for genetic disorders. Participants in the meeting will be asked to consider issues such as the timing of the screening, the best criteria to use, what screening technology or treatments may soon be available, and what issues, ethical, legal and social, need to be addressed.

#### Item

##### ***Premature ovarian failure (POF)***

The Committee supports further research efforts focused on collecting DNA and other genetic information from women who possess a mutation of the FMR1 gene as well as women who have POF. To accomplish this goal, the Committee encourages 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. Additionally, NICHD is encouraged to take steps to develop a comprehensive research strategy on POF as it relates to the FMR1 gene. (p. 144)

#### Action taken or to be taken

Premature ovarian failure (POF) is the onset of menopause before the age of 40. The Reproductive Sciences Branch (RSB) of the NICHD issued a Program Announcement (PA) in 2007 entitled *Fragile X Pre-Mutation and Ovarian Function*, which encourages basic, clinical or translational research on the effects of the Fragile X pre-mutation on ovarian function, with a focus on premature ovarian failure or early menopause. It is envisioned that studies supported through this PA will provide critical insights into the underlying mechanisms by which the FMR1 pre-mutation causes POF, and, in so doing, increase our understanding of the causes of POF and ovarian function in general. The RSB also solicits applications for centers addressing human reproductive diseases and disorders, including Fragile X-associated POF, through the Specialized Cooperative Centers Program in Reproduction and Infertility Research.

The NICHD recently established a trans-NIH coordinating group on Fragile X to develop an interdisciplinary research plan that will include studies on POF related to the FMR1 pre-mutation. In addition, the Reproductive Biology and Medicine Branch of the NICHD Intramural Program has an ongoing effort to collect DNA samples from women with POF. This collection will continue to grow through collaborations with NIH extramural investigators and can provide a resource for future research on the role of the FMR1 pre-mutation in POF.

#### Item

##### ***Traumatic brain injury (TBI)***

Congress is pleased with the work being done on TBI translational science research and rehabilitation at the NCMRR and encourages NCMRR to continue such work; especially the cooperative multi-center traumatic brain injury clinical trials network. (p. 145)

#### Action taken or to be taken

During the past 2 decades, understanding of the pathophysiology of traumatic brain injury (TBI) has increased dramatically. For instance, clinicians now recognize that not all neurologic damage occurs at the moment of injury, but rather that it evolves over time. Despite these advances, researchers have much to learn about the underlying deficits associated with TBI and the links among acute care, rehabilitation, and long-term patient outcomes. The NCMRR at the NICHD established a multi-center network of sites that has been working together to design clinical intervention protocols and measures of outcomes for TBI. Through rigorous patient evaluation, using common protocols and interventions designed for multiple points of care – including the accident scene, emergency room, intensive care unit, rehabilitation and long-term care follow-up – the NCMRR TBI Clinical Trials Network can study the required numbers of patients to provide answers to research questions more rapidly than individual centers acting alone. The Network is actively recruiting patients into the first

randomized clinical trial. At the same time, NCMRR staff is closely working in collaboration with other NIH Institutes and Centers, and other federal agencies, to discuss more cost-effective and efficient strategies for advancing our clinical knowledge regarding TBI. The NCMRR plans to issue a request for applications in FY 2009 which will solicit applications to develop the pre-clinical data necessary to launch a new approach to clinical trials in TBI.

Item

***Spinal muscular atrophy (SMA)***

The Committee encourages NICHD to support specific basic, translational, and clinical research initiatives on SMA. The Committee also encourages NICHD to coordinate funding with NINDS to ensure increased participation of investigators in SMA and developmental neurobiology relevant to SMA and to establish a cross-institute working group comprised of NICHD, NINDS, and NIGMS. (p. 145)

Action taken or to be taken

In FY 2007, NICHD committed nearly \$4 million in total award amounts to four new grants for research on SMA. This is in addition to over \$5 million already committed to SMA-related research in prior years. NICHD has also provided research infrastructure support for two SMA research projects through our Mental Retardation and Developmental Disabilities Research Centers (MRDDRC). These funding supplements have already assisted one investigator to compete successfully for two new grants in FY 2007, suggesting that NICHD investments are supporting new research in anticipation of future translational and clinical initiatives in SMA.

Currently, NICHD is supporting research to develop a newborn screening test for SMA, the most promising of which will be used for a pilot population study. Additionally, NICHD is developing a newborn screening translational research network that is intended to validate screening technologies and therapeutic interventions for rare diseases, such as SMA.

NICHD staff are actively participating with NINDS and other NIH Institutes and Centers in scientific meetings and conferences relating to SMA research. NICHD's Director and other Institute staff participated in the SMA Summit on Drug Development Logistics in September 2007. Earlier, in July 2007, NICHD organized a meeting and supported the travel of three SMA investigators to discuss potential collaborative international research opportunities. This initial meeting facilitated sharing of research findings and planning potential collaborative opportunities.

NICHD is currently co-organizing a conference entitled "Carrier Screening: Lessons learned, advancing technologies, and new opportunities" with the National Human Genome Research Institute. The February 2008 conference's intent is to engender discussion of the potential opportunities to improve health

through carrier screening for genetic disorders. This meeting seeks to determine feasibility and address issues surrounding the development of a SMA carrier screening research program. Discussion items include when to screen, criteria to use for screening, what screening technology and treatment is available and what ethical, legal and social issues need to be addressed (i.e. informed consent, family planning, access to healthcare).

Item

***Liver wellness in children***

The National Children's Study (NCS) provides a unique opportunity to study the prevalence of obesity related chronic liver disease, also known as fatty liver, from birth to early adulthood. The Committee understands that fatty liver is the most common liver abnormality in children age 2 to 19 years old, and disproportionately affects Hispanic-Americans. The Committee encourages NICHD to analyze the prevalence of fatty liver under the NCS to better understand obesity-related chronic illnesses in children and to work with other agencies in the screening and prevention of these diseases. (p. 145)

Action taken or to be taken

Consistent with the FY 2007 and 2008 President's Budgets, this budget does not continue the National Children's Study (NCS) in FY 2009. The FY 2009 President's budget requests no funds to implement or continue planning for the proposed National Children's Study.

The NICHD supports liver disease research that identifies the basic mechanisms and processes that lead to healthy liver development, as well as how liver disorders affect fetal growth and newborn complications such as necrotizing enterocolitis. The Institute is also supporting a study to better understand the physiology of glucose and lipid metabolism in overweight adolescents, which includes Hispanic-Americans. Researchers are measuring insulin sensitivity, gluconeogenesis (how the body generates glucose from sources other than glycogen), and fat content in muscle and liver. The findings will help fill the knowledge gap so that researchers can define strategies to prevent insulin resistance and impaired glucose metabolism during adolescence—a stage of life where many physiological changes are already taking place.

Item

***Primary immunodeficiency (PI) diseases***

The Committee continues to be impressed with the dedication of financial and personnel resources by NICHD to physician education and public awareness programs to reach early diagnosis of this class of 140 diseases. In addition, the Institute's focus on newborn screening research is critical as States begin to implement pilot newborn screening programs for severe combined

immunodeficiency disease (SCID), one of the most severe forms of PI. NICHD is urged to coordinate its efforts with CDC and the States in this critical implementation period. (p. 145)

#### Action taken or to be taken

Primary Immunodeficiency diseases (PI) result from inherited defects in the immune system. While individual primary immunodeficiency diseases are rare, as a group they may affect 1-2% of the population with symptoms ranging from mild to life threatening, such as in Severe Combined Immunodeficiency [SCID].

The NICHD has a long-standing interest in newborn screening and in expanding the number of conditions that can be screened for at birth, including SCID. The NIH has issued a number of funding announcements, including a program announcement, "Innovative Therapies and Clinical Studies for Screenable Disorders," which supports research on the development of therapeutic interventions for screenable conditions and a request for proposals to support the development of new screening technologies for use in newborn screening. The NICHD has also developed a Request for Proposals (RFP) to award one or more research contracts in FY 2008 for a "Newborn Screening Translational Research Network," which, by connecting and coordinating state newborn screening programs, can enhance the research agenda of NICHD and other Institutes and federal agencies by producing findings that are immediately relevant to newborn screening programs. This network will be able to draw on the experience and insight of practicing laboratorians and geneticists to help identify and frame research questions. Moreover, because this network can use the existing personnel and infrastructure of established newborn screening laboratories and clinics, certain types of studies can be conducted in a more cost-effective manner. The NICHD is taking a leadership role in developing and implementing an integrated national program for newborn screening by organizing and participating in a number of national forums, and NICHD staff members were instrumental in co-authoring an article entitled "Population-Based Newborn Screening for Severe Combined Immunodeficiency: Steps Towards Implementation."

NICHD continues to sponsor research to identify the genetic basis of PI since this knowledge is important in helping to understand the underlying causes of these conditions. For several years, the NICHD has partnered with the NIAID to fund the US Immunodeficiency Network (USIDNet), to support research on the underlying causes of these conditions. NICHD and NIAID are partnering to sponsor funding opportunities to support innovative exploratory and developmental investigations for detecting, identifying the molecular basis of, or developing innovative therapies for these devastating conditions.

### Item

***Pre-term births*** – A recent national study showed that the rate of pre-term births among first pregnancies has increased 50 percent over the past decade. The data also revealed that women in their first pregnancy are at highest risk for developing preeclampsia, which puts them at risk for devastating maternal complications and fetal death. In addition, the study also showed a racial disparity with black women at a two-fold higher risk than white women. The Committee understands that the prediction and prevention of these first pregnancy complications is problematic and that there is a shortage of research on the etiology and prevention interventions for this cohort of women. The Committee requests that NICHD conduct research on women in their first pregnancy in order to fill the gap in knowledge for the prevention of these complications. (p. 146)

### Action taken or to be taken

NICHD has identified adverse pregnancy outcomes in nulliparous women (women for whom this is a first pregnancy) as an important area requiring further research. An initiative targeted at this population is currently under consideration in FY 2009. 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, there is a racial disparity in risk for all these adverse outcomes.

Building on three ongoing NICHD-supported studies, this initiative plans to study approximately 20,000 nulliparous women with singleton gestations who will be randomized into routine care or intensive research assessments during the course of their pregnancies. To examine the role of genetic and environmental exposures, biological samples will be obtained in each trimester and at delivery. The initiative includes the following aims: (1) Determining specific aspects of the mother's genetics, epigenetics, physiological response to pregnancy, and environmental exposures that influence and/or predict poor outcome; (2) Identifying specific aspects of placental development and function that lead to preterm delivery; (3) Determining the interaction of genetic, growth, and developmental parameters of the fetus that are associated with and predict preterm delivery; (4) Validating the association of particular single nucleotide polymorphisms (SNPs) with preterm birth; (5) Determining and validating biomarkers in maternal serum that are predictive of spontaneous preterm birth and preeclampsia (a major cause of preterm birth); and (6) Determining whether assessments that improve detection of fetal growth restriction as well as increased fetal surveillance during pregnancy provide useful information to reduce the incidence of preterm delivery, stillbirth, neonatal morbidity and mortality.

This study will identify predictive markers in this unstudied population at high risk for adverse pregnancy outcomes and the results may allow clinicians to intercede before preterm birth, preeclampsia and stillbirth take a personal and economic toll.

Item

***Assisted reproductive technology (ART)***

The Committee encourages NICHD to support an initiative for a multi-site cohort study on ART that would emphasize pregnancy outcomes, and short and long term effects on children to determine if the adverse outcomes are specifically related to ART procedures. (p. 146)

Action taken or to be taken

Currently, there are over 50,000 births per year that result from the use of assisted reproductive technology (ART) in the United States. While the majority of ART pregnancies and the offspring born from these pregnancies are considered normal, emerging evidence reflects that ART pregnancies may be associated with a significantly higher risk of pregnancy complications such as perinatal death, preterm delivery, low birth weight, preeclampsia and gestational diabetes, and that the offspring may be at increased risk for birth defects.

Over the past decade, the NICHD, in collaboration with other Federal agencies, has sponsored several workshops and conferences addressing ART and its associated outcomes on maternal, infant and child health. As a result of recommendations made during these meetings and input received from NICHD-convened advisory panels, several activities addressing ART outcomes are ongoing or planned. These include: 1) an ongoing population-based prospective cohort study supported by NICHD to assess the possible effect(s) of infertility treatment (including, but not limited to ART) on children's physical growth patterns, health, and neuro-developmental status from birth through three years of age; 2) an ongoing program on Female Health and Egg Quality that in part addresses the effects of ART procedures on the health of offspring using animal models; 3) plans to publish a program announcement entitled "Adverse Outcomes of Assisted Reproductive Technologies" in fiscal year 2008; and 4) plans to perform a multi-site cohort study to investigate potential genetic and epigenetic mechanisms responsible for adverse maternal, fetal, infant and childhood ART outcomes. Investigator-initiated applications will be sought that propose basic, translational and clinical research to address the adverse consequences of ART on maternal health, pregnancy outcomes, and the overall health (biological, psychological) and development (reproductive, cognitive, language, behavioral and educational) of children whose conceptions were aided by ART. The aforementioned solicitation will also encompass demographic, behavioral and social sciences research on fertility, infertility and families, as related to long-term outcomes of ARTs.

Item

**Stillbirth**

The Committee applauds NICHD's efforts in addressing stillbirth, a major public health issue with morbidity equal to that of all infant deaths. The Committee understands that the NICHD cooperative network has an ongoing study using a standard protocol at five clinical sites and encourages NICHD to continue supporting this effort. (p. 146)

Action taken or to be taken

The NICHD's Stillbirth Collaborative Research Network (SCRN) includes five clinical centers (Brown University, University of Texas at Galveston, University of Texas at San Antonio, Emory University, and the University of Utah) and a data center (Research Triangle Institute, North Carolina). This Network is engaged in a study that will obtain a geographic, population-based determination of the incidence of stillbirth defined as fetal death at 20 weeks gestation or greater; determine the causes of stillbirth using a standard stillbirth postmortem protocol (to include a review of clinical history, protocol for autopsies and pathologic examinations of the fetus and placenta, as well as conduct other postmortem tests to illuminate the genetic, maternal, and other environmental influences that may be risk factors for stillbirth). The main study protocol has been approved by the appropriate Institutional Review Boards and all sites (including over 50 hospitals) are now recruiting and enrolling. SCRN is now working on plans for the data analysis, which will begin in the fall of 2008.

The SCRN study provides an opportunity to diagnose and classify a large number of stillbirths with extensive information on each case to compare with live born infants. The NICHD convened a workshop in October 2007 entitled "Stillbirth Classification System: developing an international consensus for research," co-sponsored by the Society for Maternal- Fetal Medicine, First Candle and the Office of Rare Diseases, National Institutes of Health. As more research into the causes of stillbirth is being conducted internationally, an internationally agreed upon classification system is urgently required for the comparison of results of these various research studies to guide the development of therapeutic and preventive strategies to reduce stillbirths.

Item

**Vulvodynia** – As a result of efforts funded by the NICHD, the number of highly qualified scientists interested in researching vulvodynia has greatly increased. The Committee commends NICHD for reissuing its program announcement in this area and suggests that a request for applications be considered. The Committee encourages NICHD to strengthen its support of vulvodynia studies in 2006, with a particular emphasis on etiology and multicenter therapeutic trials. (p. 146)

### Action taken or to be taken

Vulvodynia remains one of the poorly understood complex chronic pain syndromes, a clinical condition of unexplained vulvar pain and sexual dysfunction. While the true prevalence remains unknown, several million women in the United States are estimated to have vulvodynia. A combination of therapies is frequently utilized and, although several treatment options are available, most of the literature supports the conclusion that cures for vulvodynia are uncommon and a specific inciting cause can only be diagnosed in a relatively small percentage of patients. Consideration of these factors must be an integral part of the management of patients with vulvodynia and underscoring the need to examine this condition in a multidisciplinary context.

NICHD continues to participate in ongoing efforts to stimulate research on vulvodynia, particularly with the reissuance of its long-standing Program Announcement (PA) in fiscal year 2007 entitled *Vulvodynia – Systematic Epidemiologic, Etiologic or Therapeutic Studies*. The goal of the PA is to allow NICHD, in partnership with the Office of Research on Women's Health at the NIH, to expand its research base in basic, translational and clinical studies on vulvodynia by attracting applications in this under researched area, building a substantive scientific knowledge base related to this debilitating condition.

In an expanded effort to specifically address unexplored research questions about vulvodynia, NICHD recently partnered with NIDDK, NINDS and ORWH on a new initiative entitled *Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network* that will explore vulvodynia as a related pain condition with similarities to urologic chronic pelvic pain syndromes. Despite intense study, the underlying etiology and patho-physiology of this condition, as well as risk factors for development of the disease remain unclear, and there exists no effective clinical therapeutics for patients with urologic chronic pelvic pain syndromes. Both the PA and MAPP initiatives represent a continuation of ongoing efforts aimed at reducing the burden of chronic pain syndromes and improving the quality of life for women affected with these disorders.

In addition, to further educational outreach efforts for women with this condition and their health care providers, NICHD has partnered with ORWH, other NIH Institutes and Centers, the American College of Obstetricians and Gynecologists, the National Vulvodynia Association, and other organizations to implement a national educational program for health care professionals, patients and the general public on the symptoms, diagnosis and treatment options for vulvodynia. The Vulvodynia Awareness Campaign was presented to relevant professional societies and the public in October 2007.

### Item

**Pre-term birth** – The Committee encourages NICHD to strengthen research on the underlying causes of pre-term delivery and the development of treatments for the prevention of premature birth. Furthermore, the Committee is aware that a 2006 Institute of Medicine report found that a multidisciplinary research approach is needed to better understand premature birth, and therefore encourages NIH to use this strategy to fund research on pre-term birth. (p. 146)

Action taken or to be taken

The NICHD supports research on predicting and preventing preterm birth through investigator-initiated grants and networks such as the Maternal Fetal Medicine Units (MFMU) Network for clinical trials and the Genomic and Proteomic Network on Premature Birth Research. Ongoing trials in the MFMU Network, which comprises 14 sites across the U.S. and a data center, include several trials specifically related to preterm birth prevention and management including the BEAM trial (Beneficial Effects of Antenatal Magnesium Sulfate), a clinical trial to determine if a sulfate compound administered antenatally can reduce the risk of cerebral palsy in offspring in women at 24 - 31 weeks gestation with preterm or planned delivery. This trial has completed enrollment and is finishing the two year follow-up of the infants. Still another clinical trial is underway to determine whether 17 alpha hydroxyprogesterone prevents preterm birth in multi-fetal pregnancies (twins and triplets). The results of the twin data were recently published in the *New England Journal of Medicine*. NICHD is also supporting a follow-up study to determine whether there is a difference in the achievement of developmental milestones and physical health between children exposed to progesterone and those exposed to placebo. In addition, a clinical trial is being conducted in the network to determine whether Omega-3 fatty acids, in conjunction with 17 alpha hydroxyprogesterone, reduce the risk of preterm delivery in women at high risk. Enrollment is complete with the results presented at the January 2008 Society of Maternal Fetal Medicine meeting.

The NICHD's Genomic and Proteomic Network for Premature Birth Research aims to accelerate the pace of premature birth research by focusing on global genomic and proteomic strategies and the dissemination of genomic and proteomic data to the scientific community through: 1) the design and implementation of hypothesis-driven, mechanistic studies based on large-scale, high-output genomic and proteomic approaches, and; 2) the providing of a public, web-based, genomic and proteomic database for data mining and data deposition by the research community. The research focus of the network is to identify new biomarkers that increase the risk or are predictive of a preterm delivery and to delineate molecular mechanisms responsible for a preterm birth. Recruitment for three studies started in August 2007 and each of the studies is expected to be completed in 2010. Ultimately, this research could some day lead to relatively simple screening tests to identify pregnant women (or possibly even women contemplating pregnancy) at risk of a preterm birth and provide them with interventions enabling them to carry a pregnancy to term.

Item

***Mental Retardation/Developmental Disabilities Research Centers***

***(MRDDRC)*** – The Committee is particularly pleased with the MRDDRC contributions in the areas of autism, fragile X syndrome, Down syndrome and other genetic and environmentally induced disorders. These centers have greatly improved our understanding of the causes of developmental disabilities. However, the Committee is concerned that the centers have not been given sufficient resources to sustain the progress made in this critical area, even though they received outstanding scientific evaluations. The Committee urges NICHD to provide additional resources to the MRDDRCs so that they can conduct translational research to develop effective prevention and intervention strategies for children and adults with developmental disabilities. (p. 146/147)

Action taken or to be taken

NICHD funds the Mental Retardation/Developmental Disabilities Research Centers (MRDDRC) to provide infrastructure to investigators conducting MRDD-related research. The MRDD field is moving toward translational and clinical research that takes advantage of current knowledge of biology underlying MRDD. NICHD facilitates this renewal process by conducting open, rigorous, annual competition for continuing or new centers. The last four solicitations for applications have strongly encouraged applicants to propose infrastructure necessary for conduct of translational research towards both prevention and treatment.

In addition, NICHD has encouraged the successful centers to catalyze submission of new research applications that will further translational research. One step towards this goal is the formation of a consortium of three mid-Atlantic centers (at children's hospitals in Philadelphia and Washington DC and the Kennedy Krieger Institute in Baltimore), encouraging them to work together towards creating a national infrastructure for clinical MRDD research. For example, an effort to integrate patient registries across centers is underway, which will maximize the amount of data available on patients seen in all of the centers. Working with MRDDRC directors and their colleagues, NICHD is making significant progress towards increasing translational and clinical research to develop effective prevention and intervention strategies for children and adults with developmental disabilities.

**Senate Significant Items**

Item

***Adverse Pregnancy Outcome*** – A recent national study showed that the rate of pre-term births among first pregnancies has increased 50 percent over the past decade; women in their first pregnancy are at highest risk for developing

preeclampsia; and black women have a two-fold higher risk of these problems than white women. The Committee requests that the NICHD launch an intensive research study of first pregnancy women in order to fill the major gap in the research on the etiology, mechanisms and prevention of these complications. The Committee also urges the NICHD to investigate the rates of adverse pregnancy outcomes in pregnancies associated with assisted reproductive technology [ART]. The Committee urges the NICHD to support a multi-center cohort study on ART that would emphasize pregnancy outcomes, and short-and long-term effects on children, to determine if the adverse outcomes are specifically related to ART procedures versus underlying factors within the couple. (p. 163)

Action taken or to be taken

Please refer to page 163 of this document for the NICHD response to this significant item.

Item

**Demographic Research** – The Committee applauds the NICHD for its strong support of demographic research, which has resulted in a greater understanding of such topics as family dynamics and immigration. The NICHD is encouraged to provide additional resources on research that addresses the future of America's families, including the forces affecting birth rates and family investments in children. The Institute should also actively support opportunities for interdisciplinary research into the complex socioeconomic and biological mechanisms that produce health disparities within our population. To ensure the continued vitality of this program, the Committee urges the NICHD to maintain its levels of investment in demographic training and infrastructure support. (p. 131)

Action taken or to be taken

Please refer to page 155 of this document for the NICHD response to this significant item.

Item

**Dietary Intervention to Prevent Juvenile Diabetes** – The Committee applauds the NICHD for its oversight of the Trial to Reduce IDDM in the Genetically at Risk [TRIGR] study, which is testing whether substitution of hydrolyzed cow's milk in an infant's diet can reduce the rate of type 1 diabetes in children. The Committee urges the NICHD to continue its strong support of TRIGR to follow the study participants over the next 10 years. (p. 131)

Action taken or to be taken

The Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR), funded by NICHD, is now in its seventh year of operation at 26 sites in the United States of America, Australia, and Canada, and at 51 sites in 12 European countries. TRIGR operates under the surveillance of an

independent Data Safety Monitoring Board located in Denmark.

TRIGR is currently the only ongoing clinical trial in the world that is designed to find out if type 1 (juvenile) diabetes can be prevented by a dietary intervention in infancy. The goal of the trial is to ascertain if exposure to a hydrolyzed cow-milk-based formula (Nutramigen) instead of to an unhydrolyzed cow-milk-based formula prevents or delays the onset of diabetes. The rationale for the intervention is that cow milk proteins appear to be involved in stimulating the intestinal immune system to trigger the onset of type 1 diabetes in infants at high genetic risk. The formulas were introduced to the infants on a random basis after the babies are weaned from the breast. The intervention phase of the trial was completed in August 2007. The full TRIGR trial will end in 2016. The children who are enrolled now will continue to be examined semi-annually over the next nine years. These serial examinations are necessary in order to ascertain the incidence of diabetes during the first decade of life in children who were randomly assigned to Nutramigen or to a cow-milk based control formula in infancy and also to detect the first appearance of auto-antibodies directed against insulin and other pancreatic proteins in the two groups of children.

The NICHD and the Canadian Institutes for Health Research (CIHR) have pledged support through TRIGR Year 10 and will encourage grant renewal applications for continued support in years 11-16. If the intervention succeeds, a serious disease facing many of our young people could be ameliorated or eliminated.

#### Item

**Down Syndrome** – The Committee commends the NICHD on earlier efforts to supply mouse models of Down syndrome for the research community. It now encourages the NICHD to partner with the NINDS and other agencies to define additional mouse models needed to link important structural and functional abnormalities that underlie cognitive difficulties to the actions of specific genes and gene pathways. The Committee urges the NICHD to take a leadership role in providing a robust research portfolio that addresses the problems that affect children with Down syndrome and to work collaboratively with other Institutes to carry out this mission. (p. 131)

#### Action taken or to be taken

In 2006, the Director, NIH, designated the NICHD as the lead NIH Institute to organize and convene the trans-NIH Down Syndrome Working Group. This working group is composed of program officers at the many Institutes and Centers within NIH that support aspects of research on Down syndrome, and others with portfolios of research directly relevant to Down syndrome. After several meetings and a review of currently funded NIH research, the working group met with interested members of organizations that represent individuals with Down syndrome and their families, and non-NIH researchers, presenting

them with an overview of ongoing research efforts, and to obtain their input on future directions. To gain further information on ideas for expanded directions for the NIH, the working group, led by NICHD, convened a meeting in July 2007 of experts in Down syndrome, including researchers from a wide variety of fields, clinicians, advocates, parents and other relevant federal agencies. In addition to recommendations made at that meeting, the working group also evaluated the recommendations from three earlier expert workshops, two international meetings on Chromosome 21, and a meeting on cognitive function in Down syndrome. The working group has synthesized the ideas culled from these many sources, and formulated a draft plan for Down syndrome research that contains short, intermediate and long-term research objectives to guide NIH investment on Down syndrome over the next 10 years. This plan was made available for public comment and is being revised, incorporating suggestions made by the over 150 comments received. The plan is available at [http://www.nichd.nih.gov/publications/pubs/upload/NIH\\_Downsyntaxe\\_plan.pdf](http://www.nichd.nih.gov/publications/pubs/upload/NIH_Downsyntaxe_plan.pdf)

To carry out the earliest goals of the plan, NICHD will actively seek partnerships with participating Institutes and other federal. For example, NICHD is currently reviewing its plan for sharing model organisms to ensure that as new mouse models are developed using NIH funds, they will be deposited in a central repository so that all researchers who wish to use these models for their research have ready access to them. The NICHD is dedicating \$1.1 million to a Request for Applications related to Down Syndrome and the working group will meet to continually guide NIH's next steps in this area.

#### Item

***Early Language Development*** – The Committee applauds the NICHD's continued support of research in early language development, particularly studies that underscore the importance of social interaction as a necessary component for language learning. The Committee encourages further research to help understand which components of social interaction are critical for language development, and how this knowledge can be used to improve the linguistic skills of those with social impairments. (p. 131)

#### Action taken or to be taken

The NICHD has supported foundational work on early language development for at least three decades. Currently, this work is supported mainly by the Child Development and Behavior Branch in their programs on language development and early learning. Many of the studies that have been or are supported by these programs include the interaction of language and social skills. These studies have been foundational to our understanding of social and language impairment, in particular of the linguistic and social development of young children with autism spectrum disorder. The NICHD is a major supporter of work on autism spectrum disorder providing funds for research in this area. Through FY 2006, NICHD participated with various other NIH Institutes in funding center grants in both the

Collaborative Programs of Excellence in Autism and Studies to Advance Autism Research and Treatment networks. In FY 2007, the NICHD was a major partner in the most recent trans-NIH initiative on Autism Centers of Excellence (ACE). Some of the ACE projects are related to understanding and improving social and linguistic abilities in children with or at risk for autism spectrum disorders. The NICHD is committed to the continuation of funding for both of these studies on typical early language and social development, and to intervention studies which seek to improve these abilities in children diagnosed with or at risk for impairment.

Item

**Epilepsy** – Epilepsy often begins in childhood, and even in its mildest forms can modify brain development, with lifelong effects on cognitive processes ranging from learning disabilities to severe developmental disabilities. Recurring seizures are also common for children with autism, brain tumors, cerebral palsy, mental retardation, tuberous sclerosis and a variety of genetic syndromes and may dramatically add to the burden of these disorders. The Committee urges the NICHD to make research in epilepsy a priority, with particular emphasis on developmental effects, and to coordinate these efforts with the NINDS. (p. 132)

Action taken or to be taken

Although the NINDS traditionally funds the majority of NIH epilepsy research, the NINDS and the NICHD have a long history of collaboration in this area. The NICHD funds the Mental Retardation/Developmental Disabilities Research Centers (MRDDRC), a network of regional centers developed for research on mental retardation and related aspects of human development, including epilepsy. Many of the Centers also provide infrastructure for NINDS-supported epilepsy research projects. Both Institutes plan to continue this successful collaboration. Currently, the MRDDRCs are supporting a number of research projects related to epilepsy, including research on the effects of treating obstructive sleep apnea in patients with epilepsy on seizure frequency, daytime sleepiness, and health-related quality of life. Another study is examining category-specific recognition and naming abilities in patients with temporal lobe epilepsy before and after resective neurosurgery. In the case of childhood epilepsy, by understanding these processes better, it may be possible to determine the optimal time frame for considering resective surgery as a treatment intervention for the control of intractable seizures. Still another study on childhood absence epilepsy (CAE) indicates that the primary neuropsychological problem in children with this condition is attention.

CAE is a common pediatric epilepsy syndrome that affects 10 to 15 percent of all children with epilepsy. These seizures impair the children's ability to learn and play, and lead to higher injury rates. The goal of this study is to determine the best first choice out of three medicines used as treatment for children with CAE. The planning for the trial was developed jointly by NICHD and NINDS staff.

Knowledge gained from this study may lead to individualized treatment for children with CAE, and may also be beneficial for other pediatric and adult seizure disorders. NICHD staff have also cooperated with NINDS staff within the Interagency Epilepsy Working Group on two important meetings related to epilepsy and will collaborate on the written reports emanating from the conference as requested. Staff will also ensure the dissemination of important information on pediatric epilepsy to the scientific community and the public.

Additionally, NICHD is engaged in clinical research on epilepsy. One clinical trial, being conducted under the Best Pharmaceuticals for Children Act, is testing choices of treatment for children with status epilepticus. Four to eight children per every 1,000 will experience status epilepticus before age 15, and because the condition is life-threatening, are usually admitted to hospital emergency departments. Presently, two drugs are commonly administered in emergency rooms for children presenting with these seizures. Although both medications are regarded as standard treatment, no large-scale comparison has been conducted to determine which treatment is the safer, more effective one for these events. To answer this question, the NICHD is sponsoring a large-scale national study, "The Pediatric Seizure Study".

#### Item

***Family Formation*** – The Committee encourages the NICHD to continue to fund research on effective ways to promote and sustain healthy family formations, particularly for low-income families and families of color. (p. 132)

#### Action taken or to be taken

Healthy families are crucial to our nation's health, but recent changes in family patterns have troubled many observers. Vital issues include decisions related to marriage, teen birth rates, and infertility, an area where there is statistically a health disparity. Many young people are delaying or foregoing marriage, often opting instead for short-lived cohabiting relationships. In part because of this trend, the proportion of births that occur to unmarried couples is now well over one-third and still increasing. As a result, U.S. children experience high rates of family instability during their growing-up years. While declines in the teen birth rate have been encouraging, teen birth rates remain higher in the U.S. than in other developed countries. In addition, many Americans are experiencing infertility. Although, statistically, families of color are least likely to delay childbearing, they are most likely to experience infertility, and for many of these families affordable and effective infertility treatment remains out of reach.

NICHD research addresses the causes and the consequences of changing family patterns for children, adults, and communities. For example, recent work conducted under a major study of the effects of welfare reform on children demonstrated that women who experience domestic abuse were less able to form and maintain stable relationships throughout adulthood. Another study has

examined the outcomes of families formed through non-marital childbearing, documenting the factors that facilitate family stability and marriage, and the effects of varying family outcomes on the health and development of children. NICHD has begun to support research on innovative interventions to improve couple relationships in low-income families and families of color. These interventions complement and contribute to work done under the Healthy Marriage initiative. NICHD also supports a major study of impoverished rural families, which seeks to understand the supports and challenges for children in rural communities as they enter school; research on the relationship of poverty to child development; research on the impact of father involvement and parenting practices on children's development; and research that seeks to improve family involvement in schooling among Latino families.

In a recent review conducted under the auspices of the National Advisory Child Health and Human Development Council, NICHD was advised to continue and expand its strong program of research on the family. One important avenue for research is to expand our understanding of the causes of family change by broadening the types of interdisciplinary science brought to bear in explanatory theories and studies, because of the consequences of family change for children, but also because of the long-term impact of fertility trends on rates of old-age dependency within the population. A second avenue for research is to study family processes that reach across households to better understand the many families with multiple generations or nonresident parents involved in caretaking.

Item

***Fragile X Associated Premature Ovarian Failure [POF]*** – The Committee acknowledges the importance of furthering research into the FMR1 premutation to inform the research community about the genetic causes of infertility and disorders of altered ovarian function. The Committee supports further research efforts focused on collecting genetic information from women who possess a mutation of the FMR1 gene as well as women who have POF. To accomplish this goal, the Committee urges the NICHD to include the collection of genetic data on women who are relatives of people living with Fragile X in the development of a National Fragile X Patient Registry in order to facilitate genetic screening and counseling services for family members who may be at risk of Fragile X. Additionally, the NICHD is encouraged to address POF as it relates to the FMR1 gene in the development of a blueprint on Fragile X research opportunities. (p. 132)

Action taken or to be taken

Please refer to page 157 of this document for the NICHD response to this significant item.

Item

***Liver Wellness in Children*** – The National Children's Study provides a unique

opportunity to study the prevalence of obesity-related chronic liver disease, also known as non-alcoholic steatohepatitis [NASH], from birth to early adulthood. The Committee urges the NICHD to analyze the prevalence of NASH under the NCS to better understand obesity-related chronic illnesses in children and to work with other agencies in the screening and prevention of these diseases. (p. 132)

Action taken or to be taken

Please refer to page 158 of this document for the NICHD response to this significant item.

Item

***Mental Retardation*** – The Committee recognizes the contributions of the Mental Retardation/Developmental Disabilities Research Centers [MRDDRC] 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 MRDDRC contributions in the areas of autism, Fragile X syndrome, Down syndrome and other genetic and environmentally induced disorders. However, the Committee is concerned that the MRDDRCs do not have sufficient resources to sustain the progress made in this critical area and is especially concerned with the cut in support for recently funded centers. The Committee urges the NICHD to restore these reductions and to the extent possible provide additional resources to the MRDDRCs. (p. 133)

Action taken or to be taken

Please refer to page 167 of this document for the NICHD response to this significant item.

Item

***National Center for Medical Rehabilitation Research [NCMRR]***

The Committee notes that while the NCMRR has the lead at NIH for medical rehabilitation, 15 other institutes and centers also fund research in this area. The Committee urges the NCMRR to provide leadership for this trans-NIH research and to increase its focus on institutional and career development awards with the goal of raising the applicant success rates of the several under-represented health professions that can contribute significantly to the field, such as occupational therapists. The Committee also urges the NCMRR to support research on pulmonary rehabilitation. (p. 133)

Action taken or to be taken

The NCMRR at the NICHD continues to lead the trans-NIH Rehabilitation Coordinating Committee. The committee has analyzed the results of the applications received in response to the trans-NIH program announcement,

Research Partnerships to Improve Functional Outcomes. Based upon the scientific reviews these applications received, the committee has determined that a revised program announcement should be published to provide more guidance for the types of research needed, as well as providing support for conferences and workshops that will assist investigators in forming the kind of multi-disciplinary teams necessary to address the challenges in rehabilitation and management of chronic disease. This announcement is expected to be issued in late FY 2008 or early 2009.

Recognizing that a range of health professionals must be adequately trained to handle the myriad of issues surrounding rehabilitation, the NCMRR recently funded two new institutional career development awards for physical and occupational therapists.

Item

***Neurofibromatosis***

The Committee continues to encourage the NICHD to issue RFAs for NF research, aggressively pursue and expand funding of clinical trials for NF patients in the area of learning disabilities and support the creation of NF Centers involved with treating and curing learning disabilities. (p. 133)

Action taken or to be taken

The NICHD, along with NINDS, has funded multiple projects in recent years addressing the neurology, genetics and to a more limited extent, the behavioral consequences of neurofibromatosis (NF). As a result, a great deal is known about the genes and some of the related brain pathways involved with the cognitive deficits associated with this disorder. Research in various developmental disorders, such as NF, Fragile X, Turner Syndrome, and Velo-Cardio-Facial Syndrome, all of which involve learning disabilities and specific profiles of cognitive/learning disabilities, can inform us on gene-brain-behavior pathways toward learning disability as well as give us a better understanding of what is required for normal (or typical) cognitive development. Likewise, since we have mouse models of NF, there is an opportunity to study the development of learning disabilities from embryonic molecular effects through young adult ages.

Specific behavioral intervention trials for learning disabilities in NF patients are under consideration by several of the Mental Retardation/Developmental Disabilities Research Centers (MRDDRC), supported by NICHD. NICHD staff assisted the MRDDRC at UCLA in a recent workshop, "Treatment for NF1 – Associated Learning Disabilities." The workshop participants, convened by the Children's Tumor Foundation, "agreed it would be advantageous for all future NF1 learning disabilities trials to build upon the framework being developed by the emerging NF Clinical Consortium for such trials; and to make a commitment to close international collaboration."

The MRDDRC at the University of Alabama (UAB) supports NF Consortium Development trials targeting neurofibromatosis-associated abnormalities. Topics currently under study include the natural history, diagnosis, and management of neurofibromatosis type 1 (NF1) including using the diagnostic outcome of children presenting with multiple cafe-au-lait spots, learning disabilities in NF-1, and abdominal migraine in children with NF-1. In addition, investigators at the Center have developed a test to detect occurrence of large deletions involving the entire NF-1 gene. More than 15 patients with such large deletions have been identified and studied; they have a distinct phenotype of dysmorphic features, early onset and large number of neurofibromas, and severe developmental impairment. This is the only genotype-phenotype correlation so far established in NF-1.

NICHD is also supporting research on NF and learning disabilities. Approximately half of children with NF-1 have some form of learning disabilities, the most debilitating and common of which relate to reading. Researchers are currently working to determine specific reading-related deficits in children with NF, and to find the best interventions for particular types of learners.

#### Item

##### ***Preterm Birth***

The Committee commends the NICHD for its sustained investment in prematurity research through the Maternal-Fetal Medicine Network, the Neonatal Research Network and the Genomics and Proteomics Network. The Committee strongly encourages the NICHD to expand research on the underlying causes of preterm delivery and the development of treatments for the prevention of premature birth. (p. 133)

#### Action taken or to be taken

The NICHD supports research on predicting and preventing preterm birth through investigator initiated grants and networks such as the Maternal Fetal Medicine Units (MFMU) Network for clinical trials and the Genomic and Proteomic Network for Premature Birth Research. Ongoing trials in the MFMU Network, which comprises 14 sites across the U.S. and a data center, include several trials specifically related to preterm birth prevention and management including the BEAM trial (Beneficial Effects of Antenatal Magnesium Sulfate), a clinical trial to determine if a sulfate compound administered antenatally can reduce the risk of cerebral palsy in offspring in women at 24 - 31 wks gestation with preterm or planned delivery. This trial has completed enrollment and is finishing the 2-year follow-up of the infants. Still another clinical trial is underway to determine whether 17 alpha hydroxyprogesterone prevents preterm birth in multifetal pregnancies (twins and triplets). The results of the twin data were recently published in the *New England Journal of Medicine*. Also, NICHD is supporting a follow-up study to determine whether there is a difference in achievement of developmental milestones and physical health between children exposed to

progesterone and those exposed to placebo. Additionally, a clinical trial is being conducted in the network to determine whether Omega-3 fatty acids, in conjunction with 17 alpha hydroxyprogesterone, reduce the risk of preterm delivery in women at high risk. Enrollment is complete and results presented at the January 2008 Society of Maternal Fetal Medicine meeting.

The NICHD's Genomic and Proteomic Network for Premature Birth Research aims to accelerate the pace of premature birth research by focusing on global genomic and proteomic strategies and the dissemination of genomic and proteomic data to the scientific community through: 1) the design and implementation of hypothesis-driven, mechanistic studies based on large-scale, high-output genomic and proteomic approaches, and; 2) the providing of a public, web-based, genomic and proteomic database for data mining and data deposition by the research community. The research focus of the network is to identify new biomarkers that increase the risk or are predictive of a preterm delivery and to delineate molecular mechanisms responsible for a preterm birth. Recruitment for three studies started in August 2007 and each of the studies is expected to be completed in 2010. Ultimately, this research could some day lead to relatively simple screening tests to identify pregnant women (or possibly even women contemplating pregnancy) at risk of a preterm birth and provide them with interventions enabling them to carry a pregnancy to term.

Item

***Primary Immunodeficiency [PI] Diseases***

The Committee continues to support the NICHD's efforts to educate physicians and the public regarding this class of about 140 diseases. The Committee also encourages the Institute's focus on newborn screening research as States begin to implement pilot newborn screening programs for SCID, one of the most severe forms of PI. The NICHD is urged to coordinate its efforts with the CDC and the States in this implementation period. (p. 133)

Action taken or to be taken

Please refer to page 160 of this document for the NICHD response to this significant item.

Item

***Obstetric Systematic Reviews***

The Committee continues to encourage the NICHD to support obstetric systemic reviews, which provide an important resource to practicing physicians and the general public. (p. 134)

Action taken or to be taken

A high priority of the NICHD is the conduct of randomized clinical trials to improve the health of women and families, and the promotion of evidence-based practice of clinical medicine. NICHD is committed to acquiring an ongoing series

of systematic reviews of key obstetrical issues to disseminate to professional organizations and others interested in these topics. NICHD plans to solicit proposals for systematic, quantitative reviews of the effectiveness and safety of therapies used in the care of pregnant women. The resulting data and meta-analyses/reviews will be used to (1) facilitate exchange of information among researchers and clinicians involved in design and conduct of multi-center studies in this area, to provide information to clinicians in obstetrics/perinatology, (2) provide information upon which to base priorities for future research and allocation of health-care resources, and (3) promote investigation on the translation of research into clinical practice. NICHD will disseminate these reviews to a wide audience by posting them on its website and through other means such as professional journals. By providing ready access to these high-quality reviews, this initiative will address a core mission to support the educational needs of obstetric health care providers and the health knowledge of the general public.

#### Item

#### ***Spina Bifida***

The Committee strongly urges the NICHD to make a greater investment in the prevention and treatment of spina bifida and its associated secondary conditions.

In particular, the Committee urges a stronger emphasis on understanding the myriad co-morbid conditions experienced by children with spina bifida, including paralysis and developmental delay. (p. 134)

#### Action taken or to be taken

The NICHD is one of several Institutes at the NIH that supports research efforts to address the serious condition of spina bifida. Infants born with spina bifida have significant sensory and motor disruptions at the level of the spinal cord and higher nervous system. One NICHD-funded project on spina bifida is examining the intrinsic capacities of infants born with spina bifida during their first year of life and their responsiveness to various forms of enhanced sensory input. NICHD is also supporting studies on a variety of research questions related to spina bifida, including variations in cognitive ability, psychosocial adjustment in adolescents with spina bifida, and the effects of exercise on plasticity in a mouse model of spina bifida.

NICHD also supports research on spina bifida through the Mental Retardation and Developmental Disabilities Research Centers (MRDDRCs) that provide infrastructure for projects funded by NIH Institutes and Centers. For example, the MRDDRC at Vanderbilt University provides infrastructure for a project titled Neural Crest Contributions to the Bladder. (Myelodysplastic bladder disease is a co-morbid condition experienced by children with spina bifida.) The goal of this project is to analyze aberrations in neural crest development in mouse spina bifida models with myelodysplastic bladder disease. In addition, the MRDDRC at Kennedy Krieger Institute supports projects about bowel and bladder

incontinence in youth and among children with spina bifida.

NICHD is funding a multicenter trial, the Management of Myelomeningocele Study (MOMS), to evaluate the safety and efficacy of fetal surgical repair compared to traditional postnatal repair of open neural tube defects. The study is enrolling pregnant women with diagnosed fetal spina bifida using a rigorous and common protocol at the three sites. The effect on mother's health during that pregnancy and future pregnancies will be looked at as well as fetal and childhood outcome.

NICHD also supports two projects that investigate the effects that individuals with spina bifida have on their families. One project investigates the effect on mothers' health comparing families with children that have typical development, Down syndrome and with spina bifida. Another is investigating sibling hospitalizations of children with Down syndrome and with spina bifida.

Item

***Spinal Muscular Atrophy [SMA]***

The Committee has stated in previous years that improving the diagnosis of SMA and accelerating the development of treatments for this disease is consistent with the NICHD's mission. However, the Committee is concerned that the NICHD has dedicated only minimal resources specifically to initiate work and sustain ongoing resources for SMA. The Committee again urges the NICHD to fund specific basic, translational and clinical research initiatives on SMA. Further, the Committee urges the NICHD to coordinate its efforts with the NINDS and NIGMS. (p. 134)

Action taken or to be taken

Please refer to page 159 of this document for the NICHD response to this significant item.

Item

***Stillbirth***

The Committee applauds the NICHD's efforts to address stillbirth and urges the Institute to fully fund the cooperative network's ongoing study using a standard protocol at five clinical sites. (p. 134)

Action taken or to be taken

Please refer to page 163 of this document for the NICHD response to this significant item.

Item

***Tuberous Sclerosis Complex [TSC]***

Individuals with TSC—many of whom are infants and young children—face a lifetime of suffering with seizures, behavioral disorders, autism and mental

retardation. The Committee urges the NICHD to stimulate and support research on the link between autism and TSC, specifically the role of the TSC1/2 genes in autism. The Committee also urges the NICHD to stimulate and support research on the role of early-onset seizures in TSC and subsequent cognitive development. (p. 134)

Action taken or to be taken

NICHD supports research on the link between autism and tuberous sclerosis complex (TSC), and on the role of early-onset seizures in TSC and subsequent cognitive development, through research infrastructure grants supporting the Mental Retardation and Developmental Disabilities Research Centers (MRDDRC). For example, a new program development project at the Boston MRDDRC is indicating that axon specification and guidance is markedly abnormal in the absence of TSC genes. This preliminary data has led to a new grant, funded by NINDS, to explore this further. To investigate further the relevance of this basic science work to children with TSC, the investigator plans to develop a collaborative translational study with other MRDDRC scientists to examine visual function in children with TSC and autism.

Another MRDDRC supports investigators who have identified mutations in a protein that may regulate Tuberous Sclerosis complex (TSC1/TSC2). As autism spectrum disorders are found in up to 50% of TSC patients, studying signaling by these proteins could have implications for both TSC and autism.

The MRDDRC located in Philadelphia supports a project examining gene expression TSC (funded by NINDS), and the MRDDRC in Los Angeles supports investigators who are attempting to distinguish epileptogenic tubers in patients with TSC using combination of PET and MRI imaging. Finally, still another MRDDRC is supporting research that contributed to the consensus guidelines for the assessment of cognitive and behavioral problems in TSC.

Item

***Uterine Fibroids***

The Committee encourages the NICHD to expand, intensify, and coordinate programs for the conduct and support of research with respect to uterine fibroids. Current research and available data do not provide adequate information on the rates of prevalence and incidents of fibroids in Asian, Hispanic, and other minority women, the costs associated with treating fibroids, and the methods by which fibroids may be prevented in these women. (p. 134)

Action taken or to be taken

While uterine fibroids represent the most common gynecologic benign tumor in women, the mechanisms that initiate fibroid growth and pathogenesis are not completely understood. This disorder is clinically important because it is a significant source of abnormal uterine bleeding, anemia, pelvic pain and

pressure. Currently, no effective medical treatment exists and surgery is the standard treatment. Uterine fibroids remain the leading indication for a hysterectomy in the United States. Thus, both the economic cost and effect on quality of life can be substantial. Moreover, significant health disparities are associated with this condition, particularly for African American women.

In September 2007 and building on a major meeting held in 2002, NICHD, in collaboration with ORWH, convened the NICHD Uterine Fibroid Research Update Workshop. This meeting brought together NICHD intramural and extramural investigators to share research findings and explore future directions and collaborations, including the prevalence, disease burden, infertility risk, and genetic liability for developing uterine leiomyomata, as well as novel therapeutic strategies for treating fibroids and their co-morbidities.

In addition, NICHD's Cooperative Reproductive Science Research Centers at Minority Institutions Program, in collaboration with ORWH and the National Center for Research Resources, is supporting a clinical research study on uterine fibroids at Meharry Medical College, which further addresses the effort to find answers for increased prevalence rates in minority women. The Women's Reproductive Health Research (WRHR) Career Development Program, in collaboration with ORWH, is an ongoing training and career development program for junior physician scientists, and one of the WRHR scholars is currently conducting a research project with an emphasis on uterine fibroids. NICHD plans to publish a new program announcement in fiscal year 2008 aimed at expanding ongoing efforts to stimulate research in the field. Finally, the NICHD through its Reproductive Medicine Clinical Trials Network is poised to conduct randomized clinical trials on novel therapeutic interventions to treat fibroids, and through its intramural program, has already begun a fibroid tissue bank that will promote research on fibroid disease by providing access to tissue samples for NIH-funded investigators throughout the world.

Item

***Vulvodynia*** – The Committee commends the NICHD for supporting two new projects on vulvodynia in 2006 and strongly urges the Institute to increase the number of awards for vulvodynia studies in FY 2008, with a particular emphasis on etiology and multi-center therapeutic trials. Finally, the Committee commends the NICHD for working with the ORWH to implement an educational outreach campaign on vulvodynia, and calls upon the Institute to continue these efforts. (p. 134)

Action taken or to be taken

Please refer to page 164 of this document for the NICHD response to this significant item.

# National Eye Institute

## House Significant items

### Item

#### ***Age-Related Macular Degeneration (AMD)***

The Committee encourages further research into diagnostics for early detection and appropriate therapies. The Committee also applauds NEI for initiating the second phase of its age-related eye disease study, in which additional dietary supplements are being studied to determine if they can demonstrate or enhance their protective effects against progression to the advanced form of AMD, as shown with dietary zinc and antioxidant vitamins in the study's first phase. This research is a potentially cost-effective means by which to decrease the progression of this disease. (p.147)

### Action taken or to be taken

The original Age-Related Eye Disease Study (AREDS) demonstrated that oral supplements containing high doses of antioxidant vitamins and minerals reduced the risk of progression to the vision threatening forms of AMD by 25%. Additional studies made possible by data and samples collected in AREDS have demonstrated strong linkage with certain genetic factors, especially and somewhat unexpectedly, those related to inflammation. This contributes not only to our rapidly developing understanding of the disease, but will also help in the development of new drugs and in the exploration of existing anti-inflammatory and immunomodulating drugs for treating AMD.

The new Age-Related Eye Disease Study 2 (AREDS2), has made excellent progress in recruiting participants and is on target to reach its goal of 4000 individuals. AREDS2 is testing lutein/zeaxanthin and omega-3 fish oil to see whether these oral supplements may further delay the development of advanced AMD that causes vision loss. AREDS2 will, in addition, evaluate the effect of omega-3 fish oil on cognitive function, as well as cardiovascular disease in this elderly population.

### Item

#### ***Diabetic Eye Disease***

The Committee applauds NEI for the collaborative efforts of the diabetic retinopathy clinical research network to test innovative treatments for diabetic eye disease. The Institute is encouraged to 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. (p.147)

Action taken or to be taken

Please refer to page 183 of this document for the NEI response to this significant item.

**Senate Significant Items**

Item

***Diabetes Management Devices***

The Committee urges the NEI, in collaboration with the NIDDK and the Food and Drug Administration, to sponsor a scientific workshop that would include representatives from diabetes management device manufacturers and representatives of organizations that address the technology access needs of Americans with low vision or blindness to document and clarify the technical capabilities of the devices currently on the market and to develop standards for device accessibility for Americans with low vision or blindness. (p. 134)

Action taken or to be taken

NEI staff held an informal exploratory meeting with parties interested in accessibility issues as they relate to state-of-the-art glucose monitoring and insulin delivery devices. An agenda is being developed and other preparations are being made for an NEI-sponsored forum that will explore the accessibility of diabetes management technologies to Americans with blindness and low vision. This forum will be open to federal agencies, manufacturers, and organizations that are interested in these accessibility issues.

Item

***Diabetic Eye Disease***

The Committee applauds the NEI for the collaborative efforts of the Diabetic Retinopathy Clinical Research Network to test innovative treatments for diabetic eye disease. The Institute is encouraged to expand and extend the network by increasing the number of clinical trials with new drugs and therapeutics that can treat and prevent diabetic retinopathy. (p.135)

Action taken or to be taken

NEI continues to support the Diabetic Retinopathy Clinical Research Network (DRCR.net). The NEI has expanded DRCR.net activities through additional support provided by NIDDK, the Juvenile Diabetes Research Foundation International, and other contributors. The DRCR.net is designed to conduct multicenter clinical research on diabetic retinopathy, diabetic macular edema, and associated conditions. Currently, the DRCR.net has 11 active studies that are being conducted at approximately 150 clinical sites located in 40 States.

## National Institute of Environmental Health Sciences

### House Significant Items

#### Item

#### ***Alpha-1-antitrypsin deficiency (Alpha-1)***

Given the link between environmental factors and the onset of Alpha-1 related COPD, the Committee encourages NIEHS to develop research initiatives to explore gene-environment interaction research and to support public-private partnerships. (p. 148)

#### Action taken or to be taken

NIEHS agrees that, given the link between environmental factors and the onset of alpha-1 related COPD, research is needed to explore gene-environmental interactions and disease etiology. NIEHS is supporting both laboratory and epidemiology research projects investigating how genes and environmental factors interact to cause or exacerbate COPD. Understanding the complex mechanisms through which genes and environmental factors interact is necessary to develop preventive strategies and effective treatments.

Deficiency in the activity of alpha-1-antitrypsin is a major factor of genetic susceptibility for the development of COPD. A laboratory study using a combination of genetic linkage, microarray gene expression profiling, and genetic association studies has identified serine protease inhibitor Serpin E2 as a candidate susceptibility gene for COPD. The study is examining the physiological role of Serpin E2 in normal lung homeostasis and testing Serpin E2 for a physiological role in maintenance of lung structure following cigarette smoke exposure in mice to identify the role of this gene in lung maturation, homeostasis, and susceptibility to COPD.

Studies being conducted by NIEHS in collaboration with the University of North Carolina, National University of Singapore, Sonoma Technology, Inc., University of Minnesota and the National Cancer Institute (NCI) are investigating the role that genetic factors play in modulating the effects of diet, smoking, occupational exposures, and ambient pollution on the risk of adverse respiratory outcomes in adults. Several populations are being prospectively studied.

NIEHS and the National Heart, Lung and Blood Institute (NHLBI) are funding the Lung Lysyl Oxidase Regulation by Metal Ion Homeostasis projects. One of these projects involves exposing pregnant mice to levels of smoke consistent with environmental exposures. Pups are being monitored for lung functions and susceptibility to develop emphysema as they age. The role of stem cells is being evaluated by quantifying progenitor stem cell functions in the exposed animals using *in vivo* and *in vitro* methods. Bone marrow stem cell transplants are being

used to confirm the role of stem cells and to attempt to restore lung function. This project seeks to establish fetal environmental smoke exposure as a cause of adult COPD and provide a novel basis for therapy. A second project is investigating elevation of cellular metallothionein and glutathione, perturbation of copper homeostasis, and down-regulation of lysyl oxidase as key mechanisms in emphysema pathogenesis in rats chronically exposed to cadmium. This project will enhance our understanding of the molecular mechanisms of emphysema pathogenesis.

Variation in the levels of a component of air pollution and particulate matter (a mixture of particles and liquid droplets) correlate with an increase in asthma and COPD exacerbations. Particulate matter-exposed macrophages induce fibroblast toward myofibroblast transformation, a key phenotypic change of airway remodeling that can lead to irreversible airway disease. A study supported by NIEHS and NHLBI is investigating whether particulate matter induces airway remodeling via oxidant-mediated macrophage release of cytokines that trigger myofibroblast differentiation. Exploring the mechanisms of particulate matter-induced airway remodeling is important in providing preventive and therapeutic targets that apply to a broad range of patients.

NIEHS is also supporting the Shared Mechanisms of Pulmonary Lymphocyte Activation by Bacteria and Toxicants project. These studies will provide a better understanding of the pathways and mechanisms of immune system activation in response to environmental exposures that contribute to the pathophysiology of chronic airway diseases.

#### Item

##### ***Bone Marrow Failure Diseases***

Aplastic anemia, myelodysplastic syndromes [MDS], and paroxysmal nocturnal hemoglobinuria [PNH] are life threatening, non-contagious diseases. While there are no known causes of bone marrow failure diseases, they have been linked to environmental factors. The Committee encourages NIEHS to work with NHLBI and NCI to fund research that explores these links to determine what, if any, environmental factors may cause bone marrow failure diseases. (p. 148)

#### Action taken or to be taken

NIEHS agrees that research to determine if environmental factors may cause bone marrow failure diseases is a high priority, and, in collaboration with NCI and NHLBI, is supporting both epidemiological and laboratory projects that are investigating environmental factors affecting bone marrow.

NIEHS and NCI are supporting a joint initiative, Environmental Influences on Epigenetic Regulation, which includes studies on environmental effects on the development of acute myeloblastic leukemia. In addition, NIEHS, in partnership

with NIAAA and NHLBI, is funding a separate initiative on Comparative Biology Elucidation of Environmental Pathways and Susceptibility, to conduct myeloplasia and aplastic anemia research.

NIEHS and NCI also are supporting the Childhood Leukemia and Environmental Exposures project to identify etiologic associations between environmental exposures and childhood leukemia. To study genetic susceptibility, buccal cell specimens will be collected from cases, controls, and their biological mothers. To measure micronutrients and biomarkers of environmental chemical exposures, peripheral blood specimens will be collected from biological mothers of cases under age seven and their matched controls. Data on a wide spectrum of environmental exposures will be collected. This comprehensive information on environmental exposures and genetic characteristics, in conjunction with improved disease classification and stratification by Hispanic status, will provide significant insights into the etiology of childhood leukemia.

In addition, NIEHS and NCI are supporting a project to develop new biomarkers of exposure and early effect for benzene toxicity and provide new insights into the mechanisms of benzene toxicity. The shape of the dose-response curve for benzene-induced leukemia at exposures below 10 ppm is a key public policy and risk assessment issue involving potentially billions of dollars. Conventional epidemiology and toxicology studies are unlikely to resolve this controversy. Emerging technologies, such as microarrays and proteomics, offer a significant opportunity to develop new biomarkers and provide key mechanistic information. Affymetrix microarrays will be used to reveal changes in gene expression related to benzene exposure. A Ciphergen ProteinChip mass spectrometer will allow for differentially expressed proteins and protein modifications related to benzene exposure to be identified and a protein profile for benzene exposure to be established in serum and lymphocytes.

Using fluorescence-based and antigen-presentation assays, a study supported by NIEHS and NCI determined that significant quantities of exogenously added peptide could accumulate in “designer” chaperone-rich cell lysate (CRCL) and could stimulate T cell activation. Further, the study showed that peptide embedded CRCL, devoid of other antigens, could generate potent immunity against murine leukemia. Designer CRCL allows for the development of personalized vaccines against cancers expressing known antigens, by embedding antigens into CRCL derived from normal tissue.

- *Citation:* Kislin KL, Marron MT, Li G, Graner MW, Katsanis E. Chaperone-rich cell lysate embedded with BCR-ABL peptide demonstrates enhanced anti-tumor activity against a murine BCR-ABL positive leukemia. *FASEB J.* 2007 Jul;21(9):2173-84.

In a study supported by NIEHS and NHLBI and several foreign agencies, investigators quantified recruitment of pericytes (special elongated cells found

wrapped around some small blood vessels) in human and mouse bone marrow to see whether pericyte deficiency is associated with the vascular aberrations seen in the bone marrow of patients with myelofibrosis (MF). The study showed that pericytes cover blood vessels in bone marrows of both healthy humans and individuals with MF. Unexpectedly, the extent of vessel coverage by PC was markedly greater in bone marrow from MF patients than in that from normal individuals. The treatment of MF remains unsatisfactory. The findings of this study suggest that the pathological vessel morphology seen in MF is not due to a lack of pericytes but rather associated with a high number of these cells. Moreover, the study demonstrated a novel concept in the pathogenesis of MF, whereby the myeloproliferative disorder *per se* is for the abnormal angiogenesis and not directly the MF. Specific targeting of pericytes emerges as a potential new treatment option, particularly in view of the notion that current angiostatic drugs might have less effect on mature vessels.

- *Citation:* Zetterberg E, Vannucchi AM, Migliaccio AR, Vainchenker W, Tulliez M, Dickie R, Hasselbalch H, Rogers R, Palmblad J. Pericyte coverage of abnormal blood vessels in myelofibrotic bone marrows. *Haematologica*. 2007 May;92(5):597-604.

#### Item

##### ***Food allergies***

The Committee recognizes the potential relationship between environmental conditions and food allergies, and encourages NIEHS to fund research in cooperation with NIAID to understand the causes and potential therapies for the growing danger of anaphylaxis resulting from food allergies. (p. 149)

#### Action taken or to be taken

Recent epidemiological findings indicate that there is an increase in the use of asthma or allergy drugs in young adults who have been fed soy formula during infancy. Studies conducted by NIEHS scientists have provided evidence that the developing immune system, especially the function of T cells, is altered following oral exposure to genistein, a soy isoflavone found in soy formula, at physiologically relevant concentrations in experimental animals. NIEHS scientists are currently studying the mechanisms through which exposure to genistein leads to an increase in hypersensitivity responses to trimellitic anhydride, a respiratory allergen, in adult life. The results of this investigation will provide an understanding the health implications associated with the use of soy formula and a better insight with which to make informed decisions regarding intervention studies.

In 1993, the ICD-9-CM system introduced codes to identify specific food allergies. NIEHS and NIAID supported a study to determine the accuracy of using ICD-9-CM codes to identify emergency department visits for allergic reactions or anaphylaxis resulting from food and insect stings and determine the potential bias that might be introduced by sole reliance on these codes. The

study indicates that prevalence estimates of food allergies based on ICD-9-CM codes should be interpreted cautiously because they significantly underestimate the true prevalence of food allergies. Clinical studies identifying patients with an allergy should include both ICD-9-CM codes specific to the allergy of interest and more general allergy codes combined with chart reviews to identify the underlying cause of the allergic reaction. NIEHS will explore further scientific opportunities in collaboration with NIAID.

Item

***Effects of methylmercury exposure on pregnant women***

NIH is encouraged to continue its work on the long-term effects of the exposure of pregnant women to methylmercury, including higher than average levels of exposure, and to report to the Committee by April 1, 2008 the results of these studies. (p. 149)

Action taken or to be taken

NIH agrees that it is important to continue to support research on the long-term consequences of prenatal methylmercury exposure. The National Institute of Environmental Health Sciences (NIEHS) is continuing its support of two methylmercury studies involving pregnant women living in places with potentially much higher than average exposure to methylmercury through diet. The study in the Faroe Islands examined offspring with prenatal exposure from their mothers' consumption of contaminated whale meat. In the study in the Seychelles Islands, the source of prenatal methylmercury contamination was from the mothers' consumption of fish. Seychellois consume about 10-12 fish meals a week. Thus far, the results of the studies have not agreed on the neurodevelopmental effects of methylmercury. The Faroes study has found some evidence for mild neurocognitive damage, while the Seychelles study has not. These differences may be due to the different dietary sources of methylmercury and the protective effects of maternal fish consumption in prenatal neurodevelopment. Both projects are now at the point where it is feasible to see if there is a correlation between academic achievement and the degree of prenatal methylmercury exposure. These studies are just starting and the results should be available in the next several years.

**Senate Significant Items**

Item

***Asthma***

Given the link between environmental factors and the onset of asthma, chronic obstructive pulmonary disease [COPD], and pulmonary fibrosis, the Committee encourages the NIEHS to further develop research initiatives to understand the environmental and genetic risk factors for predisposing some individuals to and in controlling the severity of these lung diseases. (p. 136)

### Action taken or to be taken

NIEHS supports multi-pronged research approaches on lung diseases including asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. Efforts include studies on the role of environmental agents in the origin of these diseases, molecular mechanisms implicated in the initiation and progression of the disease processes, the triggering of pre-existent disease by environmental pollutants and toxicants, the genetic basis for these exacerbations, the role of “epigenetics” (mechanisms that regulate genes without changing their DNA sequence), preventive measures, such as the role of nutritional supplements, the identification of specific targets for therapy. NIEHS also supports research to understand the role of physical and social influences on the environmental impact of toxic pollutants, including the involvement of community-based organizations in educating vulnerable or susceptible populations, children, adults from poor socioeconomic status and minorities. A wide range of environmental chemicals and mixtures is studied, including particulate matter air pollutants (coarse, fine, and ultrafine) in both indoor and outdoor environmental settings, ozone, NO<sub>2</sub>, diesel exhaust particles, asbestos, crystalline silica, metals and metal mixtures, phthalates and organophosphorous pesticides.

Basic research efforts utilize state-of-the-art molecular biological approaches (genomic and proteomic) to understand molecular mechanisms. Some NIEHS-funded research studies use laboratory animal models to understand how asthma is exacerbated by environmental agents, such as particulate matter and ozone. Other animal studies are investigating the potential role of epigenetically-controlled genes to identify potential targets for treatment and prevention of asthma. Rhesus monkey models are being used to develop dosimetric models based on personal exposure data to PM, NO<sub>2</sub> and other confounders to derive precise dose estimates on the associations between exposure and the onset of pediatric asthma episodes. Animal models are also being used to understand the role of prenatal and early post-natal exposures in the onset of pediatric and adult asthma. Gene-environment interaction studies using animal models also investigate the role of differences in the gene for interleukin-4, a protein known to be important in asthma development.

NIEHS-funded researchers also are using animal models to understand the role of genetic susceptibility in the development of COPD by exploring a gene in the lungs of rats exposed to cigarette smoke and to understand the molecular mechanisms involved in asbestosis by investigating the potential role of an enzyme, to develop therapeutic strategies to prevent protein degradation and cell death in the lung caused by oxidative stress. Effective strategies to treat chronic airway fibrosis and interstitial pulmonary fibrosis that result from environmental exposures to inhaled allergens are being developed, to explore the possibility of medically increasing gene expression to speed repair of injured airways.

To complement these basic research efforts, NIEHS funds numerous epidemiological studies to better understand: (1) genetic determinants of asthma morbidity in the urban environment; (2) the role of genetic differences (such as in the glutathione S-transferase m-1 gene) on the effects of particulate air pollution in asthmatic children; (3) a disease process known as “oxidative stress” caused by diesel exhaust exposure and other pollutants; (4) community-based approaches to study the potential benefits of preventive interventions, such as the use of air filters and air conditioners in childhood asthma; (5) the relationship between exposure to environmental chemicals known as phthalates and the incidence of pediatric asthma in the inner city; (6) the influence of modifiable social and physical factors in susceptible populations; and (7) the influence of obesity on airway responses in asthmatics and use of a community partnership to reduce asthma and obesity.

#### Item

##### ***Autism - [Thimerosal exposure]***

The Committee remains strongly interested in possible environmental causes or triggers of autism. The Committee commends the NIEHS for convening an expert panel in May 2006 regarding thimerosal exposure in response to fiscal year 2006 report language. The report from the workshop, titled “Thimerosal Exposure in Pediatric Vaccines,” concluded that comparing the rates of autism in the Vaccine Safety Datalink [VSD] over the time period before, during and after the removal of thimerosal from most childhood vaccines would be “uninformative and potentially misleading.” The report also outlined three alternate studies that could address possible associations between thimerosal exposure and increased rates of autism. The Committee urges the NIEHS to evaluate the merit of conducting these alternate studies and provide an update in the FY 2009 congressional budget justifications. (p. 136)

#### Action taken or to be taken

NIEHS is committed to studying the roles of environmental exposures as potential risk factors for developing autism. The May 2006 expert panel workshop provided valuable information that helped the Institute determine the focus for its investment in this area.

The three studies recommended by the expert panel for further consideration included an expansion of the Verstraten study to add more recent data and two related study designs that focused on a high risk population, defined as the siblings of children who had been diagnosed with ASD. Competitive applications in any of these three areas are eligible for consideration for funding under the current NIEHS program announcement, Research on Autism and Autism Spectrum Disorders (<http://grants.nih.gov/grants/guide/pa-files/PA-07-085.html> ).

In addition, NIEHS is pursuing other new research opportunities examining regarding environment and autism in siblings. NIEHS is participating in a new study based at Drexel University, called EARLI (Early Autism Risk Longitudinal Investigation). This network application received from the Autism Centers of Excellence (ACE) solicitation is a joint initiative with all five NIH Autism Coordinating Committee Institutes. This multisite network longitudinal study is enrolling mothers with at least one child with autism, during subsequent pregnancies; the expected recurrence risk of around 5-10% will provide an enriched population for study of risk factors. There will be prospective collection of medical and environmental risk factor data during the prenatal and postnatal period, with collection of various biospecimens and clinical evaluations of children up to age 3.

The NIEHS-funded Center for Children's Environmental Health and Disease Prevention Research at UC-Davis is conducting research to build on their findings of immune dysregulation in autism. They have three interrelated projects spanning humans to rodents, focused on the interplay of immune, genetic and environmental factors in autism susceptibility. Their efforts also include the initiation of a new cohort study, MARBLES (Markers of Autism Risk in Babies—Learning Early Signs), a prospective study enrolling mothers of a least one child with autism when they become pregnant with another child.

Another major NIEHS investment at UC-Davis is the CHARGE (Childhood Autism Risks from Genetics and the Environment) study, which will continue enrollment of children to provide increased power for detecting gene-environment interactions in phenotypically distinct subgroups. This is a large case-control study enrolling children aged 2-5 years: cases and two control groups (children with developmental delay and children from general population). Cases and controls will be compared with respect to environmental exposures, immune function, gene transcription profiles, genetic polymorphisms, information from interviews, medical records, and current and banked specimens.

NIEHS also will capitalize on the availability of its environmental health sciences expertise at selected institutions by initiating the ENHANCES Program (Exploring Novel Hypotheses in Autism Centers and Networks through Environmental Sciences). Through this program, NIEHS will provide supplemental funds to NIEHS Core Center Grant Programs that have an ACE grant at the same institution. Funds will be used for a special pilot project solicitation involving new collaborations between environmental health scientists and ACE investigators to explore potential environmental etiologies.

#### Item

#### ***Behavioral Research***

The Committee encourages the NIEHS to maintain its steps toward integrating basic behavioral and social science research into its portfolio. The NIEHS is

urged to expand partnerships with OBSSR and other institutes to fund research on common interest including gene and environment interactions and health. (p. 136)

#### Action taken or to be taken

NIEHS has historically supported innovative projects that involve behavioral research, including those under the trans-NIH Genes, Environment and Health Initiative (GEI). The Exposure Biology Program, the NIEHS-lead component of the GEI, includes a focus on biomarkers and sensors associated with behavioral indicators. In FY 2007, NIEHS participated in nine Program Announcements (PAs), many of which are trans-NIH announcements.

NIEHS is also partnering on a variety of OBSSR-initiated programs, including two recently released PAs. One of the announcements calls for research to improve and elaborate explanations and understandings of the causes for health disparities. The announcement stresses the explicit employment of concepts and models from the behavioral and social sciences to guide basic and applied research.

In addition, NIEHS is participating in a trans-NIH global funding opportunity to support behavioral social science research. The specific goal of this initiative is to provide funding opportunities for the increasing pool of foreign social and behavioral scientists, clinical investigators, nurses and other health professionals, upon their return to their home countries, with state-of-the-art knowledge of research methods to advance critical issues in global health through social and behavioral sciences research.

NIEHS is also part of an inter-NIH Community-Based Participatory Research opportunity with OBSSR partnership. The PA will be reissued this year with the focus on vulnerable populations; to date, NIEHS has funded seven grants.

NIEHS will co-fund an R21 grant with OBSSR, in response to an NIH Roadmap Initiative, entitled "Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences."

Another important OBSSR partnership is the Centers for Population Health and Health Disparities (CPHHDs). NIEHS, the National Cancer Institute, the National Institute on Aging, and OBSSR collaboratively made awards to eight CPHHDs. The purpose of the CPHHDs is to conduct multi-disciplinary, multi-level, integrated research projects with the purpose of elucidating the complex interactions of the social and physical environment, mediating behavioral factors, and biologic pathways which determine health and disease. A key objective is to generate a research program that embraces the concept of 'multiple levels of analysis' in health sciences to examine factors operating at the social/environmental, behavioral/psychological, and biological (organ system,

cellular, and molecular) levels.

# National Institute on Aging

## House Significant Items

### Item

#### ***Down syndrome***

The Committee commends NIA for its support of studies to examine the cellular, molecular and genetic bases for age-related neuropathological and cognitive abnormalities in people with Down syndrome. It encourages NIA to further examine these abnormalities and to devise new methods for diagnosing and treating them. Given that all people with Down syndrome develop the neuropathological changes of Alzheimer's disease, and that many or most go on to suffer dementia, NIA is encouraged to consider how studies of the Down syndrome population might enhance the ability to understand, diagnose and treat Alzheimer's disease. The Committee encourages NIA to collaborate with other institutes to address the issues that face elderly adults with Down Syndrome. (p. 150)

### Action taken or to be taken

In collaboration with the National Institute of Child Health and Human Development and the National Center on Complementary and Alternative Medicine, NIA has completed recruitment for a clinical trial of vitamin E in older Down Syndrome (DS) patients with Alzheimer's disease (AD). The goal of this international three-year study is to determine whether the administration of vitamin E, which has been shown to delay the progression of AD, will slow the rate of cognitive/functional decline in persons age 50 or older with Down syndrome. Data analysis for this study is ongoing.

Another NIA-supported study in a mouse model of DS is exploring the metabolism of the amyloid precursor protein, which, when cut (or cleaved) in a certain way, gives rise to AD's characteristic amyloid plaques. NIA-supported researchers are also conducting a study of the contribution of polymorphisms in genes involved in estrogen biosynthesis and estrogen receptor function to the rate of cognitive decline and risk of AD in women with DS. Prior studies in the general population suggest that the dramatic declines in estrogen levels following menopause may play an important role in the etiology of AD. Among women with DS, the average age at onset of menopause is 46 and the average age at onset of AD is 50-55. Thus, in women with DS, the short interval between menopause and AD provides a unique opportunity to examine the influence of endogenous estrogen activity on disease risk in a prospective study.

### Item

#### ***Bone strength***

The Committee has learned that although bone mineral density has been a useful predictor of susceptibility to fracture, other properties of the skeleton

contribute to bone strength, such as geometry and composition. At this time, little is understood as to how these properties influence bone strength. The Committee encourages NIA to work with NIAMS, NIBIB, NICHD, NIDDK, NCRR and NHLBI to support research, including research on bone structure and periosteal biology, which will achieve identification of the parameters that influence bone strength and lead to better prediction for prevention and treatment of bone diseases. (p. 150)

#### Action taken or to be taken

NIA conducts a robust research portfolio in bone health and disease, and collaborates with other NIH Institutes in these efforts. Examples of NIA research efforts in FY 2007 include:

- NIA continued participation in the Study of Osteoporotic Fractures and the Osteoporotic Fractures in Men (Mr. OS) study, both co-sponsored by NIAMS, which quantify the determinants of fracture in women and men, respectively.
- NIA continues to support trans-NIH program announcements in this area, including Aging Musculoskeletal and Skin Extracellular Matrix, with NIAMS.
- Under RFA, the Adipogenic Phenotype in Aging Musculoskeletal Tissues, NIA is supporting support basic research on aging-related mechanisms of formation and function of adipocytes (or fat cells) within tissues of the aging musculoskeletal system as well as effects of those adipocytes on the function of aging bone, muscle, and cartilage.
- Adequate intake of Vitamin D is essential to maintenance of strong bones. Ongoing NIA-supported investigators are exploring the mechanisms by which Vitamin D encourages bone strength, and are working to determine the optimal daily intake of Vitamin D for African American and Caucasian women.

#### Item

##### ***Demography***

The Committee encourages NIA to sustain its commitment to the demography of centers program. These centers coordinate key data collection and dissemination activities that benefit the entire field of population aging research and inform public policy issues, such as reform of federal entitlement and health care programs. The Committee also congratulates NIA for elevating the dialogue surrounding global aging issues by hosting with the Department of State the Summit on Global Aging. (p. 134)

#### Action taken or to be taken

The NIA Centers on the Demography and Economics of Aging program was established in 1994. The purpose of the centers is to foster research in demography, economics and epidemiology of aging and to promote use of important datasets in the field. To achieve these aims, the centers support cores for infrastructure development and pilots to support seed projects. The thirteen current centers were awarded in 2004 and are entering their fifth year of support.

In 2007, NIA conducted an evaluation of the Demography Centers program intended to assess the overall effectiveness of the centers and to determine what changes might be warranted for a future funding cycle, including potential adjustments to program scope, goals, and objectives. Findings include:

- **Centers on the Demography and Economics of Aging Add Value:** The centers as a whole have met the stated objectives of the program, and the results to date have been even more creative and influential than what was expected at the outset of the centers program.
- **Interdisciplinary and Single-Disciplinary Emphases Are Appropriately Balanced:** Although there appears to be variability in balance between disciplinary and interdisciplinary research across Centers, the panel considered the Demography Centers program as a whole to be appropriately balanced.
- **Research Scope Should Be Rooted in Population Research but Informed by Other Fields:** The panel recommended that the centers continue to be rooted in population research but informed by psychological, biological, and other fields as appropriate.
- **No Major Changes Needed to Demography Centers RFA**

NIA plans to renew the Demography Centers through a solicitation for grant proposals in FY 2009.

The Summit on Global Aging, held in February 2007, provided a unique and important opportunity to catalyze greater international dialogue and encourage coordinated international studies about the health, economic, social, and security implications of this important issue. Additional information on the global aging issue is available in the report issued jointly by the Department of State and NIA: *Why Population Aging Matters: A Global Perspective*. Copies of this report have been sent to members of the NIH's authorizing and appropriations committees; the report is also available online at <http://www.state.gov/q/oes/rls/or/81537.htm>.

### Senate Significant Items

#### Item

#### ***Alzheimer's Disease***

Unless science soon finds ways to prevent, cure or more effectively treat Alzheimer's, by mid-century as many as 16 million persons will be living with this disease. To prevent this will require a stepped-up investment in a comprehensive Alzheimer research strategy that includes: basic investigator-initiated research to isolate the best targets for drug development; cost-effective interdisciplinary research across multiple institutions that shares data and

biological materials; multi-site clinical trials to test potential therapies; and larger-scale clinical studies, including neuroimaging techniques, to find early biomarkers of disease so as to speed drug discovery and to identify those at risk so treatment can start soon enough to make a difference. As the lead institute in Alzheimer research, the NIA is urged to expand its investment into finding more effective treatments and prevention strategies for at-risk individuals. (p. 138)

#### Action taken or to be taken

To expand and intensify the translation of basic research findings into clinical studies and human trials and expand its investment in AD research, NIA has launched a Translational and Drug Discovery Initiative. This ongoing initiative includes an Early Drug Discovery Program and a Preclinical Drug Development Program.

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" with SRI International.

In addition, the NIA established the AD Prevention Initiative, an intensive coordinated effort among several NIH Institutes, including the NIA, National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), and National Institute of Mental Health (NIMH), to accelerate basic research and the movement of basic research findings into clinical practice.

The Alzheimer's Disease Cooperative Study (ADCS) is a major Alzheimer's disease clinical trials effort. In October 2006, NIH announced a 6 year award for the ADCS to conduct several new clinical trials. The first clinical trial undertaken during the current award period will examine whether treatment with DHA, an omega-3 fatty acid, will slow decline in AD. This 18 month trial began in February 2007 and recently completed enrollment ahead of schedule. Other planned trials include:

- A trial of intravenous immunoglobulin (IVIg), a form of immunotherapy that boosts immune response and suppresses harmful inflammation, a possible risk factor for developing AD.
- A study of lithium, commonly used to treat bipolar disorder, to possibly reduce the risk of developing AD.
- A study of the impact of resveratrol on AD biomarkers and clinical outcomes in AD patients.

Item

***Biology of Aging***

The Committee commends the NIA for work it has done to improve understanding of the biological factors that regulate the processes of aging. These new discoveries have led many scientists to believe that it may become possible to postpone the onset of a wide range of fatal and disabling diseases, in a coordinated fashion, by retardation of the aging process. It is widely understood that chronic illness is a powerful driver of medical costs, which in the United States are expected to reach \$16 trillion annually by 2030. To alleviate this financial burden and to develop interventions that can extend health and longevity, the Committee urges the NIH to increase dramatically its annual investment in the biological basis of aging. (p. 138)

Action taken or to be taken:

NIA maintains a strong commitment to the support of studies of the biological factors involved in the aging process. Investigators supported by NIA's Biology of Aging Program (BAP) seek to better understand the basic biological mechanisms underlying the process of aging and age-related diseases. Basic biochemical, genetic, and physiological studies are carried out primarily in animal models, including both mammals and non-mammalian organisms (e.g. flies, worms, and yeast). In addition, NIA's Intramural Research Program includes highly productive laboratories devoted to cellular and molecular biology, genetics, immunology, and other areas of aging-related basic research.

A "Biology of Aging Summit" is planned for FY 2008 to review BAP's current research portfolio, identify areas of opportunity, and facilitate the formulation of cohesive and comprehensive plans for the future.

Item

***Bone Strength***

The Committee continues to encourage the NIA, in conjunction with the NIAMS, NIBIB, NICHD, NIDDK, NCRN and NHLB, to support research, including research on bone structure and periosteal biology that will achieve identification of the parameters that influence bone strength and lead to better prediction for prevention and treatment of bone diseases. (p. 138)

Action taken or to be taken:

Please refer to page 194 of this document for NIA's response to this item on bone strength.

Item

***Demographic and Economic Research***

The Committee urges the NIA to sustain its commitment to the Demography of Aging centers program and continue its current support of the economic and demographic components of the Roybal Centers for Applied Gerontology. . . .

Finally, the Committee commends the NIA for elevating the dialogue surrounding global aging issues by hosting with the Department of State the Summit on Global Aging. (p. 138)

Action taken or to be taken

Please refer to page 195 of this document for NIA's response to this item on demographic and economic research.

In 2007, the NIA conducted an evaluation of the Roybal Centers, intended to assess the overall effectiveness of the centers and to determine what changes might be warranted for a future funding cycle, including potential adjustments to program scope, goals, and objectives. The evaluators found that the Centers as a whole met the stated objectives of the program, and that the Centers' impact on specific research fields has been notable; in particular, the modeling of health and long-term health care costs conducted through the Centers is likely to be influential in future policy discussions.

There are currently ten Roybal Centers, whose long-range objectives are to improve the health, quality of life, and productivity of middle-aged and older people. NIA plans to renew the Roybal Centers through a solicitation for grant proposals in FY 2009.

Item

***Down Syndrome***

The Committee commends the NIA for its support of studies to examine the cellular, molecular and genetic bases for age-related neuropathological and cognitive abnormalities in people with Down syndrome. It encourages the NIA to further examine these abnormalities and to devise new methods for diagnosing and treating them. Given that all people with Down syndrome develop the neuropathological changes of Alzheimer's disease, and that many or most go on to suffer dementia, the NIA is encouraged to consider how studies of the Down syndrome population might enhance the ability to understand, diagnose and treat Alzheimer's disease. The Committee urges the NIA to collaborate with other institutes to address the issues that face elderly adults with Down syndrome. (pp. 138-139)

Action taken or to be taken

Please refer to page 194 of this document for NIA's response to this item on Down syndrome.

Item

***Epilepsy***

The Committee urges the NIA, working with the NINDS, to continue research on why epilepsy develops in association with diseases of the elderly and to develop

therapies to prevent the occurrence of seizures and to diminish their consequences in this population. (p. 139)

#### Action taken or to be taken

NIA supports a number of research projects related to epilepsy. For example, the Institute is currently supporting a number of basic neurobiological studies that have the potential to provide insight into the etiology and pathological mechanisms underlying epilepsy. NIA is also supporting a study looking at the impact of fluctuating anti-seizure drug levels in nursing home patients with epilepsy.

With NINDS, in 2007 the NIA re-issued a Program Announcement (PA) entitled “Collaborative Awards in Epilepsy Research for Junior Investigators,” the purpose of which is to stimulate basic, translational and clinical research in the field of epilepsy by promoting collaborations among junior investigators. The ultimate goal of this PA is to bring about meaningful advances in understanding the factors that contribute to the development of epilepsy, and to develop interventions and effective treatments that improve the quality of life of people with epilepsy. The NIA also is participating along with several other NIH Institutes on a PA entitled “Focal Cognitive Deficits in CNS Disorders.” The purpose of this PA is to promote the study of cognitive deficits experienced by persons with non-dementing disorders of the central nervous system, including epilepsy, as well as the secondary effects of these cognitive deficits on their health and quality of life. Research under this PA will also include the development of treatments for cognitive impairment in persons with non-dementing CNS disorders.

The NIA will continue to work with NINDS and other ICs via the Interagency Epilepsy Working Group to identify and support relevant research, including workshops. NIA staff participated in the NINDS conference on “Curing Epilepsy 2007: Translating Discoveries into Therapies” held in March 2007; at that conference, new “benchmarks” in epilepsy research were established. Initiatives undertaken through the NIH Neuroscience Blueprint, a framework to enhance cooperative activities among fifteen NIH Institutes and Centers that support research on the nervous system, may also facilitate progress in epilepsy research.

#### Item

##### ***Exercise and Aging***

Given the positive impact of exercise on many aspects of aging, from improved cognition and decreased depression to fewer falls and fractures, the Committee is very supportive of NIA’s taking additional steps in exercise research. (p. 139)

#### Action taken or to be taken

Several studies suggest that physical exercise may prevent physical disability, including impaired mobility, in healthy and frail older adults. To develop definitive evidence, NIA and grantee researchers have developed the LIFE (Lifestyle Interventions and Independence in Elders) study, a clinical trial testing the effects of a physical activity program vs. a health education program among older Americans. A successful pilot study (LIFE-P) showed both feasibility and positive preliminary data, permitting design and consideration of this large-scale clinical trial.

In addition, NIA is participating with several other NIH Institutes and Offices in coordinated research solicitations for basic and clinical studies of long-term weight maintenance, including clinical studies of behavioral, nutritional, exercise, or other interventions. NIA participates in the Health Maintenance Consortium (HMC), a trans-NIH activity with the goal of understanding the long-term maintenance of behavior change and effective strategies for achieving sustainable health promotion and disease prevention. NIA supports two studies under the HMC: A clinical trial to support maintenance of exercise adherence among older adults with osteoarthritis, and a trial evaluating an innovative, theory-based behavioral intervention to maintain physical activity in 50-70 year old adults who have recently become at least moderately active. Finally, NIA conducts a number of activities aimed at communicating the benefits of exercise to older Americans, including an Age Page on exercise and physical activity (see <http://www.niapublications.org/agepages/exercise.asp>) and an award-winning booklet and video, "Exercise: A Guide from the National Institute on Aging."

#### Item

##### ***Fragile X-Associated Tremor/Ataxia Syndrome [FXTAS]***

The Committee urges the NIA to expand its existing dialogue with the NINDS to fund research on FXTAS. Given the link between FXTAS and adult-onset disorders, this disease may serve as a gateway to understanding parkinsonism and dementia. The NIA is urged to participate in the NIH's efforts to develop a coordinated design of Fragile X research strategies and public-private partnership opportunities as they relate to FXTAS. (p. 139)

#### Action taken or to be taken:

Fragile X-associated tremor/ataxia syndrome (FXTAS), which involves progressively severe tremors, difficulty with walking and balance, and dementia, affects at least 1/3 of men over 50 years of age who carry certain mutations in the FMR1 gene. The NIA supports research into this disorder. For example, an ongoing NIA-supported study aims to identify the molecular basis for FXTAS, and another, supported by the NIA via the NIH Road Map, focuses on the development of targeted treatments for FXTAS. NIA staff from both the Intramural and Extramural Programs also participate in the NIH Fragile X Research Coordinating Group. This group has begun work on a trans-NIH

research plan, which will be developed in partnership with the scientific community, advocacy groups, and other pertinent Federal agencies. A scientific meeting to refine the NIH research agenda is planned for the Spring of 2008.

NIA's participation in the NIH Roadmap Epigenomics Program, which explores DNA modifications that are not the result of a change in the coding sequence of genes, may also stimulate further research in this area; notably, FXTAS is associated with abnormal DNA methylation, a type of epigenomic change. Although not directly focused on FXTAS, these basic studies have the potential to provide insight into the etiology and pathological mechanisms underlying the disease. Finally, NIA co-sponsors a trans-NIH research solicitation on drug discovery for nervous system disorders, which may well encourage the development of new treatments for this condition.

#### Item

##### **Healthy Brain**

The Committee encourages the NIA's cooperation with other Institutes and Centers on the Healthy Brain Project. (p. 139)

#### Action taken or to be taken

NIA is 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. A perspective on the Healthy Brain Initiative and related research supported by NIA and NIH was published in the April 2007 supplementary issue of *Alzheimer's and Dementia*. Also in 2007, the 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.

During FY 2008, the CEHP partners intend to complete and/or further develop/expand two resources – an online bibliography of extant literature (which will be a living document) and a database of large longitudinal and epidemiological studies that have captured data on cognitive and emotional health risk and prevention factors.

#### Item

##### **Hematology**

The Committee commends the Institute for its increased emphasis on research in

thrombotic disorders and anemia in the elderly. The frequency of other hematologic diseases, including most of the blood cancers, also increases dramatically with age. The Committee encourages the NIA to further its efforts in research in hematologic issues affecting the elderly, including hematologic malignancies and anemias of inflammation and chronic disease. (p. 139)

#### Action taken or to be taken

In follow-up to a workshop to explore the clinical implications of anemia in the elderly and identify a research agenda for this topic, a solicitation for grant applications addressing clinical translational research on anemia in the elderly was released in August 2005. Eight grants have been funded by NIA and NHLBI in FY2007 and are ongoing. The funded applications address a broad range of issues relevant to the pathophysiology of anemia in older patients, and several applications include a major translational focus in identification and testing of new therapeutic agents.

In November 2006, the NIA, in collaboration with the NHLBI and the NIH Office of Dietary Supplements, released two Requests for Applications (RFAs) on Venous Thrombosis and Thromboembolism in the Elderly. Information from the research supported by this initiative should improve understanding of factors that contribute to the age-related increase in risk of thrombosis and thromboembolism and translate to improvements in diagnosis, treatment, and prevention. NIA hopes that these RFAs will stimulate interest and lead to further collaborative activities on this topic.

#### Item

##### ***Stereotypes***

The NIA is encouraged to expand its work on the role of stereotypes in the functioning of the aging and elderly. The Committee is interested in the social and cultural transformation that is taking place as the population ages, and as the workforce ages, and encourages additional research on stereotypes that may hinder or otherwise affect how our society manages the transformation. (p. 139)

#### Action taken or to be taken

NIA recognizes that older people may be the target of inaccurate and negative stereotypes. Accordingly, NIA's revised Strategic Directions document indicates the Institute's intent to examine the bases for individual and societal attitudes toward older people and to develop effective strategies to improve them. One avenue for such research is an expanded emphasis on social and affective neuroscience, a field that addresses relations between neural, endocrine, and immune systems and aspects of emotional function, social behavior and the sociocultural environment, including stereotypes and stereotyping. NIA conducted an exploratory workshop on the social neuroscience of aging in February 2007, and is participating with the National Institute of Mental Health in a research solicitation on basic and translational opportunities in the social

neuroscience of mental health. NIA is also currently funding several research grants under a separate research solicitation on social neuroscience, this one co-sponsored by the National Institute on Drug Abuse and the National Institute on Alcohol Abuse and Alcoholism.

# National Institute of Arthritis and Musculoskeletal and Skin Diseases

## House Significant Items

### Item

#### ***Burden of skin diseases***

The Committee continues to urge NIAMS to strengthen the research portfolio on skin disease and develop partnerships with the skin disease research community to address recognized challenges and future research questions. The Committee is especially concerned about epidermolysis bullosa (EB), a rare, genetic skin disease characterized by severe blistering and sores on the skin and, in some cases, on mucous membranes, the external surface of the eye, as well as the respiratory, gastrointestinal and genitourinary tracts. The Committee also notes the importance of autoimmune diseases, such as scleroderma, in the overall burden of skin diseases. (p. 150-151)

### Action taken or to be taken

As part of the trans-NIH effort to re-engineer the clinical research enterprise, a new way to measure patient-reported outcomes such as pain, physical functioning (including itch), fatigue, emotional distress, and social interactions that have a major impact on quality-of-life across a variety of chronic diseases is under development. This effort, PROMIS, which stands for, "Patient-Reported Outcomes Measurement Information System," is one of the first initiatives supported by the NIH Roadmap for Medical Research. The major product from this initiative will be a streamlined, computer adaptive testing system, in which subsequent questions concerning patient-reported outcomes are determined by a patient's response to prior questions. This system will be very useful for researchers studying patient groups affected by any number of chronic diseases within NIAMS mission areas.

Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited blistering disease, and RDEB patients suffer from debilitating, chronic wounds of the skin over much of their bodies and the mucosal surfaces of the mouth and esophagus. RDEB is caused by a defect in the gene for type VII collagen (C7), a structural protein that is essential for keeping skin layers together. Recently, NIAMS-supported researchers engineered cells from RDEB patients to express high levels of normal human C7 and found that these cells made more C7 than cells from a healthy volunteer. Furthermore, when the engineered cells were injected into the bloodstream of injured mice, the cells took up residence directly in the wounds. These wounds also healed faster than those receiving normal cells. This accomplishment in wound healing may provide significant improvement for epidermolysis bullosa patients, due to the challenge of treating multiple, widespread lesions. Other patients with chronic wounds may benefit as

well.

NIAMS supports a diverse portfolio examining the causes of and potential treatments for scleroderma, a debilitating disease characterized by thickening of the skin (fibrosis), blood vessels, and internal organs. In addition to new research examining health-related quality-of-life in patients with scleroderma, NIAMS-supported researchers recently developed a mouse model of the disease. The model provides direct evidence that tumor necrosis factor beta (TGF- $\beta$ ), a naturally-occurring hormone-like substance, plays a role in the development of the fibrosis associated with scleroderma. It also provides a new tool to further our understanding of the mechanisms of the disease and for future testing of potential therapeutics.

#### Item

##### ***Psoriasis***

The Committee encourages NIAMS to expand and coordinate genetic, clinical, and basic psoriasis and psoriatic arthritis research, with emphasis on the cellular and molecular mechanisms of disease; understanding the genetics that lead to psoriasis susceptibility; the role of inflammation in psoriasis co-morbidities such as obesity, depression and heart disease; and studies to ascertain if aggressive early treatment of psoriasis can prevent or mitigate psoriatic arthritis, which often appears as much as a decade after psoriasis. (p. 150-151)

#### Action taken or to be taken

Psoriasis is an autoimmune disease that results in the overproduction of new skin cells. These areas or “plaques” cycle new cells to the skin surface over the course of a few days, as opposed to an entire month in healthy skin, causing unsightly regions of inflammation that can lead to significant discomfort and disability.

NIAMS supports diverse efforts to combat psoriasis. For example, stemming from the observation that psychological stress seems to cause or exacerbate psoriasis, researchers supported by NIAMS are investigating a potential mechanism that may trigger increased disease activity. This research may lead to the development of better ways to control psoriasis. Several NIAMS-funded investigators are testing novel therapeutic treatments for psoriasis. These include reagents directed against skin cells that divide too rapidly, as well as more effective ultraviolet light and topical (applied to the skin) treatments. Other NIAMS-funded investigators are studying the basic biology of skin cells in psoriasis and immune responses contributing to the disease.

In addition to these projects, other NIAMS-supported researchers are examining genetic components of psoriasis in order to develop new therapies for the disease. For example, NIAMS-supported researchers are using information recently made available through the NIH-supported Genetic Association

Information Network to identify genes associated with susceptibility to psoriasis, which may result in the discovery of biomarkers and targeted treatment options.

NIAMS also recently funded a new Center of Research Translation (CORT) in psoriasis. The CORT mechanism is designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics. Researchers at this CORT will test a novel photodynamic psoriasis therapy for safety and efficacy. Complementary studies will investigate the roles of S100 proteins which have long been known to be expressed at high levels in inflamed skin of psoriasis patients. Researchers will also use a novel mouse model of psoriasis to examine the development of the disease.

Furthermore, NIAMS sponsored a roundtable discussion in 2007 that was centered on psoriasis, psoriatic arthritis, and rheumatoid arthritis. Attendees examined the most promising scientific opportunities and critical needs as seen by the research community. Specifically, inflammation-related molecular pathways, genetic studies, co-morbidities and common biomarkers, applicable technological breakthroughs, and clinical trials were discussed. Information gathered at this roundtable will be considered during the NIAMS long-term scientific planning and priority-setting process.

#### Item

##### ***Mucopolysaccharidosis (MPS)***

In previous years, the Committee has encouraged NIAMS to support and work collaboratively with NIDDK in an effort to achieve a greater understanding of bone and joint lesions in MPS disorders. Research focused on the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored and potential therapeutic approaches continue to be of interest to the Committee. In its congressional justification, the Institute noted that it would welcome applications for musculoskeletal-related research related to MPS. It also noted its meetings with NIDDK, NINDS and MPS patient advocates to examine opportunities for collaboration. The Committee is interested in further information on the outcome of these efforts and the steps that are being taken to encourage progress in this area of study. (p. 151-152)

#### Action taken or to be taken

Mucopolysaccharidoses (MPS) are a group of genetic, progressive disorders that are caused by the absence or malfunctioning of certain enzymes needed to break down molecules called glycosaminoglycans - long chains of sugar carbohydrates in each of our cells. When mutations occur in the genes for the enzymes involved in the normal turnover of mucopolysaccharides, excess amounts of them are stored in the body, causing progressive damage to a number of different organs and tissues, and, in most cases, early death.

There are no current cures for MPS, although cell transplants and enzyme replacement therapy show potential for reducing symptom severity. Treatment for the skeletal abnormalities remains a challenge due to the difficulty of introducing replacement enzymes or transplanted cells into skeletal tissues. NIAMS continues to encourage investigator-initiated research focused on the skeletal complications associated with MPS, and welcomes the opportunity to discuss potential mission-related, trans-NIH collaborations with relevant Institutes and Centers. Although the greatest benefit is likely to be discovered through MPS research supported by other NIH components, ongoing research at the NIAMS in other areas of skeletal research may help to inform the science base and potentially improve the quality of life of patients with the disease.

#### Item

##### ***Lupus***

The Committee is aware that despite numerous important research advances, few new therapies are available to patients with lupus. Treatment with steroids, anti-inflammatory agents and immunosuppressive medications may be palliative, but these medications have numerous side effects and may become less effective over time. Advances in the identification of lupus susceptibility genes and biomarkers make it important to translate these research advances into clinically relevant treatments. The Committee encourages the Institute to develop focused programs designed to move research advances from the laboratory to the patient's bedside so that the complications of lupus and the underlying disease can be treated more effectively. (p. 151)

#### Action taken or to be taken

While lupus has long been believed to have a strong genetic component, the identification of the exact genes responsible for the disease has remained elusive. However, collaborations between researchers in the Intramural Research Program at the NIAMS and their colleagues have produced evidence that a particular gene, STAT4, may play a significant role in the onset of immune system diseases including lupus and rheumatoid arthritis. Patients who carry two copies of the variant form of STAT4 have more than double the risk for suffering from lupus. This discovery may lead to improved genetic screening for lupus.

A NIAMS-supported retrospective review of military medical records revealed that symptoms and organ-associated autoantibodies precede the diagnosis of lupus. Autoantibodies were harbingers of lupus-associated kidney disease in a subset of patients while arthritis was the most common clinical symptom observed prior to the onset of lupus. Some biological response modifier therapies for arthritis could be cause for concern in managing lupus patients. More accurate preclinical diagnosis of lupus could avoid inappropriate, and potentially harmful treatments, and possibly pre-empt emergence of disease.

Lupus patients often undergo cyclic periods of relative wellness alternating with

times of illness which are called flares. NIAMS-supported researchers have recently found the production of antibodies such as anti-dsDNA and complement C3a, a substance that aids in the breakup and removal of immune complexes from the body, foreshadowed flares of lupus. More importantly, by using these early warning signs, researchers were able to prevent flares and decrease overall lupus activity. Monthly checks of anti-dsDNA and C3a may help to predict severe flares and that therapy with a common, inexpensive treatment such as prednisone may be highly effective.

NIAMS recently funded a new Center for Research Translation (CORT) in lupus. The CORT mechanism is designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics. Research conducted at the CORT may help to identify early markers for lupus and assist in predicting disease progression. Additionally, in 2007, the NIH released The Future Directions of Lupus Research, a scientific planning document that was developed with input from experts from the lupus research community and beyond. The plan serves as a guide for the lupus research community by illustrating the scientific needs and challenges that exist, and highlighting translational research that could facilitate the development of effective clinical treatments.

#### Item

##### ***Musculoskeletal Trauma and Skeletal Pain***

The Committee recognizes that of the 29.7 million Americans who are treated for injuries at U.S. hospital emergency departments, more than 40 percent have injuries to the musculoskeletal system. In the U.S., back pain is a major reason listed for lost time from work. The Committee encourages NIAMS, NIA, NIDCR, and NCCAM to study ways to better understand the epidemiology of back pain, improve existing diagnostic techniques, as well as develop new ones. The Committee also encourages NIAMS, NIBIB, NICHD, NIDCR, NIDDK and NIA to expand research to improve diagnostic and therapeutic approaches to lower the impact of musculoskeletal traumas, as well as research on accelerated fracture healing-including the use of biochemical or physical bone stimulation, the role of hematopoietic niches to preserve bone stem cells, the use of mesenchymal bone stem cells, and biomaterials and biologicals in bone repair and regeneration- and research into repair of nonunion fractures in osteogenesis imperfecta. (p. 151-152)

#### Action taken or to be taken

Results from the largest trial to date comparing surgical and non-surgical interventions for the treatment of low back pain are shedding new light on treatment options for certain conditions. For example, degenerative spondylolisthesis is a condition in which breakdown of the cartilage between the vertebrae of the spine causes one vertebra to slip over the one below, which can put pressure on the nerves, resulting in pain in the buttocks or legs with walking

or standing. Results from a new study indicate that a surgery called decompressive laminectomy, which relieves pressure on the nerves, provides significantly better results than non-surgical alternatives. The study is the second in a series of findings from the Spine Patients Outcomes Research Trial (SPORT), a five-year, multicenter study supported by the NIAMS, ORWH, and the National Institute of Occupational Safety and Health. SPORT found that patients who were treated with non-surgical alternatives reported modest improvements in their condition. However, those who received the surgery reported significantly reduced pain and improved function. Furthermore, for the surgery group, relief from symptoms came quickly. These results will provide patients and their health care providers with valuable information when considering the best treatment option.

In addition to ongoing research designed to enhance our understanding of areas such as the effectiveness of current treatment strategies and the molecular regulation of fracture repair, NIAMS provided support for the American Academy of Orthopaedic Surgeons (AAOS) 2007 Research Symposium on “Fracture Repair: Challenges and Opportunities.” This event convened leaders in the field of fracture healing research and explored the current knowledge of the cellular, molecular and engineering aspects of bone repair and regeneration. Additionally in the spring of 2007, NIAMS sponsored a roundtable discussion that was centered on musculoskeletal injury and trauma. Attendees examined the most promising scientific opportunities and critical needs in basic, translational, clinical, and epidemiology research as seen by the research community.

Osteogenesis imperfecta (OI) results from a genetic defect that affects the body’s production of collagen, the major protein of the body’s connective tissue. A person with OI has either less collagen or a poorer quality of collagen than normal, leading to weak bones that fracture easily. Researchers supported by the NIAMS have identified a gene (cartilage-associated protein or CRTAP) that is linked to the development of OI. This finding will have a significant impact on OI diagnosis and should lead to more comprehensive genetic counseling for individuals and family members affected by the disease. NIAMS was joined by the NIDCR, NIEHS, and NIDCD in providing funding for this study.

### **Senate Significant Items**

#### Item

#### ***Congenital and Genetic Disease of Bone***

The Committee understands that the science of genetics has led to a greater understanding of numerous systems that affect bone health, but little of this technology is being applied to bone research. The Committee encourages the NIAMS and NICHD to support research focusing on mechanisms for preventing fractures and improving bone quality and correcting malformations; on innovations in surgical and non-surgical approaches to treatment; on physical

factors that affect growth; and on genetic defects that cause bone disease. Furthermore, the Committee urges the NIAMS, NICHD, NIDCR, and NIDDK to expand research on skeletal stem cell biology and the genetics and pathophysiology of rare disorders such as fibrous dysplasia, meliostosis, XLinked hypophosphatemic rickets and fibrodysplasia ossificans progressiva. (p. 140)

#### Action taken or to be taken

NIAMS supports a broad portfolio of research in bone biology and diseases. For example, researchers are examining how stem cells may be used to treat bone disorders, including the potential of using a patient's own stem cells to correct the deleterious effects of disease. Other researchers are investigating the genetic basis of skeletal fragility by identifying factors that regulate bone structure. In addition to ongoing research designed to enhance our understanding of the molecular regulation of fracture repair, NIAMS provided support for the American Academy of Orthopaedic Surgeons (AAOS) 2007 Research Symposium on "Fracture Repair: Challenges and Opportunities." This event convened leaders in the field of fracture healing research and explored the current knowledge of the cellular, molecular and engineering aspects of bone repair and regeneration.

Osteogenesis imperfecta (OI) results from a genetic defect that affects the body's production of collagen, the major protein of connective tissue. A person with OI has either less collagen or a poorer quality of collagen than normal, leading to weak bones that fracture easily. Researchers supported by the NIAMS have identified a gene (cartilage-associated protein or CRTAP) that is linked to the development of OI. This finding will have a significant impact on OI diagnosis and should lead to a more comprehensive genetic counseling for individuals and family members affected by the disease. NIAMS was joined by the NIDCR, NIEHS, and NIDCD in providing funding for this study.

X-linked hypophosphatemic rickets is a disorder in which the bones become soft and bend easily because the blood contains low levels of phosphate, which bones need in order to grow properly. NIAMS is supporting a Center of Research Translation (CORT) in X-linked hypophosphatemic rickets. This CORT is studying the various molecular contributors to this genetic form of rickets and working toward developing new treatments. The CORT mechanism provides unique opportunities to study basic and clinical facets of disease, speeding the translation of research into effective new treatments.

Fibrodysplasia ossificans progressiva (FOP) is one of the rarest genetic diseases, and results in muscles, ligaments, tendons, and other connective tissue gradually turning into bone. One critical step to understanding and eventually treating this condition was made by researchers funded in part by the NIAMS. Researchers reported the discovery of a disease-causing mutation of a gene called ACVR 1, which encodes a protein called activin receptor type 1A,

which in turn controls the formation of cartilage and bone. The discovery of the mutation immediately suggests two possible approaches to treatment: either to block the renegade proteins, or to destroy the message coming from the mutant copy of the gene that creates them. Although clinical treatments are still some years away, this is a crucial advance in understanding the disease and developing those treatments.

Item

***Lupus***

The Committee urges the NIAMS to expand and intensify genetic, clinical, and basic research on 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. 140)

Action taken or to be taken

Please refer to page 207 of this document for NIAMS' response to this significant item regarding lupus.

Item

***Lymphatic Research and Lymphatic Diseases***

The lymphatics are central to the function of bone, muscle, skin and joint tissues. The Committee urges the NIAMS to place a high priority on research in lymphatic biology and disease, with the goal of improving the understanding of inflammatory, autoimmune and fibrotic mechanisms that impact a myriad of diseases and bodily functions. (p. 140)

Action take or to be taken

The body's ability to detect infection and tissue injury occurs via immune cells that are resident in organ tissues, and immune cells that traverse the body tissues via the cardiovascular and lymphatic systems. Immune cells interact with each other and organ tissue cells in a cell-to-cell manner. Local and long distance communication is also involved via chemicals such as hormones and their respective receptors. The interrelated functions of protecting injured tissues from infection and providing for tissue maintenance and repair of injuries, puts the immune system in constant interaction with bone, muscle, skin and joint tissues.

The NIAMS has joined several other NIH components in sponsoring the Program Announcement entitled "Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases." The purpose of this funding announcement is to encourage researchers to examine the developmental, molecular, and cellular defects that cause lymphedema, and new treatments for both primary and secondary lymphedemas. NIAMS welcomes highly meritorious applications

focused on the research areas relevant to the Institute's mission.

Item

***Marfan Syndrome***

The Committee commends the NIAMS for the leading role it has played in advancing basic research on Marfan syndrome. The Committee notes with interest an NHLBI-sponsored clinical trial on the potential benefits of the drug losartan in addressing the cardiovascular manifestations of Marfan syndrome. The Committee encourages the NIAMS to partner with the NHLBI on this research where appropriate, including support for ancillary studies that fall under the mission and jurisdiction of the NIAMS. (p. 140)

Action taken or to be taken

Marfan syndrome is a genetic condition that adversely affects connective tissue throughout the body. While the most serious symptoms generally pertain to the cardiovascular system in the form of weakened heart valves and blood vessel walls, patients also suffer from skeletal abnormalities and muscle growth defects.

Currently, a mouse model is available for Marfan syndrome research. However, a larger animal model would facilitate the development of surgical and non-surgical methodologies that could potentially improve the quality of life of patients with the disease. NIAMS-supported researchers are attempting to produce a new pig model that is based on the existing mouse model made possible by the manipulation of fibrillin-1, a gene known to be mutated in people with Marfan syndrome. Through the inactivation and modification of this same gene in pigs, the researchers intend to produce a large animal model that would be a vital tool in future studies designed to increase our understanding of Marfan syndrome. NIAMS encourages additional highly meritorious applications in mission-related research in Marfan syndrome, and welcomes the opportunity to collaborate with other NIH components supporting research in this area.

NIAMS-funded researchers have also begun a new project in a separate research area that could provide significant insight into Marfan syndrome. Weill-Marchesani syndrome is a rare connective tissue disorder that stems from a mutation of the ADAMTS10 gene. Preliminary results have indicated a connection between fibrillin-1 and ADAMTS10. Consequently, scientists are monitoring fibrillin-1 in ADAMTS10 deficient mice. This research could provide additional information on the mechanisms that cause both diseases.

Item

***Musculoskeletal Trauma and Skeletal Pain***

The Committee urges the NIAMS, NIA, NIDCR, and NCCAM to study ways to better understand the epidemiology of back pain and improve existing diagnostic techniques, as well as develop new ones. The Committee also encourages the NIAMS, NIBIB, NICHD, NIDCR, NIDDK and NIA to expand research to improve

diagnostic and therapeutic approaches to lower the impact of musculoskeletal traumas, as well as research on accelerated fracture healing--including the use of biochemical or physical bone stimulation, the role of hematopoietic niches to preserve bone stem cells, the use of mesenchymal bone stem cells, and biomaterials and biologicals in bone repair and regeneration--and research into repair of nonunion fractures in osteogenesis imperfecta. (p. 140)

Action taken or to be taken

Please refer to page 208 of this document for IC's response to this significant item regarding musculoskeletal trauma and skeletal pain.

Item

***Paget's Disease***

The Committee urges the NIAMS to continue to study the prevalence, cause, and treatment of Paget's disease. (p. 140)

Action taken or to be taken

Paget's disease, the second most common bone disease after osteoporosis, is a chronic disorder that can result in enlarged and misshapen bones. Paget's disease is a disorder of bone remodeling, the process in which old bone is removed (resorption) and new bone is added to the skeleton (formation). In Paget's disease, osteoclasts - the cells that resorb bone - are increased in size and have increased resorption capacity. The increase in bone resorption triggers excessive bone formation, resulting in pain, malformation, and an increased risk of fractures in affected bone. The underlying causes of Paget's disease are complex and are poorly understood. Contributing factors likely include chronic infection with certain viruses and inherited predisposition to develop the disease in some families. However, it is clear that a key feature of the disease is excessive numbers and activity of osteoclasts.

A mutated form of the gene for a protein called p62, which is produced by osteoclasts, has been implicated in Paget's disease. However, not all people with the mutation develop the disease, and not all who have the disease have defective p62 protein. Researchers supported by NIAMS now know that defects in p62 increase the sensitivity of osteoclasts to certain cell signaling molecules that stimulate bone resorption. This finding suggests that compounds targeting the activity of p62 might be able to reduce the severity of Paget's disease in some patients. Furthermore, such compounds also might be useful in treating other disorders arising from excessive bone resorption.

Other researchers supported by NIAMS are using a newly developed mouse model of Paget's disease to determine the extent to which the p62 mutation contributes to the development of the disease. The researchers are attempting to determine the effect of the p62 mutation on the signaling pathways that regulate both osteoclast and osteoblast (bone forming cells) formation, function, and

survival. This unique mouse model will allow the researchers to determine the specific mechanisms by which the p62 mutation contributes to the development of Paget's disease, and will also serve as a valuable research tool for identifying other environmental and genetic factors contributing to it.

Item

***Psoriasis***

The Committee strongly urges the NIAMS to expand genetic, clinical, and basic research related to the understanding of the cellular and molecular mechanisms of psoriasis and psoriatic arthritis research. Moreover, additional attention is needed to conclusively identify the major psoriasis gene as well as others that contribute to psoriasis and/or psoriatic arthritis genetic susceptibility. The Committee is concerned about recent studies illustrating an elevated risk for certain chronic diseases, such as heart attack and diabetes, among individuals with psoriasis, and therefore urges the NIAMS to examine the relationship between co-morbidities and psoriasis, including shared molecular pathways. Further, the Committee encourages the NIAMS to undertake studies to understand individual response to particular therapies for psoriasis and psoriatic arthritis, determine if psoriatic arthritis can be prevented in those who are at risk, and examine joint inflammation and the associated damage caused by psoriatic arthritis. (p. 141)

Action taken or to be taken

Please refer to page 205 of this document for NIAMS' response to this significant item regarding psoriasis.

Item

***Tuberous Sclerosis Complex (TSC)***

The Committee urges the NIAMS to support clinical trials that specifically target skin manifestations of TSC (facial angiofibromas, hypomelanotic macules, Shagreen patches, etc.). The Committee also urges the NIAMS to support basic research on the mTOR signaling pathway and the role of the TSC1/2 genes in skin and muscle cells. (p. 141)

Action taken or to be taken

Tuberous sclerosis complex (TSC) is a rare genetic disease characterized by the growth of noncancerous tumors at various places in the body, including on the skin. Skin may be affected by thickened, pebbly patches (Shagreen patches), red or pink bumps (angiofibromas), or depigmented "ash-leaf" spots (hypomelanotic macules). The genes that cause TSC (TSC1 and TSC2) are known, understanding of the pathways in which they act is increasing, and animal models that mimic certain features of the disease now exist. As a result, there is an opportunity to increase our knowledge about the mechanisms that cause TSC and translate this knowledge into therapies. To further the understanding of TSC, the NIAMS joined NINDS, NIDDK, NIMH,

and NCI in reissuing a Program Announcement designed to encourage research in areas such as preclinical therapy development and clinical research. NIAMS encourages highly meritorious applications in mission-related research and welcomes opportunities to collaborate with other NIH components to support research targeted at the causes and treatment of the skin manifestations of TSC.

Additionally, NIAMS-supported researchers continue to examine the signaling abnormalities from the genes that have been identified as contributing to TSC using a novel mouse model, as well as studying the role of the mTOR (mammalian target of rapamycin) signaling pathway in the development of muscle and skin cells. This research will broaden the base of knowledge which may lead to therapies that can prevent or ameliorate the skin manifestations associated with TSC, as well as other skin disorders in humans.

# National Institute on Deafness and Other Communication Disorders

## House Significant Items

### Item

#### ***Tinnitus***

The Committee recognizes that tinnitus, characterized by loud ringing in the ears, can be a severely debilitating medical condition. While tinnitus disproportionately impacts military personnel exposed to explosive devices or loud noise, it also affects people of all ages, including children and the elderly. In 2005, the NIDCD held a workshop to explore areas of needed research for the treatment and cure of tinnitus. The Committee encourages NIDCD to follow up on the workshop's recommendations, including increasing collaboration 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. 152)

### Action taken or to be taken

Please refer to Page 225 of this section for the NIDCD response to this significant item.

## Senate Significant Items

### Item

#### ***Animal Models of Plasticity***

The Committee emphasizes the importance of research into the brain's response to and changes due to stimulation by sound or electricity, as hearing loss will increasingly be ameliorated through advanced restorative technologies such as amplification devices and cochlear prostheses. Focus should be on how hearing loss changes the central nervous system, with studies at the level of synaptic connections through studies of perceptual learning. These should include studies of neural coding, neural network function, and "critical periods" during life when central auditory processing is affected. The Committee also encourages the use of new methodologies, including computational models, emerging optical tools and new anatomical methods and models. (p. 141)

### Action taken or to be taken

NIDCD understands that animal models for human disease to study the underlying processes of communication disorders are essential. Scientists can also use these techniques to understand how the central nervous system and the sensory organs involved in human communication recover or adapt to injury or damage by reorganizing connections (synapses) among neurons – an ability known as "plasticity." NIDCD intramural scientists are using functional imaging

techniques to understand how the brain constructs networks of interacting regions (i.e., neural networks) to perform cognitive tasks, especially those associated with audition and language, and how these networks are altered in brain disorders. Brain activation patterns characterized using PET, fMRI, EEG, MEG and other brain mapping techniques are used to describe and treat human communication disorders. The scientists are also studying functional, structural and neurochemical changes in the course of recovery from stroke.

#### Item

##### ***Early Detection and Intervention***

The Committee continues to support expanded research on early detection, diagnosis and optimal intervention strategies for infants identified at birth with hearing loss and other communication disorders. The Committee urges the NIDCD to accelerate efforts to define the role of congenital exposure to cytomegalovirus in progressive hearing loss in childhood and foster research to identify novel effective intervention strategies to prevent otitis media and lessen dependence on antibiotic therapies. (p. 141-142)

#### Action taken or to be taken

The NIDCD is supporting a wide variety of research aimed at detecting, diagnosing, and intervening to help infants identified at birth with hearing loss. For example, NIDCD sponsored a workshop on Outcomes Research in Children with Hearing Loss on December 2006, to determine and prioritize research needs and discuss design considerations unique to outcomes research in children with hearing loss. The NIDCD used the information generated by this workshop to develop three funding opportunity announcements (FOAs) that focus on the contemporary population of young children with mild to severe hearing loss. Their goal is to improve understanding of the development of children with hearing loss and the evaluation of current methods to diagnose and provide interventions for these children.

With regard to cytomegalovirus (CMV) and hearing loss, NIDCD is supporting a research contract with the University of Alabama School of Medicine, Birmingham, to lead a multicenter study, entitled the CMV and Hearing Multicenter Screening (CHIMES) Study. The research investigates the role of congenital CMV in the development of hearing loss in children. A major focus is the identification of asymptomatic children and following their progress to determine if hearing loss develops. The CHIMES study is one of the largest studies of its kind with approximately 100,000 children to be screened at birth for CMV infection. Those who test positive for CMV will undergo follow-up diagnostic hearing testing to determine the onset, severity, and progression of hearing loss. The scientists will analyze the data to better understand the relationship between CMV infection and hearing loss and to determine the extent to which CMV screening together with hearing testing can improve the detection and prediction of permanent hearing loss in children.

In the area of otitis media (OM) research, NIDCD is participating in a FOA entitled “Novel Approaches To Study Polymicrobial Diseases.” Previous NIDCD-supported research demonstrated that an intricate layer of bacteria growing on a membrane in the middle ear – a so called “biofilm” could be the source of the chronic form of OM. A biofilm is a topographically and ecologically rich community composed of bacteria affixed to a surface by means of long-chained sugars that the bacteria produce. Bacteria adhering to the biofilm form towers that create a wall of protection against the bacteria-devouring cells of the body’s immune system. In addition, although bacteria living on the periphery of a biofilm may be susceptible to antibiotics, those living near the center are resistant to their killing effects. This FOA encourages scientists to explore how viral infections or other disease may facilitate bacterial colonization and enhanced attachment of infectious agents (via biofilms or other means), such as those that cause otitis media. NIDCD intramural scientists are also studying the disease-causing properties of bacterial otitis media and developing a candidate vaccine that targets the three major OM pathogens: *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, and *Moraxella catarrhalis*. If successful, this vaccine will reduce the incidence of OM caused by the major bacterial pathogens in children.

#### Item

#### **Hearing Devices**

Recognizing that more people are receiving cochlear implants, the Committee recommends tissue engineering research to improve their efficacy and, for recipients of two implants, research to improve spatial hearing. The Committee also encourages the NIDCD to support research building on developments in brain stem prostheses. (p. 142)

#### Action taken or to be taken

NIDCD-supported research to improve sound localization using bilateral cochlear implantation (Bi-CI) (a cochlear implant in each ear) and preserving/restoring nerve health is important for improving life for hearing impaired individuals. NIDCD-supported scientists have investigated the benefits of Bi-CI in adults and children. Results show that they are significantly better at localizing sounds and hearing speech in a noisy room when they wear Bi-CIs compared with a single CI. In addition, within 1 to 2 years, children with Bi-CIs learn how to locate sounds, and the majority of Bi-CI children can now localize sounds better with two ears than one.

An NIDCD-supported research team developed a new CI design capable of delivering drugs to the inner ear. A drug called brain derived neurotrophic factor (BDNF) provides significant enhancement of auditory nerve function when delivered into the inner ear of guinea pigs. This finding suggests that BDNF delivery might be used to delay the degeneration of the auditory nerve typically

seen following hearing loss. Neural sensitivity to electrical stimulation (ES) was significantly improved in animals receiving this drug as compared to those receiving electrical stimulation alone; sensitivity to ES is an important factor for the successful function of a cochlear implant. Based on these promising results, future cochlear implant designs could include a drug delivery system in order to improve the long term health of the auditory nerve and thus maximize the individual's ability to hear with this device.

Auditory brainstem implants (ABI) were developed based on cochlear implant technology. They stimulate the hearing portions of the brain to restore some degree of hearing function to people with Neurofibromatosis Type 2 (NF2) who are deafened by bilateral tumors on their hearing and balance nerves. The NIDCD is actively supporting research to improve and test ABI prototypes. These implantable devices benefit deaf individuals unable to benefit from a conventional cochlear implant. Additionally, individuals have been successfully implanted with a new modified version of the ABI called the Penetrating Electrode Auditory Brainstem Implant (PABI). The PABI is a prosthetic device has an additional assembly of microelectrodes designed to penetrate into the cochlear nucleus. Both the ABI and PABI are undergoing clinical trials for both adults and children with NF2. NIDCD plans to capitalize on these emerging technologies to design and improve devices that enhance communication, to determine the best techniques for assessing performance, and to evaluate which devices can help specific groups of people who have a communication disorder.

#### Item

##### ***Environmentally Induced Hearing Loss***

The Committee remains concerned by the number of Americans who suffer from chemical and noise-induced hearing loss. It strongly supports informing the public of the risks to the auditory system from excessive noise, with special emphasis on young individuals. Therefore, the expansion of NIDCD's "Wise Ears" Campaign is greatly encouraged. (p. 142)

#### Action taken or to be taken

NIDCD sponsors and conducts research and education related to the prevention of noise-induced hearing loss (NIHL), and for the past eight years, has overseen a public education campaign called WISE EARS!®. This national campaign is sponsored by the NIDCD and the National Institute for Occupational Safety and Health (NIOSH) along with roughly 90 public and private partners to prevent NIHL in the general public and people who work in noisy environments. The campaign's objectives are to educate the public about the risks of NIHL and to motivate individuals and organizations to increase awareness about preventing NIHL.

In the summer of 2006, NIDCD evaluated WISE EARS! to determine how well the campaign was meeting its objectives and to make recommendations for the future direction of the campaign. Based on the evaluation's findings, NIDCD now plans to expand the program to refocus its efforts to children ages 8 to 12 (the "tweens"), to forge more mutually beneficial partnerships between all stakeholders (tweens, parents, health professionals, etc.), and to make use of delivery channels with the highest potential to engage this target audience.

In addition to using the information from the evaluation, NIDCD reviewed findings from a survey of how audiologists view the prevalence of NIHL among tweens and to learn about opportunities to educate children and their parents about the causes and prevention of NIHL. NIDCD also conducted focus group testing of tweens and their parents to learn about individuals' knowledge, feelings, and habits regarding the topics of NIHL and hearing protection. Lastly, NIDCD sponsored a workshop with experts in health communication to develop communication objectives for an NIHL campaign targeting tweens.

Supported by findings from the WISE EARS! evaluation, the survey, focus group testing and the workshop, NIDCD will begin developing materials for NIHL prevention for tweens and evaluate the effectiveness of these materials through more focus group testing. NIDCD is planning to launch the expanded campaign in 2008.

#### Item

#### ***Funding Strategies***

The Committee suggests that the NIDCD consider novel funding formats such as multi-year project periods, with the first several years devoted to technology development and the second several years devoted to implementation of the technology. The Committee also encourages the NIDCD to consider funding collaborations with foundations and/or other non-government funders of deafness-related research. (p. 142)

#### Action taken or to be taken

NIDCD encourages research on technology development and implementation through several mechanisms. For example, NIDCD utilizes the Small Business Innovation Research/ Technology Transfer (SBIR/STTR) mechanisms for small businesses to compete in technology development and implementation. Phase I grants provide funding for initiating an innovative technological concept and getting it to a working stage, and Phase II grants fund implementation into a marketable product for the public.

In addition, NIDCD uses the Contracts mechanism to develop and implement scientific concepts that are high risk but if successful, show exceptional promise. The intent of using a contract is to enable NIDCD to evaluate safety and efficacy

of a specific approach thoroughly in animal models, and then translate that technology to a small group of patients in an investigative study with tight control of expenses and the direction of the research.

A new NIDCD mechanism for addressing infrastructure needs for patient-oriented research is the R21/R33 grant. This mechanism may include technology development (biomedical informatics and information technology support such as data collection and management tools as well as electronic import and export of data) or administrative support (regulatory compliance, patient recruitment, informed consent and Institutional Review Board issues). These grants are phased with piloting and development occurring first in the R21 period and then expansion and translation of the application to clinical use in the R33 period. In addition, NIDCD participates in the BECON (Bioengineering Consortium) group, which is a trans-NIH committee that promotes technology development and implementation in a range of biomedical fields.

The NIDCD recognizes the potential benefits of collaborations with foundations and other non-government supporters of deafness-related research. [However, federal law determines how NIDCD can award its research funds to non-federal organizations. Subject to Section 429 of the Public Health Service Act, NIDCD may only obligate extramural research funds after each application for grant funds has undergone technical and scientific peer review and has been reviewed by the NIDCD Advisory Council. Thus, the NIDCD must issue each grant award to the applicant organization directly, and NIDCD may not transfer funds to an outside organization for the purpose of making grant awards. Some non-government foundations independently make small awards expressly to provide resources for otherwise unfunded investigators who need pilot data to submit a grant application to NIDCD, and this “leveraging for success” from small funds often benefits the whole research and clinical community.]

The NIDCD is permitted to partner with outside organizations when funds are gifted to the NIDCD. These gift funds and may be accepted on a conditional or an unconditional basis within established policy. The awarded grant projects remain solely an NIH/NIDCD grants and overall administration of the project(s) would be retained by the NIDCD. Each award would cite support or partial support from the partnering organization.

#### Item

#### ***Hereditary Hearing Loss***

The Committee urges the NIDCD to continue to support molecular and cellular research to identify the structure, regulation and function of genes whose mutation results in human communication disorders. In addition, acknowledging the progress of the HapMap Project, the Committee encourages the NIDCD to

consider large-scale screening of patients with hearing and other communication disorders to determine the loci of mutant genes relevant to susceptibility to manifestation of various outcomes. (p. 142)

#### Action taken or to be taken

NIDCD recognizes that one of the most rapidly developing areas of research is functional genomics, which involves determining the identity, structure, and function of genes whose mutation results in susceptibility to communication disorders. NIDCD-supported scientists are capitalizing on the wealth of knowledge available from the Human Genome Project to identify and/or describe inherited genetic mutations that cause communication disorders or play a role in susceptibility to conditions that impair communication. Some areas of active investigation include hereditary hearing loss, gene variants that predispose an individual to develop age-related hearing loss or noise-induced hearing loss, genetic mutations that cause syndromes that include hearing loss, balance disorders, loss of the sense of smell and/or taste, or other communication disorders, genes inherited by individuals who stutter, and identification of genes that permit detection of tastants (sweet, sour, salty, bitter) and odors.

With regard to deafness, NIDCD-supported scientists are examining target populations (for example, inbred families that carry deafness genes) to identify regions of DNA that may carry the mutation that causes deafness. Once a putative mutation-carrying region is identified, NIDCD-funded scientists compare as much DNA as possible from different families carrying deafness genes to published human DNA sequences found in databases. This helps them identify with more precision which region on the chromosome carries a mutation. The scientists must then sequence the mutated gene from the target population. In this way, they are identifying new genes responsible for hearing and for the maintenance of our ability to hear. When these important hearing genes are mutated, they disrupt hearing and result in hearing loss. By comparing normal and mutated genes involved in hearing, NIDCD-supported scientists are able to describe how the protein produced by that gene functions in the normal and mutated states.

#### Item

##### ***Inner Ear Hair Cell Regeneration***

The Committee applauds past support of regenerative studies and urges the NIDCD to continue to give a high priority to biological molecular and genetic research aimed at preventing the loss of hair cells and replacing lost and dying inner ear hair cells and other cells compromised by aging, drugs, noise and genetic conditions. The Committee encourages the NIDCD to build on animal studies demonstrating the possibility of regenerating lost sensory cells and the potential use of stem cells or endogenous precursors to replace lost sensory cells or auditory nerve cells. (p.142)

### Action taken or to be taken

More than 90 percent of hearing loss is sensorineural, which occurs when either sensory hair cells of the inner ear or auditory nerve cells are destroyed. Until recently, scientists believed that auditory hair cells in mammals could never be replaced if they were injured or destroyed. NIDCD-supported scientists continue to explore the biological, molecular, and genetic modalities that have the potential to prevent the loss of hair cells and to replace damaged and dying inner ear hair cells. In a recent landmark study, NIDCD-supported scientists treated deafened guinea pig ears with a harmless virus carrying the gene *Ato1*. Eight weeks after treatment the researchers found new hair cells in the ears treated with the *Atoh1* gene, and auditory testing confirmed that the generation of hair cells coincided with restoration of auditory threshold levels. This is the first demonstration of gene therapy that improved hearing in deafened animals.

Following this discovery, NIDCD-supported scientists are determining if the gene therapy approach used to deliver the corrected genes to the inner ear is safe and could be used in human therapy. Scientists are also working to identify the key groups of cells involved in the therapy, their interactions, and the molecules necessary to coordinate and regulate hair cell regeneration. In addition to the research highlights described above, NIDCD is supporting researchers investigating mammalian hair cell regeneration in several other laboratories.

NIDCD is planning several research initiatives to enable scientists to continue to study how supporting cells and stem cells in the inner ear interact with their immediate microenvironment. By understanding what molecular and cellular events stimulate hair cell regeneration, NIDCD-supported scientists hope to restore the ability to detect sound to individuals who have lost some or all of their hearing.

Additional NIDCD-supported scientists throughout the country are also working to understand what enables hair cell regeneration in non-mammalian systems, such as chickens and zebrafish. We anticipate that each year, information generated by NIDCD-funded researchers will bring us closer to an important goal: to regenerate functional hair cells in humans and restore hearing to those who have lost it.

### Item

#### ***Mouse Models***

The Committee recommends developing new mouse genetic models for in vivo studies of hair cell development, regeneration, and damage/protection, including models of hair cell damage not caused by aminoglycosides. (p. 142)

### Action taken or to be taken

Aminoglycosides are a class of antibiotics sometimes prescribed for a variety of severe bacterial infections. Unfortunately, aminoglycoside treatment can cause

degeneration of inner ear hair cells (ototoxicity) resulting in hearing loss. This kind of hearing loss is caused by environmental exposure to a drug, rather than by inheritance of a particular gene.

The NIDCD has developed a substantial research portfolio to study existing mouse mutants as well as creating new mouse models to facilitate the discovery and analysis of genes whose mutation causes hereditary hearing impairment in humans. Some of these mouse models have abnormal hair cells or develop hair cell degeneration with age. The NIDCD participates in the Knockout Mouse Project (KOMP). KOMP is a trans-NIH initiative that aims to generate a comprehensive and public resource comprised of mouse embryonic stem (ES) cells containing a null mutation in most of the genes in the mouse genome. The NIDCD is also pursuing research to increase the understanding of so-called susceptibility genes, which make an individual more susceptible to conditions such as noise-induced hearing loss, for example.

Mouse models are also playing an important role in our understanding of age-related hearing loss. An NIDCD-supported study discovered that mutated genes in mouse mitochondria significantly alter the severity of age-related hearing loss. This model system should provide important information regarding age-related hearing loss in humans, a relatively common and debilitating health problem within the aging U.S. population.

#### Item

##### ***Neurofibromatosis***

NF2 accounts for approximately 5 percent of genetic forms of deafness. The Committee therefore encourages the NIDCD to expand its NF2 research portfolio. (p. 142)

#### Action taken or to be taken

Neurofibromatosis Type 2 (NF2) is part of a group of inherited disorders and NF2 occurs in about one out of every 40,000 Americans. NF2 causes non-malignant tumors (called acoustic neuromas or vestibular schwannomas) to grow specifically in 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. A mutation on chromosome 22 is strongly associated with the development of NF2 bilateral nerve tumors.

The NIDCD supports ongoing research projects on how regulation of gene transcription is involved in vestibular schwannoma tumor genesis and how specific biochemical signaling pathways for growth are deregulated in vestibular schwannomas. NIDCD also continues to support technologies to enhance the successful treatment of individuals with NF2. Treatment of these bilateral acoustic neuromas often requires removal of these important sensory nerves on both sides, which renders the individual deaf and suffering a significant loss of

balance. NIDCD supports a R&D contract to develop a cochlear nucleus auditory prosthesis (Auditory Brainstem Implant or ABI) for individuals who have lost their hearing from NF2. This implantable device would be a benefit to deaf individuals that are unable to gain benefit from a conventional cochlear implant. The ABI has completed both Phase I and II clinical trials for both adults and children with NF2. Additionally, scientists have successfully implanted individuals with a new modified version of the ABI called the Penetrating Electrode Auditory Brainstem Implant (PABI). The ABI and PABI, based on cochlear implant technology, stimulates the hearing portions of the brain to restore some degree of hearing function to people deafened by bilateral tumors on their hearing and balance nerves. Furthermore, the NIDCD encourages further research applications in this area through Funding Opportunity Announcements for Patient-Oriented Research (PA-07-095), for Cell Lineage and Developmental Research (PA-07-127), and for Epidemiological Research on Disorders (PA-07-251).

#### Item

#### ***Tinnitus***

The Committee recommends that the NIDCD expand its research into causal mechanisms underlying peripheral and central tinnitus and pursue research to develop therapies for treatment. In 2005, the NIDCD held a workshop to explore areas of needed research for the treatment and cure of tinnitus. The Committee urges the Institute to devote additional resources to follow up on the workshop's recommendations, including increasing collaboration with the Department of Defense, and the Veterans Administration to support a multi-disciplinary research approach that promotes accurate diagnosis and treatment to cure tinnitus. (p. 143)

#### Action taken or to be taken

Tinnitus is a disorder without a cure. Because scientists do not fully understand the causes or know how to successfully treat this disorder, the NIDCD hosted a Tinnitus Research Workshop in 2005 and has implemented several of the recommendations from this workshop. There were many opportunities identified at the workshop, both immediate and longer-term (see [http://www.nidcd.nih.gov/funding/programs/wkshp\\_tinnitus.htm](http://www.nidcd.nih.gov/funding/programs/wkshp_tinnitus.htm)).

NIDCD published a Request for Applications (RFA) in response to the recommendations from the tinnitus workshop on Collaborative Research on Tinnitus (<http://grants.nih.gov/grants/guide/rfa-files/RFA-DC-08-002.html>). The RFA requires collaborative team efforts (including at least two distinct disciplines) in tinnitus research for a variety of topics and approaches identified at the workshop. Research opportunities exist for projects that use electrical stimulation in the brain to understand tinnitus; develop models to better predict which drugs and devices will work in humans; develop animal models that separate the effects of hearing loss from tinnitus; use models to establish

methods such as high-throughput analyses of transcripts and proteins to identify the genomic and proteomic changes in cell processes involved in tinnitus; conduct image studies to include brainstem structures and to include new techniques and/or combinations of techniques; develop objective measures of tinnitus that can be used in the clinic; study genetic factors that contribute to tinnitus; and develop clinical studies of promising pharmacologic treatments, dietary supplements and complementary and alternative methods to treat tinnitus, and chemoprotective (e.g., antioxidants) agents or other means (e.g., education) to prevent tinnitus.

NIDCD funded two new grants in FY 2007 in response to the first round of applications for the tinnitus RFA. These two new grants complemented the 21 existing projects that study the cause and possible therapies for tinnitus. The first project is studying the effectiveness of magnetic stimulation on individuals with tinnitus. The second project is studying the effects of drugs or noise exposure in causing tinnitus in an animal model. The next round of applications was due October 2007, from which NIDCD will consider additional projects. In addition, NIDCD and representatives from the Department of Veterans Affairs and the Department of Defense have been in discussions about their respective tinnitus research portfolios with the hope of exploring possible research collaborations in the future.

#### Item

##### ***Translational Research***

The Committee applauds the NIDCD's establishment of a Translational Research Branch and urges the continuation of research activities and clinical trials that can be used in treatments of communication disorders. (p. 143)

#### Action taken or to be taken

An important aspect of NIH's mission is to ensure that basic research discoveries are quickly transformed into drugs, treatments, or methods for prevention. As part of the Roadmap for Medical Research, NIH has embarked on a initiative to "re-engineering the clinical research enterprise," to stimulate a recasting of the system of clinical research that will foster translational research, taking discoveries from bench to bedside, and from bedside to widespread clinical practice.

In keeping with this trans-NIH initiative, NIDCD established a Translational Research Branch (TRB) in 2004. NIDCD's existing clinical trials program was included in this branch. NIDCD held a workshop on Translational Research (TR) in Hearing and Balance in April 2004, to facilitate the translation of basic biomedical or behavioral research discoveries into new clinical and research tools, prostheses and assistive devices, behavioral, pharmacotherapeutic, and surgical therapies. The workshop sought to identify barriers to and opportunities in translational research and to consider new initiatives in support of translational

research. This information was used to formulate a more targeted approach in delineating NIDCD's translational research agenda. A TR Program Announcement with Special NIDCD review was issued in 2004. This program announcement, bringing basic and clinical scientists together, was active for three years. NIDCD funded several applications in response to this initiative, and is planning to reissue it again in the very near future as a means to continue building NIDCD's translational research portfolio.

In order to maximize research capacity and to build upon existing resources, NIDCD sought and developed active partnerships with leaders from academia, professional organizations, as well as other federal agencies. As a result of this partnership, NIDCD sponsored a workshop on *Clinical Research/Clinical Trials in Otology: Setting the Research Agenda for Development of an Intervention* in 2006. The workshop's purpose was to review the state of NIDCD's clinical trials and translational research portfolio, and to develop a strategic roadmap. It is expected that this information will help guide future NIDCD clinical trials and translational research initiatives.

# National Institute of Mental Health

## House Significant Items

### Item

#### ***Adolescent Depression and Suicide***

Suicide is the third leading cause of death among teenagers; for the first time in sixteen years, teen suicide rates have increased in the U.S. Depressive disorders, one of the major risk factors for suicide, continue to be very common in adolescence. The Committee therefore strongly encourages NIMH to strengthen 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. 155)

### Action taken or to be taken

NIMH will continue to invest in research that promises to strengthen our ability to achieve safe and effective approaches to identify and treat diverse youth at risk for suicidal behavior and related depressive disorders. NIMH currently devotes significant effort to this area of research.

For example, in one NIMH-funded longitudinal study, researchers found that individuals with a particular combination of genetic variation were more susceptible to suicidal thinking when undergoing antidepressant treatment than those who did not have this genetic variation. Although this study was conducted with adults, these findings could lead to increased early-life detection for individuals most vulnerable to suicide, as well as better customization of treatment strategies for addressing depression and suicide in youth and adults. Other NIMH-supported researchers have found that for children of parents with mood disorders, the warning signs of early-onset suicidal behavior include mood disorder, self-reported depression, impulsive aggression, parental history of suicide attempt, and sexual abuse.

NIMH continues to support research on interventions to improve suicide risk detection and to facilitate treatment among youth at elevated risk for suicide. Two recently funded studies will test distinct intervention models to increase problem recognition, facilitate treatment, and prevent repeat suicide attempts among adolescents seen in emergency service settings. The recently completed Treatment for Adolescents with Depression Study (TADS) found that when adolescents received fluoxetine alone or in combination with cognitive behavioral therapy (CBT), they recovered faster than those who were receiving CBT alone. However, those taking fluoxetine alone had higher rates of suicidal thinking than those in combination treatment and those in CBT alone, particularly in the early stages of treatment. Thus, while treatment with fluoxetine may speed

recovery, adding CBT provides additional safeguards for individuals vulnerable to suicidality.

A recently completed NIMH-funded multi-site clinical trial, Treatment of Resistant Depression in Adolescents (TORDIA), tested the effectiveness of antidepressants alone or in combination with CBT for adolescents with treatment-resistant depression; results are expected in early 2008. In addition, the first pilot study to evaluate the feasibility of testing specific pharmacological and psychosocial interventions for adolescents who have recently attempted suicide was completed under an NIMH cooperative agreement with five academic sites [the Treatment of Adolescent Suicide Attempters (TASA) study]. Results are expected in early 2008.

#### Item

##### ***Geriatric Mental Health***

By the year 2010, there will be approximately 40 million people in the United States over the age of 65, and 20 percent of them will experience mental health problems. A national crisis in geriatric mental health care is emerging, and action must be taken to avert serious problems in the future. For the past five years, this Committee has urged NIMH to strengthen research devoted to older adults; however, the geriatric mental health research portfolio supported by NIMH continues to be dramatically disproportionate to the increasing number of older Americans. The Committee requests that NIMH provide data on funding targeted toward geriatric mental health research in 2002-2006 and the amount of funding provided to new investigators in late-life mental health research. In addition, the Committee urges NIMH to place a stronger emphasis on research on adults over age 65 to reflect the growth in numbers of this population. (p. 155)

#### Action taken or to be taken

NIMH is highly committed to geriatric mental health research and invests significantly in research on late-life mental disorders. To maintain robust support for aging related research, in 2003, NIMH and its National Advisory Mental Health Council (NAMHC) examined the Institute's extramural aging research and training portfolio and identified strategies for strengthening this area of research, resulting in the report *Mental Health for a Lifetime: Research on the Mental Health Needs of Older Americans*. It found that research grant applications on aging fared equally well or better in the peer review and funding process relative to comparison research areas. However, the field suffers from a low number of applications. The report included recommendations that NIMH develop a clearer programmatic focus for aging research within its organizational structure. In 2004, NIMH established a new Geriatrics Research Branch as a focal point for much of its clinical research on issues of aging. The Institute supports numerous research projects in geriatric mental health, including studies to better understand relevant brain mechanisms and risk factors for late-life mental disorders; to develop new animal models and assessment tools; and to improve

the diagnosis and treatment of mental disorders in older adults.

In FY 2007, NIMH reissued two Program Announcements [(PAs) originally released in FY 2006] entitled “Clinical Research in Mental Illnesses in Older Adults,” and “Pathophysiology and Treatment Response in Late-Life Mood and Anxiety Disorders.” These PAs encourage research grant applications that address high priority issues on the mental health of older Americans, The Institute conducted workshops with leading researchers in FY 2005 and FY 2006 to help articulate and refine foci for future translational research efforts on geriatric depression and on psychosocial intervention research in late-life mental disorders.

The table provides NIMH funding on aging research.

**National Institute of Mental Health**  
**Aging Research**  
(Dollars in Thousands)

Fiscal Year	New Investigators	Total Aging Research
2002	\$1,740	\$106,090
2003	\$2,503	\$100,055
2004	\$3,022	\$97,418
2005	\$3,120	\$91,686
2006	\$2,580	\$85,164

In FY 2007, NIMH continued to support research training programs and career development awards designed to expand the pipeline of future generations of scientists in the field of mental health and aging research. To further address the low base of applications, NIMH supports several annual technical assistance workshops to mentor junior investigators in research design, research implementation, and grant-writing in order to establish successful careers in geriatric mental health research.

Item

***Suicide Prevention Research***

Suicide is a major, preventable public health problem. In 2004, it was the eleventh leading cause of death in the U.S., accounting for 32,000 deaths. An estimated eight to 25 attempted suicides occur per every suicide death. The Committee is pleased to note that NIMH is supporting three developing centers for interventions to prevent suicide and encourages NIMH to strengthen its investment in suicide prevention research. (p. 155)

### Action taken or to be taken

NIMH continues to expand its efforts in suicide prevention through investment in research studies and in career training opportunities. Ongoing studies have been expanded to address more diverse groups at risk for suicide, as well as under-researched settings where high risk individuals are seen, such as emergency rooms. Investment in research infrastructure, such as centers, has been leveraged with support by the American Foundation for Suicide Prevention, which has funded a pilot suicide attempter registry study across the three Developing Centers for the Intervention and Prevention of Suicide. These centers are co-funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA). NIAAA and NIDA have also co-funded research projects and career development efforts.

The result of this investment is an increasing understanding of who is most prone to suicidal behavior. For example, a recent NIMH-supported study found that male veterans in the general U.S. population are twice as likely as their civilian peers to die by suicide.

Studies solicited by an NIMH-supported Request for Applications (RFA) on suicidality side effects of medications have led to a number of highly publicized reports on patterns of suicide attempts before and after treatment, primarily showing a benefit of medication treatment in defined private health care systems as well as in the Veterans Health Administration. NIMH-funded researchers have also studied individual differences in risk for treatment emergent suicidality. Collaborations among NIMH-funded extramural and intramural scientists found that specific variations in two genes associated with the brain's glutamate chemical messenger systems are linked to suicidality side effects among adults in a clinical trial who were administered the selective serotonin reuptake inhibitor (SSRI) citalopram.

NIMH participates in several cross-agency efforts to facilitate Federal coordination of suicide prevention. For example, in collaboration with staff from the Centers for Disease Control and Prevention (CDC) and outside experts, a consensus on common definitions of suicide attempts and deaths was developed, which will lead to more accurate surveillance of both suicide attempts and deaths. Another example of cross-agency collaboration is NIMH's support of a study examining the effectiveness of a training program for crisis counselors supported by the Substance Abuse and Mental Health Services Administration (SAMHSA). The training program is designed to improve crisis counselors' ability to adequately assess suicide risk during crisis calls and increase the number of successful mental health referrals for distressed callers. NIMH's support of the effectiveness study for this program is critical, given the widespread referrals to this particular national hotline by every Health and Human Services (HHS) agency and an increasing number of health care system providers, such as the Department of Veteran Affairs.

Item

***Down Syndrome***

The Committee encourages NIMH to develop new strategies for cataloging, diagnosing and treating behavioral disorders that are common in people with Down syndrome, including autism, pervasive developmental disorder, obsessive compulsive disorder, depression, and psychosis. The Committee encourages NIMH to coordinate its research on Down syndrome with NICHD, NINDS, NIA and other institutes. (p. 156)

Action taken or to be taken

NIMH continues to work collaboratively with other NIH Institutes to advance research on the identification, prevention, and treatment of common psychiatric disorders in individuals with Down syndrome. In particular, two PAs (“Research on Autism and Autism Spectrum Disorders” and “Research on Psychopathology in Intellectual Disabilities”) encourage new grant applications for research on the emotional and behavioral aspects of developmental disorders and conditions, including Down syndrome. NIMH is specifically interested in research investigating behavioral or psychopharmacological interventions for comorbid disorders within this population.

In addition to these PAs, NIMH participates in a trans-NIH Down Syndrome Working Group to plan joint activities for research on Down syndrome and related disorders. In December 2006, the Working Group hosted an outreach meeting with key Down syndrome advocacy organizations in order to learn about their efforts and provide a foundation for future partnerships. In July 2007, the Working Group held a scientific workshop titled “Factors that Affect Cognitive Function in Down Syndrome Throughout the Lifespan.” This meeting was helpful in assessing the current research gaps and opportunities in this area. After consultation with the scientific research community and national organizations that focus on Down syndrome, the Working Group developed the NIH Research Plan for Down Syndrome. The purpose of the plan is to build on current NIH-supported research and to take advantage of emerging scientific opportunities. A draft plan was posted on the National Institute of Child Health and Human Development (NICHD) website for public comment in September 2007.

**Senate Significant Items**

Item

***Alzheimer’s Disease***

The NIMH plays a vital role in efforts to develop new treatment strategies for Alzheimer’s disease, from basic neuroscience studies to treatment and services research. For example, the Institute is supporting a large practical clinical trial examining the effectiveness of antipsychotic medications for treating agitation and other behavioral disturbances in Alzheimer patients. The Committee

encourages the NIMH to continue to advance understanding of Alzheimer's disease. (p. 148)

Action taken or to be taken

NIMH places major emphasis on studies of the psychiatric, behavioral, and emotional disturbances associated with Alzheimer's disease and related dementias, including depression, anxiety, psychosis, agitation, and aggressive behavior. This work encompasses a breadth of research areas, such as basic neuroscience studies on the genetics and pathophysiology of these aspects of dementia, studies of treatments for such syndromes, and services research aimed at improving care for Alzheimer's patients and their family members. These studies complement the work of NIA, which directs NIH's primary program of research on the neuropathology and cognitive decline that occurs in Alzheimer's disease,

In December 2006, the initial outcomes of the NIMH-funded practical clinical trial titled "Clinical Antipsychotic Trials in Intervention Effectiveness-Alzheimer's Disease" (CATIE-AD) were published in the *New England Journal of Medicine*. This 42-site study compared a number of antipsychotic medications for effectiveness in treating agitation and other behavioral disturbances in Alzheimer's disease. The major finding was that several of the atypical antipsychotic medications commonly used to treat Alzheimer's disease were no more effective than an inactive medication, or a "placebo," in managing agitated behavior for most people with this disease. The limited benefits seen in some patients were generally offset by adverse side effects. Additional analyses are being conducted on results from subsequent treatment phases of this trial; publication of those findings is expected within the next year.

In another NIMH-funded multi-site clinical trial, investigators are examining the effectiveness of antidepressant medication in treating the specific syndrome of depression that is associated with Alzheimer's disease. In addition, this study aims to further validate the utility of consensus criteria for diagnosing the depression syndrome. NIMH will continue to collaborate with other NIH institutes in Alzheimer's related research initiatives.

Item

**Basic Behavioral Science**

The Committee urges the NIMH to put a higher priority on the study of basic behavioral functions such as cognition, emotion, decision-making, and motivation, and to maintain its support for research on the promotion of mental health and the study of basic psychological factors that influence behavior. (p. 148)

Action taken or to be taken

NIMH continues to support basic science, including basic behavioral science, as

an essential component of the Institute's program to advance its public health mission. The Institute's priorities for basic behavioral research have been shaped significantly by a 2004 report from the NAMHC. The report, titled "Setting Priorities for Basic Brain and Behavioral Science Research at NIMH," provided strategies for sharpening the focus and impact of the Institute's basic science portfolio, including basic behavioral science, so that it better serves the Institute's mission. Based on these strategies, NIMH strives to support basic research that (1) links the brain with behavior and experience; and (2) takes into account how mental and behavioral disorders begin, how they are best diagnosed, and how they are best prevented. Since the 2004 NAMHC report, NIMH has worked with basic social science grant recipients to help them redirect their work into basic and translational research more relevant to NIMH's mission.

The fields of social psychology, cognitive science, and affective neuroscience have all addressed key issues concerning the role of behavioral processes in human health. These fields, however, have not had a strong tradition of significant interaction with each other. In FY 2007, NIMH sponsored the first in a series of three annual grant solicitations in an emerging scientific discipline that brings scientists together from across these distinct areas; this multidisciplinary field is referred to as social cognitive neuroscience. The RFA, titled "Basic and Translational Research Opportunities in the Social Neuroscience of Mental Health," seeks to encourage and stimulate multidisciplinary research that examines the brain's role in social behaviors that are affected in many mental disorders. This includes, but is not limited to, autism and schizophrenia. Also in FY 2007, NIMH was a cosponsor for a PA titled "Methodology and Measurement in the Behavioral and Social Sciences." This announcement seeks to support grant applications that will improve the quality of data collected within the social and behavioral sciences. These targeted efforts, in addition to NIMH's ongoing support of basic research within its Division of Neuroscience and Basic Behavioral Science, seek to provide a greater understanding of behavior and its underlying relationship with the brain, thereby providing greater insight into the causes, trajectories, and possible prevention of many mental disorders.

#### Item

#### ***Clinical Research***

The Committee applauds NIMH's continued commitment to the goals of the NIH Roadmap Initiative on reengineering the clinical research enterprise through the new clinical trials networks on bipolar disorder, depression, and schizophrenia. The Committee strongly supports these efforts and urges the NIMH to examine treatments of mental disorders across the lifespan, with particular attention paid to aging populations and youth, and to the effects of psychopharmacological treatments on cognition, emotional development, and other co-morbid conditions.

The Committee further urges the NIMH to examine cultural factors, such as stigma, that influence the diagnosis and treatment of mental disorders. (p. 148)

### Action taken or to be taken

During FY 2007, NIMH sought input from a wide variety of sources, including mental health researchers, the advocacy community, and the NAMHC to inform the future directions of research conducted on the NIMH Clinical Trials Networks in schizophrenia, depression, and bipolar disorder.

The Schizophrenia Trials Network, an outgrowth of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project, already supports two studies: a study of side effects linked to heart disease, and a study of the outcomes of switching from first to second generation medications or from multiple to only one medication.

New trials will be implemented through the Bipolar Trials Network (BTN) and the Depression Trials Network (DTN) whose infrastructures emerged from the Systematic Treatment Enhancement Program for Bipolar Disorder study and the Sequenced Treatment Alternatives to Relieve Depression study, respectively. Each network will design, develop, implement, and complete, within three years, one clinical trial each. The BTN will conduct a study on the use of moderate-dose lithium for the treatment of bipolar disorder. The DTN will study the use of combination medication therapy as initial treatment. The DTN is currently conducting a study to develop a method for assessing the emergence of suicide in people taking antidepressants.

NIMH continues to support a six-site collaborative research study to examine the effects of ethnicity on the diagnosis and treatment assignment in African-American, Latino, and white patients with mood disorders. NIMH also supports a growing number of studies to develop or tailor interventions to the needs and preferences of diverse, often underrepresented groups. These smaller studies will provide the scientific basis for full-scale trials to assess the effectiveness of targeted, culturally sensitive treatments.

NIMH has supported studies of cultural factors and stigma influencing mental illness. In FY 2007, NIMH issued a PA to foster partnerships between community-based, clinical/services settings and research institutions in order to bridge the gulf between what treatments exist for mental illness and what is available to people in the community who need care, especially racial/ethnic minorities and other underrepresented groups. NIMH also funded two new projects in FY 2007 that encourage collaboration between consumer, advocate, or state or local groups with expertise in developing and implementing anti-stigma programs, and behavioral and communication researchers. The goal is to identify effective approaches and better ways of reducing or eliminating the stigma and discrimination associated with mental illness and its treatment.

### Item

### ***Down Syndrome***

The Committee encourages the NIMH to develop new strategies for cataloging, understanding, diagnosing and treating behavioral disorders that are common in people with Down syndrome. They include autism, pervasive developmental disorder, obsessive compulsive disorder, depression and psychosis. The Committee urges the NIMH to coordinate its research on Down syndrome with the NICHD, NINDS, NIA and other Institutes. (p. 148)

#### Action taken or to be taken

Please refer to page 232 of this document for NIMH's response to this item on Down syndrome.

#### Item

### ***Epilepsy***

The connections between epilepsy and depression as well as the cognitive burden of epilepsy are of particular importance to the Committee. The Committee strongly urges the Institute to coordinate research into this area with the NINDS and to intensify efforts at understanding the etiology and treatment of co-morbid mental and neurological disorders. (p. 148)

#### Action taken or to be taken

NIMH and NINDS continue ongoing collaboration and coordination in research on the cognitive burden of epilepsy and on the relationship between epilepsy and co-occurring mental disorders, including depression. Research applications received in these areas are regularly discussed by staff from both Institutes to ensure coordination of the Institutes' scientific agendas and to optimize the probability of a successful outcome of the research efforts undertaken.

NIMH supports substantial research portfolios in both cognitive science and cognitive neuroscience and has an active research program focused on disorders that co-occur with the major mental disorders. For example, one NIMH-funded study is examining the affect of neurogenesis (the birth of new brain cells in the adult) on brain circuits that may be involved in both depression and epilepsy. Another NIMH-funded project is using an animal model to study how epilepsy and seizures in the early stages of postnatal brain development may increase predisposition to schizophrenia. In addition, NIMH-funded clinical researchers are investigating safe and effective treatment for attention-deficit hyperactivity disorder in children who have co-occurring epilepsy.

In March 2007, NIMH scientists participated in the NINDS-sponsored meeting "Curing Epilepsy 2007: Translating Discoveries into Therapies." One of the meeting sessions was devoted to the topic *Beyond Seizures: Cognitive and Psychological Issues in Epilepsy*. Of the three featured speakers, one was an NIMH senior intramural scientist and another was an NIMH grantee.

Item

***Fragile X***

The Committee urges the NIMH to enhance its Fragile X translational research efforts that were identified during focused meetings from November 2001 through July 2004. These include 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. The Committee also urges the NIMH to include Fragile X in its studies of related neuropsychiatric disorders and to work with other Institutes such as the NICHD and NINDS to develop cooperative research support mechanisms in this area. In addition, the Committee encourages the NIMH participate in the scientific session described under the section on the NICHD. (p. 149)

Action taken or to be taken

NIMH issued a PA in May 2005 titled “Shared Neurobiology of Fragile X Syndrome and Autism” which remains active. This PA represents a public-private partnership between NIMH, NINDS, and NICHD, as well as the Canadian Institutes of Health Research, the Health Research Board - Ireland, Cure Autism Now, the National Alliance for Autism Research, Autism Speaks, and the FRAXA Research Foundation. The goal of the PA is to promote research that aims to characterize and understand mechanisms common to both Fragile X syndrome and autism, with the ultimate goal of developing treatments. Studies are expected to focus on understanding neural processes that play a role in the etiology or pathophysiology of Fragile X and that may be implicated in autism and related disorders. Studies to identify drug targets for new treatments are encouraged. Through another PA titled “Research on Psychopathology in Intellectual Disabilities,” NIMH solicits research designed to elucidate the epidemiology, etiology, treatment, and prevention of mental disorders in persons with intellectual disabilities, including Fragile X.

NIMH-funded research on Fragile X aims to understand the biological mechanisms underlying the disorder. For example, NIMH continues to support a magnetic resonance imaging (MRI) study that follows a cohort of patients in order to examine the relationships between Fragile X mental retardation 1 gene (FMR1) expression, brain abnormalities, and behavior throughout development. Another longitudinal study is examining 120 school-age children with Fragile X as well as their families to assess the biological and environmental factors contributing to clinical outcomes. NIMH continues to support programs focused on training post-doctoral and clinician researchers with an interest in developmental disabilities, including Fragile X.

NIMH is helping to facilitate research efforts in support of Fragile X syndrome and related disorders by participating with NICHD and other NIH Institutes in the NIH Fragile X Research Coordinating Group. The group consists of scientists from both NIH intramural and extramural programs working to expand research opportunities to further the study of Fragile X syndrome and associated disorders. Over the next year, the NIH Fragile X Research Coordinating Group will convene a series of meetings with stakeholders to outline and develop a research plan for advancing this research.

#### Item

##### ***Frontier Mental Health Needs***

The Committee commends the NIMH on its outreach efforts to determine the unique mental health needs that may exist in remote frontier communities, including Alaska. The Committee encourages the NIMH to expand its research efforts into these communities, which are often ignored in research projects but continue to suffer from high incidences of mental health problems including depression, suicide and co-occurring disorders with substance abuse. (p. 149)

#### Action taken or to be taken

In 2007, the NIMH Office of Rural Mental Health Research (ORMHR) conducted several activities designed to improve the competitiveness of research grant applications submitted by rural mental health researchers. For example, ORMHR conducted two technical assistance workshops on the NIH grant writing process for investigators planning to submit an application concerning frontier mental health research. The meetings were held in Anchorage, Alaska and Denver, Colorado. Seasoned investigators with NIH peer-review experience provided junior investigators with valuable advice on how to prepare a grant application. The experienced investigators provided scientific, peer review feedback on a study proposed by each meeting participant. The junior investigators indicated they benefited from hearing critiques of all applications discussed at each meeting. The participants also received summary statements of the reviewers' comments to assist them in revising their research plan. The investigators were also encouraged to submit draft applications to NIMH program staff in order to obtain additional feedback prior to formal submission to NIMH.

NIMH also supports a PA titled "Research on Rural Mental Health and Drug Abuse Disorders" that invites grant applications to stimulate research on mental health, HIV/AIDS, and/or drug abuse problems in rural and frontier communities.

The goal of this PA is to support research that will (1) improve understanding of community, cultural, and individual factors that may enhance the provision and utilization of prevention and treatment services in these communities; and (2) generate knowledge to improve the organization, financing, efficiency, effectiveness, quality, and outcomes of mental health and drug abuse services for diverse populations in rural and frontier populations.

## Item

### ***Immigrant Health***

The Committee recognizes that immigrants to the United States experience unique stresses, prejudice, and poverty and can be considered at-risk subpopulations for health, emotional and behavioral problems as well as, in the case of children, learning and academic difficulties. The effects of immigration on the psychological and social well-being are especially profound for certain populations, including children, women, individuals with disabilities, and those with limited financial resources. To address this, the Committee urges the NIMH to partner with other Institutes to boost research on the adaptation, development, health, and mental health needs of diverse immigrant children, youth, and families. (p. 149)

### Action taken or to be taken

NIMH continues to support research to elucidate the effects of the immigration process on mental illness. Several epidemiological studies funded by NIMH examine the influence of immigration on mental illness and mental health care across various age groups. These studies explore the distribution and prevalence of mental disorders among immigrants, in addition to studies of risk, resiliency, protective factors, diagnosis, and treatment. An important focus of the research is sub-ethnic analysis (countries of origin within Latino, Black, and Asian American groups) and nativity analysis (U.S. born/non U.S. born) of the distribution of mental illness and access to care, as well as mechanisms that might influence prevalence and access, such as language, socioeconomic status, insurance coverage, time in the United States, and use of alternative therapies.

For example, the NIMH-funded National Latino and Asian American Study (NLAAS) reported that age at immigration appears to affect the onset of mental disorders in Asian Americans and Latinos. Asian immigrants who arrived at age 12 or younger had a greater risk for psychiatric disorders during childhood than their U.S. born counterparts. In general, Latinos arriving between ages 0-6 had very high risks of onset shortly after immigration, but after several years, their lifetime prevalence rates approached those of Latinos born in the United States. In general, past age 7, Latinos who arrived later in life had lower lifetime prevalence rates than younger immigrants or U.S. born Latinos.

NIMH also supports research that examines the social, familial, and psychological processes that may increase risk or protect against mental illness among immigrants. These studies will provide critical information for the development of culturally appropriate clinical practices, diagnostic tools, and interventions.

Item

**Older Adults**

The Committee urges the NIMH to place a stronger emphasis on research on adults over age 65 to reflect the growth in numbers of this population. The Committee requests that the Institute provide data in the fiscal year 2009 congressional budget justifications on the amount of NIMH funding directed toward geriatric mental health research over the past 5 years. (p. 149)

Action taken or to be taken

NIMH is highly committed to geriatric mental health research and invests significantly in research on late-life mental disorders. To maintain robust support for aging related research, in 2003, NIMH and its National Advisory Mental Health Council (NAMHC) examined the Institute's extramural aging research and training portfolio and identified strategies for strengthening this area of research, resulting in the report *Mental Health for a Lifetime: Research on the Mental Health Needs of Older Americans*. It found that research grant applications on aging fared equally well or better in the peer review and funding process relative to comparison research areas. However, the field suffers from a low number of applications. The report included recommendations that NIMH develop a clearer programmatic focus for aging research within its organizational structure. In 2004, NIMH established a new Geriatrics Research Branch as a focal point for much of its clinical research on issues of aging. The Institute supports numerous research projects in geriatric mental health, including studies to better understand relevant brain mechanisms and risk factors for late-life mental disorders; to develop new animal models and assessment tools; and to improve the diagnosis and treatment of mental disorders in older adults.

In FY 2007, NIMH reissued two Program Announcements [(PAs) originally released in FY 2006] entitled "Clinical Research in Mental Illnesses in Older Adults," and "Pathophysiology and Treatment Response in Late-Life Mood and Anxiety Disorders." These PAs encourage research grant applications that address high priority issues on the mental health of older Americans. The Institute conducted workshops with leading researchers in FY 2005 and FY 2006 to help articulate and refine foci for future translational research efforts on geriatric depression and on psychosocial intervention research in late-life mental disorders.

In FY 2007, NIMH continued to support research training programs and career development awards designed to expand the pipeline of future generations of scientists in the field of mental health and aging research. To further address the low base of applications, NIMH supports several annual technical assistance workshops to mentor junior investigators in research design, research implementation, and grant-writing in order to establish successful careers in geriatric mental health research.

The table summarizes NIMH funding for total aging research for Fiscal Years 2002 to 2006.

**National Institute of Mental Health**  
**Aging Research**  
(Dollars in Thousands)

Fiscal Year	Total Aging Research
2002	\$106,090
2003	\$100,055
2004	\$97,418
2005	\$91,686
2006	\$85,164

Item

***Suicide Prevention***

The Committee is pleased that the NIMH is supporting two developing centers for interventions to prevent suicide. The Committee encourages the NIMH to increase its investment in suicide prevention research by supporting advanced centers for this purpose and creating new developing centers. (p. 149)

Action taken or to be taken

NIMH, with co-funding from NIAAA and NIDA, has worked to leverage the NIH investment in the three Developing Centers for the Intervention and Prevention of Suicide. Through the leadership provided by NIH staff, a number of cross-center projects have been developed to address challenges in research methodology. For example, projects have addressed the identification of valid measurement of suicide ideation, and the development of treatment models that target possible aggression and impulsivity mediators of suicide risk. Each of the centers provides extensive suicide research consultation nationally and internationally, as well as training opportunities for new investigators. For example, at the most recent July 2007 centers meeting, consultation was provided to investigators from an institution outside of the funded centers, along with their partners funded through the Indian Health Service, to strengthen their efforts at implementing and evaluating an intervention delivered by paraprofessionals to screen and refer White Mountain Apache tribal members at risk for suicide. Also participating in the centers meeting were representatives from the Department of Veterans Affairs (VA) and several VA medical centers interested in developing further collaborations in suicide prevention research. The centers also work with the CDC to assist in the development of common definitions of suicidal behavior and

have provided technical assistance to SAMHSA in the development of best practices in suicide risk and monitoring for community-based practitioners.

The research conducted by the centers has been further enhanced by support from the American Foundation for Suicide Prevention. The Foundation has provided support for cross-center studies that test the feasibility of developing patient registries of individuals seen for a suicide attempt in psychiatric emergency departments. A common patient assessment protocol was agreed upon across sites, with some variation across sites where interventions are also being tested to improve follow-ups and outcomes of the patients.

# National Institute on Drug Abuse

## House Significant Items

### Item

#### ***Drug Abuse and Brain Development***

The Committee notes neuroimaging research by NIDA and others showing that the human brain does not fully develop until about age 25. The Committee encourages NIDA to continue its emphasis on adolescent brain development to better understand how developmental processes and outcomes are affected by drug exposure, the environment, and genetics. (P. 154)

### Action taken or to be taken

The adolescent period of development presents vulnerabilities for long-term drug abuse problems and addiction since this is the time when drug experimentation and subsequent drug abuse and addiction typically occur. Research that expands our understanding of the developing brain, the specific effects of drug exposure on developmental trajectories, and the influence of environmental and genetic factors will help to develop and improve prevention and treatment approaches for youth. Neuroimaging research is allowing us to identify the brain circuits involved in adolescent motivation, decision-making, impulsivity and risk-taking—processes that influence the decision to take or resist taking drugs.

For example, studies using functional magnetic resonance imaging (fMRI) are comparing reward processing in adolescents with that of adults and younger children, noting that a combination of heightened responsiveness to rewards and immaturity in behavioral-control areas may impel adolescents to seek immediate rewards rather than long-term gains—and also may leave them vulnerable to risky decision-making. The influence of social factors in individual and group decision-making is being studied using a social neurobiological perspective, which looks at the mechanisms underlying adolescents' increased sensitivity to social influences (i.e., peers) and decreased sensitivity to negative consequences of their behavior that together make them particularly vulnerable to drug abuse.

In addition, the application of modern brain imaging technologies to NIDA's multiple longitudinal study cohorts is beginning to generate unprecedented structural and functional views of the dynamic changes occurring in the developing brain, shedding light on the role of brain development in decision-making processes and responses to a variety of stimuli, including media messages about drug abuse prevention (see Brain Imaging, p 248). Collectively, these longitudinal studies, with new imaging and genetics tools applied to them, promise a greatly enhanced ability to interpret the effects of environmental variables (e.g., quality of parenting, drug exposure, socioeconomic status, and

neighborhood characteristics) on brain development and behavior— including vulnerability to substance abuse.

#### Item

##### ***Minority Populations***

The Committee notes that the consequences of drug abuse disproportionately impact minorities, especially African American populations. The Committee is pleased to learn that NIDA continues to encourage researchers to conduct more studies in this population and to target their studies in geographic areas where HIV/AIDS is high and/or growing among African Americans, including in criminal justice settings. (p. 154)

#### Action taken or to be taken

Multiple NIDA studies are examining drug use patterns and their consequences among particular ethnic minority populations, including African Americans and American Indians, where striking health disparities exist.

As the Committee recognizes, HIV/AIDS and criminal justice involvement as a result of drug abuse disproportionately affects African Americans, an effect further amplified in women. For although African Americans comprise 12-13 percent of the U.S. population, they account for the majority (over half) of new AIDS cases and two-thirds of all new HIV/AIDS diagnoses in women. Moreover, since the 1980s, African Americans have been increasingly represented among prison and jail populations, with about 75 percent of this increase estimated to be drug-related.

In FY 2006, NIDA funded research grants to investigate HIV/AIDS and criminal justice involvement as a consequence of drug abuse among African Americans. Topics include understanding the roles of drug abuse, violence, and insurance coverage in HIV/AIDS among African American women; addressing the health service needs and improving health care utilization among drug-involved African American women; and preventing drug abuse and other risk behaviors among vulnerable populations (e.g., pregnant women, incarcerated juveniles, and rural African American youth). Given the need for additional studies, in FY 2007, NIDA re-issued a call for studies addressing these issues. In 2006, NIDA organized a workshop to identify ways to increase acceptance of HIV screening in African Americans, since research shows that screening is cost effective and improves individual outcomes while helping to curb the epidemic. In 2006, NIDA and SAMHSA also cosponsored a workshop to address research-related issues on the disproportionate occurrence of criminal justice involvement and HIV/AIDS among African Americans as a consequence of substance abuse.

There has also been a growing concern about methamphetamine abuse among Native American populations (i.e., American Indians [AI] and Alaskan Natives [AN]). According to national datasets, AI/AN methamphetamine abuse is higher

than in any other subgroup. However, very few datasets are available to characterize the problem. In addition, due to their rural nature, reservations have been prime places for drug distribution and clandestine labs. To determine the best responses to these issues, NIDA held a scientific meeting in 2007 to assess the data available to characterize this problem and the data collection plans under way, identify existing data collection infrastructures, and begin to plan a research agenda to address the serious public health issue.

#### Item

##### ***HIV/AIDS and Drug Abuse***

The Committee understands that drug abuse and addiction continue to fuel the spread of HIV/AIDS in the United States and abroad, and that drug abuse prevention and treatment interventions can be very effective in reducing HIV risk.

Research should continue to examine every aspect of HIV/AIDS, drug abuse, and addiction, including risk behaviors associated with both injection and non-injection drug abuse, how drugs of abuse alter brain function and impair decision making, and HIV prevention and treatment strategies for diverse groups. The Committee applauds the Institute for holding a spring 2007 conference titled “Drug Abuse and Risky Behaviors: The Evolving Dynamics of HIV/AIDS,” and urges the Institute to continue supporting research that focuses on developing and testing drug abuse-related interventions designed to reduce the spread of HIV/AIDS. (p. 154)

#### Action taken or to be taken

Drug abuse continues to be a major vector for the spread of HIV/AIDS, owing in large part to the connection between drug abuse and other risky behaviors, including the sharing of needles by intravenous drug users. NIDA-supported research, from basic to clinical to health services, has increased the understanding of this nexus and shown the value of drug abuse treatment in preventing HIV spread. Notable recent findings include: the ability of contingency management to increase adherence to HIV treatment; the potential of selenium supplementation to suppress HIV-1 progression and offer a safe, inexpensive adjunct therapy for HIV disease; the discovery that methamphetamine abuse among HIV-infected individuals can magnify neuropsychological impairment and brain pathology, which can be further exacerbated by HCV co-infection; and that voluntary, rapid HIV testing appears to be feasible for implementation in jail settings.

NIDA-supported modeling research has contributed to broadening CDC guidelines for providing HIV screening to at-risk populations. Screening for HIV can mean early detection and better outcomes, reducing the spread of the disease; therefore, NIDA plans to investigate rapid screening within the National Drug Abuse Treatment Clinical Trials Network (CTN) to identify obstacles to acceptance of HIV screening and to investigate whether counseling plus testing

leads to greater reductions in risk behavior than testing alone. NIDA also intends to use the Criminal Justice–Drug Abuse Treatment Studies (CJ-DATS) research network (see Criminal Justice Population, p. 250 ) to investigate the utility of HIV screening and to promote the adoption of medications to treat intravenous and other drug use in criminal justice settings.

NIDA is also increasingly shifting its research focus to align with the evolving HIV epidemic, centering on the linkages between non-injection drug abuse and risky sexual behaviors prompted by impaired judgment and decision-making. Thus, NIDA’s drug abuse prevention efforts also go toward HIV prevention. As the committee mentioned, to raise awareness of these linkages, NIDA hosted a conference, “Drug Abuse and Risky Behaviors: The Evolving Dynamics of HIV/AIDS,” which brought together more than 500 scientists, clinicians and public health specialists to discuss the latest research findings. NIDA also recently expanded its public service announcement campaign for youth, “Learn the Link”, to include announcements designed specifically for the Latino community—messages that will be widely distributed through partnerships with media, agencies, and targeted groups.

#### Item

##### ***Research Translation***

The Committee commends NIDA for its outreach and work with State substance abuse authorities to reduce the current 15–20-year lag between the discovery of an effective treatment intervention and its availability at the community level. In particular, the Committee applauds NIDA for continuing its work with the Substance Abuse and Mental Health Services Administration (SAMHSA) to strengthen State agencies’ capacity to support and engage in research that will foster statewide adoption of meritorious science-based policies and practices. The Committee encourages NIDA to continue collaborative work with States to ensure that research findings are relevant and adaptable by State substance abuse systems. (p. 154)

#### 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 continues to strengthen this partnership through multiple activities to close the 15–20 year lag between research and practice.

A collaborative initiative—the NIDA-SAMHSA RFA, “Enhancing State Capacity to Foster Adoption of Science-Based Practices”—encourages state agencies to team with research organizations to optimize their research infrastructure and

examine the delivery of publicly supported drug abuse treatment or prevention services. Several grants have received funding in both prevention and treatment areas. They are looking at innovative ways to measure and track program fidelity, promote adoption of research-based practices, and monitor patient recovery statewide in outpatient substance abuse treatment programs, among other efforts.

Another NIDA research solicitation seeks to enhance practice improvement in community-based substance abuse care. Funded grants will evaluate a new electronic health information system (integrated medical record) in New York City opioid treatment centers, implement a chronic pain management intervention (behavioral plus physical therapies) in patients addicted to opioid analgesics, evaluate technology enhancements to improve co-occurring disorder care in rural areas, and enhance substance abuse treatment services for women criminal 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 (CTPs) 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 (ATTCs) 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 motivational enhancement therapy. The adoption of buprenorphine by a growing number of CTPs treating patients with opioid addiction is an example of real culture change issuing from NIDA's translation efforts, and is garnering growing support from state agencies. To fortify communication with our stakeholders and to further the adoption of research-based practices by state-based systems, NIDA cosponsors regular meetings with the National Association of State Alcohol and Drug Abuse Directors (NASADAD) and SAMHSA. NIDA is also working to improve delivery of drug abuse treatment for those involved with the criminal justice system (see p. 250 NIDA- Criminal Justice Population).

#### Item

#### ***Centers of Excellence For Physician Information***

The Committee is pleased that NIDA has created centers of excellence for physician information, and understands that these centers will serve as national models to support the advancement of addiction awareness, prevention, and treatment in primary care practices. The NIDA centers of excellence will target physicians-in-training, including medical students and resident physicians in

primary care specialties. The Committee urges the Institute to continue its focus on activities to provide physicians and other medical professionals with the tools and skills needed to incorporate NIDA-funded research findings into their clinical practices. (p. 154)

#### Action taken or to be taken

To help integrate substance abuse and addiction diagnosis, referral, and treatment into standard medical practice, NIDA has launched a project specifically targeting physicians in training. In 2006, NIDA established four Centers of Excellence for Physician Information (CoEs) at several medical institutions across the country: the University of Pennsylvania School of Medicine in collaboration with Drexel University College of Medicine; Creighton University School of Medicine; the Massachusetts Consortium of Medical Schools (University of Massachusetts Medical School; Boston University School of Medicine; Harvard Medical School/Cambridge Health Alliance; Tufts University of Medicine); and the University of North Dakota School of Medicine and Health Sciences. The CoEs are being developed in collaboration with the American Medical Association's (AMA) Research Education Consortium and are part of NIDA's ongoing Physician Outreach Program.

The purpose of these centers is to develop research-based educational materials for medical students and resident physicians to advance their understanding of drug abuse and addiction. The CoEs have collaboratively developed a survey to measure students' exposure to coursework dealing with drug addiction, self-efficacy in diagnosing and treating addiction, attitudes/beliefs regarding drug addiction, and preferred method of receiving educational information. Each CoE will focus on a different area of drug abuse and addiction education. Areas of interest include: prescription drug abuse, methamphetamine abuse, inhalant abuse, general substance abuse disorders, and comorbidity. Additionally, a few of the individual CoEs have implemented data gathering specific to their subject by either conducting focus groups or developing a content-specific survey. Further, the AMA conducted interviews with key faculty to identify current drug abuse and addiction curricula offerings at the NIDA CoE medical schools and resident training programs.

In year 2 of this project, sites will work both individually and collaboratively to develop products to raise future primary care physicians' awareness of drug addiction as a chronic, treatable disease and to further facilitate the dissemination of knowledge on how best to prevent, diagnose, and treat patients struggling with prescription and illicit drug abuse.

#### Item

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.

be taken

NIDA established an AAPI Workgroup in 1999, which continues to hold meetings and issue guidance and recommendations. The workgroup is composed of researchers, scholars, practitioners, and community advocates who make recommendations 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 drug abuse research. NIDA uses its Diversity Supplement program to encourage AAPI researchers and scholars to pursue research in drug abuse. Currently NIDA supports five Asian Americans and one Pacific Islander American through this program.

NIDA also encourages investigators to study drug abuse in AAPI populations, supporting studies to investigate health disparities and drug use patterns among AAPI subgroups. NIDA's investment recently produced published findings on drug use among specific AAPI subgroups (Chinese, Filipino, Japanese, and Pacific Islander/Native Hawaiian). Using data from school surveys of nearly 82,000 9<sup>th</sup> grade students in California and nearly 5,000 10<sup>th</sup> grade students in Hawaii, researchers showed that rates of alcohol, tobacco, and other drug use were lowest for Chinese adolescents and highest among White and Pacific Islanders/Native Hawaiians. These results contradict previous research suggesting that AAPIs have the lowest rates of alcohol, tobacco, and other drug use compared to Whites, a finding likely explained by use of samples with little AAPI representation or insufficient inclusion of subgroups. Additional studies are aiming to identify various genetic variations underlying racial differences in nicotine metabolism. Results will inform targeted approaches for smoking prevention and cessation.

NIDA recently joined other NIH Institutes participating in a Program Announcement, "Methodology and Measurement in the Behavioral and Social Sciences," which encourages innovative study designs that improve the inclusion of under-represented groups, such as Asian Americans, in research and that allow for the meaningful integration of biological, behavioral, and social

science data (e.g., to study gene-biology-social interactions). Indeed, AAPIs clearly constitute heterogeneous groups characterized by a wide range of substance use behaviors, making the treatment needs of each subgroup unique.

To enable researchers to glean useful information from existing data sets on AAPI populations, NIDA has awarded a professional services contract that will help frame a more accurate picture of the needs of this diverse population.

### **Senate Significant Items**

#### Item

#### ***Adolescent Brain Development***

The Committee encourages NIDA to continue its emphasis on adolescent brain development to better understand how developmental processes and outcomes are affected by drug exposure, the environment and genetics. (p. 145)

#### Action taken or to be taken

Please refer to page 243 of this document for NIDA's response to this item on Drug Abuse and Brain Development.

#### Item

#### ***Brain Imaging***

The Committee applauds the Institute's efforts to find new and important uses for brain imaging technologies—such as through the new RFA titled “Brain Imaging Drug Use Prevention Messages”—and urges the Institute to continue work in this area. (p. 145)

#### Action taken or to be taken

Modern brain imaging technologies are increasingly being used as part of drug abuse and addiction research to provide real-time insight into how the brain interacts with social influences in the context of drug abuse or decision-making. Gaining a better understanding of the mechanisms underlying peer influences, for example, and whether or not and how they might be reversed, will be important in terms of prevention in adolescents.

NIDA's recent RFA, “Brain Imaging Drug Use Prevention Messages,” seeks to stimulate exploratory research on neurobiological responses to substance abuse prevention messages across developmental stages and age groups. Although brain imaging has been used to investigate brain processes to emotional or persuasive stimuli (e.g. consumer or political advertisements), little research has been done using functional brain imaging methods to evaluate prevention messages in the health field. Brain imaging may reveal biological markers of the impact of prevention messages, along with information that could help increase or even predict their effectiveness. Findings may also elucidate the relative contributions of individual personality factors (e.g., sensation-seeking tendency) and preexisting behavioral disorders

(e.g., attention deficit disorder) to the differential processing of messages among different populations—adolescents, young adults, and parents—varying by factors such as age, gender, and propensity for risk-taking. For example, messages high in sensation value have been shown to be more effective at attracting high sensation-seeking teens and promoting behavioral responses among them. Resulting studies may spawn a new generation of effective, tailored, anti-drug messages.

Brain imaging technologies are also helping researchers investigate the effects of chronic drug abuse in humans, building on animal studies to assess whether and how drug abuse causes measurable long-lasting changes in the brain. Current studies are using a variety of imaging tools to study the effects of different types of drugs and exposure, including studies of cue-induced craving and the biological effects of drug use in adolescents; studies to see how prenatal cocaine exposure correlates with brain abnormalities and cognitive dysfunction, particularly language; and studies of brain development in adolescent chronic marijuana users, particularly effects on cognition and brain structure and function.

#### Item

##### ***Co-occurring Disorders***

The Committee encourages NIDA to continue to work with other agencies to stimulate new research to develop effective strategies and to ensure the timely adoption and implementation of evidence-based practices for the prevention and treatment of co-occurring disorders. (p. 146)

#### Actions taken or to be taken

Drug abuse can co-occur with various kinds of illnesses, such as HIV/AIDS (see, HIV/AIDS and drug abuse p. 243). Drug abuse and addiction are also associated with increased risks for other infectious diseases, such as hepatitis C, as well as with greater risk for cancer, cardiovascular and pulmonary disease, and accidents and injuries. However, the most pervasive type of co-occurring condition is that between substance use disorders (SUDs) and other mental illnesses. Certain mental disorders are established risk factors for subsequent drug abuse, and some evidence suggests that drug abuse may increase an individual's risk for a range of other mental disorders. Although historically, addiction has been perceived as a moral failing, recent findings in neuroscience clearly show that addictive substances disrupt many of the brain functions also disrupted by other types of mental disorders, including areas of the brain involved in self-control. Understanding the common neural bases of these disorders may help in developing effective interventions to prevent and treat co-occurring disorders and disseminating this information may help lessen the social stigma that makes people reluctant to seek treatment.

NIDA has a broad and active comorbidity research portfolio. For example, NIDA-supported research in the Clinical Trials Network (CTN) is testing the

effectiveness of a behavioral intervention simultaneously targeting Post Traumatic Stress Disorder symptoms (“Seeking Safety”) and drug abuse. Other ongoing CTN studies are examining whether treating adults with attention deficit hyperactivity disorder (ADHD) enhances their ability to stop smoking (via a standard nicotine patch/behavioral intervention) and whether medications to treat ADHD improve outcomes of behavioral therapy for SUD in adolescents (under 21). In addition, NIDA is intensely focused on criminal justice systems populations, among whom psychiatric comorbidities have a particularly negative effect on rehabilitation and recidivism.

Findings issuing from NIDA’s comorbidity research portfolio and the high rate of comorbidity between drug abuse and addiction and other mental disorders make a strong argument for a comprehensive approach to intervention that identifies, evaluates, and treats *both* disorders. In spite of significant obstacles, steady progress is being made through evaluation of existing treatment options for SUDs in comorbid populations. Also, several existing treatments for other mental disorders have been modified for people with comorbid substance use. The number of psychotropic medications and behavioral therapies that can be applied either singly or in combination to improve comorbidity treatment outcomes continues to rise.

Advances in genetic research now make it feasible to investigate genetic variants (polymorphisms) as well as epigenetic processes (modifications of gene expression by the environment) that may account for the high rates of comorbid substance abuse and other mental illness.

To promote a better understanding of the complex issues that contribute to comorbidity between substance abuse and other mental disorders, NIDA is about to launch a new publication on comorbidity as part of its Research Report Series.

NIDA also actively participates in a broad Federal Partnership to motivate, facilitate, and compel mental health transformation at all levels, in line with the vision of the President’s New Freedom Commission on Mental Health.

#### Item

##### ***Criminal Justice Population***

The Committee commends NIDA for the success of its Criminal Justice Drug Abuse Treatment Studies program. By providing evidence-based training to judges about the neurological and behavioral underpinnings of substance abuse and treatment, this program helps ensure that addicted offenders will receive appropriate treatment. The Committee encourages NIDA to continue its support of behavioral research that can further our understanding about the underlying cognitive, emotional, and behavioral factors that lead to drug abuse relapses in prisons and how to prevent them. (p. 146)

### Action taken or to be taken

The connection between drug abuse and crime is well known, as drug abuse is associated with theft, violence, and child abuse and neglect. A nationally representative survey of State correctional agencies conducted in 2005 estimates that nearly 8 million adults are involved in the justice system,<sup>1</sup> with substance abuse or dependence rates among offenders more than four times that of the general population.<sup>2</sup> Left untreated, drug-abusing offenders have high rates of relapse to drug abuse, crime, re-arrest, and incarceration—a cycle that jeopardizes public health and public safety and further taxes an already overburdened criminal justice system.

NIDA is using a multipronged strategy to address this problem. In addition to our ongoing National Criminal Justice Drug Abuse Treatment Studies (CJ-DATS) program, we continue to support research to evaluate and develop medication and behavioral interventions for substance abuse in the criminal justice setting. We also continue to sponsor initiatives to educate judges and others in the criminal justice system on the science of drug addiction. Our integrated public health-public safety response advances the knowledge that chronic drug abuse causes long-lasting changes in brain chemistry and function that contribute to an addict's compulsion to use drugs despite catastrophic consequences—and that ongoing treatment is needed to achieve recovery and stop the cycle. Studies show that community-based treatment cuts drug abuse in half and greatly decreases criminal activity and arrests.

Building on these efforts, NIDA has recently published the 2<sup>nd</sup> edition of its landmark publication, *Principles of Drug Abuse Treatment for Criminal Justice Populations: A Research Based Guide*. This guide, designed for a wide variety of audiences, synthesizes NIDA-supported research on what works and what does not work with regard to drug treatment services in criminal justice settings. Approximately 1.3 million copies of the initial publication have been downloaded from NIDA's website, and more than 40,000 hard copies have been circulated. Outreach efforts to judges and other stakeholders are being met with great enthusiasm.

Meanwhile, CJ-DATS, designed to improve outcomes for abusing offenders by improving the integration of drug abuse treatment with other public health and

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<sup>1</sup> Taxman, F.S.; Young, D.W.; Wiersema, B.; Rhodes, A.; and Mitchell, S. The National Criminal Justice Treatment Practices survey: multilevel survey methods and procedures. *Journal of Substance Abuse Treatment* 32(3):225–238, 2007.

<sup>2</sup> U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. *National survey on drug use and health, 2005*. Ann Arbor, MI: 2006-11-16.

public safety systems, has multiple studies under way with criminal justice populations on varied topics, including: drug abuse and related risk behaviors among juvenile detainees; co-occurring substance use and mental disorders; standards needed to assess drug treatment practices in correctional settings; and targeted interventions to address needs in community re-entry treatment programs, including HIV/AIDS.

Item

***Health Disparities***

The Committee notes that the consequences of drug abuse disproportionately impact minorities, especially African American populations. The Committee encourages NIDA to conduct more studies in these populations, especially in criminal justice settings and geographic areas where HIV/AIDS rates are high. (p. 147)

Action taken or to be taken

Please refer to page 244 of this document for NIDA's response to this item on Minority Populations.

Item

***Hepatitis Prevention***

The Committee urges NIDA to work with voluntary health organizations to promote liver wellness, education, and primary prevention of both hepatitis and substance abuse. (p. 147)

Action taken or to be taken

Current incidence and prevalence data reveal hepatitis C virus (HCV) infection as a substantial health problem in this country that is likely to linger for some time. Nearly 4 million people in the United States are believed to be infected with HCV, the leading cause of liver disease; approximately 400,000 are also co-infected with HIV. Chronic HCV and HIV co-infection results in an accelerated progression to end stage liver disease and death, compared to HCV infection alone.

NIDA is committed to continuing support for research on liver disease among drug using populations, with a major emphasis on HCV. The broad spectrum of NIDA-supported HCV research is contributing to both primary prevention and prevention of morbidity and mortality through improved clinical management of chronic HCV and HCV/HIV co-infection. For while therapeutic programs and treatment models have been developed for drug users with chronic HCV infection, multiple treatment barriers prevent most active or recovered drug abusers from receiving HCV therapy, requiring better education both of affected individuals and of health care providers.

Working with its partners, NIDA continues to educate the community about prevention measures. To this end, outreach to partners, voluntary organizations, and grassroots groups is critical. NIDA has relationships with several organizations (e.g., the Liver Foundation) with whom it works to translate and disseminate science research on HIV, hepatitis, and co-occurring problems into user friendly information for community coalitions.

NIDA also supports dissemination and translation of research findings through sponsorship of meeting symposia on drug use and liver disease. At the annual meeting of the American Association for the Study of Liver Disease (AASLD), NIDA presented a symposium on Liver Disease in Drug Users and, in collaboration with other NIH institutes (NIDDK & NCI), co-sponsored a meeting on HIV and Liver Disease. In addition, NIDA also sponsored a symposium at the Congress of Drug Addiction, Hepatitis, and AIDS on the intersections of drug abuse, HIV, and HCV. This session provided attendees, including clinicians and researchers with information on the latest scientific developments in how to best treat drug abuse and HIV/HCV co-infection. NIDA supports publication of meeting symposia to further disseminate information on hepatitis and drug use, including a recent summary article by NIDA staff reflecting the latest thinking about clinical management of HIV and HCV co-infection in drug users.

NIDA is also participating in the Trans-NIH Action Plan for Liver Disease Research. This congressionally mandated NIH task force has developed and is assessing progress on an action plan for coordinating and developing the liver research agenda for NIH. This year, the task force issued a Progress Review (year two analysis).

#### Item

##### ***Inhalant Abuse***

The Committee urges the Institute to continue its support of research on prevention and treatment of inhalant abuse, and to enhance public awareness on this issue. (p. 147)

#### Action taken or to be taken

Inhalants are often among the first drugs that young children abuse. According to the 2006 Monitoring the Future survey, past-year inhalant abuse was reported by 9.1 percent of 8<sup>th</sup> graders, 6.5 percent of 10<sup>th</sup> graders, and 4.5 percent of 12<sup>th</sup> graders. NIDA recognizes the need to continue supporting research on the consequences, prevention, and treatment of inhalant abuse, as well as increase public awareness of the dangers associated with these drugs.

Despite the pernicious nature of this form of substance abuse, little is known about long-term health and social consequences, functional impairments, psychiatric comorbidities, and treatment needs of inhalant abusers in the general population. To fill this gap—and in response to persistent levels of inhalant

abuse among youth—NIDA supports a diverse research portfolio on the topic and has intensified efforts to inform the public about the damaging effects of inhalant abuse. NIDA-supported researchers have recently drawn attention to two important topics: (1) the relationship between inhalant abuse and suicide among incarcerated youth and (2) the role of social context in the abuse of inhalants by adolescents. To design effective prevention programs, it is vital to understand the contexts in which these substances are typically abused. To further encourage research on all aspects of inhalant abuse, NIDA has issued a Program Announcement titled “Inhalant Abuse: Supporting Broad-Based Research Approaches.” It is designed to encourage broad-based research that can inform prevention and treatment interventions for inhalant abuse, particularly for children and adolescents.

To educate students about the risks associated with inhalant abuse, NIDA-supported researchers are adding an inhalant-related component to the award-winning website called “The Reconstructors” (<http://reconstructors.rice.edu/>). The website is designed for middle school students to use either at home or in the classroom. Recent studies have shown that students’ knowledge of drug effects increases significantly after using the website. This approach represents yet another avenue through which NIDA can reach youth about the dangers associated with inhalant abuse.

NIDA continues to enhance public awareness regarding inhalant abuse through its participation in events such as the annual press conference held by the National Inhalant Prevention Coalition. During this press conference, families speak openly about the deadly impact inhalants have had on their children and share information about the latest trends in inhalant abuse and ways to prevent it.

#### Item

##### ***Marijuana Use***

The Committee urges NIDA to continue to support research on the long-term consequences of marijuana use and work with the private sector to develop medications focusing on marijuana addiction. (p. 147)

#### Actions taken or to be taken

Smoking marijuana (the most commonly abused illicit drug among teenagers in the United States) can produce adverse physical, mental, emotional, and behavioral changes, and—contrary to popular belief— can be addictive. Scientists continue to learn about the ways in which marijuana affects the brain and other organs. In general, the acute effects of marijuana abuse are more studied and better understood than the consequences of chronic abuse, which are often difficult if not impossible to disentangle from many other confounding factors. Therefore, NIDA is committed to better understanding the long-term consequences of marijuana abuse, including its effects on mental and physical

health. Furthermore, NIDA has implemented an aggressive program of medications development, which targets addiction to all drugs of abuse, including marijuana.

NIDA's portfolio on the potential consequences of long-term marijuana abuse has an important preclinical component. Indeed, animal studies have proven particularly suitable to identify the potential effects of chronic marijuana on the immune, endocrine, reproductive, and cardiovascular systems. NIDA's marijuana research portfolio also includes a growing number of human studies, several of which have indicated possible associations between heavy marijuana abuse and the triggering or exacerbation of mental illness symptoms, particularly in individuals with a genetic predisposition. Several ongoing NIDA grants are investigating a range of possible effects from chronic marijuana abuse, using neuroimaging studies that assess whether abuse causes measurable long-lasting changes in the brain. For example, although there is little evidence that chronic cannabis use might result in altered brain structure, specific imaging studies (i.e., BOLD fMRI) in chronic users have recently revealed consistent changes in brain networks responsible for higher cognitive functions. Other projects are assessing possible sleep disturbances during marijuana withdrawal syndrome and the magnitude of chronic and residual effects of smoked marijuana on job productivity.

NIDA-funded studies are also investigating marijuana's effects from the prenatal period to adulthood. One of these is a longitudinal study that has shown prenatal exposure to marijuana to be a significant predictor of marijuana abuse at age 14. Another project has recently found that prenatal exposure to cannabis can differentially disrupt opioid-related gene expression in the human brain, which could have long-term effects on cognitive and emotional behaviors.

NIDA continues to focus a substantial amount of its research on the identification of effective treatments as growing numbers of people in treatment report marijuana as their primary drug of abuse. A better understanding of the cannabinoid system, for example, has opened the way for the development of a medication to block the intoxicating effects of marijuana's active ingredient, THC, and prevent relapse.

#### Item

##### ***Methamphetamine Abuse***

The Committee urges NIDA to continue supporting research to address the medical consequences of methamphetamine abuse. (p. 147)

#### Action taken or to be taken

Methamphetamine (METH) abuse continues to be a problem in the United States, persisting at high levels in western parts of the country, with reports of

increases among youth, women, and Hispanic populations throughout 2006-2007. NIDA recognizes the myriad problems posed by meth abuse and addiction and has redoubled its research efforts since 2000 in response.

NIDA supports a comprehensive research portfolio that aims to understand how METH affects the brain and body and to develop effective prevention and treatment interventions. In 2006, NIDA research demonstrated that prevention interventions designed to target all drugs of abuse can significantly reduce METH abuse as well. Effective prevention interventions are critical given the devastating consequences of meth addiction. For example, NIDA-supported research has shown that METH abuse can lead to cardiovascular problems, such as rapid and irregular heartbeat, increased blood pressure, and stroke. Chronic METH abusers can also exhibit violent behavior, anxiety, depression, confusion, insomnia, and psychosis. In fact, NIDA's research portfolio addresses a range of METH abuse consequences—behavioral, cognitive, physiological, and medical—as well as developmental outcomes associated with prenatal and childhood exposure.

NIDA-supported research has also demonstrated that prolonged abstinence can reverse some of the brain changes associated with METH abuse, making effective treatment critical for those addicted. To this end, NIDA-supported research has demonstrated several effective treatment approaches to help people recover from METH addiction. For example, a recent study conducted through NIDA's CTN showed that incentive-based behavioral therapy is effective in achieving sustained abstinence. Building on the positive outcomes and lessons learned from this study, NIDA (through its collaborative Blending Initiative with SAMHSA) recently released a toolkit entitled "Promoting Awareness of Motivational Incentives," which includes a video, PowerPoint presentations, sample materials, and additional resources, to inform practitioners about successful approaches in the use of motivational incentives. NIDA is also invested in the development of medications for METH addiction. Preliminary data suggest that bupropion, the antidepressant marketed as Wellbutrin, in combination with behavioral group therapy, is effective in increasing the number of weeks of abstinence in male patients with low-to-moderate METH dependence. This medication and others are currently in clinical trials, while new compounds are being developed and studied in preclinical models (including monoclonal antibodies).

Given the devastating consequences of METH abuse, NIDA will continue to support research not only on medical consequences, but also on prevention and treatment interventions for methamphetamine abuse and addiction.

Item

***Primary Care Settings and Youth***

The Committee encourages NIDA to continue to support health services research on effective ways to educate primary care providers about drug abuse, develop brief behavioral interventions for preventing and treating drug use and related health problems; and develop methods to integrate drug abuse screening, assessment, prevention and treatment into primary health care settings. (p. 147)

Action taken or to be taken

Research indicates that adolescence is not only the time when most drug abuse starts, but it is also a period of remarkable structural and functional maturation of the brain. Since drugs of abuse target many of these developing brain systems, exposure to drugs could have potentially life-long consequences, in addition to the already well characterized detrimental impact on academic achievement, social integration, and family function. Primary care settings and the implementation of screening and brief interventions for illicit and prescription drug abuse offer a tremendous opportunity to reach this population at a critical time—between experimentation and addiction.

Integrating substance abuse education into medical settings has the potential to not only refer clearly symptomatic drug-addicted patients to specialized treatment, but to identify and possibly *prevent* risk of addiction in those patients who do not yet exhibit extreme symptoms. Moreover, because drug abuse can be a factor in the course and progression of a variety of other medical diseases (including adherence to treatment regimens), assessing a patient's level of drug abuse can assist healthcare providers in treating a number of other conditions.

To further the goal of creating reliable and valid screening and brief intervention tools conducive to primary care medical settings, NIDA joined with the Substance Abuse and Mental Health Services Agency (SAMHSA) to cohost a scientific meeting in 2007. The goals of the meeting were to review the current state of the science; assess the feasibility, validity, and reliability of current screening and assessment instruments; examine the impact of brief interventions in medical settings on health outcomes; and explore models for implementing screening within communities. Building on the momentum generated by this collaborative meeting, NIDA has announced its intent to publish an RFA seeking applications to develop and test the effectiveness of systems-level models of care that integrate drug screening, brief intervention, and referral to specialized treatment (SBIRT) for individuals entering primary care medical settings. This RFA will be a joint effort between NIDA and SAMHSA, with applicants encouraged to work with participants in SAMHSA's SBIRT program, currently operating at seven different sites around the country. This research is expected to contribute to an evidence base for determining the effectiveness of drug abuse screening followed by brief interventions in primary care practices.

Item

**Social Neuroscience**

The Committee encourages the Institute to continue its focus on the interplay between genes, environment, and social factors and their relevance to drug abuse and addiction. (p. 147)

Action taken or to be taken

Neuroscientific methods have already contributed to major advances in research on basic cognitive processes such as memory, attention, and learning. Still, there is little understanding of the neural basis of social cognition, emotion and behavior, and much less research on intermingled alcohol and/or drug abuse. NIDA recognizes that the social environment is itself multifaceted, comprising a dynamic set of environmental and behavioral interactions that influence connections among individuals (e.g., parent and child, husband and wife, groups, institutions, and societies). These connections form social networks that can have an impact on brain development and function, cognition, emotion, and behavior. Research is needed to identify the specific pathways by which social behavioral processes and experiences influence and are influenced by brain function across life stages. This is particularly true today because we now have the tools to investigate how genetics, epigenetics, and brain chemistry can change social behavior and how the social interactions of an individual can change his or her brain.

NIDA is committed to address the research gap by taking advantage of modern imaging and genetics tools, and has spearheaded, in concert with the NIAAA and the NIA, a broad initiative to encourage the kind of interdisciplinary research required to examine the neurobiological mechanisms of social behavior and how these influence, mediate, or are influenced by alcohol and drug abuse, along with social, economic, and health-related decisions that people make. Recent meetings devoted to “Mapping the Social Environment” and “Social Neuroscience: Developing More Powerful Behavioral Interventions” reflect this commitment.

Current grants under NIDA’s Social Neuroscience RFA investigate a range of complex issues, including the neurobiology of emotion relative to drug abuse, the neurobiology of risk-taking behaviors and peer pressure, and how social context influences the way people react to drug abuse cues. NIDA is particularly interested in targeting the influence of social factors both in individual and group decision-making, a critical focus to understand drug abuse and other health behaviors. For instance, a social neurobiological perspective is being applied in NIDA studies investigating the mechanisms underlying adolescents’ increased sensitivity to social influences (e.g., peers) and decreased sensitivity to negative consequences of their behavior that together make them particularly vulnerable

to drug abuse. On a related note, a recent fMRI study has established the foundation for investigating whether drug abusers display impairment in brain systems involved in emotional appraisal of groups. Since many treatment approaches involve group therapy, dysfunction in these areas could have substantial implications for treatment.

NIDA is similarly committed to efforts designed to better characterize social environments and to understand their interaction with other factors, such as genetics. One approach is to map community risk factors for drug use (e.g., parental practices, family structure, school systems, socio-economic status, neighborhood characteristics, and drug availability) and use that knowledge to mitigate the impact of social stressors that elevate drug abuse risk.

# National Institute on Alcohol Abuse and Alcoholism

## Senate Significant Items

### Item

#### ***Alaska Natives***

The Committee is aware of serious problems with alcohol and substance abuse among Alaska Natives and of the need for translating research into clinical applications for this population. The Committee urges the NIAAA to sponsor a research-to-practice forum with SAMHSA and other experts to focus on bridging the gap between researchers and practitioners and translating scientific research into clinical applications. (p. 144)

### Action taken or to be taken

NIAAA worked closely with the Office of the Surgeon General and SAMHSA to develop *The Surgeon General's Call to Action to Prevent and Reduce Underage Drinking* and we have continued to partner to promote and disseminate the *Call to Action*. As part of this effort, with funding and staff support from NIAAA and SAMHSA, former Acting Surgeon General RADM Moritsugu visited individual states, presenting the findings from and strategies within the *Call to Action* and meeting with state officials, community leaders and prevention practitioners until his retirement in September 2007. Following his appointment in October 2007, the current Acting Surgeon General RADM Galson announced he would continue to promote the *Call to Action* in individual states. In early December, 2007 he participated in the Alaska Health Summit in which he presented the science behind the Surgeon General's *Call to Action*, met with members of the Alaska Coordinating Committee for the Prevention of Underage Drinking, and participated in the release of their Plan to Prevent and Reduce Underage Drinking to the public. The overall theme of the Summit was *Making Alaska Healthy: Individuals, Communities, Policies and Environment* and the theme for the Behavioral Health/Public Health track was *Making the Brain and Body Connection—Integrating Behavioral Health and Public Health*. The overarching focus was on developing a coordinated approach to address protective factors, risk factors and opportunities for intervention that promote physical and emotional health for all Alaskans. In addition to its work with the Office of the Surgeon General, NIAAA also continues to support the translation of scientific research into culturally appropriate clinical applications for the Alaska Native population. NIAAA is currently funding the development of a culturally based alcohol prevention intervention program for Alaskan Native youth in the extremely isolated rural areas of Alaska. The intervention is based on the findings of previous NIAAA-supported research that revealed how culturally based activities, attitudes, and beliefs were at the center of maintaining sobriety for many rural Alaskan Natives. Pilot data will be collected with the intent of

conducting a large scale test of the intervention. Recently, analyses of clinical data with the medication naltrexone have indicated the drug is effective in treating alcohol dependence in Alaska Natives. This study may inform healthcare options for individuals who live in remote areas with limited access to health care facilities.

#### Item

##### ***Clinician's Guide***

The Committee commends the NIAAA for widely disseminating its publication "Helping Patients Who Drink Too Much: A Clinician's Guide." The Committee encourages the NIAAA to further develop guide materials, including information for clinicians about how to best use the guide, and short pamphlets that are targeted toward special subpopulations, and to work with professional organizations, SAMHSA, and other international organizations to further disseminate this important resource. The Committee also encourages the NIAAA to develop supporting training materials for physicians and other health care providers. (p. 144)

#### Action taken or to be taken

In response to the Committee's suggestion, NIAAA will launch an online, interactive program that features four video scenarios that demonstrate the clinical approach in NIAAA's *Helping Patients Who Drink Too Much: A Clinician's Guide*. The videos depict screening, assessment, and management of at-risk and dependent patients in different states of readiness to change. Engaging learning activities have been developed for each case study. In addition, nationally recognized experts will lead participants through the case studies. NIAAA is working with Medscape to provide continuing education credits for physicians and nurses. The online training program will be available in early 2008. Outreach for the *Guide* has included the following professional association partnerships:

- NIAAA worked with the American Medical Association (AMA) targeting a direct mailing of the *Guide* to 10,000 members registered as medical school faculty. A letter jointly signed by the AMA President and NIAAA Director Dr. Li accompanied the *Guide*. In addition, the AMA publicized the *Guide* on its Web site, in several specialized e-newsletter announcements, and in a news brief in *JAMA*.
- An article about the *Guide* and its "family of products" (including the PowerPoint CD and dedicated Web Page) was published in the April/May 2007 issue of *American Society of Addiction Medicine News*. NIAAA also supported mailing copies of the *Guide* along with the newsletter to 3500 ASAM members and subscribers.
- NIAAA provided content and artwork to the Association for Medical Education and Research in Substance Abuse and the American Academy of Addiction Psychiatrists (AAAP) for e-announcements and newsletter articles, and issued a direct mailing of the *Guide* to AAAP members.

- A direct mailing of the *Guide* was also sent to 680 deans of nursing schools and an e-announcement to 230 organizations: 71 substance abuse; 97 medical; 43 mental health, and 19 criminal justice.

Item

***Collaboration with Single State Authorities [SSAs]***

The Committee urges the NIAAA to work with State substance abuse agencies, also known as Single State Authorities [SSAs], on collaborative initiatives to ensure that research findings are relevant and adaptable by publicly funded State substance abuse systems. (p. 144)

Action taken or to be taken

NIAAA will participate in SAMHSA's CSAP Community Prevention Day that will be attended by community prevention organizations, including SSAs. NIAAA will take advantage of this platform to share alcohol-related research findings with SSAs to inform programs and practices in the substance abuse systems at the State level.

Item

***Hepatitis Prevention***

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. 144)

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* and one issue of *Alcohol Alert* 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 most sure way to reduce the risk of organ damage is to reduce alcohol exposure in children and adolescents, thus preventing 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

***Patterns of Alcohol Consumption***

The Committee encourages the NIAAA's efforts to include measurement of quantity and frequency of alcohol consumption in new classification systems of alcohol problems. The Committee also encourages the NIAAA to continue to fund research that defines both safe and hazardous levels of alcohol consumption for various segments of the population. (p. 144)

Action taken or to be taken

Analysis of data from NIAAA's National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and other research studies continue to show the importance of quantity, frequency as well as patterns of drinking as measures for assessing: risk for alcohol dependence, potential for tissue and organ pathology, severity of disease, and for guiding therapeutic approaches. Defining both safe and hazardous levels and patterns of drinking continues to be an issue of importance and data to address these questions are emerging from on-going NIAAA-supported research.

Item

***Underage Drinking***

The Committee notes that the Surgeon General calls for measures to decrease the availability of alcohol to youth. The Committee urges the NIAAA to conduct further research on the most effective means of reducing youth access to alcohol and increasing the cost of obtaining it. (p. 145)

Action taken or to be taken

If we are to prevent and reduce underage drinking, it is essential that we reduce youth access to alcohol and increase the cost of obtaining it (broadly defined to include the price of alcohol, the difficulty of getting it, and the negative consequences of being caught drinking underage). To do this, it will be important that all who interact with young people act in concert and do not provide alcohol to underage youth. This includes parents, older siblings and friends, merchants and others from whom youth may potentially seek to obtain alcohol. This is important because studies on shoulder tapping, whereby an underage individual approaches an adult with a request to purchase alcohol, indicate a significant percentage of adults will agree to buy alcohol for someone under age 21. In terms of retail access, compliance checks can be successful at reducing underage drinking. Further, comprehensive community interventions that involve multiple elements of the community, e.g., school, health, police and alcohol beverage control departments, alcohol sellers, media advocacy, parents, private citizens and organizations and community organizations, have been shown to be effective at reducing underage drinking. A less specific, but extremely critical part of reducing access will involve changing attitudes about underage drinking,

so that it is no longer viewed as a rite of passage, but rather as a behavior that can derail healthy development in multiple domains. Adults who have incorporated this information into their thinking will be less likely to provide alcohol to minors. It will also be important as we move forward to understand more about parental attitudes and how they influence parental decisions about underage alcohol consumption. NIAAA also tracks underage drinking policies through the Alcohol Policy Information System (APIS) that will allow researchers in the future to determine which policies are most effective at reducing underage drinking.

#### Item

##### ***Understanding the Processes of Change in Drinking Behavior***

The Committee understands that a number of distinct treatment approaches have been developed to address alcohol use disorders. While each approach is useful in reducing alcohol consumption, research suggests that these approaches have similar levels of effectiveness. Recent research has also demonstrated that many individuals transition out of alcohol dependence without professional treatment, while others drink heavily but never develop complications required for a diagnosis of dependence. The Committee applauds recent NIAAA research initiatives supporting mechanisms of behavioral change using professional treatment mechanisms. The Committee encourages the NIAAA to further expand research in this area by stimulating interdisciplinary research that integrates biomedical, psychological and social science perspectives on mechanisms of behavior change. (p. 145)

#### Action taken or to be taken

In FY 2007, NIAAA funded 12 exploratory/developmental projects to investigate the underlying psychological, social, and neurophysiological processes that drive behavior change within the context of evidence-based behavioral treatments for alcohol use disorders. These studies are expected to lay the groundwork for understanding the causal relationship between potential mechanisms of behavior change and treatment outcomes.

## National Institute of Nursing Research

### House Significant Items

#### Item

#### ***End of Life Science***

Improving the care of terminally ill patients at the end of life continues to be an urgent public health need, along with the need to improve the end-of-life experience for the patient's loved ones. Additional research is needed into improving palliative care, reducing caregiver burden, and improving the interactions between patients, loved ones, and clinicians. The Committee recognizes NINR's continued leadership in end-of-life sciences and encourages the Institute's continued focus in this area. (p. 152)

#### Action taken or to be taken

NINR designated end-of-life research as a major priority in its strategic plan. As enumerated in the plan, NINR will focus its end-of-life research efforts, in part, on: developing strategies to improve decision-making and treatment at the end of life; developing interventions to improve palliative care and enhance quality of life for the dying patient and to support family and informal caregivers; communicating factors related to the end of life to underserved groups, including those who are vulnerable and unable to express their own end-of-life preferences; and increasing efforts to expand end-of-life research through research training and other mechanisms.

Having created an important foundation of end-of-life science, NINR will begin to move its end-of-life research program to the next stage of development in FY 2008. The Institute will increasingly focus its efforts on clinical, interdisciplinary studies that test the effectiveness of innovative end-of-life/palliative care interventions with the goal of transitioning these interventions into general use. While the initial development and testing of new interventions will continue to occupy an important position in NINR's research program, larger clinical studies will promote the continued advancement of end-of-life science and ensure that successful interventions reach the patients and caregivers whom they could benefit.

The advancement of end-of-life research also will require the development of enhanced research capacity, in terms of both people and organizations. Accordingly, NINR will focus in the coming years on the training of new investigators in end-of-life/palliative care research, and will support the development of collaborative resources at institutions committed to furthering the science. Consistent with this focus, NINR recently solicited applications for the Nursing Science Centers of Excellence in Self-Management or End-of-Life Research. The first awards under this program were made in late FY 2007. It is anticipated that these Centers will serve as a nexus for the emergence of end-of-

life research as an interdisciplinary science, training investigators from multiple backgrounds and enhancing collaboration to increase the quality and quantity of innovative, interventional research projects in end-of-life and palliative care science. Support for these Centers will continue.

#### Item

##### ***Nursing Shortage***

The shortage of nurses in the U.S. is a great concern for the field of healthcare. The nursing shortage threatens our nation's healthcare delivery systems, and shortages of nursing faculty impair the ability of schools of nursing to train new nurses. The Committee is concerned about the potential impact of the nursing shortage on nursing research and encourages NINR to explore innovative strategies for recruiting and developing additional nurse scientists. The Committee encourages NINR to support training programs that will develop the next generation of nurse scientists, especially those with multidisciplinary research skills and those from underserved populations. (p. 152)

#### Action taken or to be taken

NINR training strategies seek to enhance the pipeline of nursing faculty, which will have a direct impact on improving the ability of schools of nursing to educate new nurses. These strategies focus on the training of new nurse scientists, many of whom go on to become nursing faculty. NINR supports innovative training programs such as the NINR Career Transition Awards, in which awardees receive postdoctoral research training in the NINR intramural laboratories in Bethesda, Maryland, followed by two years of extramural support as they begin tenure-track faculty positions. NINR also participates in the NIH Pathway to Independence Award program, designed to shorten the amount of time trainees spend as post-doctoral fellows and facilitate their transition to independent research careers. Awardees receive one to two years of mentored research training, followed by three years of independent support once the awardee has secured an independent research position. In addition, NINR participates in the NIH Graduate Partnership Program (GPP), in which the Institute partners with schools of nursing to support the research training of doctoral students in symptom management, genetics, or end-of-life/palliative care at the NIH intramural laboratories. Currently, five schools of nursing partner with NINR on the GPP. Finally, NINR will continue to support career development opportunities for underserved and disadvantaged investigators. These opportunities provide new investigators from such backgrounds with an intensive, supervised career development experience in the nursing sciences leading to research independence.

Considering its long history of collaboration with other disciplines, nursing science is well-positioned to serve as an agent of change for a research community in which multidisciplinary collaboration must become the norm and not the exception. In order to further scientific leadership in this area, NINR

will increasingly support training programs and opportunities that encourage participants not only to develop expertise in diverse topic areas, but also to employ interdisciplinary collaborations as part of their standard research practice. These efforts will include taking full advantage of current NIH-wide initiatives to expand interdisciplinary research opportunities, including the NIH Roadmap. NINR's commitment to innovative training programs to improve the pipeline of nursing faculty will continue into FY 2009 and beyond.

Item

***Health Disparities***

The Committee continues to encourage NINR to support research into the causes of health disparities and into the development of innovative methods for overcoming such disparities. In addition, NINR is encouraged to develop new nurse scientists from underserved populations as a way to encourage new health disparities research. (p. 153)

Action taken or to be taken

The elimination of health disparities is a cross-cutting area of health care science that is a significant part of every program of research funded by NINR.

Consistent with the Institute's focus on this area of research, the elimination of health disparities is highlighted as an Institute research priority in NINR's new strategic plan, and all centers currently funded by NINR include some aspect of health disparities research in their program plan. In FY 2007, NINR funded projects to study: the promotion of asthma self-care in urban African-American adolescents; the testing of interventions to improve end-of-life care for homeless persons; and the development of interdisciplinary programs targeted to ethnic minority children and their parents to improve nutrition and exercise habits. NINR also recently renewed an institutional training program to train pre- and post-doctoral investigators in the conduct and dissemination of research in the area of health disparities and vulnerable populations.

In addition, NINR supports the Mentored Research Scientist Development Awards for Underrepresented or Disadvantaged Investigators. These career development opportunities provide new investigators from such backgrounds with an intensive, supervised career development experience in the healthcare sciences leading to an independent research career. In supporting the scientific development of these investigators, NINR seeks to stimulate new and innovative lines of research into the elimination of health disparities. Support for the projects described here, and many others like them, demonstrate NINR's continuing commitment to reducing, and ultimately eliminating, health disparities. This commitment will continue.

## 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. 143)

### Action taken or to be taken

NINR supports research to establish the scientific basis of care across the lifespan. Improving health outcomes for newborn children and their parents is an important focus of NINR's research programs. One recent study by NINR-supported investigators assessed the effect of an educational program on the psychological care needs of parents of preterm infants. Utilizing the Creating Opportunities for Parental Empowerment (COPE) educational program, parents were taught about prematurity, infant behaviors, and infant development. In FY 2007, investigators reported that parents who participated in the COPE program demonstrated improved parenting behaviors and decreased stress levels. Meanwhile, infants averaged 3.8 fewer days in a neonatal intensive care unit (NICU) than controls, which translated to a savings of roughly \$5,000 per infant. In FY 2009, NINR will support a new initiative to conduct research on biobehavioral interventions to reduce the incidence of preterm delivery and low birth weight and improve associated outcomes.

### Item

#### ***Nursing Shortage***

The nursing shortage has an adverse effect on the health care delivery system as well as the health of our Nation's citizens. A shortage of nurse faculty caused schools of nursing to turn away thousands of qualified students last year. The NINR confronts this issue by directing 8 percent of its budget to research training to help develop the pool of nurse researchers who also become faculty. Training support for fast-track baccalaureate-to-doctoral program participants is one important initiative. The 17 recently funded Nursing Partnership Centers to Reduce Health Disparities is another initiative that helps produce an adequate number of nurse researchers. The Committee encourages these ongoing efforts. The Committee also encourages the NINR to facilitate research projects located in rural areas that serve minority nursing students through community colleges. (p. 143)

### Action taken or to be taken

Please refer to page 268 of this document for NINR's response to this item on the nursing shortage.

## National Human Genome Research Institute

### House Significant Items

#### Item

##### ***Fragile X syndrome***

Finally, there are important aspects of Fragile X to be studied in genomic research. FMRP, the protein whose absence results in fragile X syndrome, is a regulator of translation of many genes, including those involved in learning and memory. A genomic approach to understanding the diverse pathways regulated by FMRP would aid in the understanding of human cognition and identify potential targets for drug design to alleviate the symptoms of fragile X and related disorders. The Committee encourages NHGRI to strengthen its research activities on fragile X and to coordinate these efforts with other Institutes working on related activities, including NIMH, NINDS, NIDDK, NICHD and FIC.

#### Action taken or to be taken

NHGRI funds 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 just completed the pilot phase of ENCyclopedia Of DNA Elements (ENCODE), a multi-phase project that seeks to identify all functional elements of the human genome, and has begun broad expansion of the project. The ENCODE pilot study, which examined just 1 percent of the human genome, produced strong evidence that the organization, function and evaluation of the genome appears to be far more complicated than was commonly suspected. The full-scale ENCODE project will survey the entire genome and provide a more extensive analysis of the relationships between, and impact of, all the functional aspects of the genome. NHGRI has recently funded multiple ENCODE grants totaling more than \$80 million over the next four years.

ENCODE is designed to encourage broad scientific collaboration, and all ENCODE data will be deposited into public databases and made available to researchers around the world. This research is expected to provide valuable information for many diseases such as Fragile X.

#### Item

##### ***Spinal muscular atrophy (SMA)***

The Committee is supportive of the development of a carrier screening program for SMA and the trans-institute collaborative effort initiated by NHGRI to develop a strategic plan addressing research-related needs to improve carrier screening technology. The Committee encourages NHGRI to work collaboratively and cooperatively with the advocacy community in this effort.

Action taken or to be taken

On February 6-7, 2008, NHGRI will hold a conference to engage a variety of organizations in a discussion of emerging opportunities and obstacles in carrier screening for single gene disorders. This conference framed a vision that participating organizations may use to inform their scientific activities and policy development regarding carrier screening. The conference was cosponsored by NICHD, ORD, HRSA, CDC, the Genetic Alliance and the American College of Medical Genetics. Representatives from the advocacy community have actively participated in the planning committee and were represented among the speakers at the conference.

**Senate Significant Items**

Item

***Fragile X***

FMRP, the protein whose absence results in Fragile X syndrome, is a regulator of translation of many genes including those involved in learning and memory. A genomic approach to understanding the diverse pathways regulated by FMRP would enhance the understanding of human cognition and identify potential targets for drug design to alleviate the symptoms of Fragile X and related disorders. The Committee urges the NHGRI to consider expanding its research activities on Fragile X and to coordinate these efforts with other Institutes working on related activities.

Action taken or to be taken

Please refer to our response on page 271 of this document.

Item

***Spinal Muscular Atrophy [SMA]***

The Committee supports the development of a pan-ethnic carrier screening program for SMA and commends the NHGRI and NICHD for their plans to jointly convene a workshop in early 2008 to stimulate carrier screening technology development, enhance education and awareness among professional and patient communities, and promote policy discussions regarding the ethical and social issues related to implementing new carrier screening programs for disorders such as SMA. The Committee requests an update on the workshop in the fiscal year 2009 congressional budget justifications. Furthermore, the Committee urges the NHGRI to work collaboratively and cooperatively with the advocacy community in this effort.

Action taken or to be taken

Please refer to our response on page 271 of this document.

Item

***Tuberous Sclerosis Complex [TSC]***

The Committee urges the NHGRI to provide assistance and advice to the TSC research community on TSC gene and genome-wide sequencing projects

Action taken or to be taken

NHGRI funds 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 tuberous sclerosis complex (TSC). As always, the NHGRI welcomes discussions with the TSC community to provide education, assistance, and advice about research relevant to TSC, and to explore the potential implications of genome-wide association studies for TSC research.

# National Institute of Biomedical Imaging and Bioengineering

## House Significant Items

### Item

#### ***Imaging Beta Cells***

The ability to painlessly and non-invasively visualize pancreatic islets in people with type 1 diabetes has the potential to revolutionize diagnosis and therapy of type 1 diabetes. The Committee recognizes the NIBIB, along with the NIA, NIAID, and NIDDK, for their collaborative efforts to promote research on the development of new islet imaging technologies. The Committee encourages the NIBIB and NIDDK to support translational research efforts to convert advances made in imaging of islets in animal models into technologies that can be applied to human type 1 diabetes patients.

### Action taken or to be taken

The NIBIB, began collaborating with the NIDDK, NIAID, and NIA in 2003, to develop imaging approaches that could be clinically useful for type 1 diabetes patients. For example, in 2006, NIDDK, NCI, NIBIB, and NIAID, along with the Juvenile Diabetes Research Foundation International, hosted a workshop on “Imaging the Pancreatic Beta Cell in Health and Disease.” and supports research through an initiative entitled “Toward Imaging the Pancreatic Beta Cell in People.”

We are closely monitoring scientific progress in these grants, and in the next two years will use this information to design initiatives that will enable new scientific research focused on providing better translation of novel molecular imaging approaches to type1 diabetes patients.

### Item

#### ***Positron emission tomography [PET]***

The Committee continues to encourage the NIBIB to devote significant resources to molecular imaging technologies such as PET and microPET to take advantage of the capacities of molecular imaging to detect disease process at the molecular level and to monitor the effectiveness of targeted gene therapies now under development. The Committee also encourages the NIBIB to collaborate with other, disease-specific Institutes at NIH, so that new imaging technologies are closely tied to the research projects being undertaken throughout the NIH.

### Action taken or to be taken

The NIBIB supports the research and development of technologies for PET in order to further advances in molecular imaging and early detection and localization of diseases such as cancer. Two particularly active areas of research are the combining of PET (or SPECT - single photon emission computed tomography) with CT or MRI scanners. These devices will combine the three-dimensional anatomical precision of MR or CT with the functional (biochemical) specificity of PET. The NIBIB is also supporting the development

and design of higher resolution, lower cost PET and SPECT devices. Other research includes the development of better radiopharmaceuticals, crystal scintillators (radiation and light detection materials), collimators (radiation focusing device), and novel approaches to dual-isotope imaging.

#### Item

##### ***Artificial Pancreas***

A fully automated pancreas that responds rapidly to changes in diet, physical activity, and metabolic status has the potential to improve daily glucose control and dramatically reduce the risk of long-term diabetic complications. The NIBIB is urged to foster research on algorithms that can replicate normal glucose control and accurately close the loop between glucose monitoring and insulin treatment.

#### Action taken or to be taken

The NIBIB is working with the Food and Drug Administration and the NIDDK as a member of the Artificial Pancreas Working Group to accelerate the development of an artificial pancreas or a “closed-loop” insulin delivery system. The artificial pancreas algorithm development is intimately tied to the development of glucose sensors and the NIBIB currently supports projects aimed at accurate, reliable glucose sensing. In 2008, the NIBIB along with the Artificial Pancreas Working Group will hold a workshop to identify critical needs and a path forward to the artificial pancreas. Research on algorithms such as traditional proportional-integrative-derivative (PID) control as well as feed-forward and non-linear control that integrate physical activity and food consumption will be fostered, especially in the context of developing algorithms that are matched to existing and emerging glucose sensor and insulin pump systems. The NIBIB has also funded in FY 2007, under its Quantum Projects initiative, research to develop a new source of insulin secreting cells as a replacement strategy for treating diabetes. This entails the development of tissue engineered islets for human implantation.

## National Center for Research Resources

### House Significant Items

#### Item

##### ***Image Guided Therapy***

The committee applauds NCRR for its development and support of a national image guided therapy center (IGT) for research, training, and services related to novel imaging tools for disease diagnosis and therapy. NCRR is encouraged to work with NIDDK and NIBIB to ensure that this unique resource center engages with the diabetes research community to accelerate the development of new methods for the non-invasive imaging of pancreatic islets for applications in type 1 diabetes research and treatment. (p. 156/157)

#### Action taken or to be taken

The National Center for Image Guided Therapy (IGT) is planning a workshop to be held in Spring 2008 in Bethesda, Maryland to identify and encourage collaborations with scientists working on pancreatic cells. NIDDK, as well as other NIH-supported scientists involved in this line of research, will be invited to participate in order to explore ways that IGT technologies developed at the center can be adjusted/refined to advance applications in type 1 diabetes research.

#### Item

##### ***Rare Diseases***

The Committee commends NCRR for the development of the rare disease consortium, including rare lung diseases such as LAM, and urges the continuation of the program. (p. 157)

#### Action taken or to be taken

The NCRR is committed to providing infrastructure support for the entire range of research from basic pathogenesis of disease to reliable diagnostic, preventive, and treatment approaches to all diseases. In particular, NCRR has a long history of ensuring these resources, including clinical research support services and human tissues, are readily available to those studying rare diseases. The Rare Diseases Clinical Research Network (RDCRN), a collaboration among the Office of Rare Diseases, NCRR, and multiple institutes and centers, has demonstrated the value of collaboration across diseases and specialties. For example, the RDCRN's contact registration system provides a mechanism to connect potential participants with studies in their particular diseases. It also allows individuals with rare diseases to receive periodic updates and information about new findings and research activities related to their diseases. Another benefit of the RDCRN is the incorporation of standards in data collection throughout the network. These standards have increased the value of the longitudinal data being collected across multiple diseases and will improve current and future

analyses. At this time, the RDCRN supports over 25 research studies and trials in various rare diseases (<http://rarediseasesnetwork.epi.usf.edu/study-overview.htm>), including lymphangioleiomyomatosis (LAM). The currently funded consortia will continue through 2009. A renewal of the program is planned for another 5 years through a collaboration led by the Office of Rare Diseases with participation by multiple NIH institutes and centers.

#### Item

##### ***Research Centers in Minority Institutions Program (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 proposed RCMI translational research network (RTRN) and its focus on strengthening ties between minority institutions, and encourages NIH to designate specific resources for the RTRN apart from the existing RCMI program. (p. 157)

#### 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 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 on 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 and the seven medical schools included in this group produced 20 percent of the minority M.D.'s in the United States in FY 2006.

In FY 2007, NCCR funded the RTRN, a cooperative research network to facilitate clinical and translational research in health disparity areas. This Network consists of a consortium of clinical investigators from the various RCMI programs; other academic health centers; relevant organizations, including community health centers; and a data and technology coordinating center. The goal is to facilitate

development of multi-site clinical and translational research in health disparity areas; distributed clinical data management, incorporating approaches and technologies for data management that are interoperable with other networks; and access to information related to health disparities for researchers, academic and practicing physicians, patients, and the lay public. NCRB will continue to provide the resources necessary to support the RTRN in FY 2008.

### **Senate Significant Items**

#### Item

#### ***Clinical and Translational Science Awards [CTSAs]***

The Committee strongly endorses the CTSA initiative and urges the NCRB to adhere to its goal of supporting 60 CTSAs by 2012. In doing so, the Committee urges the NCRB to maintain or strengthen the clinical research infrastructure component currently provided by the longstanding General Clinical Research Centers [GCRC] program. The Committee requests an update on these activities in the fiscal year 2009 congressional budget justifications. (p. 151)

#### Action taken or to be taken

In 2005, NCRB supported 78 GCRCs that were associated with 66 universities across the United States. The GCRCs provided facilities for 14,760 investigators who had, in total, 9,257 active clinical research protocols that yielded over 3,245 publications per year. In response to investigators' needs, NCRB launched the CTSA-program in 2006 with the aim of updating clinical research infrastructure to address the needs of clinical researchers in the post-genome era. The increased range of support being provided has been made possible by a 40 percent increase in the average size of grant awards. Examples of new areas of support include: an integrated multidisciplinary career development program; patient recruitment cores; outreach to increase community participation; enhanced bioinformatics; and support for regulatory knowledge and compliance. Twelve CTSA awards were made in FY 2006 and another 12 were made in FY 2007. Additional awards will be made in FY 2008, and a funding opportunity announcement was recently released for awards that will be made in FY 2009.

NCRB anticipates that most GCRC awardees will be successful in competing for a CTSA and has allowed a 5-year transition period for this process. The activities of the CTSA consortium are posted on a Website ([www.ctsaweb.org](http://www.ctsaweb.org)) and every effort is made to provide potential applicants with the information they need to put together a CTSA application.

#### Item

#### ***Imaging***

The committee applauds NCRB for its development and support of a national Image Guided Therapy (IGT) Center for research, training, and services related to novel imaging tools for disease diagnosis and therapy. The NCRB is

encouraged to work with the NIDDK and NIBIB to ensure that this unique resource center engages with the diabetes research community to accelerate the development of new methods for the non-invasive imaging of pancreatic islets for applications in type 1 diabetes research and treatment. (p. 151/125)

Action taken or to be taken

Please refer to page 276 of this document for NCRR's response to this significant item on Image Guided Therapy.

Item

***Positron Emission Tomography [PET]***

The Committee continues to urge the NCRR to support research resource centers for the development and refinement of PET as a unique imaging technology to diagnose [end] stage diseases of the brain, including Alzheimer's disease. (p.152)

Action taken or to be taken

In FY 2007, NCRR provided funds to acquire PET scanners for use in research on animal models of human diseases as well as funds for supportive computing hardware and instruments that produce the radionuclides essential for PET studies. The PET scanners are being used in research environments which pursue new applications of PET technology in preclinical studies, e.g., for assessing the efficacy of experimental drugs in animal models of human diseases.

Item

***Rare Disease Initiative***

The Committee understands that obtaining adequate human biospecimen tissues and clinical data for research for many of the more than 7,000 rare diseases known today has been a major barrier to adequately expanding research aimed ultimately to treat and cure these rare diseases. The Committee, therefore, encourages the NCRR and the Office of Rare Diseases to expand their emphasis on rare diseases human tissue/biospecimen procurement and storage activities for rare diseases research. (p. 152)

Action taken or to be taken

The NCRR agrees that the availability of multiple resources is necessary to advance new diagnostic, preventive, and treatment modalities for rare diseases. The Office of Rare Diseases is in process of establishing a compendium of repositories of samples and specimens available for rare disease research. The availability of this information will be critical for increased utilization of already available resources and data.

Item

### ***Research Centers at Minority Institutions***

The Committee continues to recognize the critical role played by minority institutions at both the graduate and undergraduate level in addressing the health research and training needs of minority populations. The Committee encourages the NIH to strengthen participation from minority institutions and increase resources available in this area. The Committee recommends that the NCRR direct supplemental funds to high-impact, high-risk research activities within the RCMI program such as creating an integrated translational research network to help reduce health disparities. (p.152)

### **Action taken or to be taken**

Please refer to page 277 of this document for NCRR's response to this significant item on Research Centers in Minority Institutions Program (RCMI).

## National Center on Minority Health and Health Disparities

### House Significant Items

#### Item

##### ***Glomerular Disease***

The Committee understands that a type of glomerular disease, focal and segmental glomerulosclerosis, which is a group of diseases affecting the filtering mechanisms of the kidneys, is more common in African Americans than the general population. The Committee encourages NCMHD to include glomerular disease in its research portfolio. (p. 157-158)

#### Action taken or to be taken

Glomerular disease is an area of research emphasis for the National Center on Minority Health and Health Disparities (NCMHD). In addition to the research on end-stage renal disease conducted in one of its Centers of Excellence, the NCMHD has co-funded two National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) extramural research prospective studies of chronic kidney disease (CKD) in minority populations and a cross-sectional epidemiologic study on urologic diseases. The two CKD cohort studies' primary objectives are to examine risk factors for rapid progression of chronic kidney disease. One of these projects seeks to decrease the number of Hispanics with CKD.

#### Item

##### ***Research Endowment***

The Committee commends NCMHD for its leadership in addressing the longstanding problem of health status disparities in minority and medically underserved populations. For fiscal year 2008, the Committee continues to encourage NCMHD to implement its successful research endowment program as an ongoing initiative in a manner consistent with the authorizing legislation. The Committee also commends NCMHD for its successful Project EXPORT initiative and urges continued support for this important program. (p. 158)

#### Action taken or to be taken

NCMHD's Research Endowment program continues to be instrumental in enhancing the training and research capacity of academic institutions as part of the continuing nationwide effort to address health disparities. The research endowment grants provide multi-year awards to support activities such as basic and clinical research, faculty and student training, research infrastructure, and endowed faculty chairs. Seventeen grants have been awarded since the program's inception in 2001, with ten currently active. NCMHD endowment funding has assisted in the recruitment of distinguished scientists in cancer, cardiovascular disease, diabetes, neuroscience, women's health, and Native Hawaiian health at eligible institutions; the creation of an Institute of Public Health at the University of New Mexico School of Medicine to address chronic health

issues among low income and racial and ethnic minority populations; and the development of scholarship and fellowship programs for students.

Item

***Minority Training***

The Committee encourages the NIH to strengthen participation from minority institutions with a track record of producing minority scholars in science and technology. (p. 174)

Action taken or to be taken

The NIH is committed to strengthening the research infrastructure at minority health professions institutions and has identified this as a primary goal of its five-year Health Disparities Strategic Plan for all of the ICs to support. The NCMHD will continue working with the NIH Office of the Director, the ICs, and the Health Resources Services Administration, the Office of Minority Health in the Office of the Secretary, the Indian Health Service, and other federal agencies to strengthen the research infrastructure at minority health professions schools. Some of NIH's programs that are helping to build the research capacity at these institutions include: Research Infrastructure in Minority Institutions (RIMI) Program; DHHS-Hispanic Association of Colleges and Universities (HACU) Professions Capacity Building Program; and Bridges To The Future Programs.

Loan Repayment Program (LRP): The purpose of the program is to recruit and retain highly qualified health professionals with doctorate degrees to pursue health disparities or clinical research by repaying their loans to alleviate the financial barriers that often discourage many health professionals from health disparity populations from pursuing a research career. Since 2001, NCMHD has provided loan repayment program awards to 1,460 LRP recipients. The majority of these recipients (66%) are members of a racial/ethnic minority population with 35% African-Americans, 15% Hispanics, 9% Asians and Pacific Islanders, and 3% American Indians and Native Alaskans. These individuals are located at majority and minority-serving institutions in more than 42 states nationwide.

Diverse Institutions Drug Abuse Research Program is a National Institute of Drug Abuse (NIDA) capacity-building program that provides research support to minority institutions to increase the capacity of their faculty, staff and students. The grants enable minority institutions to conduct rigorous drug abuse research in all areas of research supported by the NIDA including neuroscience, behavioral, clinical, social science, public health, biological, HIV/AIDS and health service areas.

Research Scientist Awards for Minority Institutions of the National Heart, Lung, and Blood Institute (NHLBI) seeks to augment and strengthen the research capabilities and resources of minority institutions for the conduct of biomedical and/or behavioral research by recruiting an established research scientist with

expertise in areas related to cardiovascular, lung, or blood health and disease, transfusion medicine, or sleep disorders.

Research Centers in Minority Institutions (RCMI) Program: NCMHD is involved in a collaborative effort with the National Center for Research Resources (NCRR) in enhancing the research infrastructure at minority colleges and universities that offer doctorates in health sciences. The program serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health.

Research Endowment: The mission of the NCMHD Research Endowment is to build research and training capacity at institutions that have been designated as Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals by the Health Resources and Services Administration. A total of 6 Historically Black Colleges and Universities and 5 Hispanic Serving Institutions have benefited from the program thus far.

#### Item

##### ***Minority Research Training Programs***

The Committee supports the recommendations put forward in the 2005 National Academy of Sciences (NAS) report NIH minority research training programs. The Committee believes that the training of research scientists is a critical component of the NIH mission, and the Committee urges NIH to improve its data systems so that more complete information about NIH-supported graduate and post-doctoral research assistants and trainees is available. Without adequate data, the NIH programs cannot be properly evaluated or monitored. As proposed by the NAS, the Committee recommends the NIH develop an integrated NIH-wide trainee and research assistant data tracking system. The Committee further encourages NIH to engage trainees and research assistants in the data tracking process to document outcomes such as future funding awards, including those programs that are targeted to underrepresented minorities. (p. 165)

#### Action taken or to be taken

The NIH has established a committee of representatives from each Institute and Center to address the recommendations of the NAS report which is chaired by the directors of the NCMHD and the National Institute of General Medicine Sciences (NIGMS). The committee was created to provide guidance and recommendations to the NIH Director on strategies for developing a diverse biomedical research workforce. Consistent with the recommendations of the NAS report, the goals of the committee include:

- Assembling an inventory of existing and proposed programs that target the training of underrepresented minorities.
- Proposing appropriate guidelines and measures for evaluating NIH Minority training programs.

- Providing advice on the development of a data tracking system on trainees, fellows, research assistants, or postdoctoral fellows receiving NIH funding, including those programs targeted or non-targeted to underrepresented minorities.

As a part of the committee's work, the NIH has conducted a web-based inventory of its diversity programs to enhance its understanding of the program goals, objectives, targeted populations, outcomes, and identify gaps and opportunities. This will result in the launch of the NIH Diversity Program website that provides a comprehensive overview of programs aimed at promoting diversity in education and research and will provide several ways to review the list of programs. The committee will issue a final report during the second quarter of FY 2008.

#### Item

#### ***Disparities In Clinical Trials***

The Committee encourages NIH to revisit the issue of health disparities in clinical trials with a goal of increasing participation from under-represented populations. (p. 174)

#### Action taken or to be taken

Increasing the participation of racial and ethnic minorities, and medically underserved populations in clinical trials remains a priority for the NIH. Several of the Institutes and Centers (ICs) are working on this as an area of emphasis in the NIH FY2004-2008 Health Disparities Strategic Plan. For example, the National Cancer Institute (NCI) and the National Institute of Arthritis and Musculoskeletal and Skin Disease (NIAMS) have partnered to increase minority accrual to clinical trials working with the NIAMS Community Health Center facility in the District of Columbia. Results from clinical trials of the National Eye Institute (NEI), confirmed the value of reducing intraocular pressure (IOP) in patients with ocular hypertension or glaucoma to prevent the onset of glaucoma in individuals with ocular hypertension, and the progression of disease in those with glaucoma. The Ocular Hypertension Treatment Study (OHTS), a study cosponsored by the NEI and NCMHD, noted that lowering IOP at least 20 percent produced a 50 percent protective benefit over baseline among those individuals who had elevated IOP without optic disc or visual field deterioration. Analysis of the African American subgroup revealed that daily pressure-lowering eye drops also reduced the development of primary open-angle glaucoma in African Americans by almost 50 percent.

All NIH (ICs) support NIH's policy on the inclusion of minorities and women in clinical trials; every two years the Office of Research on Women's Health releases a report affirming IC participation. To facilitate these efforts, NIH staff receives on-going training and provide outreach to the scientific community to help increase understanding of policy and OMB requirements. Program officials provide technical assistance to investigators throughout the preparation, development and application process. Review officials discuss with reviewers the

guidelines/instructions for Inclusion of Women and Minorities in Clinical Research as well as the requirements for designing Phase III Clinical Trials so that valid analyses can be conducted for sex/gender and ethnic/racial differences. The policy provides a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and racial/ethnic minorities and their subpopulations.

The NIH Clinical Center (CC) spearheads the agency's clinical trials activities and provides support to the other Institutes and Centers with their patient recruitment activities including the recruitment of racial and ethnic minorities. Strengthening the clinical trials infrastructure is a priority for the CC. Through individual and collaborative initiatives, the ICs implement various strategies to increase participation of racial and ethnic minorities in clinical trials. Activities include cultural competency programs focused on provider-patient communication; audio news releases; clinical research centers/networks; symposia; consensus conferences; minority clinical trials outreach programs at medical schools; and promotion of databases such as [www.clinicaltrials.com](http://www.clinicaltrials.com). Planned activities to increase participation of underrepresented populations in clinical trials include research programs aimed at identifying the factors that influence the decision of these communities to enroll or not to enroll in certain clinical trials and to identify innovative solutions and strategies to increase the future enrollment of these populations in clinical trials. Efforts to increase collaborations across NIH conduct clinical trials in racial and ethnic minorities will continue to be enhanced to facilitate the timely translation and dissemination of clinical trials results to the targeted communities.

### **Senate Significant Items**

#### Item

#### ***Glomerular Disease***

The Committee understands that glomerular disease, a group of diseases affecting the filtering mechanisms of the kidneys, is more prevalent among African Americans than the general population. The Committee urges the NCMHD to explore collaboration with the NIDDK to support research activities related to glomerular injury. (p. 153)

Please refer to page 281 (Glomerular Disease) of this document for the NCMHD response to this significant item regarding glomerular disease.

#### Item

***Research Endowment*** -The Committee commends the NCMHD for its leadership in addressing the longstanding problem of health status disparities in minority and medically underserved populations. The Committee continues to encourage the NCMHD to implement its research endowment program in a manner that is consistent with the authorizing legislation. (p. 154)

Please refer to page 281 of this document for the NCMHD response to this significant item regarding Research Endowment.

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, Extramural Biomedical Research Facilities, and the NCMHD. The Committee encourages the Director to work closely with the NCMHD to establish a program of coordination among these various mechanisms and partner with minority health professions schools to address their infrastructure needs. (p. 160/161)

Please refer to page 282 (Minority Training) of this document for the NCMHD response to this significant item regarding Minority Institutions.

Item

***Ethnic Minorities and Research***

The Committee encourages the NIH to invest in training programs that seek to prepare ethnic minorities and others for research and services careers that address the needs of the Nation's racial and ethnic diverse populations and to ensure, whenever feasible, that psychology is recognized as an eligible discipline for funding applications for such training programs. (p. 153)

Action taken or to be taken

The National Center on Minority Health and Health Disparities (NCMHD) supports several projects that address research training for racial and ethnic minority populations through its programs, and collaborations with other NIH or HHS entities. In addition to being the cornerstone of the NCMHD research effort, the Centers of Excellence (COE) program also seeks to increase the number of researchers from health disparity populations in the biomedical research enterprise. The NCMHD programs have established some unique partnerships that support research training.

Community Partnerships: Through its COE and Community-Based Participatory Research (CBPR) programs, more than a hundred research collaborations and partnerships have been supported by NCMHD. Examples of COE partnerships between research intensive and non-research intensive institutions are the partnerships between Johns Hopkins University and Morgan State University in Maryland; the partnerships between University of North Carolina (UNC) Chapel Hill and Shaw University in North Carolina. Examples of CBPR partnerships between academic research institutions and community-based organizations are the partnerships between Aberdeen Chairmen Health Board and University of Iowa; the partnerships between Rio Grande Valley Coalition and University of

Texas Pan American in Texas.

NCMHD Loan Repayment Program (LRP): NCMHD supports two of the five LRP's at NIH. These two programs are the health disparities research LRP and the clinical research for individuals from disadvantaged background LRP. Since 2001, 1,460 individuals have received LRP awards. The purpose of the program is to recruit and retain highly qualified health professionals from health disparity populations with doctorate degrees who are pursuing careers in health disparities or clinical research careers by repaying their loans in alleviating financial barriers that often discourage many health professionals from health disparity from pursuing their career goals. Many individuals with doctoral training in psychology have received support from NCMHD LRP Program, and are conducting research on topics such as:

- *Post Traumatic Stress Disease (PTSD) and exposure to trauma and violence in Low-Income, Urban, Sexually Abused Girls and their Mothers*
- *Health Promotion and Disease Prevention*
- *Neurobehavioral Outcomes in HIV+ Latinos*
- *The Influence of Atlanta's Neighborhoods on Health*

DHHS-Hispanic Association of Colleges and Universities (HACU) Professions Capacity Building Program: This program is aimed at building the capacity of Hispanic Serving Institutions to enable their faculty to secure more federal grants to address the health care needs of Hispanic Americans through research, education, and outreach. The program is a partnership between the DHHS Office of Minority Health, NCMHD. The program provides skills development through three program components: workshop presentations, experiential training, and participation in an online course. To date, 169 faculty and staff from 55 Hispanic Serving Institutions have benefited from the program.

#### Item

##### ***Lupus***

Lupus is two to three times more common among African American, Hispanic, Asian American, and Native American women than Caucasian women -- a health disparity that remains unexplained. Moreover, lupus mortality has increased over the past three decades and is higher among older African American women. The Committee urges the NCMHD to prioritize lupus research with a particular focus on exploring the associated health disparities and co-morbidities such as heart disease, depression, and renal disease. (p. 154)

#### Action taken or to be taken

Lupus has been included and will continue to be one of the research areas of emphasis in future NCMHD Funding Opportunity Announcements (FOAs).



# John E. Fogarty International Center

## House Significant Items

### Item

#### ***Chronic obstructive pulmonary disease (COPD)***

The Committee notes that COPD is the fourth leading cause of death worldwide, and encourages FIC to enhance its COPD research and training activities. (P. 158.)

### Action taken or to be taken

The Fogarty International Center (FIC) continues to address chronic obstructive pulmonary disease (COPD) with the establishment in FY 2003 of the International Tobacco and Health Research and Capacity Building Program (Tobacco). This program enhances the ability of scientists in low- and middle-income nations to understand risk factors for smoking uptake, particularly in youth, to develop effective prevention and mitigation programs, and to identify the most effective health service and communications policies to reduce the negative impacts of smoking on populations. The knowledge gained and interventions developed abroad through the Tobacco Program can benefit the United States since risk factors are often similar in communities at home and abroad, and since interventions developed overseas may be particularly effective in specific U.S. populations. This program is unique in supporting both trans-disciplinary research and research involving partnerships between primarily U.S. tobacco scientists and scientists in developing countries (*American Journal of Public Health*, Lando, Borrelli et al. 2005). In FY 2007, and in partnership with the National Cancer Institute (NCI) and the National Institute for Drug Abuse (NIDA), FIC re-competed Tobacco. A total of 11 competing awards were made to support tobacco control research in a wide variety of countries, including India, Indonesia, China, Panama, Brazil, Hungary, and Turkey.

FIC is also addressing COPD under its International Training and Research in Environmental and Occupational Health (ITREOH) Program. The ITREOH is a collaborative program involving FIC and the National Institute of Environmental Health Sciences (NIEHS) within the NIH, and the National Institute for Occupational Health and Safety (NIOSH) within the Centers for Disease Control and Prevention (CDC). In FY 2007 this program was re-competed, with expanded support from the CDC, Agency for Toxic Substances and Disease Registry, and the U.S. Department of State. Competing awards related to COPD include prevention of respiratory disease among mining populations in Southern Africa; prevention of respiratory disease in China; and prevention of indoor air pollution in Peru, China, and India.

#### Item

##### ***Malaria and Tuberculosis (TB)***

The Committee appreciates the important and unique role that FIC plays in addressing global health challenges. The Committee commends the Center for the success of its programs to strengthen science and public health research institutions in low-income countries, specifically in malaria, TB, and neglected tropical diseases. The Committee urges FIC to continue supporting research training focused in these areas to enable developing country scientists to develop effective, evidence based strategies to prevent, treat, and diagnose these debilitating diseases. While major investments in biomedical research by the National Institutes of National Institute of Allergy and Infectious Diseases (NIAID) and others are resulting in new tools and medical advances, the Committee realizes that improvements in health outcomes will be delayed without local scientific expertise to translate research findings into practice. The Committee encourages FIC to promote applied health research in developing countries to speed the implementation of new health interventions for malaria, TB, and neglected tropical diseases. (p. 158)

#### Action taken or to be taken

Contributions continue in TB, malaria, and neglected tropical diseases in strengthening research and public health capacity in low- and middle-income countries, including promoting applied research to speed implementation of new health interventions. Accomplishments include development of a new assay in Peru to diagnose drug-resistant TB; the assay is now being transferred to several FIC research training programs in Uganda, Zimbabwe, and South Africa. Such investments help countries identify effective interventions specific to local needs, and provide better implementation and scale-up of treatment through local health care. For example, Haiti's FIC-supported research training program is designed specifically to provide training for monitoring and evaluation for the scale-up of HIV prevention services supported by the President's Emergency Plan for AIDS Research (PEPFAR) and the Global Fund.

The President's Malaria Initiative (PMI) is also supported through planning grants in Malawi and Uganda. Several tools to prevent and treat malaria are available and proven; how to best deliver malaria interventions to large populations and evaluate their impact remains a challenge, so developing expertise in operational and health services research is an urgent priority. Grantees are planning comprehensive research training programs that can help to build capacity in PMI countries to address malaria control and to translate research findings into public health policy and interventions.

A number of projects related to neglected tropical diseases are also supported. Leptospirosis is a bacterial disease carried by animals that contaminate standing water. Brazilian scientists, with partners at Cornell, sequenced the genome, developed a patented diagnostic test, and are currently testing an experimental

vaccine. Cysticercosis kills 50 million people every year. Collaborations in Peru have developed a highly specific and sensitive diagnostic assay. Currently, testing is being done on a veterinary tapeworm vaccine to break the cycle of transmission. Lastly, cholera is an acute diarrheal illness caused by intestine bacterial infection; existing vaccines confer brief and incomplete immunity. FIC currently funds a research training program grant at the Massachusetts General Hospital to train Bangladeshi scientists to conduct research on cholera vaccine candidates.

### **Senate Significant Items**

#### Item

**Global Health Challenges** - The Committee commends the Center for the success of its programs to strengthen science and public health research institutions in low-income countries, specifically in malaria, TB, and neglected tropical diseases. The Committee urges the FIC to continue supporting research training, focused in these areas, to enable developing country scientists to develop effective, evidence-based strategies to prevent, treat, and diagnose these debilitating diseases. While major investments in biomedical research are resulting in new tools and medical advances, the Committee is concerned that improvements in health outcomes will be delayed without local scientific expertise to translate research findings into practice. The Committee urges the FIC to promote applied health research in developing countries to speed the implementation of new health interventions for malaria, TB, and neglected tropical diseases. (p. 154)

#### Action taken or to be taken

Please refer to page 290 of this document for the FIC's response to this significant item regarding Malaria and Tuberculosis.

#### Item

**Training Programs**- The Committee is pleased with the FIC's leadership in training American researchers in global health research through its International Clinical Research Scholars Program and the International Research Scientist Development Award Program. The Committee encourages the expansion of the FIC's training programs that support junior U.S. scientists. The Committee is also pleased with the Center's efforts to supplement grants in AIDS International Training and Research Program [AITRP] or International Training and Research Program in Emerging Infectious Diseases [EID], which trains tuberculosis experts in the developing world. The Committee encourages the FIC to support activities, such as the Pan-African Thoracic Society's Methods in Epidemiologic, Clinical and Operations Research [MECOR] program, to expand training opportunities for physicians in Africa. (p. 154)

#### Action taken or to be taken

FIC has taken significant steps to expand the Clinical International Research Scholars program by bringing in new collaborative partners: National Institute of Nursing Research (NINR), National Center on Minority Health and Disparities (NCMHD), National Institute of Dental and Craniofacial Research (NIDCR), NCI, National Institute of Alcohol Abuse and Alcoholism (NIAAA), NIAID, NIDA, Office of AIDS Research (OAR), and National Institute of Mental Health (NIMH) by adding components to provide for training of medical residents and fellows. In FY 2007 FIC made an award to Vanderbilt University to assist FIC in expanding and strengthening this program. The Clinical Scholars Program is expected to increase interest among junior U.S. Scientists to apply for awards under the International Research Scientist Development Award (IRSDA) program and the Center anticipates making a number of competing awards under this program in FY 2008. FIC also distributed information about and encouraged awardees under our training programs to attend the expanded MECOR program for physicians in Africa.

#### References:

Lando, H. A., B. Borrelli, et al. (2005). "The landscape in global tobacco control research: a guide to gaining a foothold." Am J Public Health **95**(6): 939-45.

# National Library of Medicine

## House Significant Items

### Item

#### ***Health information technology***

The Committee encourages NLM to conduct outreach activities to all public and private sector organizations which have demonstrated capabilities in health information technology. The Committee is particularly interested in disease management technology as it relates to saving health care dollars, and improving care for chronically ill individuals and the workforce.

### Action taken or to be taken

The NLM is working with the Disease Management Association of America to improve disease management technology information by including their Program Evaluation Guide on the NLM Bookshelf, a database of digitized books, which provides free access for all health professionals and organizations in both the public and private sectors. NLM also plans to review the DMAA Dictionary of Disease Management Terminology for inclusion in our Unified Medical Language System and is investigating including their meeting abstracts in the NLM Gateway. In addition, representatives from the National Network of Libraries of Medicine conducted online training on PubMed and MedlinePlus at the DMAA Annual Leadership Conference. We will continue to look for additional opportunities to collaborate with DMAA and its member organizations and to expand our outreach activities related to health information technology.

### Item

#### ***Outreach***

The Committee encourages NLM to continue its outreach activities aimed at educating health care professionals and the general public about the Library's products and services, in coordination with medical librarians and other health information specialists.

### Action taken or to be taken

The medical librarians and other health information specialists in the more than 5,800 libraries in the National Network of Libraries of Medicine (NN/LM) continue to be key players in NLM's efforts to educate health professionals and the general public about the Library's products and services. The basic goals of the NN/LM are to: (1) develop collaborations among network members and other organizations to improve access to biomedical information; (2) promote awareness of, access to, and use of biomedical information resources for health professionals and the public, with a particular emphasis on contributing to the Healthy People 2010 goal of eliminating health disparities; and (3) develop, promote and improve electronic access to health information by network

members, health professionals, and organizations providing health information to the public.

In Fiscal Year 2006, new 5-year contracts were awarded to 8 health sciences libraries to serve as Regional Medical Libraries in the National Network of Libraries of Medicine (NN/LM). During the first and second years of the 5-year contract, 144 outreach projects have been. In Fiscal Years 2008 and 2009, these contracts will award 80-90 projects involving academic health sciences, hospital, public and state libraries, public health departments, K-12 schools, and community based organizations to improve electronic access to health information. The projects will focus on priority initiatives related to health disparities, health information literacy, and public health. Emphasis will continue to be on projects that target minority and underserved populations.

#### Item

##### ***PubMed Central***

The Committee encourages NLM to work with the medical library community regarding issues related to copyright, fair use, and classification of information on PubMed Central.

#### Action taken or to be taken

NLM continues to work closely with the medical library community in the development of PubMed Central. In addition to the librarians who are integral members of the PubMed Central development team at NLM, medical librarians have played an active role on the PubMed Central National Advisory Committee since its formation, effectively representing the needs and concerns of academic health centers, hospitals, health professionals, patients, and the general public. Medical librarians have been invaluable in promoting awareness and use of PubMed Central, in convincing editors and publishers to deposit additional journals, and in supplying back issues to be digitized for inclusion in this heavily used archive. More than 1,100,000 articles are now freely available in PubMed Central, some dating back to the 19th century. In an average month, more than 3 million unique users retrieve more than 12 million copies of articles from the archive. The free availability of this material has improved library service across the country and has also enabled some libraries to free up valuable space previously devoted to older volumes of journals.

As PubMed Central has become the repository for NIH-funded research as part of the NIH Public Access policy, medical librarians have been instrumental in educating the research community on how authors can make their publications more accessible. The Scholarly Communication Committees of the Medical Library Association (MLA) and the Association of Academic Health Sciences Libraries (AAHSL) have provided valuable insights to NIH on barriers to participation by scientists in their institutions. Members of these groups have made numerous presentations about PubMed Central and the NIH public access

policy at a wide range of professional meetings. NLM works closely with both the MLA and AAHSL on matters related to copyright, fair use, and peer review and their potential impact on PubMed Central, other NLM activities, and services provided through the National Network of Libraries of Medicine.

Item

***Registry of liver toxicities***

The Committee applauds NLM's plan to create an accessible, on-line registry of the liver toxicity of medications and sees this as an important step to help physicians and patients avoid the devastating consequences of liver failure. . . . The Committee encourages the inclusion in the registry of information from databases that catalog information on the interrelationship between environmental toxins and genes.

Action taken or to be taken

The Specialized Information Services (SIS) Division of the National Library of Medicine (NLM) and the Liver Disease Research Branch (LDRB) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have established a collaborative effort to design and build a multilayered, informational and interactive web resource on drug- and herbal medication-induced liver disease. The resource is tentatively named and referred to as **LiverTox**. Design and development of a prototype is in progress. The website is expected to be fully operational December 2008. It 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, family practitioners and internists who are likely to see occasional cases of drug-induced liver injury. The website will also be helpful for experts in liver disease and toxicology, as well as for patients seeking information on the web.

**Senate Significant Items**

Item

***Communication of Research Findings***

One of the fundamental charges to the NIH is to facilitate the translation of research findings into practice. In this regard, the Committee is pleased that the NLM has helped to launch NIH MedlinePlus magazine, which provides consumers and health professionals authoritative health information based on the latest NIH-supported research in a user-friendly format. The Committee strongly urges the NLM to substantially expand the distribution of this new publication.

Action taken or to be taken

The NLM, together with the support of the National Institutes of Health and the Friends of the National Library of Medicine, has greatly expanded the distribution

of the *NIH MedlinePlus* magazine. This magazine provides consumers and health professionals with authoritative health information based on the latest NIH-supported research in a user-friendly format. Approximately 300,000 copies of the Summer, 2007 issue of the magazine were sent to physicians, community health centers, and medical/health science libraries nationwide to share with patients and patrons – a 600% increase over the distribution of the previous year's issues. The NLM will continue to increase the readership of this free publication by encouraging its member libraries to share copies with the public they serve and by reaching out to Spanish speaking Americans with a bilingual version of the magazine beginning in FY 2008. NLM also hopes to partner with hospitals to distribute the magazine in their waiting rooms and to discharged patients and their families.

Item

***Disease Management Technology***

The Committee urges the NLM to conduct outreach activities to all public and private sector organizations which have demonstrated capabilities in health information technology.

Action taken or to be taken

The NLM is working with the Disease Management Association of America to improve disease management technology information by including their Program Evaluation Guide on the NLM Bookshelf, a database of digitized books, which provides free access for all health professionals and organizations in both the public and private sectors. NLM also plans to review the DMAA Dictionary of Disease Management Terminology for inclusion in our Unified Medical Language System and is investigating including their meeting abstracts in the NLM Gateway. In addition, representatives from the National Network of Libraries of Medicine conducted online training on PubMed and MedlinePlus at the DMAA Annual Leadership Conference. We will continue to look for additional opportunities to collaborate with DMAA and its member organizations and to expand our outreach activities related to health information technology.

Item

***Native Hawaiian Healthcare Resources***

The Committee urges the NLM to work with Native Hawaiian organizations to increase access to health information and health resources for Native Hawaiians.

Action taken or to be taken

NLM is working to both increase access to and use of health information resources for Native Hawaiians as well as supporting the development and preservation of collections of traditional Native Hawaiian health and healing practices. For example, NLM has been working with Papa Ola Lokahi (POL), a federally-funded non-profit, community-based organization, authorized by the Native Hawaiian Health Care Act of 1988 (PL 100-579), as amended. NLM has

funded POL to work with the Miloli'i Native Hawaiian community (on the Big Island) to develop a wireless mobile computer lab that will enable the community to increase knowledge about available health information. This project also includes training for the community librarian and other members of the community as well as support for other community-developed related initiatives such as an after school tutoring program. The Waimanalo Community Health Education Project included placing computers in the waiting areas of the Waimanalo Community Health Center with access to MedlinePlus and other high quality health sites for use by patients and community members. The project also plans to include provider referrals to the computers through the use of an Information prescription. NLM continues to work with the Native Hawaiians from POL who participated in NLM's Information Fellowship for Native Americans in 2004-2006. This is an ongoing relationship to support their efforts to implement programs within Native Hawaiian communities. NLM's American Indian Health Web site contains information about all Native peoples of the U.S. including Native Hawaiians. NLM has also refined and expanded its collection development policy to include materials related to traditional Hawaiian (and other Native American) health and healing practices. The Library also encourages the digitization and preservation of these materials by local institutions. To highlight traditional Native health and healing practices, NLM is planning to mount a major exhibition on this topic in 2010. The Library is actively seeking input and participation from Native tribes and communities.

#### Item

#### ***Registry of Liver Toxicities***

The Committee applauds the NLM's plan to create an accessible, online registry of the liver toxicity of medications and sees this as an important step to help physicians and patients avoid the devastating consequences of liver failure. The registry will include information regarding the liver toxicity of more than 400 drugs. The Committee urges the inclusion in the registry of databases that develop information on the interrelationship between environmental toxins and genes

#### Action taken or to be taken

The Specialized Information Services (SIS) Division of the National Library of Medicine (NLM) and the Liver Disease Research Branch (LDRB) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have established a collaborative effort to design and build a multilayered, informational and interactive web resource on drug- and herbal medication-induced liver disease. The resource is tentatively named and referred to as **LiverTox**. Design and development of a prototype is in progress. The website is expected to be fully operational December 2008. It 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, family practitioners and internists who are likely to see

occasional cases of drug-induced liver injury. The website will also be helpful for experts in liver disease and toxicology, as well as for patients seeking information on the web.

## Office of the Director

### House Significant Items

#### Item

##### ***Nanosystems Biology***

The Committee encourages the Director, along with the NCI, to support a collaborative effort to bring nanotechnology, systems biology and molecular imaging together to examine the molecular basis of cancer, consistent with the Director's Roadmap Initiative. Bringing these three disciplines together may allow researchers to identify specific sub-types of cancer and to better target new interventions. Successful results of such an effort could lead to a molecular classification of many types of cancer and to targeted molecular treatments for molecular-specific disease. (p. 161)

#### Action taken or to be taken

Please refer to page 29 of this document for NCI's response to this significant item regarding Nanosystems Biology.

#### Item

##### ***Microbicide Research Branch***

Women and girls are the new face of HIV/AIDS and are increasingly affected by the disease in every region of the world. The Committee has long advocated that NIH accelerate and better coordinate its microbicide research and notes with approval that NIH has stated its intent to establish a dedicated microbicide branch at NIH with clearly identified leadership, funding and staffing. The Committee strongly supports establishment of this branch and requests that NIH prepare within six months of passage of this bill a report detailing progress made in establishing a microbicide branch, including detailed information on staff and funding dedicated to this effort. (p. 163)

#### Action taken or to be taken

The NIH Office of AIDS Research (OAR) continues to be the point of coordination for all federally-funded microbicide research among the various components of the NIH as well as other Federal agencies such as the Centers for Disease Control and Prevention (CDC) and the United States Agency for International Development (USAID). Within the NIH, the National Institute of Allergy and Infectious Diseases (NIAID) provides leadership and coordination of microbicide research outlined in the NIAID Topical Microbicide Strategic Plan.

In fiscal year 2007, the NIAID Division of AIDS (DAIDS) established a new Prevention Sciences Program (PSP) that includes a Microbicide Research Branch. This Branch is a dedicated unit responsible for coordinating all DAIDS-supported microbicide research and providing oversight of the NIAID-sponsored

Microbicide Trials Network. There are currently five full-time equivalent staff within the Microbicide Research Branch and NIAID is recruiting for two additional positions; one recruitment is for Director of the PSP and the second recruitment is for Chief of the Microbicide Research Branch.

NIAID coordinates microbicide research within the Institute through a cross-divisional topical microbicide working group, known as the Microbicide Evaluation Group. This working group allows for harmonization of solicited microbicide research programs and for sharing and coordination of preclinical resources. For example, contracts for research support services, such as those to screen compounds, can be procured through a single Institute contract, compared to the previous approach in which each division would maintain separate contracts for similar services.

Item

***National Children's Study***

The Committee strongly supports full and timely implementation of the National Children's Study that aims to quantify the impacts of a broad range of environmental influences, including physical, chemical, biological, and social influences, on child health and development. The Committee urges NIH to coordinate the involvement of the Department, the lead Federal partners, and other interested non-Federal partners conducting research on children's environmental health and development. (p. 164)

Action taken or to be taken

Consistent with the FY 2007 and FY 2008 President's Budget, the NIH OD FY 2009 President's budget request does not continue the National Children's Study (NCS). The FY 2008 appropriated support of \$110.9 million within the Office of the Director sustains the support for existing activities of the vanguard centers, study sites and the data coordination center and provides funding for the laboratory and bio-specimens repository. To phase out this study, existing contracts for pilot studies and other activities will be allowed to expire when the FY 2008 funds provided for planning are exhausted and no additional contracts will be awarded.

Item

***Clinical and Translational Science Awards (CTSA)***

The Committee is pleased with the extensive planning and consultation that NIH has conducted in the development of the CTSA program, and it will be very interested in the progress report due July 1, 2007 that was requested in the fiscal year 2007 House Appropriations Committee report. The Committee understands that a national CTSA evaluation is being developed, along with evaluations of each CTSA site. The Committee believes it is important that the national evaluation include the expertise of external reviewers not affiliated with the CTSA grants or NIH. These reviewers would provide credibility grounded in

independent experience with the challenges of clinical and translational research. Such viewpoints would contribute to a candid assessment of the successes and shortcomings of the CTSA research model and its impact on the clinical research enterprise. The Committee recommends that NIH include such reviewers in the evaluation of CTSA's impact. The Committee suggests that participants in the Institute of Medicine's Clinical Research Roundtable who are not affiliated with the CTSA program would be useful additions to the program's evaluation. (p. 164/165)

#### Action taken or to be taken

Given the complexity, challenges, and scope of the CTSA program, NCRP recognizes that multiple inputs into the national evaluation process are critical. To design an independent evaluation, NCRP has hired evaluation experts from The Madrillon Group, Inc. through a subcontract to MasiMax Resources. This group is conducting a feasibility study, which will determine the optimal approach for evaluating the CTSA Program by assessing which evaluation design and data collection strategies should be used.

NCRP also recognizes the importance of seeking external advice. As such, NCRP seeks input on the National CTSA Evaluation from its National Advisory Research Resources Council (NARRC), comprised of 17 external researchers and institutional officials. NARRC will review the national CTSA evaluation goals and indicators and provide recommendations to improve the evaluation plan and ultimately, the CTSA program. Feedback and recommendations from the external research community are actively being solicited by The Madrillon Group through interviews with CTSA stakeholders, including more than 20 advocacy groups that represent a wide range of basic, translational, clinical research and patient communities.

#### Item

##### ***Minority research training programs***

The Committee supports the recommendations put forward in the 2005 National Academy of Sciences (NAS) report on NIH minority research training programs. The Committee believes that the training of research scientists is a critical component of the NIH mission, and the Committee urges NIH to improve its data systems so that more complete information about NIH-supported graduate and post-doctoral research assistants and trainees is available. Without adequate data, the NIH programs cannot be properly evaluated or monitored. As proposed by the NAS, the Committee recommends the NIH develop an integrated NIH-wide trainee and research assistant data tracking system. The Committee further encourages NIH to engage trainees and research assistants in the data tracking process to document outcomes such as future funding awards, including those programs that are targeted to underrepresented minorities. (p. 165)

#### Action taken or to be taken

The NIH has established a committee of representatives from each Institute and Center to address the recommendations of the NAS report which is chaired by the directors of the NCMHD and the NIGMS—Drs. John Ruffin and Jeremy Berg. The committee was created to provide guidance and recommendations to the NIH Director on strategies for developing a diverse biomedical research workforce. Consistent with the recommendations of the NAS report, the goals of the committee include:

- Assembling an inventory of existing and proposed programs that target the training of underrepresented minorities.
- Proposing appropriate guidelines and measures for evaluating NIH Minority training programs.
- Providing advice on the development of a data tracking system on trainees, fellows, research assistants, or postdoctoral fellows receiving NIH funding, including those programs targeted or non-targeted to underrepresented minorities.

In the near future, as a part of the committee's work, the NIH will conduct a web-based inventory of its diversity programs to enhance its understanding of the program goals, objectives, targeted populations, outcomes, and to identify gaps and opportunities. This will result in the launch of the NIH Diversity Program website that provides a comprehensive overview of programs aimed at promoting diversity in education and research and will provide several ways to review the list of programs. The committee is expected to have a final report on its work by the second quarter of 2008.

#### Item

***Fragile X syndrome*** -- This syndrome has many characteristics and features that make it important to the research portfolios of multiple NIH institutes and centers. The Committee places most of the report language pertaining to fragile X in the NIH Office of the Director to emphasize the cross-disciplinary nature of many of the disease's research questions. For example, the symptoms of fragile X syndrome include digestive difficulties. Some affected individuals also show hyperphagia and obesity. Understanding this disorder may permit the development of treatments to relieve these fragile X symptoms and may also help understanding disorders with similar symptoms. The Committee encourages NIDDK to coordinate its efforts with other Institutes working on related activities, including NIMH, NINDS, NICHD, NHGRI and FIC. (p. 166)

#### Action taken or to be taken

The NICHD is the lead NIH institute in funding of research in the of area Fragile X syndrome (FX) and its portfolio has grown to include the associated disorders of Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) and Premature Ovarian Failure (POF) related to Fragile X premutation. In fiscal year 2007, the NICHD funded about 35 research grants and other awards that support research

in FX and associated disorders, including newborn screening. The NICHD is funding three Fragile X Research Centers, which are currently in the process of recompeting. The Fragile X research portfolio is continually updated with new applications and investigators, ensuring the vitality of the research effort. The NICHD also interacts regularly with other NIH Institutes and Centers (ICs) that fund FX research, including NIMH and NINDS, as well as key research advocacy groups that represent families concerned about Fragile X and researchers who are doing work in this area. The NICHD is participating in a cooperative agreement with NIMH, NINDS, advocacy groups, and a small pharmaceutical company on a project that focuses on the *Development of mGluR5 Antagonists to Treat Fragile X Syndrome and Autism*. Another common initiative is the Program Announcement “Shared Neurobiology of Fragile X Syndrome and Autism” that has attracted numerous grant applications.

In the spring of 2007, the NICHD established a Fragile X Research Coordinating Group and invited representatives from interested ICs that fund research on Fragile X and associated disorders to participate. Representatives from NICHD, NINDS, NIMH, NIA, NCI, NIGMS, NIDDK and NIDCD have joined. Most recently, the Fragile X Research Coordinating Group has begun working on a trans-NIH Research Plan for Fragile X. The Coordinating Group plans to work with the scientific community, advocacy groups, and other pertinent federal agencies to develop a comprehensive, yet realistic, plan to build upon and expand Fragile X research at NIH in a meaningful manner. The NICHD has agreed to take the lead role and will assume administrative responsibility. The group has discussed a tentative timeline that includes a planning meeting in Washington in the spring of 2008 and a completed draft of the research plan by September 1, 2008.

#### Item

##### ***Fragile X syndrome***

In the research field of aging, the Committee encourages NIA to expand its existing dialogue with NINDS to fund research on fragile X-associated tremor/ataxia syndrome (FXTAS). NIA is encouraged to strengthen its existing research portfolio into this newly identified neurological disorder, which involves progressively severe tremors and difficulty with walking and balance that specifically affect some older premutation carriers, generally grandfathers of children with fragile X syndrome. The Committee suggests that NIA include FXTAS among its priorities in the area of adult-onset disorders. Given the link, FXTAS may serve as a gateway to understanding other aging disorders including parkinsonism and dementia. In addition, the Committee encourages NIMH to include fragile X in its studies of related neuropsychiatric disorders and to work with other Institutes such as NICHD and NINDS to develop cooperative research support mechanisms in this area. (p.166)

#### Action taken or to be taken

Fragile X-associated tremor/ataxia syndrome (FXTAS), which involves progressively severe tremors, difficulty with walking and balance, and dementia, affects at least 1/3 of men over 50 years of age who carry certain mutations in the FMR1 gene. The NIA does support research into this disorder. For example, an ongoing NIA-supported study aims to identify the molecular basis for FXTAS, and another, supported by the NIA via the NIH Roadmap, focuses on the development of targeted treatments for FXTAS. NIA staff from both the Intramural and Extramural Programs also participate in the NIH Fragile X Research Coordinating Group. This group has begun work on a trans-NIH research plan, which will be developed in partnership with the scientific community, advocacy groups, and other pertinent Federal agencies. A scientific meeting to refine the NIH research agenda is planned for the spring of 2008.

NIA's participation in the NIH Roadmap Epigenomics Program, which explores DNA modifications that are not the result of a change in the coding sequence of genes, may also stimulate further research in this area; notably, FXTAS is associated with abnormal DNA methylation, a type of epigenomic change. Although not directly focused on FXTAS, these basic studies have the potential to provide insight into the etiology and pathological mechanisms underlying the disease. Finally, NIA co-sponsors a trans-NIH research solicitation on drug discovery for nervous system disorders, which may well encourage the development of new treatments for this condition.

#### Item

##### ***Fragile X syndrome***

Finally, there are important aspects of Fragile X to be studied in genomic research. FMRP, the protein whose absence results in fragile X syndrome, is a regulator of translation of many genes, including those involved in learning and memory. A genomic approach to understanding the diverse pathways regulated by FMRP would aid in the understanding of human cognition and identify potential targets for drug design to alleviate the symptoms of fragile X and related disorders. The Committee encourages NHGRI to strengthen its research activities on fragile X and to coordinate these efforts with other Institutes working on related activities, including NIMH, NINDS, NIDDK, NICHD and FIC.

#### Action taken or to be taken

NHGRI funds 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 just completed the pilot phase of ENCyclopedia Of DNA Elements (ENCODE), a multi-phase project that seeks to identify all functional elements of the human genome, and has begun broad expansion of the project. The ENCODE pilot study, which examined just 1% of the human genome, produced strong evidence that the organization, function and evaluation

of the genome appears to be far more complicated than was commonly suspected. The full-scale ENCODE project will survey the entire genome and provide a more extensive analysis of the relationships between, and impact of, all the functional aspects of the genome. NHGRI has recently funded multiple ENCODE grants totaling more than \$80 million over the next four years. ENCODE is designed to encourage broad scientific collaboration, and all ENCODE data will be deposited into public databases and made available to researchers around the world. This research is expected to provide valuable information for many diseases such as Fragile X.

#### Item

#### **Autism**

The Committee recognizes the growing public health crisis represented by the dramatic rise in autism, which according to CDC now strikes one in 150 of our nation's children. Autism causes serious hardships to families of children with autism, as well as to the children themselves, and also creates an extreme financial burden to families and our nation. The care of a child diagnosed with autism is estimated to cost \$3,200,000 in direct and indirect costs over his/her lifetime; all individuals diagnosed with autism are projected to cost the nation an estimated \$35,000,000,000 annually. In response to this crisis, the Combating Autism Act was signed into law last year, which expanded autism activities at CDC and HRSA, authorized increased funding for autism, created centers of excellence and called for the establishment of an inter-agency autism coordinating committee (IACC), charged with the preparation of a strategic research plan for autism. The Committee encourages HHS's prompt appointment of the IACC and looks forward to its completion of an autism strategic research plan. In addition, the Committee encourages NIH to use its research funds to implement the recommendations of that strategic plan. (p. 166)

#### Action taken or to be taken

NIH continues to focus attention and resources on a number of ongoing and new programs directed at understanding and treating autism spectrum disorders (ASD). In response to the Combating Autism Act (CAA), the Secretary of HHS delegated the responsibility for establishing a new Interagency Autism Coordinating Committee (IACC) to the Director of NIH, who designated the National Institute of Mental Health (NIMH) as the lead for this responsibility. The Secretary of HHS retained the authority to appoint public members described in the CAA. This newly authorized IACC will operate under the provisions of the Federal Advisory Committee Act.

The CAA requires the IACC to include both Federal and non-Federal members. The Committee includes the following Federal members or their designees: the Director of the NIH and relevant NIH Institutes, the Director of the Centers for

Disease Control and Prevention, and representatives of other Federal agencies that serve individuals with ASD, such as the Department of Education. Public members include an individual with an ASD diagnosis, a parent or legal guardian of an individual with an ASD diagnosis, and a representative of a leading research, advocacy, or service organization for individuals with ASD. A primary goal for the new IACC is the development of a strategic plan for the conduct of, and support for, autism spectrum disorder research. NIMH took initial steps to formulate a strategic planning process, and the proposed process was presented to the IACC for discussion and adoption at its inaugural meeting in November 2007. The goal of the process will be for the IACC to complete the first strategic plan for autism spectrum disorder research in May 2008. As described in the CAA, the IACC will update the strategic plan annually, and NIMH will provide the staff necessary for the IACC to accomplish its functions as defined in the CAA.

As the strategic plan for autism spectrum disorder research is being drafted, it is important to note that NIH is continuing its strong commitment to advancing autism research. For example, in 2007, NIMH, NICHD, NINDS, NIDCD, and NIEHS implemented the new Autism Centers of Excellence (ACE) Research Program, addressing a major requirement of the CAA. The ACEs are designed to maximize coordination and cohesion of NIH-sponsored efforts in order to involve a large number of investigators, avoid duplication, and allow the most efficient use of resources. The ACEs focus on priority areas identified in the IACC Autism Research Matrix, specifically in the areas of causation and treatment. To facilitate data sharing among the ACEs, as well as other autism researchers, NIH created the National Database for Autism Research (NDAR). Beginning in FY 2008, NDAR will allow scientists to access and share research data and to collaborate toward reaching consensus on common measures and methodologies in autism research. NDAR will also coordinate research data with other Federal databases, such as the NIMH Genetics Repository (<http://www.nimhgenetics.org/>). The NIMH Genetics Repository stores DNA, cell cultures, and clinical data—serving as a national resource for researchers studying the genetics of complex mental disorders, including autism spectrum disorders.

#### Item

#### ***Congenital and Genetic Disease of Bone***

The Committee is aware that thousands of children and adolescents nationwide suffer from musculoskeletal disorders and malformations, many of which have devastating effects on mortality and disability. Diseases such as osteogenesis imperfecta, fibrous dysplasia, osteoporosis, and Paget's disease are caused by poorly understood genetic mutations. In Paget's disease, underlying genetic defects can also be exacerbated by environmental factors. The Committee understands that the science of genetics has led to tremendous advances in our understanding of numerous systems that affect bone health, but little of this technology is being applied to bone research. The Committee encourages

NIAMS and NICHD to support research focusing on mechanisms of preventing fractures and improving bone quality and correcting malformations, on innovations in surgical and non-surgical approaches to treatment, on physical factors that affect growth, and on genetic defects that cause bone disease. Furthermore, the Committee urges NIAMS, NICHD, NIDCR, and NIDDK to expand research on skeletal stem cell biology and the genetics and pathophysiology of rare disorders such as fibrous dysplasia, meliostosis, XLinked hypophosphatemic rickets, and fibrodysplasia ossificans progressiva. (p. 167-168)

#### Action taken or to be taken

NIH supports a diversified portfolio of research focusing on the genetics of bone biology. For example, NIAMS-supported investigators are examining the genetic basis of bone strength and fragility, as well as the potential use of a patient's own stem cells to treat bone disease. By studying the functional interactions among skeletal traits, researchers will be able to determine how various genes are related to the structure of bone, allowing for the development of early diagnosis and preventive treatments for diseases of bone fragility and malformation. NICHD also supports a number of investigator-initiated projects on the genetic causes of structural birth defects, including those of the skeleton, and recently issued two Program Announcements to expand this work. In addition to this targeted work, the NIDDK supports bone-related genetic research in diseases such as lysosomal storage disorders which often cause serious complications in bone. Additionally, many genetic diseases of bone have distinct craniofacial and oral manifestations that significantly impact daily function and quality of life. NIDCR's intramural and extramural research portfolios address basic and applied research to uncover the knowledge required to understand the causes, treat the effects, and to one day prevent such diseases.

NIH-supported researchers recently identified mutations in the human gene known as cartilage-associated protein (CRTAP) that is linked to the development of osteogenesis imperfecta (OI). Previously, OI was thought to be caused only by mutations in type I collagen, the major protein of bone, but researchers demonstrated that mutations in the CRTAP gene cause a form of OI that is characterized by low bone mass, bone fragility, and long-bone deformities. This finding will have a significant impact on OI diagnosis, and should lead to more comprehensive genetic counseling for individuals and family members affected by the disease. Support for this research was provided by NIAMS, NIDCR, NIEHS, and NIDCD. In other OI-related efforts, investigators in the intramural program at NICHD are conducting genetic bone diseases research aimed at characterizing the molecular mechanisms of heritable connective tissue disorders and applying this information to the treatment of affected patients, specifically individuals with OI and Ehlers-Danlos Syndrome. These researchers recently uncovered two mutations in genes for a form of OI.

X-linked hypophosphatemic rickets is a disorder in which the bones become soft and bend easily because the blood contains low levels of phosphate, which bones need in order to grow properly. NIH is supporting a Center of Research Translation (CORT) in X-linked hypophosphatemic rickets. This CORT is studying the various molecular contributors to this genetic form of rickets and working toward developing new treatments. The CORT mechanism provides unique opportunities to study basic and clinical facets of disease, speeding the translation of research into effective new treatments.

Fibrodysplasia ossificans progressiva (FOP) is one of the rarest genetic diseases, and results in muscles, ligaments, tendons, and other connective tissue gradually turning into bone, rendering the person permanently unable to bend or even move. One critical step to understanding and eventually treating this condition was made by researchers funded in part by the NIH. Researchers reported the discovery of a disease-causing mutation of a gene called ACVR 1, which encodes a protein called activin receptor type 1A, which in turn controls the formation of cartilage and bone. The discovery of the mutation immediately suggests two possible approaches to treatment: either to block the renegade proteins, or to destroy the message coming from the mutant copy of the gene that creates them. Although clinical treatments are still some years away, this is a crucial advance in understanding the disease and developing those treatments.

#### 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 MD centers of excellence and advancement of a conference focusing on translational research opportunities. The Committee urges NIH to continue to provide sufficient funding to advance the work of the centers, encourage greater collaboration and resource sharing between centers, and to further additional DBMD research opportunities. Given increasing concerns about cardiac complication in both DBMD patients and carriers, the Committee suggests that the muscular dystrophy coordinating committee be broadened to include the Director of NHLBI. (p. 168)

#### Action taken or to be taken

NIH currently funds six Wellstone Centers, with two Centers each supported by the National Institute of Neurological Disorders and Stroke, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institute of Child Health and Human Development. The Wellstone Centers program has built-in set-aside funds to promote new collaborations, and a total of 14 projects have been approved for funding using these collaborative funds, 10 in 2007. To further enhance ongoing and collaborative activities, the Wellstone Centers provided supplemental funds to support senior postdoctoral fellows or non-tenure track investigators affiliated with the Centers, or to support small workshops or conferences focused on specific topics in muscular dystrophy research. Four

fellowships and two workshops have been funded through this supplement program. To further promote and disseminate information related to the activities of the Wellstone Centers, a new Web site (<http://www.wellstonemdcenters.nih.gov/index.htm>) is available to investigators and patients interested in muscular dystrophy research, including new NIH funding opportunities. This website also provides information for muscular dystrophy investigators interested in using resources, facilities and reagents that the Centers share with the rest of the research community.

The National Heart, Lung, and Blood Institute (NHLBI) supports a number of research grants focused on ultimately improving heart and lung health for children and adults with muscular dystrophy. The range of research support NHLBI provides in this area includes investigations of muscular dystrophy gene regulation and mutations, development of new treatments and diagnostic approaches, and access for investigators to patient data through a registry. NHLBI recently joined NINDS, NIAMS, and NICHD in reissuing the Request for Applications for the selection of the next set of Wellstone Centers. These new Centers will each contain one core facility providing services, data, or biological specimens that will be available for use by other Centers and the broader muscular dystrophy research community, and another core facility focused on training new investigators and engaging patients in research and education activities. NHLBI will support meritorious projects or cores associated with these Centers that are relevant to the Institute's mission. Additionally, the Director of NHLBI was recently invited to join the Muscular Dystrophy Coordinating Committee (MDCC). Although representatives from NHLBI have been actively participating in committee activities, the addition of the Director of NHLBI to the MDCC further emphasizes the importance of NIH-supported research on the cardiopulmonary complications associated with muscular dystrophy and greater collaboration between Institutes.

#### Item

##### ***Musculoskeletal Trauma and Skeletal Pain***

The Committee encourages NIAMS, NIA, NIDCR, and NCCAM to study ways to better understand the epidemiology of back pain and improve existing diagnostic techniques, as well as develop new ones. The Committee also encourages NIAMS, NIBIB, NICHD, NIDCR, NIDDK and NIA to conduct research to improve diagnostic and therapeutic approaches to lower the impact of musculoskeletal traumas, as well as research on accelerated fracture healing and research into repair of nonunion fractures in osteogenesis imperfecta. (p. 168)

#### Action taken or to be taken

While methods to diagnose and treat musculoskeletal trauma constantly improve, there are few solutions for the severe damage that leaves gaps too large for the body's innate healing mechanisms. Such "critical-sized" defects require novel approaches to repair and replace the damaged tissue. The NIBIB is actively

addressing such problems by supporting research in tissue engineering and regenerative medicine. NIBIB is leading NIH's collaboration with the United States Army in an initiative to establish an Armed Forces Institute of Regenerative Medicine (AFIRM). Therapies for compartment syndrome (a painful condition that results when pressure within the muscles builds to dangerous levels), large osseous defects, and lost limbs, digits, muscles and tendons will be sought.

The NICHD continues to study the Brittle Mouse (Brtl) model, created in its intramural research program, to understand factors that increase bone strength. These researchers have found that uncoupling of the normal balance between bone formation and bone breakdown in this model results in decreased formation of the bone matrix, which in turn leads to the hypothesis that changes in the composition of the matrix of the bone itself may be the cause of increased bone strength. NICHD investigators plan to pursue this hypothesis in subsequent research. In its extramural program, the NICHD has been supporting studies related to understanding fracture risk and bone health in children. Additionally, since the elderly also experience problems associated with the musculoskeletal system, the NICHD, NIA and NIAMS continue to support a Program Announcement focused on the effects of aging on structures such as cartilage and bone.

The NIAMS, in collaboration with the NIH Office of Research on Women's Health and the National Institute of Occupational Safety and Health, continues to study low back pain and its treatment through the Spine Patients Outcomes Research Trial (SPORT). Researchers recently published findings that patients treated with surgery for degenerative spondylolisthesis, a condition in which breakdown of the cartilage between the vertebrae of the spine causes one vertebra to slip over the one below, experienced significantly reduced pain and increased function compared to those who received non-surgical treatments. These results will provide patients and their health care providers with valuable information when considering the best treatment option. NIAMS also supported research that recently identified a gene – cartilage-associated protein or CRTAP – linked to the development of osteogenesis imperfecta (OI). This finding will have a significant impact on OI diagnosis and should help lead to comprehensive genetic counseling for individuals and family members affected by the disease. NIAMS was joined by the NIDCR, NIEHS, and NIDCD in providing funding for this study.

NCCAM continues to fund a variety of basic and clinical research studies on the use of complementary and alternative medicine (CAM) to address musculoskeletal trauma, skeletal pain, and bone health. For example, NCCAM-supported scientists are also investigating massage, chiropractic, and acupuncture for low back pain. In October 2007, NCCAM, in collaboration with NIAMS, supported the *First International Congress*

*on Fascia Research: Basic Science and Complementary Medicine*, a scientific symposium on the role of acupuncture and other CAM therapies in musculoskeletal disorders. In addition to maintaining its leadership role in the NIH Pain Consortium, the NIDCR continues to support basic and applied research on chronic pain. For example, NIDCR recently awarded 10 new grants emanating from the announcement titled “New Models of Pain Relevant to the Trigeminal System.” Many of the findings from NIDCR-supported studies may prove to be applicable towards back pain as well as craniofacial pain.

#### Item

##### ***Psoriasis***

In addition to the research priorities the Committee has identified for psoriasis in NIAMS, the disease has relevance to the research portfolios of several other institutes. The Committee encourages NHLBI to undertake research on the link between severe psoriasis and increased risk of heart attack, as this may help advance the understanding of both heart disease and psoriasis. Secondly, since the Committee understands that while psoriasis manifests itself on the skin, it may be an auto-immune disease. The Committee encourages NIAID to identify and study immune cells and inflammatory processes involved in psoriasis. Lastly, because it is a disease involving both genetic and environmental/lifestyle components, the Committee encourages NIEHS to identify environmental and lifestyle triggers associated with psoriasis onset, flares, and disease state which will help in the development of appropriate therapies and interventions. The Committee encourages NIEHS to expand its biomarker work to include efforts to identify psoriasis and psoriatic arthritis genetic susceptibility. (p. 168)

#### Action taken or to be taken

Several NIH components are supporting research aimed at uncovering the cellular and molecular processes that contribute to psoriasis and psoriatic arthritis, expanding our knowledge of genes that play a role in the development of these diseases, and creating more effective treatments in order to help increase the quality of life for patients. For example, the NIAMS recently funded a new Center of Research Translation (CORT) in psoriasis. The CORT mechanism is designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics. Researchers at this CORT will test a novel photodynamic psoriasis therapy for safety and efficacy. Complementary studies will investigate the roles of S100 proteins, which have long been known to be expressed at high levels in inflamed skin, in the development of psoriasis. Researchers will also use a novel mouse model of psoriasis to examine the development of the disease.

NHLBI funds several studies examining the link between inflammation, immune activity, and heart disease. Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus have long been known to be associated with higher risks of heart and vascular disease through inflammatory mechanisms.

NHLBI recognizes that the auto-immune disorder of psoriasis has also been found to be associated with heart disease, and will plan to include psoriasis in ongoing and future investigations of risk factors for heart disease.

NIAID supports a broad 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 FY 2007, NIAID continued to support development of two clinical trials to study the safety and efficacy of immune cell modulators in lessening the symptoms of psoriasis and psoriatic arthritis. NIAID also supported studies to develop a test to characterize cytokines (chemical messengers) produced by individual immune cells in healthy skin and psoriatic skin, as well as studies to understand how immune cells are recruited to inflamed and healthy skin. An additional project is currently investigating 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. It is anticipated that these projects may provide insight into the pathogenesis and treatment of psoriasis.

NIEHS is supporting several research projects related to psoriasis to help develop appropriate therapies and interventions, as well as to identify psoriasis and psoriatic arthritis genetic susceptibility. Psoriatic arthritis can erode cartilage and bone, a condition that is currently irreversible. To better understand the pathways leading to this erosion, and thus develop targeted therapies, scientists conducted studies in a mouse model for erosive arthritis, as well as clinical trials in psoriatic arthritis patients. These studies showed that natural tumor necrosis factor (TNF), a chemical messenger that plays a key role in the pathogenesis of inflammatory disorders such as psoriasis and psoriatic arthritis, induces the migration of critical osteoclast (cells that break down bone) precursors from the bone marrow into circulating blood. When these precursors enter joints through blood vessels, they initiate a cascade of events that disrupts the normal balance of bone creation and destruction. This insight into how joint damage occurs will help identify events leading to psoriatic arthritis and, hopefully, will be useful in future development of effective therapies to counteract this destruction.

#### Item

#### ***Amyloidosis***

The Committee encourages NIH to continue to intensify its research efforts into the amyloidoses, 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 understands that NIH has held a U.S. seminar on amyloidosis and participated in an international conference on the disease. The Committee urges NIH to pursue the recommendations from these meetings and identify steps that need to be

taken to increase the understanding, prevention and treatment of this devastating group of diseases. (p. 169)

#### Actions taken or to be taken

The Office of Rare Diseases (ORD) worked with the Trans-NIH Rare Diseases Research Working Group and its Subcommittee on Amyloidosis. ORD and NIH institutes and centers (ICs) supported a number of amyloidosis-related scientific conferences in 2005 and 2006, and ORD held two small targeted workshops. The June 2006 workshop offered guidance to NIH in expanding its amyloidosis research. The results of this workshop were shared with the participants at the "XI<sup>th</sup> International Symposium on Amyloid and Amyloidosis" held in November 2006. A summary report of the workshop, including research recommendations, was published in the journal *Amyloid* in June 2007.

In July 2006, following the workshop, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reissued a relevant broad-based program announcement, "Targeting Diseases Caused by Protein Misfolding and Misprocessing." NIDDK was joined by two other NIH institutes on this announcement. Applications underwent scientific review in June 2007 and were reviewed by the institute councils in September 2007. The applications that were reviewed as meritorious will be funded in accordance with research priorities and sufficient availability of funds. A second multi-institute program announcement, focused specifically on the systemic amyloidosis workshop recommendations, is being prepared for review. We anticipate that the review and issuance of this program announcement will be completed in early 2008. Both program announcements inform the scientific community of NIH interest in supporting research in this area.

#### Item

##### ***Neurofibromatosis (NF)***

Recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages the NCI to substantially increase its NF research portfolio in such areas as further development of animal models, natural history studies, genetic drug screening, therapeutic experimentation, and clinical and pre-clinical trials. The Committee also encourages the NCI to create, fund, and implement NF clinical and pre-clinical trial infrastructures including NF centers, pre-clinical mouse consortiums, patient databases, and tissue banks. The Committee further encourages the NCI to apply existing cancer drugs to NF patients in clinical trials both extramurally and intramurally, and to develop new drugs for NF which could then apply to the general population. (p. 169/170)

#### Action taken or to be taken

Neurofibromatosis (NF), which encompasses neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2), are distinct genetic disorders that mainly impact the growth and development of nerve cells as well as cells in other tissues such

as bone and skin. Patients with NF1 (the more common type) and NF2 are predisposed to benign and malignant nerve sheath, myeloid, and other tumors, which are the primary cause of mortality. Children with NF1 are also prone to juvenile myelomonocytic leukemia (JMML).

NCI's basic research portfolio consists of a number of grants, including one that investigates novel functional aspects of NF1 and NF2 genes and proteins, and the consequence of their deregulation. Other supported grants are examining a dynamic process that regulates neurofibromin activity and its relationship to the fine-tuning of Ras activity; how repression of the NF1 gene contributes to leukemia formation, a form of which affects children with NF1; and the use of a novel murine model developed by an investigator within the NCI Mouse Models of Human Cancer Consortium, to perform translational studies on Ras regulation in bone marrow cells and understand leukemia formation.

The NCI Mouse Cancer Genetics Program also uses mouse models to increase the understanding of the biology and genetics of certain tumors associated with NF1, with the ultimate goal of using this model to improve current treatments, as well as to design and test new therapies.

NCI is coordinating a number of trials including a study of tipifarnip that target children and young adults with NF1. In addition to the tipifarnip trial, NCI has five other trials ongoing with other experimental drugs. All of these trials have multiple participating sites in order to ensure that enough participants enroll to complete the trials in a timely fashion. In collaboration with the National Human Genome Research Institute, NCI is participating in a study of the natural history and biology of dermal neurofibromas in NF1. One of the study goals is to develop methods, which allow defining the growth rate of dermal neurofibromas, a requirement for the development of treatment trials for dermal neurofibromas. Since studies are becoming more successful, NCI looks to expand clinical and pre-clinical trial infrastructures.

#### Item

#### ***Vulvodynia***

In the last decade, NIH has supported three important research conferences on vulvodynia, as well as the first prevalence study and clinical trial of the disorder. These efforts demonstrated the need for additional research and served to heighten the research community's interest in studying vulvodynia. The Committee recommends that the Director build upon these initial successes by coordinating through ORWH collaborative extramural and intramural research into the causes of, and treatments for, vulvodynia. This effort should involve ORWH, NICHD, NINDS, and other relevant ICs, as well as the NIH pain consortium. The Committee also commends ORWH for working to plan an educational outreach campaign on vulvodynia. The Committee encourages the Director to work with the Center for Scientific Review and

the institutes 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. 309)

#### Action taken or to be taken

On October 24, 2007, the Office of Research on Women's Health (ORWH), together with NICHD, NINDS, the NIH Pain Consortium, and NLM, and other HHS and non-federal partners launched the *Vulvodynia Awareness Campaign*. ORWH and its 11 HHS and 23 non-federal partners have targeted this campaign at both health care providers and consumers. These partners represent a wide-range of interests, including consumers, physicians, nurses, midwives, researchers and advocacy groups as well as organizations representing African-American, Hispanic, and Native American women and health care providers. A complete list of partners is available at the ORWH website, <http://orwh.od.nih.gov>. The campaign is designed to increase awareness of this pain syndrome, which may affect up to 18% of women in their lifetime, and which while frequently not discussed, can greatly affect the lives and personal relationships of women of all races, ethnic groups, and ages. It includes links to websites of all partners, and also a packet of information available on-line or by mail that includes a Fact Sheet, Frequently Asked Questions, a Resource Guide, and key journal articles outlining current research on vulvodynia.

ORWH continues to work with the NIH institutes and centers (ICs) to develop strategies for addressing the causes of, and treatments for, vulvodynia through extramural and intramural research. For example, NICHD and ORWH have cosponsored the *PA-07-182, Vulvodynia—Systematic Epidemiologic, Etiologic or Therapeutic Studies*, which is designed to promote interdisciplinary research, with the goal of reducing the burden of this disease and ultimately improving the quality of life for women affected by this disorder. Other active program announcements have been released by the National Institute of Nursing Research, on behalf of the NIH Pain Consortium, to stimulate research in the field of pain and share the title, *Mechanisms, Models, Measurement, & Management in Pain Research*. These PAs include vulvodynia in their target areas for research. In the past five years, a number of researchers have been funded through these and other NIH mechanisms. Their work includes research on the epidemiology and prevalence of vulvodynia among women; clarification of the clinical definition of vulvodynia as well as determining effective treatments; assessing the pathophysiology of pain for women suffering from vulvodynia; and assessing the link between irritable bowel syndrome and vulvodynia.

ORWH, in coordination with most of the ICs of NIH, also recently launched two program announcements, entitled *Advancing Novel Science in Women's Health Research* – to which vulvodynia researchers are encouraged to apply. Finally, ORWH continues to work across the ICs to ensure that women's health issues

such as vulvodynia are adequately addressed on peer review panels.

Item

***Spinal Muscular Atrophy***

The Committee encourages the Director of NIH to monitor the progress of the SMA Project at NINDS. The Committee notes that the SMA Project is an excellent example of high risk, high reward research that was a focus of the recent reauthorization of the NIH by Congress. The current SMA project is scheduled to reach its near-term milestones in 2007 and thus it is important that the OD participate in planning for the successive stages of the project, including clinical trials and the infrastructure that will be needed to support drug development. Specific attention by the OD is necessary to ensure that the results of this innovative project are maximized, as well as to ensure that it serves as a model for other diseases as an innovative program to accelerate actual treatments for disease. (p. 171)

Action taken or to be taken

The NIH Director closely monitors the NINDS SMA Project, which is showing encouraging progress toward its goal of developing a drug to readiness for clinical testing. The project recently filed its second patent, and has advanced to the next stage by selecting a clinical candidate drug that is moving forward to safety studies. If successful, this could lead to an Investigational New Drug (IND) application to begin human studies in the next year. Because this drug acts by counteracting a general type of gene defect that also occurs in other genes and causes many other genetic diseases, the drug may be useful for several other diseases, including muscular dystrophy, Rett syndrome, ataxia-telangiectasia, and lysosomal storage disorders, to name a few. The NINDS is already applying the lessons of the SMA Project by developing similar medicinal chemistry resources for other diseases. The NINDS is also heavily engaged in and brings its experience with the SMA project to the NIH Roadmap Molecular Libraries Screening Center Network, Clinical and Translational Science Awards (CTSA's), and other translational research efforts. So, the lessons from the SMA Project will certainly receive appropriate attention in other NIH translational research efforts.

In addition to monitoring the development of infrastructure for drug development, the NIH Director has been paying close attention to the preparations for clinical trials in SMA. The Therapeutics Advancement Program for SMA (TAP-SMA) systematically examined whether any currently available drugs might warrant clinical trials for SMA, and NINDS convened an international scientific workshop on the development of clinical trials for SMA to discuss SMA clinical trials, including the TAP-SMA analysis. Among other SMA clinical activities, NINDS is developing a pilot clinical trial of phenylbutyrate for SMA, based on the TAP-SMA analysis, that will provide valuable information on conducting future SMA clinical trials, including biomarker and natural history data. The institute has also funded

research to improve animal models and better define the “therapeutic window” when intervention can be effective. The NICHD supports research on quantitative testing of muscle strength in SMA, which will be important for assessing trial outcomes, and on the development of both newborn and carrier screening tests for SMA, which will be critical for the success of clinical trials for infants.

Item

***Dystonia***

The Committee is very pleased with progress demonstrated by the NIH intramural research program in the treatment and understanding of dystonia. NIH intramural researchers have successfully utilized injections of Botox to treat many patients who otherwise would be severely debilitated by dystonia. The Committee urges continued work in this important area of study and treatment. (p. 171)

Action taken or to be taken

NINDS has a strong commitment to dystonia research in both its intramural and extramural programs. The Human Motor Control Section and the Laryngeal and Speech Section in the intramural research program continue to have a major focus on dystonia, including treatment with botulinum toxin. Intramural investigators have found a number of changes in how the brain controls movement in dystonia, including abnormal plasticity and defective sensory function, and are now working to identify structural pathology in dystonia using magnetic resonance imaging and to identify genetic mutations that cause focal dystonia. As research continues on the mechanisms of the abnormal movement in dystonia, investigators are developing novel treatments informed by insights about how the normal brain controls movement and what goes wrong in dystonia.

In June 2006, the NINDS and the Dystonia Medical Research Foundation (DMRF) brought together intramural and extramural researchers, clinicians, industry scientists, and representatives from patient advocacy groups in a scientific workshop that focused on recent advances and future directions for dystonia research. To follow up the workshop, the NINDS extramural program issued a program announcement in July 2007, together with the 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 DMRF and the Bachmann-Strauss Dystonia and Parkinson Foundation, Inc. The announcement, which is scheduled to be active through July 2010, encourages basic, translational and clinical research studies that will advance the understanding and treatment of generalized and focal dystonias.

## Item

### ***Gene therapy research***

The Committee is encouraged by promising research being undertaken in gene therapy, especially regarding thalassemia, or Cooley's anemia. NIH has indicated that human clinical trials could begin between 2008 and 2010. The Committee encourages that every step be taken to assure that this research moves forward without delay at the earliest possible date, consistent with safety (p. 172)

### Action taken or to be taken

During the past 5 years, much progress has been made in developing gene therapy for hemoglobinopathies, including Cooley's anemia (beta-thalassemia). Four U.S. laboratories have reported a gene therapy cure in mouse models, one using human thalassemic blood cells. The first human trial of gene therapy for hemoglobinopathies (funded by industry in France) enrolled two patients, one with Cooley's anemia and the other with sickle cell disease. The patients were treated with lentiviral vectors developed by NHLBI-supported U.S. investigators. To assess when a similar trial might occur in the United States, the NHLBI convened a working group of leading investigators with representatives from the Cooley's Anemia Foundation, the Sickle Cell Disease Association of America, the FDA, and the extramural hematology and bioethics communities. Barriers to starting a U.S. trial were identified as funding, lentiviral vector production, and preparation of applications to the FDA and the Recombinant DNA Advisory Committee (RAC). Since the meeting, some investigators have made progress toward obtaining approval for their protocols from the RAC and the FDA.

The NHLBI has created a Gene Therapy Resource Program (GTRP) to facilitate translation of preclinical research into clinical interventions. Its objective is to provide resources to produce preclinical and GMP (good manufacturing practices) vectors and to complete pharmacology and toxicology studies. The program also includes resources to assist investigators with the regulatory process. To promote the translation of basic research to the clinic, GTRP funds are provided for a maximum of two phase I/II gene transfer clinical trials per year that have successfully met all regulatory requirements and are ready to enroll patients within 12 months of application approval. Other ongoing NHLBI programs to facilitate trials in this area include the Production Assistance for Cellular Therapies (PACT), the Comprehensive Sickle Cell Centers, the Thalassemia Clinical Research Network, and the Center for Fetal Gene Transfer in non-human primates.

Through its programs, the NHLBI is establishing a foundation for U.S. human gene therapy trials for hemoglobinopathies. The NHLBI already has assembled experienced staff and a safety monitoring committee, and has developed

standard operating procedures to monitor patient safety. Depending on the quality of proposals received, we anticipate that the first U.S. trial of human gene therapy for Cooley's anemia could start between 2008 and 2010.

Item

***Interdisciplinary genetic research***

The Committee commends NIH for supporting independent investigators studying chromosome abnormalities and for partnering to sponsor meetings on many conditions. However, the Committee encourages NIH to sponsor mechanisms to support multidisciplinary, multi-institute research focused on devising treatments for the 20,000 babies born every year with a chromosome abnormality, especially those involving chromosome 18. (p. 172)

Action taken or to be taken

The research area including chromosomal abnormalities has long been at the heart of the NICHD's portfolio. Although the research funded to date continues to elucidate aspects of many of these rare conditions, methods of treating or ameliorating many of these conditions and their developmental and health consequences remain elusive. The NICHD supports research efforts on nearly 70 rare genetic disorders, including those syndromes of chromosome duplication and deletion.

Multidisciplinary research efforts undertaken include both research and program project grants on a wide range of disorders, including Prader Willi, Angelman, Williams and Rett syndromes, and urea cycle disorders. The NICHD supports the three Fragile X "centers within centers." Additionally, the Institute supports clinical trials that address a number of these conditions, including trials on Rett syndrome, Down syndrome, X-linked Adrenoleukodystrophy, Fragile X syndrome and gene therapy for several lysosomal disorders.

The Mental Retardation and Developmental Disabilities Branch of the NICHD currently supports one research project on chromosome 18 disorders that is up for competitive renewal. The NICHD received no applications during fiscal year 2007 to support meetings in this research area which can serve to stimulate research proposals. The NICHD will continue to encourage a wide variety of applications to address these conditions through ongoing outreach to the scientific community through professional societies and scientific meetings and conferences.

Item

***Peer review***

The Committee is concerned that individuals with surgical expertise are sometimes not assigned to surgical research grant application review. The Committee urges the Center for Scientific Review to ensure that there is an adequate number of specialty-specific peer reviewers, especially cardio-thoracic

surgeons, in organ-specific or system-specific study sections reviewing surgical research applications. (pp. 173-174)

#### Action taken or to be taken

The Center for Scientific Review (CSR) has recently implemented an evaluation process for all of the Integrated Review Groups (IRGs) and their study sections on a two year cycle. To date, approximately half of CSR IRGs, including the Cardiovascular Sciences IRG, have been evaluated in this manner. The evaluation covers a broad range of topics, including a review of the meeting and membership rosters for committees and a discussion of areas of particular concern.

In the three most recent Council Rounds (January 2006, May 2006, and October 2006) CSR reviewed approximately 60 cardiac (including general cardiovascular, cardiopulmonary and cardiothoracic) surgery applications. Two-thirds of these applications were for Research Project Grants (R01s) and Exploratory/Developmental Grants (R21s), with the balance for small business innovation projects. Within the research grant application pool, the surgery applications did extremely well in peer review compared to their competition, with over 35% receiving percentile scores of 20 or better. Depending on the scientific questions being asked, these applications were primarily assigned to one of three study sections, Myocardial Ischemia and Metabolism (MIM), Clinical and Integrative Cardiovascular Sciences (CICS) and Bioengineering, Technology and Surgical Sciences (BTSS).

The Director of CSR and the Scientific Review Administrators (SRAs) that manage these study sections have had meetings with surgeons representing the American Association of Cardiothoracic Surgeons. At that time the Society expressed their concerns for representation on study sections. CSR agreed to cluster such applications to the extent that the subject matter and the expertise of the panel warranted and to include surgeons with appropriate expertise on those study sections. CSR requested and received a recommended list of potential reviewers from the Society.

Scientific Review Officers (SROs) consult this list in selecting reviewers for their study sections. The MIM study section has one active member of that society as a regular member and additional reviewers with surgical expertise are routinely recruited as needed to accommodate the applications under review. On the BTSS panel, the chair and one regular member are cardiothoracic surgeons. Temporary cardiothoracic surgeon reviewers are also added to this panel as needed. Finally, several Scientific Review Administrators will be participating in a Grantsmanship Workshop in March 2007 that is being organized by the American Association of Cardiothoracic Surgeons.

In summary, CSR's evaluation indicates that cardiothoracic surgery applications are being clustered according to the science proposed, with the assistance of

professional societies, such as the American Association of Cardiothoracic Surgery, to ensure that appropriate expertise is routinely recruited for the panels to assist in the review of these applications, and that the peer review outcomes for this cohort of applications are quite positive.

Item

***Disparities in clinical trials***

The Committee encourages NIH to revisit the issue of health disparities in clinical trials with a goal of increasing participation from under-represented populations (p. 174)

Action taken or to be taken

Increasing the participation of racial and ethnic minorities, and medically underserved populations in clinical trials remains a priority for the NIH. Several of the Institutes and Centers have identified this issue as an area of emphasis in the NIH FY2004-2008 Health Disparities Strategic Plan. All NIH Institutes and Centers are required to comply with the agencies policy on the inclusion of minorities and women in clinical trials, and every two years the Office of Research on Women's Health releases a report affirming that each IC is in compliance. The NIH Clinical Center (CC) spearheads the agency's clinical trials activities and provides support to the other Institutes and Centers with their patient recruitment activities including the recruitment of racial and ethnic minorities. Strengthening the clinical trials infrastructure is a priority for the CC. Through individual and collaborative initiatives, the ICs implement various strategies to increase participation of racial and ethnic minorities in clinical trials. Activities include cultural competency programs focused on provider-patient communication; audio news releases; clinical research centers/networks; symposia; consensus conferences; minority clinical trials outreach programs at medical schools; promotion of databases such as clinicaltrials.gov. Some of the activities that are planned to address this issue include research programs aimed at identifying the factors that influence the decision of these communities to enroll or not to enroll in certain clinical trials and to identify innovative solutions and strategies to increase the future enrollment of these populations in clinical trials. There are a number of NIH programs that focus on the training of investigators from health disparity populations who will eventually conduct clinical trials and partnerships among majority and minority-serving institutions where the research intensive institution conducts the clinical trials and the minority-serving institutions leads the recruitment process. Efforts will continue in order to increase collaborations across Institutes and Centers that conduct clinical trials in racial and ethnic minorities to facilitate the timely translation and dissemination of trial results to the targeted communities.

Item

***Tuberous Sclerosis***

TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple

organs of the body, including the brain, heart, kidneys, lungs, liver, eyes and skin. Because of the effects of TSC on multiple organ systems, the Committee urges NIH to continue coordinating TSC research activities through the trans-NIH tuberous sclerosis coordinating committee. The Committee also encourages the various institutes that fund TSC research to place increased emphasis on this important research, and to increase coordination with the TSC community as future research plans are developed and executed. (p. 174)

#### Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) leads the Trans-NIH Tuberous Sclerosis Working Group, composed of representatives from nine other NIH Institutes and Centers, the Department of Defense (DoD), and representatives from the TS Alliance patient voluntary organization. The working group meets on an annual basis, and serves as a forum for NIH Institutes to coordinate research activities particularly those relevant to the NIH Research Plan for Tuberous Sclerosis. The working group also represents a way for federal agencies to share and learn about activities with areas of possible collaboration with the patient community, through representation of the TS Alliance.

At the most recent meeting in August 2007, members gave updates on their activities, including recent NIH-funded research and a DoD effort to compile and publicize DoD-funded TSC research resources and research highlights. Two meetings organized by members of the working group were also discussed. The first, "Tuberous Sclerosis Complex: From Genes to New Therapeutics," held in September 2007, was supported in large part by an NIH conference grant together with the TS Alliance. The workshop brought together prominent researchers to discuss recent advances in understanding the molecular basis of TSC and opportunities for therapy development. The second, "mTOR Signaling: From Cancer to CNS Function," sponsored by NINDS and planned for January 2008, will focus on a specific molecular pathway - the mTOR pathway - which has been implicated in TSC as well as other cancers and disorders of the nervous system.

NIH recognizes the importance of coordinating activities on TSC given its effects on multiple organ systems of the body, and will continue to coordinate activities and identify opportunities for collaboration with other agencies and groups through the NIH TSC Working Group.

#### Item

##### **Minority training**

The Committee encourages NIH to strengthen participation from minority institutions with a track record of producing minority scholars in science and technology. (p. 174)

### Action taken or to be taken

The NIH is committed to strengthening the research infrastructure at minority health professions institutions and has identified this as a primary goal of its five-year Health Disparities Strategic Plan for all of the ICs to support. The NCMHD will continue working with the NIH Office of the Director, the ICs, and the Health Resources Services Administration, the Office of Minority Health in the Office of the Secretary, the Indian Health Service, and other federal agencies to strengthen the research infrastructure at minority health professions schools. Some of NIH's programs that are helping to build the research capacity at these institutions include:

Research Infrastructure in Minority Institutions (RIMI) Program: The purpose of the RIMI Program is to establish and 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. From an initial cohort of seven institutions, the program has advanced to support a total of 26 institutions. In FY 2007, seven new and 19 non-competing grants were awarded.

Loan Repayment Program (LRP): The purpose of the program is to recruit and retain highly qualified health professionals with doctorate degrees to pursue health disparities or clinical research by repaying their loans to alleviate the financial barriers that often discourage many health professionals from health disparity populations from pursuing a research career. Since 2001, NCMHD has provided loan repayment program awards to 1,460 LRP recipients. The majority of these recipients (66%) are members of a racial/ethnic minority population with 35% African-Americans, 15% Hispanics, 9% Asians and Pacific Islanders, and 3% American Indians and Native Alaskans. These individuals are located at majority and minority-serving institutions in more than 42 states nationwide.

Bridges To The Future Programs: The programs (Bridges to the Baccalaureate Degree and Bridges to the Doctoral Degree) provide support to institutions to help students make transitions at a critical stage in the development of their careers as scientists. The NCMHD co-funds the programs with National Institute of General Medicine Sciences (NIGMS).

DHHS-Hispanic Association of Colleges and Universities (HACU) Professions Capacity Building Program: This program is aimed at building the capacity of Hispanic Serving Institutions to enable their faculty to secure more federal grants to address the health care needs of Hispanic Americans through research, education, and outreach. The program is a partnership between the DHHS' Office of Minority Health and NCMHD. To date, 169 faculty and staff from 55 Hispanic Serving Institutions have benefited from the program.

Diverse Institutions Drug Abuse Research Program is a National Institute of Drug Abuse (NIDA) capacity-building program that provides research support to minority institutions to increase the capacity of their faculty, staff and students. The grants enable minority institutions to conduct rigorous drug abuse research in all areas of research supported by the NIDA including neuroscience, behavioral, clinical, social science, public health, biological, HIV/AIDS and health service areas.

Research Scientist Awards for Minority Institutions of the National Heart, Lung, and Blood Institute (NHLBI) seeks to augment and strengthen the research capabilities and resources of minority institutions for the conduct of biomedical and/or behavioral research by recruiting an established research scientist with expertise in areas related to cardiovascular, lung, or blood health and disease, transfusion medicine, or sleep disorders.

Research Centers in Minority Institutions (RCMI) Program: NCMHD is involved in a collaborative effort with the National Center for Research Resources (NCRR) in enhancing the research infrastructure at minority colleges and universities that offer doctorates in health sciences. The program serves the dual purpose of bringing more minority scientists into mainstream research and enhancing studies of minority health.

Research Endowment: The mission of the NCMHD Research Endowment is to build research and training capacity at institutions that have been designated as Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals by the Health Resources and Services Administration. A total of 6 Historically Black Colleges and Universities and 5 Hispanic Serving Institutions have benefited from the program thus far.

#### Item

##### ***Bridging the 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. 174)

#### Action taken or to be taken

In response to language in the NIH Reform Act of 2006, a Bridging the Sciences Demonstration Oversight Group was created. This group consists of four NIH Institute Directors and representatives from key offices throughout NIH, as well as representation from the NIH Bioengineering Consortium (BECON) and the Biomedical Information Science and Technology Initiative (BISTI). The Group is

charged with overseeing the development of projects and programs that illustrate a synergistic bridging of the physical and life sciences, consistent with statutory provisions dealing with technical and scientific peer review and advisory council review. To assist the Oversight Group, an Implementation Group will be created and charged to prepare candidate demonstration project concepts for the Oversight Group's consideration, report to the Oversight Group as input or information exchange is needed, and advise the Oversight Group on any implementation strategies or other developments that would impact demonstration project selection or execution. The Implementation Group will have participation from NIH, NSF, NIST, DOE and other federal agencies as needed.

### **Senate Significant Items**

#### Item

#### ***Stem Cell Research***

The Committee strongly urges the NIH to support human embryonic stem cell research to the greatest extent possible under the current guidelines. The Committee also expects the NIH to explore all other avenues of stem cell research, including adult stem cells and stem cells from the placenta, amniotic fluid, cord blood and other sources; and alternative methods of establishing pluripotent stem cell lines that do not involve the destruction of an embryo. (p.109)

#### Action taken or to be taken

The National Institutes of Health (NIH) leads the federal effort in supporting all types of stem cell research. In FY 2006, NIH spent approximately \$38 million in research studying human embryonic stem cells (hESCs) and \$206 million studying human non-embryonic stem cells, including fetal, umbilical cord blood, bone marrow, and adult stem cells. In addition, NIH spent approximately \$399 million on non-human stem cell research, bringing total NIH support of stem cell research to approximately \$643 million. NIH continues to stimulate stem cell research through numerous initiatives and announcements for research funding, as well as scientific workshops and training programs. The amount of stem cell research that NIH supports is based on the number of grant applications from the research community that are deemed meritorious by peer review; NIH does not limit to the amount of funding set aside for this research.

Among major NIH hESC programs are the Exploratory Centers and Program Projects for Human Embryonic Stem Cell Research, the National Stem Cell Bank, and the Centers of Excellence in Translational Human Stem Cell Research. NIH's continued support of hESC infrastructure grants has resulted in 21 hESC lines listed on the NIH Human Embryonic Stem Cell Registry available for distribution to scientists worldwide. To further advance the field of research, NIH awarded training grants to support seven hESC short-term training courses,

enabling scientists to learn hESC culturing techniques.

To reinforce NIH's leadership in pursuing stem cell research, President George W. Bush issued Executive Order 13435 on June 20, 2007 which requires that *"The Secretary of Health and Human Services shall conduct and support research on the isolation, derivation, production, and testing of stem cells that are capable of producing all or almost all of the cell types of the developing body and may result in improved understanding of or treatments for diseases and other adverse health conditions, but are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus."*

The NIH is taking several steps to implement the Executive Order. NIH plans to Issue Funding Opportunity Announcements (FOAs) to accelerate research on human pluripotent stem cells from non-embryonic sources and to offer Administrative Supplements to existing grants for studying pluripotent stem cells from non-embryonic sources. NIH will rename the NIH Human Embryonic Stem Cell Registry as the Human Pluripotent Stem Cell Registry and add other lines deemed pluripotent by scientifically valid criteria. NIH will also convene scientific workshops on the state of the current science in pluripotent stem cell biology and on alternative ways to derive pluripotent stem cells. These meetings will inform future FOA's and help the NIH prioritize research with the greatest potential for clinical benefit.

#### Item

##### ***Gene-Environment Interactions and Health***

The Committee encourages the OBSSR to work with other Institutes and Centers to spur progress on understanding the interactions among genetic and environmental factors, especially regarding how they might contribute to health disparities in minority populations. (p. 156)

#### Action taken or to be taken

The Office of Behavioral and Social Sciences Research (OBSSR), in collaboration with multiple Institutes and Centers, is developing Funding Opportunity Announcements (FOAs), *Studying Interactions among Social, Behavioral, and Genetic Factors in Health*. These FOAs invite applications from NIH grantees to supplement their currently funded projects with additional research to study how interactions among genetic and behavioral/social factors influence health and disease. This program is focused on questions concerning the effects of (1) the interaction of genetic and social and/or behavioral factors (2) gene-environment-behavioral interactions; and (3) how the interaction of behaviors and social environmental factors affect gene expression, disease and behavior phenotypes and health outcomes. This activity follows on a 2006 Institute of Medicine (IOM) report, *Genes, Behavior, and the Social Environment. Moving beyond the Nature/Nurture Debate*, sponsored by OBSSR, the National

Institute of General Medical Sciences (NIGMS) and the National Human Genome Research Institute (NHGRI). In addition, OBSSR led the development of FOAs, *Behavioral and Social Science Research on Understanding and Reducing Health Disparities* (R21 and R01 grant mechanisms; <http://grants.nih.gov/grants/guide/pa-files/PAR-07-379.html>). These FOAs, released in June, 2007, are collaborative efforts among OBSSR, 19 Institutes and Centers and the Centers for Disease Control and Prevention (CDC). Their purpose is to encourage behavioral and social science research on the causes and solutions to health and disabilities disparities in the U. S. population. Emphasis is placed on research in and among three broad areas of action: 1) Public policy, 2) health care, and 3) disease/disability prevention. Since the understanding of health disparities requires consideration of the full range of factors that determine health – biological (including genetic), medical, behavioral, social, and environmental – and of their complex interrelationships, proposals that utilize an interdisciplinary research approach at the intersections of these disciplines is encouraged. Approaches utilizing multiple levels of analysis, from the molecular to the social/environmental, are also encouraged. Awards in response to these FOAs are anticipated to start in late 2008.

#### Item

**CETT Program:** The Collaborative, Education and Genetic Test Translation [CETT] Program promotes the translation of rare disease genetic tests from research to clinical laboratories. The Committee believes that this program can be enhanced by using microarray technology in the development of new tests and by close collaboration with and support from those Institutes whose research agendas already relate to specific rare diseases. The Director is urged to assure such trans-institute collaborations are aggressively fostered. (p. 156)

#### Action taken or to be taken

In the two years since the Office of Rare Diseases initiated the Collaboration, Education and Genetic Test Translation for Rare Genetic Diseases (CETT) Program, nearly three dozen new tests for rare genetic diseases have either become available or are under development. The CETT Program is a pilot project of ORD, designed to move tests for rare genetic diseases from the research laboratory to clinical settings by establishing collaborations among clinicians, researchers, laboratories and patient advocates. Recently, the CETT Program has expanded to include all technologies, including molecular and biochemical testing as well as the use of microarray technology in the development of new tests depending on the rare disease and the appropriate method of genetic test development.

At the two most recent meetings of the Trans-NIH Rare Diseases Research Working Group that is chaired by the Director, Office of Rare Diseases (ORD), NIH has begun discussing means by which the CETT program can be

incorporated into the programs of those Institutes, Centers, and Offices whose research agendas already relate to specific rare diseases. As the CETT program begins transitioning from its pilot phase to broader applications across the NIH, trans-institute collaborations will emerge and thereby make more genetic tests available to patients with rare diseases and their families.

Item

***Chronic Fatigue Syndrome [CFS]*** - The Committee commends the Office of Research on Women's Health for its leadership on CFS research, particularly the coordination of the request for applications that culminated in the October 2006 announcement of seven new awards for in this area. The Committee recognizes the opportunity created by the requirement that the investigators funded under this initiative meet annually and encourages the NIH to use this meeting to stimulate new research initiatives and build multi-center collaborations. The Committee again urges the NIH to develop an intramural CFS research program and to implement the recommendation made by the CFS Advisory Committee to "establish five Centers of Excellence within the United States that would effectively utilize state of the art knowledge concerning the diagnosis, clinical management, treatment and clinical research of persons with CFS." The Committee also urges special attention to CFS research as part of the NIH effort to refine its disease/research categories. (p. 527)

Action taken or to be taken

NIH thanks the Committee for recognizing its successful efforts to pursue an integrated, interdisciplinary research approach to CFS research and assures that it will continue to further and stimulate such research until there are definitive answers to this devastating illness. NIH understands the Committee's wish to establish five Centers of Excellence. We anticipate that the findings from the seven new awards, continued stimulation and support of new and ongoing research projects conducted at the NIH, and clinical epidemiologic studies at the Centers for Disease Control and Prevention will help to create a scientific base of evidence which is necessary to support future action on this recommendation.

The NIH also recognizes the Committee's wish to develop an intramural program and continues its efforts to increase interest and awareness within the NIH scientific community through the Intramural Scientific Interest Group. The Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG) will also consider other options, such as the establishment of a fellowship, to attract intramural researchers. The climate for building the collaborations necessary for such a venture is improving. For example, the CFSWG held a grantsmanship workshop that attracted several new intramural scientists and resulted in the addition of three institutes (John E. Fogarty International Center, National Institute on Aging, and National Institute of Digestive and Kidney Disorders) to membership in the CFSWG. Further information about the workshop can be found at <http://orwh.od.nih.gov/cfs/cfsFundingGMWs.html>. It is expected that this

interest in CFS as well as other similar disorders that cut across the missions of many ICs, will continue to grow as the new interdisciplinary culture of the NIH gains momentum.

Item

**Irritable Bowel Syndrome [IBS]**-- The Committee is pleased with the focus on IBS at the Office of Research of Women's Health and urges additional research in this area.(p. 156)

Action taken or to be taken

Irritable bowel syndrome (IBS), a functional gastrointestinal disorder that disproportionately affects women, is a major priority of both the NIH Office of Research on Women's Health (ORWH) and the NIDDK. Consequently, the ORWH and the NIDDK frequently partner in supporting initiatives to foster innovative IBS research. For example, the ORWH led the development and implementation of the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health (SCORs) program to support interdisciplinary research on sex/gender factors that affect the health of women. One such center, the Center for Neurovisceral Sciences and Women's Health (CNS/WH) at the University of California, Los Angeles, focuses on identifying sex- and gender-related factors that play a role in the development, clinical manifestation, and treatment response of IBS and interstitial cystitis (IC). Both disorders are characterized by pelvic visceral pain, exhibit sex differences in prevalence and response to treatment, and cause a diminished quality of life for those affected.

The NIDDK-led National Commission on Digestive Diseases, (<http://www2.nidk.nih.gov/AboutNIDDK/CommitteesAndWorkingGroups/NCDD/>) is currently developing a long-range plan for digestive diseases research. The Commission is composed of leading experts in the field who are reviewing the state-of-the-science in digestive diseases and identifying research goals and challenges that will be part of the plan. An ORWH representative is contributing to this planning process by serving as an ex officio member of the Commission. The goals and challenges for IBS research will be addressed extensively in the plan's Functional Gastrointestinal Disorders and Motility Disorders chapter. The plan is scheduled to be completed in 2008.

Item

**Vulvodynia**

In the last decade, the NIH has supported three important research conferences on vulvodynia, as well as the first prevalence study and clinical trial on the disorder. These efforts have both clearly demonstrated the need for substantial additional research and served to heighten the research community's level of interest in studying vulvodynia. The Committee calls upon the Director to build upon these initial successes by coordinating through the ORWH an expanded, collaborative extramural and intramural research effort into the causes of, and

treatments for, vulvodynia. This effort should involve the NICHD, NINDS and other relevant ICs, as well as the NIH Pain Consortium. The Committee also commends the ORWH for working with patient groups, other relevant ICs and women's health offices in other governmental agencies to plan an educational outreach campaign on vulvodynia, as previously requested by the Committee. Finally, the Committee encourages the Director to work with the Center for Scientific Review and ICs to ensure that experts in vulvodynia, and related chronic pain and female reproductive system conditions, are adequately represented on peer-review panels. (p.157)

Action taken or to be taken

Please refer to page 314 of this document for the NIH response to this item on Vulvodynia.

Item

***Antibacterial Therapy***

The Committee is concerned about the alarming rates of antibiotic resistance and the related increase in morbidity, mortality and health care costs. Little research has been devoted to defining optimal dosing regimens, particularly in defining the minimal duration of therapy necessary to cure many types of infections. The Committee recognizes that studies of this type require a long-term commitment and are not likely to be funded by pharmaceutical manufacturers since the products are already approved by the FDA. The consensus of many experts is that infections are frequently treated for longer periods of time than are necessary, needlessly increasing the antimicrobial resistance. Therefore, the Committee urges the NIH to support a Clinical Trials Network devoted to defining optimal antibacterial therapy. Multi-center randomized controlled trials to define the necessary length of therapy would create an excellent basis of evidence from which coherent and defensible recommendations could be developed. (p. 157 -158)

Action Taken or to be taken

Research to better characterize the public health threat posed by antibiotic-resistant infections and to develop therapeutics that minimize the emergence of drug resistance remains a priority for the National Institutes Health, and in particular, the National Institute of Allergy and Infectious Diseases (NIAID), the NIH component responsible for research on infectious diseases. NIAID co-chairs the Federal government's Interagency Task Force on Antimicrobial Resistance together with the Centers for Disease Control and Prevention and the Food and Drug Administration.

Rather than supporting a clinical trial network focused on antimicrobial resistance, NIAID supports the conduct of clinical trials in settings optimal for the specific scientific questions being examined. For example, in FY 2007, NIAID awarded two five-year contracts through the "Clinical Trial for Community-

Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA)” initiative to study whether selected oral, off-patent antibiotics can effectively treat uncomplicated cases of skin and soft tissue infections caused by CA-MRSA bacteria. Because CA-MRSA may be more susceptible to antibiotics than hospital-acquired MRSA, the overarching goal of this study is to determine the optimal treatment, including duration of therapy, for CA-MRSA infections. Should the data from these studies demonstrate that off-patent antibiotics are effective, final-option drugs such as vancomycin and linezolid could be preserved for treating hospital-acquired MRSA.

A second NIAID-supported clinical trial is comparing a "short course" antibiotic regimen of three days to the common practice of eight days or more in persons with suspected respiratory infections in the Intensive Care Unit (ICU). The results of the multicenter study could inform the use of antimicrobials in ICUs and have an impact on the emergence of antimicrobial resistance in these wards. Another clinical study, which began in October 2006 and is expected to be completed in May 2008, is evaluating the efficacy of antimicrobials in young children with acute ear infections. The study will compare the resolution of symptoms in children receiving the drug versus placebo.

Rapid diagnostic tests currently are not available for many infections; in lieu of these tests, healthcare providers commonly prescribe broad-spectrum antimicrobial drugs, the overuse of which has been attributed to the accelerated development of resistance. Research initiatives such as “Sepsis and CAP: Partnerships for Diagnostics development” and “Partnerships to Improve Diagnosis and Treatment of Selected Drug-Resistant Healthcare-Associated Infections” are supporting the development of new diagnostics that may facilitate the optimization of antimicrobial therapy.

In FY 2008, the NIAID anticipates making awards through the “Pharmacological Approaches to Combating Antimicrobial Resistance” initiative, which will support research to apply pharmacokinetic and pharmacodynamic principles to studies on the prevention of emergence of antimicrobial drug resistance. This initiative is also 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.

#### 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 urges the Director to give high priority to the program and to urge

active consultation and collaboration 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 appropriation, multidisciplinary peer review panels and the unique type of research envisioned. (P. 158)

Action taken or to be taken

Please refer to page 324 of this document for the response to this significant item regarding Bridging the sciences.

Item

***Chromosome Abnormalities***

One out of every 180 babies born has a chromosome abnormality that by its very nature is multisystemic because it involves a copy number change in dozens of contiguous genes. The frequency and complexity of these conditions have a major impact on childhood morbidity and mortality. The key to helping these children is creating interdisciplinary, multi-institute research teams. The Committee commends the NIH for supporting some independent investigators studying chromosome abnormalities and for partnering to sponsor meetings on many conditions, as described in the fiscal year 2008 congressional budget justification. The Committee also encourages the NIH to sponsor mechanisms to support multidisciplinary research focused on devising treatments for the 20,000 babies born every year with a chromosome abnormality, especially those involving chromosome 18. (p. 158)

Action taken or to be taken

The research area including chromosomal abnormalities has long been at the heart of the NICHD's portfolio. Although the research funded to date continues to elucidate aspects of many of these rare conditions, methods of treating or ameliorating many of these conditions and their developmental and health consequences remain elusive. The NICHD supports research efforts on nearly 70 rare genetic disorders, including those syndromes of duplication and deletion.

Multidisciplinary research efforts undertaken include both research and program projects on a wide range of disorders, including Prader Willi, Angelman, Williams and Rett syndromes, and urea cycle disorders. The NICHD supports three Fragile X "centers within centers." In addition, the Institute supports clinical trials to address a number of these conditions, including trials on Rett syndrome, Down syndrome, X-linked Adrenoleukodystrophy, Fragile X syndrome and gene therapy for several lysosomal disorders.

The Mental Retardation and Developmental Disabilities Branch of the NICHD currently supports one research project on chromosome 18 disorders, and it is up for competitive renewal. The NICHD received no applications during fiscal year 2007 to support meetings in this research area, which can serve to stimulate

proposals. The NICHD will continue to encourage a wide variety of applications to address these conditions.

Item

***Class B Animal Dealers***

While the Committee recognizes that the use of animals in research, under certain circumstances, has been beneficial to the advancement of biomedical research, the Committee would like assurances that such research is conducted as humanely as possible. In the case of the use of dogs and cats used in research and obtained from Class B dealers, the Committee is concerned that such dealers have the potential to provide animals that have not been treated in accord with USDA regulations for use in federally supported research. The Committee asks the NIH to seek an independent review by a nationally recognized panel of experts of the use of Class B dogs and cats in federally supported research to determine how frequently such animals are used in NIH research and to propose recommendations outlining the parameters of such use, if determined to be necessary. (p.158)

Action taken or to be taken

The NIH mandates that all animals used in research it supports come from legal sources, which include Class B dealers, pounds, and owner-donated animals. The actual source used depends upon availability. For example, some research facilities purchase dogs and cats from Class B dealers because the local pounds by state or local statute are prohibited from providing unwanted animals for research. The NIH does not distinguish animals by source, and the source may change during the course of the grant. The NIH plans to seek an independent review by the National Academy of Sciences, Institute for Laboratory Animal Research (ILAR) on the use of Class B dogs and cats in federally supported research in the Spring 2008. The NIH plans to request that the expert panel also include additional sources of non-purpose bred cats and dogs in the study, e.g., cats and dogs from pounds and owner-donated animals.

Item

***Cooley's Anemia***

The Committee is encouraged by promising research being undertaken in gene therapy, especially regarding thalassemia, or Cooley's anemia. The NIH has indicated that human clinical trials could begin between 2008 and 2010. The Committee urges that this research move forward without delay at the earliest possible date, consistent with safety. (p. 159)

Action taken or to be taken

Please refer to the significant item entitled, *Gene therapy research* on page 317 of this document for the response to this significant item regarding *Cooley's Anemia*.

## Item

### ***Distribution of Resources***

In light of the doubling of the agency's budget over the past 5 years and the rapid encroachment of new medical research challenges such as SARS and threats of bioweapons, the Committee believes that the NIH should encourage funding of large-scale collaborative efforts to address these and other medical challenges. In addition, while the pace of new challenges has increased, review time for proposals submitted to the Institutes at NIH continues to average about 18 months. The Committee strongly encourages the Director to develop means of encouraging large-scale, multi-institution projects to address significant areas of medical research and to devise means of reducing the time frames between submission of proposals and awarding of grants. (P. 159)

### Action taken or to be taken

The NIH is now several years past the end of the period of doubling and the NIH Director has continued the NIH Roadmap Initiative to encourage funding of large-scale collaborative efforts to address medical research challenges. The NIH has just completed the second year of funding Clinical Translational Science Awards (CTSAs) which are designed to transform clinical and translational research by stimulating collaboration and leadership. The CTSAs serve as engines of discovery to translate basic and clinical research into prevention and treatment strategies. At the same time, CTSAs prepare the next generation of clinical researchers that will be necessary to meet the challenges of the future. In addition, the NIH made twelve new Pioneer Awards and thirty New Innovator Awards in 2007 to encourage biomedical and behavioral research with a strong potential to lead to significant advances in human health. New cross-cutting Roadmap Initiatives launched in 2007 include the Human Microbiome Project and the Epigenomics Initiative. Multi-institution collaboration is being encouraged by the NIH multiple PI initiative which stimulates collaboration within and between institutions by providing consistent recognition of all of leaders on a research project. All of these efforts enhance the ability of the NIH and the larger research community to address emerging medical challenges. More information on the multiple PI initiative can be found at [http://grants.nih.gov/grants/multi\\_pi/index.htm](http://grants.nih.gov/grants/multi_pi/index.htm) and information on other Roadmap initiatives can be found at <http://nihroadmap.nih.gov/>.

At the current time, the average time between receipt of an application and award is slightly more than 10 months. Although this is a much shorter time period than described in the question, the NIH believes it is still too long. The NIH Director in collaboration with the directors of several institutes has developed several initiatives to enhance peer review and eventually reduce the time between the submission of a proposal and funding. The Shortened Review Cycle initiative began in early 2006, when 40 study sections in Center for Scientific Review (CSR) began posting new investigator, R01 summary statements within 10 days of the study section meeting. In the February 2007

review cycle, the pilot was expanded to 100 study sections. It is expected that all study sections reviewing new investigator R01 applications will participate by the end of 2007.

The expedited posting of summary statements means that all new investigators, who are not anticipating funding of the original application, may apply for an R01 at the next deadline. For those investigators who are not funded, it means that they can apply about four months earlier than the current timeline for re-submission. In a second initiative, CSR has started posting 97 percent of all summary statements within 30 days of the review. Other work underway will expedite the referral of new applications to the study section. Text and concept mining will assist with the assignment of new applications and will help identify reviewers with appropriate expertise. The NIH expects these tools to reduce the time required to refer applications from several weeks to several days. This will allow a compression of the time between receipt of an application and review. This system is currently being studied. Other ideas under discussion include shortening the length of the standard grant application and the use of computer-assisted technology for managing virtual study section meetings. All of these ideas have the potential to reduce the time between the receipt of an application and award even more.

#### Item

##### ***Down Syndrome***

The Committee is deeply concerned by the significant decrease in funding for Down syndrome research since fiscal year 2003, and it strongly urges the NIH to increase its investment in this area. Due to recent studies and advances, the Committee believes that further research into how to successfully reduce the many adverse health effects of Down syndrome, including eradicating all the ill effects of the extra chromosome 21 of Down syndrome, is an emerging area of study that deserves NIH's immediate attention. The Committee urges the Director to take note of recent advances in the neurobiology of Down syndrome, especially concerning the structure and function of neural circuits that mediate cognition. These advances point to Down syndrome as a fertile area for research investments that could lead to effective treatments for cognitive difficulties in both adults and children with this disorder. Because the responsibility for researching Down syndrome rests with multiple Institutes, the Committee notes that it is an ideal candidate for a trans-NIH initiative. The Committee requests an update on these efforts in the fiscal year 2009 congressional budget justifications. (p. 159/160)

#### Action taken or to be taken

In 2006, the Director, NIH, designated the NICHD as the lead NIH Institute to organize and convene the trans-NIH Down Syndrome Working Group. This working group is composed of program officers at the many Institutes and Centers within NIH that support aspects of research on Down syndrome, and

others with portfolios of research directly relevant to Down syndrome. After several meetings and a review of currently funded NIH research, the working group met with interested members of organizations that represent individuals with Down syndrome and their families, and non-NIH researchers, presenting them with an overview of ongoing research efforts, and to obtain their input on future directions. To gain further information on ideas for expanded directions for the NIH, the working group, led by NICHD, convened a meeting in July 2007 of experts in Down syndrome, including researchers from a wide variety of fields, clinicians, advocates, parents and other relevant federal agencies. In addition to recommendations made at that meeting, the working group also evaluated the recommendations from three earlier expert workshops, two international meetings on Chromosome 21, and a meeting on cognitive function in Down syndrome. The working group has synthesized the ideas culled from these many sources, and formulated a draft plan for Down syndrome research that contains short, intermediate and long-term research objectives to guide NIH investment on Down syndrome over the next 10 years. This plan was made available for public comment and is being revised, incorporating suggestions made by the over 150 comments received. The plan will be published in the fall of 2007, and submitted to Congress in the fiscal year 2009 Congressional Justification.

To carry out the earliest goals of the plan, NICHD will actively seek partnerships with participating Institutes and other federal agencies. For example, NICHD is currently reviewing its plan for sharing model organisms to ensure that as new mouse models are developed using NIH funds, they will be deposited in a central repository so that all researchers who wish to use these models for their research have ready access to them. The working group will continue to meet to guide NIH's next steps in this area.

#### Item

#### ***Hereditary Hemorrhagic Telangiectasia [HHT]***

The Committee encourages the Director to coordinate the development of an HHT Research Plan with the NINDS, NIDDK, NHLBI, NHGRI, and NICHD and to issue an RFA to optimize opportunities for research identified at the NIH workshop on HHT vascular biology and pathophysiology. The Committee also encourages the NIH to establish an HHT tissue registry through coordination with the Office of Rare Diseases. (*Senate p. 160*)

#### Action taken or to be taken

Recognizing that additional research on HHT is needed, the NHLBI, in concert with the NHGRI, the NIH Office of Rare Diseases (ORD), and the HHT and Grace Nolan Foundations, held the second trans-NIH HHT workshop on June 8-9, 2006. The meeting culminated in recommendations for HHT-related research on transforming growth factor- $\beta$  pathways, vascular and endothelial cell biology, and organ physiology. The participating NIH components reviewed the recommendations to determine how their respective portfolios might specifically

address HHT, as well as other areas of vascular biology important for understanding the molecular underpinnings of HHT. As a first step toward developing an appropriate and effective research initiative to optimize opportunities for research for HHT and avoid duplication of existing programs, the NIH is analyzing institute portfolios, active initiatives, and initiatives in development that broadly target vascular diseases, including HHT.

The NHLBI currently supports a wide spectrum of research on vascular and endothelial cell biology and bleeding disorders that provides the foundation for developing new therapeutic approaches for vascular and hemorrhagic diseases such as HHT. Although the NIDDK does not fund HHT research *per se*, it does support grants that seek to expand knowledge of angiogenesis in the mucosa of the gastrointestinal tract—work which may ultimately advance the HHT field. The Trans-NIH Angiogenesis Research Program, led by the National Cancer Institute, includes the NHLBI, the NINDS, the NIDDK, and the NICHD in its membership and addresses issues relevant to HHT. At this time, establishing an HHT tissue registry would be premature; additional research by ORD and the other NIH components should be completed first.

#### Item

##### ***Human Tissue Supply***

The Committee understands that there is an increased need to provide NIH intramural and extramural researchers with human tissues and organs to study human diseases. The Committee strongly urges the Director, NCCR, and Institutes such as the NCI, NHGRI, NHLBI, NICHD, NIMH, and NINDS to identify and expand support for nonprofit organizations that supply human tissues to NIH-funded researchers. (p. 160)

#### 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 (NCCR) is the lead Institute/Center for the cooperative agreement that funds the Human Tissue and Organ Resource, which is a division of NDRI. In the past year, 4,568 normal and diseased tissues and organ specimens were 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 413 active biomedical researchers this past year including those that are NIH-funded.

NCCR maintains the core funding for the HTOR cooperative agreement, now in its seventeenth 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 funds for mission-specific resources.

Item

***Lymphatic Research and Lymphatic Diseases***

Lymphatic system research falls within and between numerous IC missions, a situation that contributes to its relative neglect as an investigative focus. Therefore, the Committee once again strongly urges that the NIH foster lymphatic research initiatives and awareness across all relevant NIH Institutes and Centers. The Committee also reiterates its earlier requests that relevant ICs specifically cite lymphatic system research in related funding mechanism requests where a lymphatic research component is appropriate. (p.160)

Action taken or to be taken

The NHLBI and the Trans-NIH Coordinating Committee for Lymphatic Research, which includes representatives from the NCI, NIAID, NIDDK, NIAMS, NEI, NINR and other NIH components, continue to develop research programs in lymphatic biology. The NIH has renewed the program announcement “Pathogenesis and Treatment of Lymphedema and Lymphatic Diseases” with continued participation of the NHLBI, NCI, NICHD, NIAMS, NCCAM, NIBIB, and NINR. In 2007, the NHLBI, NCI, NICHD, NIDDK, and NINR issued a new program announcement on “Lymphatic Biology in Health and Disease.” We will amend this solicitation by issuing a notice in the NIH Guide for Grants and Contracts encouraging grant applications that address congenital lymphatic malformation-induced pulmonary dysfunction, pulmonary lymphatic biology, and pulmonary lymphatic development in the hope of generating new research in these areas.

To stimulate additional research, the Trans-NIH Coordinating Committee for Lymphatic Research, with NHLBI leadership, convened a working group of experts representing a variety of disciplines to discuss future research directions.

The NHLBI continues to support a research program in lymphatic biology, including studies of mechanisms that control lymphatic development, defects in lymphatic growth, and lymphatic regeneration after injury in the lung.

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, Extramural Biomedical Research Facilities, and the NCMHD. The

Committee encourages the Director to work closely with the NCMHD to establish a program of coordination among these various mechanisms and partner with minority health professions schools to address their infrastructure needs. (Senate pp. 160/161)

Action taken or to be taken

Please refer to page 322 of this document and the item, **Minority Training** for the response to this significant item.

Item

**Mitochondrial disease**

The Committee encourages the NIH to intensify its research efforts into primary mitochondrial disease, which is also implicated in numerous other diseases such as Parkinson's, Alzheimer's, heart disease, diabetes and cancer. The Committee understands that intensified research into primary mitochondrial disease will help to further understanding these other conditions. (p. 161)

Action taken or to be taken

Mitochondria are the compartments within the cell that generate energy. Nerve cells require a great deal of energy and are therefore particularly susceptible to mitochondrial damage. The National Institute of Neurological Disorders and Stroke (NINDS) supports basic and clinical research focused on mitochondrial dysfunction in neurodegenerative diseases including Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). The goal of this research is to understand the specific changes in mitochondrial structure, mutations in mitochondrial genes, and alterations in mitochondrial energy dynamics that contribute to neurodegeneration, and to test potential therapies that target the mitochondria. NINDS-funded researchers are also characterizing mutations in mitochondrial genes that lead to mitochondrial myopathy and a particular form of peripheral neuropathy. Other studies are underway to understand the relationship between mitochondrial dysfunction and neuronal cell death following stroke, epileptic seizures, or traumatic injury to the brain or spinal cord.

Because the onset of primary mitochondrial disease often occurs before the age of 20, the National Institute on Aging supports only a few grants in this area. These grants focus primarily on the basic molecular and cellular mechanisms that may be involved in the mitochondrial dysfunction of muscle fibers.

However, "secondary" mitochondrial dysfunction is implicated in a number of age-related diseases and conditions including Alzheimer's disease (AD), Parkinson's disease, heart disease, and others, as well as in the process of aging itself. NIA supports a robust portfolio of research on the causes of and possible treatments for mitochondrial dysfunction, including several large program projects and investigator-initiated studies of the role of mitochondrial

dysfunction in AD, anemia, and heart disease and the basic biology of aging. In addition, the Laboratory of Molecular Gerontology, within NIA's Intramural Research Program, has as a major focus the study of changes in mitochondrial function with age.

Mitochondrial biology is the focus of a number awards funded through the NIH Roadmap. The Structural Biology Program, through its support of improved technologies for analysis of membrane proteins, includes awards to investigators who seek to understand the function and regulation of mitochondrial proteins. These proteins contribute to the control of cell death, misregulation of which contributes to cancer and degenerative diseases. The Molecular Libraries and Imaging Program includes support for investigators working to develop imaging methods for improved detection and analysis of mitochondrial proteins; this program also supports a number of investigators who are seeking to identify small molecular compounds that can modulate mitochondrial function, both in the control of cell death and in metabolism. Finally, the Interdisciplinary Research Program includes support for the analysis of mitochondrial dysfunction in diabetes as part of a larger, interdisciplinary effort to understand causes and complications of obesity.

Item

***Neurofibromatosis (NF)***

Recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages the NCI to substantially increase its NF research portfolio in such areas as further development of animal models, natural history studies, genetic drug screening, therapeutic experimentation, and clinical and pre-clinical trials. The Committee also encourages the NCI to create, fund, and implement NF clinical and pre-clinical trial infrastructures including NF centers, pre-clinical mouse consortiums, patient databases, and tissue banks.

The Committee

further encourages the NCI to apply existing cancer drugs to NF patients in clinical trials both extramurally and intramurally, and to develop new drugs for NF which could then apply to the general population. (p. 169/170)

Action taken or to be taken

Please refer to page 313 of this document for the response to this significant item on *Neurofibromatosis (NF)*.

Item

***National Children's Study***

The Committee strongly supports full and timely implementation of the National Children's Study that aims to quantify the impacts of a broad range of environmental influences, including physical, chemical, biological, and social influences, on child health and development. The Committee urges NIH to coordinate the involvement of the Department, the lead Federal partners, and other interested non-Federal partners conducting research on children's environmental health and development. (p. 164)

Action taken or to be taken

Please refer to page 300 of this document for the response to this significant item on National Children's Study.

Item

***Osteoporosis***

The Committee urges the NIH to support research into the pathophysiology of bone loss in diverse populations in order to develop targeted therapies to improve bone density and bone quality and to identify racial differences in bone and the origin of racial differences in fracture patterns. Furthermore, the Committee urges research to identify patients at risk for fracture who do not meet current criteria for osteoporosis, as well as to study the effects of current and developing osteoporosis treatments on these patients. (p. 161)

Action taken or to be taken

Osteoporosis is a disease characterized by low bone mineral density (BMD) that leads to bone fragility and an increased risk of fractures. Osteoporosis affects women and men of all races and ethnic groups but is most prevalent in white women and least common in men of African origin. African American women have a lower risk of developing osteoporosis, but they are still at significant risk. For Hispanic and Native American women, the data are not clear. Among men, osteoporosis is more common in non-Hispanic whites and Asians than in men of other ethnic or racial groups. Examining differences among these groups could help to identify new treatment or prevention strategies in individuals at greatest risk for fracture.

For example, results from the Tobago Bone Health Study have indicated that a population of 2,500 West African men, ranging in age from 40 to 92 years old, have the highest BMD ever reported. Follow-up studies are monitoring the change of BMD with age, as well as the effects of sex steroids, hormones, and growth factors on BMD to better evaluate bone health in men of African descent. In contrast, a study focusing on osteoporosis in Asian men has sampled 2,000 men from Hong Kong aged 65 years and older. Researchers observed that these individuals tend to have lower BMD than similar populations of Caucasian

men, yet also have fewer instances of vertebral fracture. Researchers continue to examine the potential environmental factors that may contribute to this phenomenon.

As mentioned, data associated with bone health in Native Americans is unclear. To address this issue, researchers in the Navajo Bone Health Study are examining bone health within the Navajo Native American Community. Information on body size, diet, and lifestyle factors and their influence on fracture rate and BMD are being examined. Additionally, education and intervention programs are being provided in order to raise the awareness of osteoporosis in this population.

Another NIH-supported research effort is specifically looking at osteoporosis in premenopausal women, a population not traditionally considered at risk for developing the disease. Researchers are examining a particular patient population that demonstrates increased bone breakdown and markedly decreased formation, despite not meeting current osteoporosis criteria. This research will provide information related to abnormal skeletal microarchitecture and remodeling, and the associated increased risk for fracture.

Additionally, the NIH maintains an active outreach program through the NIH Osteoporosis and Related Bone Diseases ~ National Resource Center (NRC). The NRC has recently developed and launched an interactive Web tool called *Check Up on Your Bones* ([http://www.niams.nih.gov/Health\\_Info/Bone/Optool/index.asp](http://www.niams.nih.gov/Health_Info/Bone/Optool/index.asp)). Visitors are invited to fill out a questionnaire in order to receive tailored information based on their individual profiles about bone health and osteoporosis, including their personal “red flags” factors like the presence of other diseases or medication use that may increase risk for the disease. Information provided through the Web tool is relevant to men, and those of diverse racial and ethnic backgrounds.

#### Item

##### ***Pain Consortium***

The Committee is pleased with the increased activity of the NIH Pain Consortium, including the recent meeting showcasing NIH-funded pain research projects. However, the Committee believes that much more needs to be done to realize the Consortium’s full potential. The Committee urges the NIH to convene a conference of outside experts in pain research and care to review the current pain research portfolio at NIH and make recommendations with respect to gaps in pain research that still need to be explored as the end of the congressionally declared Decade of Pain Control and Research approaches. The Committee also suggests that the Pain Consortium have a mechanism for ongoing extramural participation and input, such as an advisory committee consisting of outside experts. (p.161)

### Action taken or to be taken

The NIH Pain Consortium has continued to be active in trans-NIH efforts to enhance awareness of pain research. The Consortium sponsored the Second Annual NIH Pain Consortium Symposium on May 1, 2007. The topic of this year's Symposium was generalized pain conditions. Twelve speakers presented their latest results on a broad range of topics and 15 young investigators presented their findings in a poster session. The Symposium was attended by over 375 participants and the Symposium was also videocast to approximately 250 more. A subcommittee is currently planning the third Symposium to be held in the spring of 2008.

The Pain Consortium has an initiative planned for a Pain Progress Review Group. The initiative will establish a collaborative group among NIH Institutes, academic researchers, industry representatives, health care providers, and patient advocates interested in research, prevention, and treatment of pain. The purpose of the initiative is to identify priorities, develop a long term plan to advance pain research and management, and establish collaborative efforts among interested parties. This review group proposal is based on similar review groups established by other Institutes at NIH to examine important topics in health research.

### Item

#### **Pharmacy**

The Committee is pleased that the NIH recognizes the importance of doctors of pharmacy across the research spectrum as evidenced by the newly created "PharmD Gateway" on the NIH website. The Committee encourages interested organizations to find opportunities that will increase the participation of colleges and schools of pharmacy and doctor of pharmacy clinical scientists in NIH post-graduate training programs such as the clinical pharmacology research (T32) program. (p. 162)

### Action taken or to be taken

NIGMS, through its Division of Pharmacology, Physiology and Biological Chemistry (PPBC), supports and encourages PharmDs who wish to pursue additional research training in clinical pharmacology. The website, PharmD Gateway to NIH (<http://www.nigms.nih.gov/Training/PharmD/>), was developed to provide information about NIH funding opportunities for Pharm.D students, postdoctoral researchers, and faculty interested in biomedical and behavioral research. It welcomes research intensive pharmacy schools to submit T32 institutional clinical pharmacology postdoctoral training grant applications to train PharmDs who wish to obtain research experience in biomedical and behavioral research in areas of clinical pharmacology. This training grant program had

emphasized that trainees would normally be MDs, but applications to train MDs and/or PharmDs will be accepted.

NIGMS also encourages newly appointed clinical faculty who are in clinical pharmacology programs to seek guidance and support from NIH-funded investigators and apply for Mentored Clinical Scientist (K08) or Mentored Patient-Oriented Clinical Scientist (K23) Research Career Development Awards that meet the mission of NIGMS.

Item

**Spinal Muscular Atrophy-** The Committee strongly urges the OD to ensure the success of the SMA Project at the NINDS by providing active and ongoing support from the OD as well as from other related Institutes. The current SMA Project is scheduled to reach its near-term milestones in 2007 and thus it is imperative that the NIH begin planning and budgeting for the necessary successive stages of the project, including funding for clinical trials and the infrastructure that will be needed to support of each of the stages of drug development. (p.162)

Action taken or to be taken

Please refer to page 316 of this document for the response to this significant item regarding spinal muscular atrophy.

Item

**Statistics**

The Committee encourages the Office of Extramural Research to update and improve its data-gathering capacity so that it may better track and analyze grant and training award success rates by the academic discipline of the principle investigator.

Action taken or to be taken

At this point, the NIH has no plans to begin collecting additional data on the academic discipline of our trainees or PIs. The NIH has had considerable experience collecting information on the academic discipline of the individuals we train. The discipline or field of training is captured on every trainee and fellow supported by Ruth L. Kirschstein National Research Service Awards (NRSA). Information on the taxonomy for this data collection is available at <http://grants.nih.gov/training/phs2271.pdf>. A similar data collection is carried out by the National Science Foundation (NSF) with support from the NIH. Nearly every individual who earns a domestic research doctorate completes a Survey of Earned Doctorates, which includes an item about the primary field of degree (see <http://www.nsf.gov/statistics/srvydoctorates/survey2005/sed2005.pdf>). This information is used on a recurrent basis for studies by the National Academies of Science (NAS) including *Advancing the Nation's Changing Needs for Biomedical, Behavioral and Clinical Personnel* (see

[http://grants.nih.gov/training/nas\\_report\\_2005.pdf](http://grants.nih.gov/training/nas_report_2005.pdf)). Such studies combine discipline data into large aggregates that might include clinical, or biomedical, or behavioral types of research training.

There is continual change in disciplinary designations and a lack of consistency across institutions. For example, most universities have now merged departments that were prevalent 20 years ago; including immunology, genetics, biophysics, microbiology, pharmacology, biochemistry, and physiology that have typically merged into single departments of cell and molecular biology. These new departments combine the technical approaches that previously characterized the individual departments. Departments of psychology also vary across institutions. In some cases psychology departments are behavioral and may be largely practice-focused. In other cases they may be merged with neuroscience and take on a more molecular and physiological orientation. Individuals with domestic doctorates or who have participated in NRSA programs constitute a substantial proportion of the NIH Principal Investigator (PI) pool. It therefore would be possible to examine success rates for individuals with degrees from the any number of disciplines but the information would be difficult to interpret and could be misleading.

#### Item

#### ***Temporomandibular Joint and Muscle Disorders [TMJDs]***

The Committee remains encouraged by actions taken over the last year by NIH to expand research on TMJDs. However, significant additional work is necessary.

Because TMJDs are a complex family of diseases and disorders influenced by genetics, gender and environmental and behavioral triggers, research should involve collaborations between many ICs, including the OD, ORWH, NIDCR, NIAMS, NINDS, NIBIB, NIDCD, NIAD, NIDDK, NIMH, NCRR, and NHLBI, as well as the NIH Pain Consortium. The NIH is urged to take quick action to implement the recommendations of the Fourth Scientific Meeting of the TMJ Association, especially its call for the establishment of regional TMJD Centers of Excellence. The Committee again urges the NIBIB to work with the NIDCR to develop bioengineering approaches that will improve diagnostics as well as treatments for TMJD problems. Complex disease research calls for team efforts involving engineers, computer scientists and medical scientists to study the jaw anatomy, physiology and the complex nervous, endocrine and immune system interactions that orchestrate jaw function. The Committee calls on the Director to coordinate the work of all relevant ICs and give priority to collaborative, cross-cutting research. While the Committee is pleased that the NIH has developed a new brochure for TMJD patients, it once again calls on the NIH to develop informational materials directed to medical, dental and allied health professionals to improve understanding of TMJDs and their frequent co-morbidities such as mitral valve prolapse, irritable bowel syndrome, chronic fatigue syndrome and fibromyalgia. (p. 162)

### Action taken or to be taken

The NIH is aware of the continued need for inter-IC support of research on TMJDs. To this end, and at the urging of the House and Senate Appropriations Subcommittee, we established the TMJD Interagency Working Group (TMJDIWG), a group led by the NIDCR and consisting of representatives from the ORWH, NIAMS, NINDS, NIBIB, NIDCD, NIAID, NIDA, NINR, AHRQ, NCHS, FDA, CMS, DOD (National Naval Medical Center), as well as representatives from private organizations including the TMJ Association, the Jaw Joints & Allied Musculoskeletal Disorders Foundation, the American Alliance of TMJ Organizations and the Society for Women's Health Research. In addition, there are close interactions between the TMJDIWG and the NIH Pain Consortium insofar as Dr. Tabak, the Chairman of the TMJDIWG, is also a co-chair of the NIH Pain Consortium and many of the IC representatives to the TMJDIWG also serve on the NIH Pain Consortium. It is through the interagency working group that the Director expresses his commitment to and support of cross-cutting and collaborative support of research on TMJDs by NIH. In addition, it is through collaborations facilitated by the TMJDIWG that the NIDCR and NIBIB, as well as ORWH, have co-funded since FY2002 a TMJ implant registry, the purpose of which is to analyze failed TMJ implants as a means of identifying modifications in the design and engineering processes needed to improve the next generation of implants.

The Director is very appreciative of the TMJ Association for working with the NIDCR and other ICs to organize and hold bi-annual scientific meetings on TMJDs, the latest being on the topic of a comprehensive systems approach to studying TMJDs. Based on the recommendations from that meeting the NIDCR, in conjunction with the TMJDIWG, held a meeting on September 16-18, 2007 of leading systems researchers to determine, in part, whether there is a sufficient science base to justify the expansion of current research activities to mega-centers of the scope proposed at the TMJ Association's meeting. A report will be presented at the January 25 meeting of the National Advisory Dental and Craniofacial Research Council for review and discussion.

Finally, NIH is committed to providing information on all diseases, including TMJDs, to health care providers as well as to patients. The content of these materials is based only on the most current scientific information available. Currently, we are aware that some patients report the presence of conditions such as mitral valve prolapse, irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and perhaps others that appear to be co-existent with TMJDs. Additional information from systematic population-based surveys is needed to insure that the correlation among these conditions is, in fact, characteristic of TMJD patients and to determine the extent of the overlap among them. It is important to know if all or only a subset of these conditions co-occurs with TMJDs and if there are other similar conditions which may be involved. In addition, it would be helpful to health care providers in selecting the most

appropriate treatment regimen to know the underlying biological mechanism(s) that connect the various co-morbid conditions. As we approach this level of knowledge, the NIH will take appropriate steps to inform both the public and health professionals.

Item

***Tuberous Sclerosis***

Because of the effects of TSC on multiple organ systems, the Committee urges the Office of the Director to continue the coordination of TSC research activities through the Trans-NIH Tuberous Sclerosis Coordinating Committee. (p.162)

Action taken or to be taken

Please refer to pages 321 of this document for the response to this significant item regarding tuberous sclerosis.

Item

***Urological Research***

The Committee strongly urges the Director to continue to increase and accelerate the research portfolio in urology. The Committee further urges the Director to coordinate and stimulate urology-related research across the NIH and other Federal agencies. (OD, p. 163)

Action taken or to be taken

The NIH has taken several recent steps to accelerate urology research. In February 2007, the NIH hosted a urology strategic planning meeting to obtain recommendations that could help the NIH bolster its urology research program. The meeting brought together basic and clinical researchers in urology, as well as researchers outside the field of urology to help provide other perspectives and suggestions regarding scientific opportunities and challenges in urology research. In March 2007, the NIH hosted the “Urology O’Brien’s Center Joint Meeting” to obtain input from the center investigators with respect to urology research priorities and new directions. As a result of these meetings, the NIH has developed two new initiatives. The first, entitled “Urological Research Career Development,” is an institutional K12 program to provide the necessary institutional infrastructure to support viable integrated career development of M.D., M.D./Ph.D., and Ph.D. researchers interested in basic, translational, and clinical urological research. The second, the George M. O’Brien Urology Research Centers Request for Applications, was significantly re-conceptualized and re-issued in September 2007. In addition, the NIH has recently increased support of the Urinary Incontinence Treatment Network, which will permit funding of two additional studies on the evaluation and treatment of urinary incontinence.

With input obtained from a national meeting (Frontiers in Painful Bladder Syndrome and Interstitial Cystitis, October 2006) and the trans-NIH Pain Consortium, the NIH has developed a multi-center, multidisciplinary basic and

clinical science research initiative, entitled “Multi-disciplinary Approach to Chronic Pelvic Pain (MAPP).” This initiative will address many of the unanswered questions that impede progress in understanding the major urological chronic pelvic pain disorders, such as interstitial cystitis and chronic prostatitis. Awards for this research are expected to be made in 2008.

NCCAM had no Significant Items