



DEPARTMENT of HEALTH and HUMAN SERVICES

FISCAL YEAR
2008

NATIONAL INSTITUTES OF HEALTH - Volume III

Overview -- Significant Items

*Justification of
Estimates for
Appropriations Committees*

SIGNIFICANT ITEMS (SIs)
FY 2007 House Appropriations Committee Report 109-515
and
FY 2007 Senate Appropriations Committee Report 109-287

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National Cancer Institute

House Significant Items

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 support the establishment of a comprehensive center at a minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 86)

Action taken or to be taken

The NCI is committed to addressing the disproportionate burden of cancer in minority populations, increasing the number of researchers from minority and underserved populations, and continuing to build the research capabilities of Minority-Serving Institutions (MSIs) through a variety of strategies, such as the development of NCI-designated Cancer Centers in minority institutions.

NCI's Minority Institution/Cancer Center Partnership Program (MI/CCP) builds and sustains relationships between MSIs and existing NCI-designated Cancer Centers in order to stimulate high quality research, education, outreach, and training activities that address the unique needs of minorities and underserved populations in the region of the partner institutions. Specifically, the program provides significant training opportunities for minority scientists in cancer research and encourages a high level of involvement of the MSIs in competitive cancer research. Through collaborative cancer research and MSI involvement, this program is improving our understanding of cancer health disparities, their impact on minority and underserved populations, and our ability to overcome them. This program is also ensuring that successful cancer outreach approaches addressing these differences are shared with other Cancer Centers and other key cancer networks such as the Cancer Genetics Network, Clinical Cooperative Groups, the Early Detection Research Network, and the Community Network Program.

The Meharry-Vanderbilt Alliance has forged a highly productive and esteemed research alliance between Meharry Medical College and the Vanderbilt-Ingram Comprehensive Cancer Center, which collaborates on research, education, and clinical care initiatives focused on cancer health disparities. This work includes the landmark Southern Community Cohort Study which is enrolling more than 100,000 people (two-thirds of them African American) in six southeastern states in order to understand the causes of cancer disparities and ultimately eliminate racial and regional gaps in cancer incidence and mortality.

Cancer Center Planning Grants provide support for minority institutional planning activities intended to position these institutions to compete for NCI Cancer Center designation. Several of these are located in states with significant minority populations, including South Carolina, Georgia, Texas, Kentucky and Oklahoma. NCI is also encouraging the development of new Cancer Center models that would extend centers'

geographic and demographic influence. This is particularly important in regions of the country with insufficient institutional infrastructure and/or expertise to compete successfully for NCI Cancer Center designation at this time

Item

Cancer Metastasis to Bone – A frequent complication of cancer is its spread to bone (bone metastasis), causing severe bone pain and pathologic fractures. The Committee encourages NCI, in collaboration with NIAMS, NIA, and NIDDK to support research to determine mechanisms and 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. (P. 86)

Action Taken or to be taken:

The NCI continues collaborate with other federal institutions to promote research and clinical trials in cancer metastasis to the bone as well as in osteosarcoma. NCI is an active participant in the Federal Working Group on Bone Diseases, and in supporting major scientific meetings on bone cancer, and bone metastasis. NCI has funded a new large multi-institutional program, the Tumor Microenvironment Network which includes research in bone metastasis.

Research into signaling pathways in general and the pathogenesis of bone metastasis in particular have helped to assemble a mechanistic picture of signaling networks that help to explain the complex interactions among tumor cells, bone stromal, endothelial cells, osteoblasts and osteoclasts. The resulting new information helped not only to explain the so-called "vicious cycle" of mutually supportive growth factors and cytokines that converge to stimulate tumor growth, but has also identified unique therapeutic opportunities to abrogate or reduce bone metastases with several drugs in various stages of clinical development.

Item

Osteosarcoma research - 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. (P. 86)

Action Taken or to be taken

The NCI supported Children's Oncology Group (COG) Bone Tumor Committee has conducted several clinical trials including: (a) a phase-3 randomized treatment trial for children and adolescents with newly diagnosed resectable osteosarcoma. Therapy involves interferon treatment for patients who responded positively to chemotherapy and high dose chemotherapy for those who have failed prior therapy (work done in conjunction with European pediatric cooperative group); (b) a pilot study of herceptin antibody (anti-HER2) and combined chemotherapy for newly diagnosed metastatic osteosarcoma patients; and (c) a phase-2 trial of GM-CSF treatment for osteosarcoma patients with lung metastases. In addition, they have created a tumor bank of tumor and normal tissue samples for improving understanding of osteosarcoma biology, for

diagnostic and prognostic determinations, and for identifying new potential molecular therapeutic targets.

Item

Gynecologic Cancers - Today, in the United States, one woman will be diagnosed with a gynecologic cancer every seven minutes. That is almost 200 per day and 80,000 in a given year. Furthermore, almost 30,000 women die from a gynecologic cancer each year. 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. 87)

Action taken or to be taken

NCI and the Gynecologic Oncology Group are fostering translational research into biologic prognosticators and therapeutic effects of chemotherapy to speed the development of new gynecologic cancer treatments. The NCI has established a public-private partnership with the pharmaceutical/biotechnology industry, NCI-sponsored Cancer Centers and cooperative groups. Ovarian, lung and brain cancers were recently chosen as the 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 these three tumors -- especially those that can serve to differentiate cancer subtypes. NCI continues to support ovarian cancer research through funding of Centers of Cancer Nanotechnology Excellence (CCNEs). For example, the MIT-Harvard (CCNE) and the Nanomaterials for Cancer Diagnostics and Therapeutics, at Northwestern University are working to develop and apply nanotechnology and nanoscience solutions to the diagnosis and treatment of ovarian cancer.

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, initiated in 1999 and recently expanded to 5 sites, 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 oncogenic Human Papilloma Virus (the main cause of cervical cancer) types. The current vaccine protects against about 70% of cases. The new vaccine will protect nearly 100% cases of cervical cancers.

Item

Gynecologic Oncology Clinical Trials - Organized in 1970, the Gynecologic Oncology Clinical Trials Cooperative Group (GOG) has conducted over 300 clinical trials involving almost 100,000 patients. With over 550 manuscripts in peer reviewed literature, the GOG is recognized as the leader in the development of new therapies for women with gynecologic cancer. The Committee encourages NCI to support 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. 87)

Action taken or to be taken

NCI supported research by the Gynecologic Oncology Group (GOG) has helped define optimal management for women with gynecologic cancer. Based primarily on large NCI-sponsored trials, the Institute issued a 2006 Clinical Announcement recommending that women with optimally debulked stage III ovarian cancer be counseled about the increased survival benefits of intraperitoneal chemotherapy.

NCI has established a public-private partnership with the pharmaceutical/biotechnology industry, and NCI-sponsored Cancer Centers and cooperative groups. Through this partnership bevacizumab (Avastin) was identified as a promising gynecologic cancer agent. Through an agreement between NCI and Genentech, GOG opened a 2002 phase II trial of bevacizumab among women with ovarian cancer. Based on the successful outcomes seen in that trial, GOG began a phase III ovarian trial in 2005 to evaluate the addition of Genentech's bevacizumab to carboplatin and paclitaxel.

An ovarian SPORE and the NCI intramural program are conducting a multi-institutional Proteomics Remission Monitoring Trial to create a serum repository allowing proteomic signature profiles of epithelial ovarian cancer remission and relapse to be developed. This trial will determine if proteomic evaluation is better able to classify patient disease progression than the biomarker CA125.

Additionally, two SPOREs are collaborating with NCI's Early Detection Research Network in a Phase III study to develop a panel of ovarian cancer biomarkers for testing specimens from the Prostate, Lung, Colon and Ovarian Cancer Trial. A positive outcome could allow early detection of ovarian cancer two or more years prior to onset.

Item

Liver Cancer - The Committee is pleased that NCI has issued program announcements requesting research projects on hepatocellular carcinoma. The Committee remains concerned, however, with the increasing incidence of primary liver cancer, and the small number of effective treatments, which is in sharp contrast to many other forms of cancer where the incidence is declining and the treatment options are rapidly increasing. The Committee encourages NCI to continue to support the NIDDK sponsored HALT-C clinical trial, which has particular relevance to the NCI mission. NCI is further encouraged to collaborate with the National Institute for Biomedical Imaging and Bioengineering on the development of improved early liver cancer diagnostic techniques. (p. 87)

Action taken or to be taken

NCI is constantly reviewing its entire research portfolio in order to ensure that it is funding research that is of the highest programmatic priority to the institute. As a result, NCI is no longer contributing to extended follow-up of the Halt-C trials directly. NCI will however continue to follow the cohort for an additional period of time because of the important work in this area. It is anticipated that biomarker and natural history data acquired from the trial will lead to further cancer research studies.

Item

Lung Cancer - The Committee remains concerned that the five-year survival rate for lung cancer is only 15 percent, thirty-five years after the passage of the National Cancer Act. The Committee recognizes that lung cancer is the leading cause of cancer deaths for both men and women—accounting for nearly one in every three deaths. The Committee encourages the National Cancer Institute to work with CDC, the Centers for Medicare & Medicaid, the Food and Drug Administration, the Agency for Healthcare Quality and Research, the Department of Defense and other federal agencies to coordinate federal efforts on lung cancer in areas including research, early and late state diagnosis, treatment, and disease management, with goal of increasing five-year survival rates and, ultimately, curing lung cancer. (p. 87)

Action taken or to be taken

NCI has made lung cancer an Institute priority through the establishment of the Lung Cancer Program, a Director's level program to support research into early detection and treatment-efforts we believe are most likely to provide more immediate benefits for lung cancer patients. Included in this program are efforts such as the recent public-private partnership called the Biomarker Consortium that NCI has joined along with FDA and CMS. One of the first projects of the Consortium is a study of FDG-PET/CT as a predictive marker of tumor response and patient outcome in non-small-cell lung cancer (NSCLC), the most common form of the disease. Studies have shown that lung cancer tumors have very high rates of glucose utilization and can be imaged efficiently by FDG-PET. The availability of such a sensitive measurement could streamline clinical trials of new treatments for lung cancer and, accelerate new drug approvals. This project emerged from discussions among NCI, FDA, and CMS under the auspices of the Oncology

Biomarker Qualification Initiative announced earlier this year. Tobacco use remains the leading preventable cause of lung cancer and other diseases in the United States, with more than 400,000 Americans dying prematurely each year of tobacco-related disease. The best evidence indicates that effectively reducing tobacco use requires a balanced and comprehensive approach, which has led NCI to initiate or join in key collaborations with various NIH Institutes, CDC, and other partners.

NCI and CDC have a 5-year memorandum of agreement outlining specific collaborations to facilitate prevention research and applications of research findings to address tobacco-related activities in the behavioral, social, and population sciences. In addition, NCI has provided technical assistance to the CMS Healthy Aging Demonstration Project on Smoking Cessation which tested three different smoking cessation benefit packages for Medicare recipients.

The National Network of Tobacco Cessation Quitlines has seen major collaborative success by NCI, CDC, and the North American Quitline Consortium. The initiative provides funding to states to enhance or establish smoking “quitlines” and established a single, national toll-free telephone number 1-800-QUIT-NOW and Smokefree.gov web site. Since the program was implemented in 2004, there have been over 420,000 calls to QUIT-NOW.

Item

Neurofibromatosis (NF) - The committee is pleased that NCI conducted clinical trials of NF patients and encourages it to continue its commitment to NF research. Recognizing NF’s connection to many of the most common forms of cancer, the Committee encourages NCI to strengthen its NF research portfolio in such areas as further development of animal models, natural history studies, genetic and drug screening, therapeutic experimentation, and preclinical and clinical trials. The Committee further encourages NCI to apply existing cancer drugs to NF patients in clinical trials both extramurally and intramurally, and to develop new drugs for NF that could then apply to the general population because of NF’s connection to many forms of human cancer. The Committee encourages NCI to continue to coordinate its efforts with other NIH institutes and government agencies. (p. 88)

Action taken or to be taken

Neurofibromatosis which encompasses type 1 (NF1) and type 2 (NF2), are distinct genetic disorders that affect the growth and development of nerve cells as well as cells in bone and skin. NF1 (the more common type) and NF2 patients are predisposed to benign and malignant nerve sheath, myeloid, and other tumors, which are the main cause of mortality. NCI is funding ten grants that are investigating NF1 and NF2 gene and protein functions and their deregulation in NF. These include: outlining the fine-tuned regulation by the NF1 protein of a key cell communication protein termed Ras, which is lost in NF1; examining the regulation of bone marrow cell formation by the NF1 gene, which should help in understanding juvenile myelomonocytic leukemia in NF1 children; and generating/using unique NF animal models, such as mice and zebrafish, to analyze how mutations in growth control genes cause cancer. In collaboration with NINDS, NCI funds

an annual NF international meeting of basic scientists and clinical investigators that helps to establish very effective research collaborations.

The NCI Intramural Program is coordinating several clinical trials for children and young adults with NF1 and plexiform neurofibromas:

- A phase II trial of the farnesyltransferase inhibitor tipifarnib.
- A phase I trial of the antifibrotic agent pirfenidone for inoperable plexiform neurofibromas.
- A phase II trial of pirfenidone for progressive plexiform neurofibromas.
- A four-center clinical study to assess centralized volume analysis for plexiform neurofibromas as a primary endpoint.
- A study of the natural history and biology of dermal neurofibromas in NF1. One study goal is to define the growth rate of dermal neurofibromas.
- A multi-institutional clinical trial for the treatment of sporadic and NF1-related malignant peripheral nerve sheath tumors with chemotherapy.
- As a member of the Department of Defense-sponsored NF1 Consortium NCI will help to develop new studies as well as enter patients on consortium studies.

Item

Specialized Programs for Research Excellence (SPOREs) - The Committee has long supported NCI's Specialized Programs of Research Excellence (SPOREs), and encourages NCI to provide support for the important work done by SPOREs at a level as close to the amount provided in fiscal year 2004 as possible, and in the current form, until such time as the Translational Research Working Group concludes its evaluation and provides recommendations to support translational research more effectively. (P. 88)

Action taken or to be taken

NCI is committed to the SPORE, a vital component of its translational research efforts. This program is dedicated to accelerating the development of new diagnostics, early detection technologies, cancer treatments, and other interventions benefiting cancer patients and populations at risk for cancer. The SPOREs capitalize on basic discoveries by funding high caliber integrative teams of researchers to move significant laboratory findings through early phase clinical trials and validation studies.

NCI has made every effort to sustain funding of cancer research and most especially translational research programs such as the SPORE. Since FY 2004, NCI has maintained its cadre of researchers and made steady progress in translational research. In FY 2005, 195 clinical research studies including early phase clinical trials were conducted in the SPORE Program; and in FY 2006, 255 clinical research studies were supported. The number of disease sites covered, the number of awards given, and the total funding for the SPORE program have all increased exponentially since the program began in FY 1992. Indeed, the growth in funding for this program has far outpaced increases in NCI funding. The commitment of the Institute and the cancer community to this program is evident in the significantly increased investment over this relatively short time interval. In FY 2004 the SPORE program totaled \$134 million. In FY 2005 there was a slight reduction to \$133 million, and in FY 2006 the amount was \$125 million. The decrease in

FY 2006 was connected, in part, to the overall decrease in the NCI budget. NCI continues to welcome high quality investigator-initiated applications. SPORes are open to any scientific approaches that can have an impact on the disease and are dependent upon team approaches in the design and implementation of the research. For the future, like the rest of the NCI budget, decisions regarding the funding level and number of SPORes will continue to be based on scientific merit and programmatic priorities.

Senate Significant Items

Item

Breast Cancers - The Committee strongly urges the NCI to give increased attention to areas of research that focus on helping women to more fully restore and improve their quality of life after treatment, including further breast cancer research on lymphedema, stress, nutrition, exercise, weight, and the environment. The Committee strongly 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. 104)

Action taken or to be taken

To research outcomes after treatment for breast cancer and to determine means for helping to improve quality of life (QOL), NCI is supporting more than 14 studies in breast cancer with QOL objectives. These studies will address QOL in the elderly, as well as in patients with brain metastases. This year, QOL measures in breast cancer patients undergoing high dose chemotherapy versus patients receiving intermediate dose chemotherapy were published in the August 2005 issue of *Cancer*. NCI recently funded a review of an intervention that provided women with audio-taped cognitive behavioral strategies and self-help manuals to help women manage uncertainty about cancer recurrence and understand and manage long-term treatment side effects and symptoms. Findings indicated that women regularly used the intervention components to deal with triggers of breast cancer recurrence and long-term treatment side effects, and most women found the strategies very helpful.

NCI supports research to measure the incidence of upper extremity lymphedema, understand risk factors for its occurrence, and determine the impact on quality of life in the years after diagnosis of breast cancer. The knowledge gained from these studies may impact recommendations for therapeutic regimens, participation in activities of daily living, and recommendations for exercise for health promotion in cancer survivors. The NCI is committed to funding research that improves technologies for breast cancer screening. The Breast Cancer Risk Assessment Tool is a new resource developed by NCI for clinicians to determine appropriate screening and prevention strategies for breast cancer. NCI investigators are currently adapting the tool to provide breast cancer risk estimates for African-American and Hispanic women.

The NCI recognizes the importance of expanding technologies to improve early diagnosis, health outcomes and survival of particular note is the Trial Assigning Individualized Options for Treatment (TAILORx) to determine whether adjuvant

hormonal therapy alone is as effective as adjuvant hormonal therapy in combination with chemotherapy for certain women with early-stage breast cancer.

Item

Cancer Metastasis to Bone - frequent complication of cancer is its spread to bone (bone metastasis), which occurs in up to 80 percent of patients with myeloma, 70 percent of patients with either breast or prostate cancer, and 15 to 30 percent of patients with lung, colon, stomach, bladder, uterine, rectal, and renal cancer, causing severe bone pain and pathologic fractures. Only 20 percent of breast cancer patients and 5 percent of lung cancer patients survive more than 5 years after discovery of bone metastasis. The Committee urges NCI, in collaboration with NIAMS, NIA, and NIDDK to support research to determine mechanisms and to identify, block, and treat cancer metastasis to bone. Furthermore, the Committee urges 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 (p. 104)

Action taken or to be taken

Please refer to page 2 of this document for NCI's response to this significant item regarding Cancer Metastasis to Bone.

Item

Cancer Vaccines - The Committee has recently become aware of emerging vaccine technologies, including a vaccine for the treatment of nicotine addiction, which could prevent carcinogenesis. The Committee urges NCI, in collaboration with NIDA, to support clinical trials to make available to the public vaccines to prevent cancer. (p. 105)

Action taken or to be taken

NCI with support from NIDA is currently funding a large, multicenter Phase II clinical trial of a nicotine vaccine, NicVAX, manufactured by Nabi Biopharmaceuticals. The nicotine vaccine is designed to stimulate production of antibodies that would bind nicotine molecules and prevent them from reaching the brain, thus diminishing the pleasure associated with smoking. Discussions are underway between NIDA and NCI to support a Phase III trial. In addition, NCI and NIDA are currently planning future collaborations to examine progress and future directions in the translational development of medications for nicotine dependence. These efforts are part of a comprehensive NCI Lung Cancer program.

Item

Chronic Lymphocytic Leukemia (CLL) - This incurable disease is the most common form of adult leukemia in the United States. The Committee once again urges the NCI to increase research into CLL, including improved therapies and their rapid movement from the laboratory to the bedside. The Committee strongly urges the NCI to give favorable consideration to continuing and expanding the scope of research activities funded through the CLL Research Consortium as it works to defeat this blood disorder. (p. 105)

Action taken or to be taken

The NCI continues to support Chronic Lymphocytic Leukemia (CLL) research. The Chronic Lymphocytic Leukemia Research Consortium (CRC) brings together the nation's top scientists from different disciplines to conduct an integrated program of basic and clinical research focused on CLL, the most common, and currently incurable, adult leukemia. The CRC, which was originally funded in 1999 and received new funding in fiscal year 2006, is a multi-center collaboration of investigators and contains 6 projects and 4 cores. Some consortium project leaders were also successful in obtaining NCI funding for another grant on epigenetic regulation of CLL gene expression. This grant will fund research on CLL treatment with certain classes of drugs that affect DNA. Developments in CLL research this year include:

- A new immunotoxin, HA22, has been shown to kill CD22-expressing CLL cells obtained directly from patients. The agent has been licensed to Cambridge Antibody Technology for clinical development. Phase I trials in CLL, B-cell lymphoma, and Hairy Cell Leukemia will open in late 2006 at two sites in the United States, including one at NIH, and two sites in Europe
- A new vaccine, MVA-TRICOM, designed to enhance expression of key co-stimulatory molecules in B cells of CLL patients has recently been shown in vitro to stimulate effective antitumor T-cell responses. In these preclinical studies, a vaccinia virus was successfully used to deliver genes to B-lymphocytes harvested from the peripheral blood of CLL patients. The modified cells were subsequently shown to have obtained the ability to stimulate T cell proliferation and cytotoxic T cell activity against CLL cells in vitro. Planning is underway for an early phase clinical trial of MVA-TRICOM in CLL patients.
- Gene expression profiling studies have led to the identification of several genes uniquely expressed by CLL tumor cells. Scientists have analyzed the cell surface expression of the protein derived from one such gene, ROR1. The ROR1 protein expression analysis suggests that, based on its highly restricted, consistent, and constitutive expression on the surface of CLL tumor cells, ROR1 protein is a promising target antigen for monoclonal antibody therapy of CLL. Monoclonal antibodies to ROR1, engineered for faster clinical translation are currently under development.

Item

Gynecologic Cancers – The Committee encourages NCI to give priority to gynecologic cancers and to work with the National Human Genome Research Institute on the Cancer Genomics project. The Committee further encourages the NCI to support 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. (page 105)

Action taken or to be taken

Please refer to Page 10 this document for NCI's response to this significant item regarding Gynecologic Cancers.

Imaging Systems Technologies - The Committee is encouraged by progress made by the NCI following its August 1999 conference on biomedical imaging, and it urges the NCI to continue to take a leadership role with the Centers for Medicare and Medicaid Services [CMS] and the Food and Drug Administration to avoid duplicative reviews of new imaging technologies which may prevent their benefits from reaching patients on a timely basis. The Committee is aware of the great 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 continues to encourage the large-scale 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.

Action taken or to be taken

Biomedical imaging is necessary to improve the early detection, accurate diagnosis, and appropriate therapy monitoring of cancer. Several projects are validating imaging as an endpoint for treatment evaluation. Confirming that imaging techniques effectively assess treatment efficacy will lead to either a reduction in the number of subjects needed in a clinical trial, or a reduction of the length needed for a trial. Functional imaging tests can give an early indication of whether a drug is effective or whether the dose used is appropriate. In FY07, as part of the Oncology Biomarkers Qualification Initiative, NCI will test FDG-PET as an early marker of therapeutic response in lymphoma and lung cancer. FDG-PET correlative studies will also be incorporated into trials of brain and kidney cancers. The NCI is undertaking trials of fluoro-L-thymidine (FLT), a new PET imaging agent. NCI intramural scientists recently began a brain cancer trial, and other breast and lung cancer trials are expected to begin soon.

The NCI Intramural Program is constructing the next generation of a microPET camera for animal research using new flat-panel detector technology, which will allow greater sensitivity and higher spatial resolution than previously possible. The new camera will permit preclinical testing of novel PET agents. Dynamic-contrast-enhanced MRI, is being tested with magnetic resonance spectroscopy in a trial of advanced breast cancer. Imaging clinical trials are also underway to determine the value of MRI and ultrasound in screening for breast cancer in high-risk women. NCI continues to support 10 Small Animal Imaging Research Resources where new technologies for animal imaging are developed. Optical imaging technologies have proven invaluable in basic research to image cells in mouse models. To exploit the potential for transfer of optical imaging technologies to humans, NCI funds the Network for Translational Research in Optical Imaging (NTROI). Nanoparticles afford a higher density of imaging beacons (MRI, optical, PET), resulting in an increased sensitivity in detection of cancer or precancerous

lesions. Nanoparticle imaging agents developed by NCI grantees are being further studied in the NCI Nanocharacterization Laboratory. One nanoparticle, called is currently being tested for feasibility in animal imaging tests. Once the appropriate dose is determined, a phase 1 imaging trial in humans could begin in fiscal year 2007.

Item

Liver Cancer - The Committee remains concerned about the increasing incidence of primary liver cancer and the small number of effective treatments—a situation that stands in sharp contrast to many other forms of cancer for which the incidence is declining and the treatment options are growing. The Committee urges the NCI to continue to support the NIDDK-sponsored HALT-C clinical trial and to collaborate with the NIBIB on the development of improved early liver cancer diagnostic techniques. The Committee welcomes NCI's program announcements on hepatocellular carcinoma but urges the Institute to set aside specific funds for research on this disease. (p.106)

Action taken or to be taken

Please refer to page 5 of this document for NCI's response to this significant item regarding Liver Cancer.

Item

Lung Cancer - Lung cancer remains a major public health issue and is the leading cause of cancer death among women and minority populations. The death rate is expected to escalate as the population ages. 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. 106)

Action taken or to be taken

The NCI is promoting studies that examine surgical improvements in the management of early stage non-small cell lung cancer (NSCLC), the most common form of the disease. A new trial will compare standard lobectomy versus sublobar resection for small peripheral tumors, and another will explore radiofrequency ablation as a valid option to surgery. A new adjuvant trial for early NSCLC, testing angiogenesis inhibition in combination with standard chemotherapy is slated to begin.

Through the development of better screening technologies for lung cancer patients will be diagnosed at earlier stages creating more opportunity for surgical treatment. The ongoing National Lung Screening Trial, conducted by the American College of Radiology Imaging Network and NCI, will determine if screening using spiral computerized tomography reduces lung cancer mortality in a high-risk population of former smokers. The screening portion of the trial has ended, but researchers will continue to contact participants yearly through 2009 to monitor their medical outcomes. The NCI is also planning a new trial using gene arrays to identify early stage lung cancer patients with different relapse risks after primary surgical treatment, and to predict subsets of patients who will benefit most from adjuvant chemotherapy.

This year NCI scientists made the following advances in lung cancer:

- Found a new miRNA molecular signature for lung cancer prognosis. MiRNAs are a class of small noncoding RNA genes known to be abnormally expressed in several types of cancer. In a study of early-stage lung cancer patients treated with surgery, a molecular signature of 10 miRNAs was correlated with both tumor type and patient survival. Validation of these markers in other lung cancer cohorts is in progress.
- Developed a new mouse model for squamous cell carcinomas. This pre-clinical model will provide a valuable tool for developing novel targeted therapies.
- Developed a prognostic marker for lung cancer therapy using the Akt gene, which confers poor prognosis. The new marker will be used to identify patients with poor prognosis and to design new therapies targeting the gene.
- Found that UGRP1, a protein secreted in the lungs, is also a growth factor that can repair pulmonary fibrosis in preclinical studies. Current studies are focusing on UGRP1 as a potential new treatment for lung cancer.

Item

Lymphatic Research and Lymphedema - The Committee urges NCI to support research on Lymphedema, a chronic, progressive and historically neglected condition faced by many cancer survivors. The Committee also urges the Institute to devote increased resources toward the study of lymphangiogenesis and lymphatic imaging, which are critical to a greater understanding of cancer metastasis and lymphedema. (p. 106)

Action taken or to be taken

The NCI recently sponsored a melanoma study comparing removal of the melanoma, (followed by patient observation) versus removal of the lymph nodes if the cancer recurred, versus surgical removal of the melanoma with a sentinel lymph node evaluation and taking out the lymph nodes immediately if positive for cancer cells. This study showed that sentinel-node biopsy was beneficial as it provides important prognostic information and identifies patients whose survival can be prolonged by immediate removal of lymph nodes.

NCI is also sponsoring 2 large trials in breast cancer, using sentinel lymph node mapping and biopsy, one of the most important advances in the surgical treatment of early-stage breast cancer. This minimally invasive procedure may reduce the morbidity of surgical treatment and improve staging of the axillary lymph node basin. These trials include measures of lymphedema as well as survival without evidence of disease recurrence.

The use of super-paramagnetic iron oxide nano-particles may improve the accuracy of lymphatic imaging in Gynecologic Cancer. NCI is sponsoring a study evaluating the diagnostic accuracy of 2 imaging techniques in identifying metastases in patients with cervical carcinoma. NCI has also supported a randomized clinical trial in patients with vulvar cancer designed to study the safety and efficacy of a fibrin sealant applied to the inguinal wound after lymph node dissection as part of treatment for vulvar cancer.

Several NCI supported studies are following cohorts of women who have undergone surgery for breast cancer to determine what percentage develop lymphedema after surgery and the effects of lymphedema on arm function. In addition, the studies include evaluations using genetic markers and impact on quality of life in the 3rd to 5th years after diagnosis of breast cancer. NCI is also conducting randomized clinical trials to test interventions, including education and strength training, to prevent lymphedema in women who have undergone surgery for breast cancer. Patient assessments include signs and symptoms of lymphedema as well as lymphedema knowledge, health-related quality of life, fear of cancer recurrence, self-efficacy, body-image, self-report of range of motion, and demographics. Treatments of interest include methods of massage and the use of non-elastic compression "sleeves". NCI is planning to study an extract of the bark of the French maritime pine tree as a treatment for arm lymphedema in breast cancer survivors.

Item

Lymphoma Research - The Committee urges the National Cancer Institute [NCI] to capitalize on the recent basic research investment by accelerating the translation of basic research findings into new treatment strategies for lymphoma. This may require a greater investment in lymphoma translational and clinical research initiatives, including more clinical trials focused on innovative lymphoma therapies. The Committee believes that the substantial impact of the disease on individuals, families, and society requires a more urgent lymphoma therapeutic development effort. The Committee recommends that NCI devote resources to: (1) studies of adequate scope to assure the identification of environmental risk factors for specific subtypes of lymphoma; (2) small studies designed to improve detection and quantification of historically difficult-to-measure environmental factors; (3) studies that are directed toward enhancing the understanding of the role of the immune system in the initiation and progression of lymphoma; and (4) studies that examine the simultaneous presence of a wide profile of infectious agents among individuals with lymphoma. The Committee also notes that lymphoma survivors may face significant long-term effects from their treatment. The Committee urges NCI to dedicate some of its survivorship research funds on research issues related to problems confronted by lymphoma survivors. (p. 106)

Action taken or to be taken

NCI investigators, together with their extramural colleagues, have conducted the largest U.S. case-control study of Non Hodgkin's Lymphoma ever assembled, examining a wide range of possible environmental risk factors that may be associated with this disease. In order to achieve the necessary statistical power to examine lymphoma subtypes, NCI founded the Interlymph international consortium <http://epi.grants.cancer.gov/InterLymph>. Evidence of differential susceptibility to NHL was also found in relation to genetic variation in acetylation capacity, suggesting a role for exposures to carcinogenic aromatic and/or heterocyclic amines such as cigarette smoke, dietary intake of well-done meats cooked at high-temperatures, hair dyes, and occupations within industries using aniline. Other studies have focused on the role of smoking, alcohol, and family history, as well as infectious agents, including Epstein-Barr virus, HIV, Kaposi Sarcoma-associated herpes virus (KSHV), hepatitis C, and SV-40.

The persistence of PCBs and other organochlorines was examined in clinical studies of lymphoma patients, environmental marker studies were carried out in farmers at increased risk of lymphoma, and a database was developed for pesticide exposures. Advances in the treatment of lymphoma have resulted in a large number of long-term survivors at risk for the serious late effects of therapy, including new malignant neoplasms. NCI's Childhood Cancer Study involves a large cohort of over 20,000 individuals in which former Hodgkin as well as non-Hodgkin lymphoma patients are well represented. NCI is committed to the development and application of interventions that will prevent or reduce adverse outcomes of cancer and its treatment and optimize the physiologic, psychosocial, and functional outcomes for cancer survivors and their families.

Item

Mesothelioma Research- The Committee is concerned with the pace of mesothelioma research. To address these concerns, the Committee strongly encourages the NCI to establish up to 10 mesothelioma centers, increase research, including clinical trials, detection and prevention methods, palliation of disease symptoms and pain management. (P. 107)

Action taken or to be taken

Mesothelioma is a disease in which malignant cells are found in the sac lining of the chest, the lining of the abdominal cavity, or the lining around the heart. Most commonly linked to exposure to asbestos, the disease usually remains asymptomatic for many years until reaching late stages that limit treatment options and result in poor rates of success. The NCI is currently sponsoring a research project intended to develop a fully automated, computerized system to assist radiologists in the quantitative assessment of pleural-based diseases using helical computed tomography (CT) scans. Currently, assessment of mesothelioma severity is based on manual measurements of the pleural thickness at different locations in the lung.

Automated methods such as those under research through the NCI will bring a level of standardization to the diagnostic process. By delineating the chest wall, lung border, and other anatomical features, measurement of the pleural thickness, and therefore mesothelioma tumor, is facilitated. Eventually, this computerized method will aid in the monitoring of the progression of the disease and provide objective assessment of response to specific modes of treatment.

NCI is continuing to develop, test, and refine immunotherapeutic agents for treatment of patients with mesothelioma. Promising recent advances include:

NCI- 01-C-0011: In this Phase I trial of SS1P, a recombinant immunotoxin designed to target mesothelin; SS1P was given to patients by continuous infusion over 10 days, as a means to saturate the tumor with the drug. One patient had a partial response and several other patients had indications that the drug was working to kill the cancer cells targeted. Scientists were able to detect significant levels of SS1P in the blood during the 10 days of treatment, at dose levels that were safe for the patients. Further development of SS1P is

continuing using the simpler technique of bolus dosing (individual doses rather than continuous infusion) on alternate days.

NCI-03-C-0243: In this phase I study of SS1P testing bolus dosing, anti-tumor activity was observed in several heavily pretreated patients. Out of 33 patients treated, 4 had minor response and 18 had stable disease (including 2 with resolution of ascites). One patient with peritoneal mesothelioma had complete resolution of abdominal ascites lasting > 5 years. NCI plans to open a phase II clinical trial of SS1P in combination with chemotherapy for newly diagnosed patients with mesothelioma. The goal of this study is to determine if SS1P improves upon the results of chemotherapy.

NCI # 06-C-0196: Several patients with mesothelioma who have failed chemotherapy have been treated on this phase I study of MORAb-009, a humanized monoclonal antibody to mesothelin. Based on laboratory studies which show synergy between MORAb-009 and chemotherapy NCI plans to conduct clinical trials of this agent in combination with chemotherapy after completion of the present phase I study.

At this time, NCI has no plans to expand the current portfolio of sites to include Specialized Programs of Research Excellence (SPOREs) solely dedicated to mesothelioma research. The number of disease sites covered, the number of awards given, and the total funding for the SPORE program have all increased exponentially since the program began in FY 1992. Indeed, the growth in funding for this program has far outpaced increases in NCI funding. The commitment of the Institute and the cancer community to this program is evident in the significantly increased investment over this relatively short time interval. In FY 2004 the SPORE program totaled \$134 million. In FY 2005 there was a slight reduction in funding to \$133 million, and in FY 2006 the amount was \$125 million. The decrease in FY 2006 was connected, in part, to the overall decrease in the NCI budget. NCI continues to welcome high quality investigator-initiated applications. SPOREs are open to any scientific approaches that can have an impact on the disease and are dependent upon team approaches in the design and implementation of the research. For the future, like the rest of the NCI budget, decisions regarding the funding level and number of SPOREs will continue to be based on scientific merit and programmatic priorities.

Item

Nanosystems Biology -The Committee encourages the Director, along with 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. 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 that 10 percent may represent a specific type of the disease, where the drug in question may be 100 percent effective. 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. 165

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 pathways and targets for treatment. The NCI continues to synergize the efforts in these disciplines to accelerate 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. NCI has established eight centers of excellence, 12 technology platform developmental partnerships, and multidisciplinary career training / teams. The aim is to develop nanotechnology and integrate it into cancer research to accelerate molecular-level assessment / intervention based on the new technology and systems approaches. Furthermore, NCI's Nanotechnology Characterization Laboratory (NCL) formed a partnership with the National Institute of Standards and Technology and the Food and Drug Administration in 2005 to perform rigorous physical, in vitro, and in vivo characterization of nanomaterials. Characterization data is now being disseminated to the community on the NCL website (<http://NCL.cancer.gov>). NCI's Integrative Cancer Biology (ICB) program researchers 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 ICB 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. NCI's Cancer Imaging Program (CIP) is leading clinical testing for the imaging agents ferumoxytol and Combidex. These iron oxide nanoparticles can be used to image lymph nodes, brain tumor margins and vasculature. An exploratory trial has been completed to assess the ability of ferumoxytol to better delineate brain tumor margins and new blood vessel growth. Additionally, a multicenter trial with Combidex to assess its utility in evaluation of lymph node metastases in cervical cancer will open soon. NCI's CIP and NCL collaborate to combine complementary expertise and resources to more effectively develop and translate nanomaterials for both imaging and therapy applications. They are currently working together to assist a small company in bringing a multifunctional nanostructure with both imaging and drug delivery capabilities to the clinic.

Item

Neurofibromatosis - The committee commends NCI for conducting clinical trials of NF1 patients and encourages NCI to increase funding for NF research. Recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages NCI to substantially increase its NF research portfolio in such areas as further development of animal models, natural history studies, genetic and drug screening, therapeutic experimentation, and pre-clinical and clinical trials. The Committee encourages NCI to create, fund, and implement NF clinical and pre-clinical trials infrastructures including NF centers and pre-clinical mouse consortiums, patient databases, and tissue banks. The Committee further encourages 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 because of NF's connection to most forms of human cancer. The Committee encourages NCI to

continue to coordinate its efforts with other NIH institutes and government agencies.
(p. 107)

Action taken or to be taken

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

Item

Pediatric Cancer - The NCI is currently partially funding a portfolio of studies looking at the causes and most effective treatments for childhood cancers. The Children's Oncology Group [COG] is conducting important laboratory research on cancer cells to discover the reasons children get cancer, developing and making available new treatments that destroy cancers, and improving the quality of life and long-term survival for pediatric cancer patients. However, the NCI is only funding approximately 50 percent of the approved collaborative pediatric cancer research projects. The Committee understands the COG acts as a cancer center without walls and reimburses hospitals for enrolling pediatric cancer patients into the best available clinical trials. The Committee encourages the NCI to increase the percentage of approved funding directed to the COG in order to open additional treatment protocols and make more treatment options available to physicians and families. (P. 108)

Action taken or to be taken

The National Cancer Institute is strongly committed to funding clinical and translational research focused on improving the diagnosis, treatment outcome and treatment-related late effects of childhood cancer through a variety of cooperative research efforts one of which is the Children's Oncology Group (COG). COG develops and conducts national, multi-institutional pilot, phase 2 and phase 3 clinical trials at over 200 pediatric oncology centers. COG is currently conducting ~50 clinical treatment trials including virtually all childhood cancers. The COG Phase 1 Consortia, a separately funded clinical research effort by 20 select pediatric oncology institutions, performs the first trials of experimental anti-cancer agents in children with relapsed cancer and is able to initiate 6-7 new clinical trials per year that introduce novel agents into the pediatric setting.

In addition to COG NCI supports other programs such as the Pediatric Brain Tumor Consortium (PBTC) whose purpose is to rapidly conduct phase 1 and 2 clinical evaluations of new therapeutic drugs, biological therapies and radiation treatment strategies in children with brain tumors. The New Approaches for Neuroblastoma Treatment (NANT) is a consortium of 12 institutions that conduct early phase drug and treatment regimen trials for children with high risk neuroblastoma. The Childhood Cancer Survivor Study (CCSS), the largest investigation of its kind, follows the late-effects of treatment for more than 14,000 survivors diagnosed and treated between 1970 and 1986 through 26 participating pediatric cancer centers. The Childhood Cancer TARGET Initiative aims to systematically apply a set of state of the art methods to childhood cancer tumor specimens with the objective of identifying new therapeutic targets that will help utilize the advances in molecularly targeted agents in three initial areas:

- Application of high throughput, cost-effective technologies to map and comprehensively characterize genomic alterations
- Application of targeted high-throughput resequencing to identify genes or chromosome regions that are consistently mutated in specific childhood cancers.
- Application of high-throughput RNA interference (RNAi) and small molecule screening methods to identify and validate therapeutic targets

Item

Prostate Cancer - The Committee commends the NCI for the considerable investment in prostate cancer and encourages NCI to continue to support research to improve the accuracy of screening and early detection of prostate cancer. (p. 108)

Action taken or to be taken

A new DCTD-sponsored study addresses the emerging issue of over diagnosis and over treatment of men based on Prostate Specific Antigen alone. Patients with low-risk prostate cancer will be randomized to either immediate definitive treatment (prostatectomy or radiation) or active surveillance. Based on changes in the biologic behavior of the prostate cancer determined by PSA doubling time as well as prostate biopsies over time, patients on the surveillance arm will either continue conservative monitoring or cross over to treatment. The study is designed to determine whether overall survival and prostate cancer mortality will be the same in both arms, suggesting that patients with stable disease as defined by readily available tests may avoid radical intervention. As a companion study, tissue from the serial prostate biopsies will serve as a platform for discovery of molecular biomarkers that are more accurate at discriminating patients within the category of low risk who warrant treatment (risk stratification). The Prostate Cancer SPOREs are sustaining their intensive translational research and development in the areas of prostate cancer diagnosis, prognosis, and treatment. While PSA continues to evolve in its utility for clinical care and research, new markers are emerging that show improved clinical performance. This is exemplified by the recent demonstration that a panel of auto-antibodies of prostate cancer provides diagnostic specificity and sensitivity that is markedly superior to that of PSA. Among the most significant translational research achievements in the last year is the landmark discovery in prostate cancer of what is likely to be the most common causally-related gene rearrangement yet identified in human malignancies and the only rearrangement present in the majority of prostate cancers.

The ongoing discovery and development of various genomic and proteomic analyses associated with different stages of prostate cancer not only enhances the prospects for detection and monitoring of prostate cancer, but is also leading to the development of new therapeutic modalities that target molecular constituents of prostate cancer. The Prostate Cancer SPOREs are currently testing a number of different targeted therapeutic approaches in early phase clinical trials with regimens that include immunotherapy, genetic therapy and other novel therapeutic molecules. Correlative studies with emerging new biomarker analysis are being incorporated into these intervention studies in order to leverage the biomarker data in the evaluation of the efficacy of new therapeutic approaches.

Item

Specialized Programs for Research Excellence [SPORE] - The Committee encourages the National Cancer Institute to fund the SPOREs at fiscal year 2004 funding levels and administer the program following fiscal year 2004 guidelines, providing for grant renewals until such time that the Translational Research Working Group [TRWG] concludes its evaluation and provides recommendations to more effectively support translational research. (P.108)

Action taken or to be taken

Please refer to page 1 of this document for NCI's response to this significant item regarding Cancer Centers.

Item

Tuberous Sclerosis Complex- Tuberous Sclerosis Complex, or 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. 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 cures and treatments for cancer as well. The Committee encourages NCI to expand its clinical trial network to include more sites and additional trials, and to assist in the development of protocols for additional clinical trials for tumor growth in TSC. Also, the Committee urges NCI to collaborate with NIDDK to conduct research on the needs identified in a recent conference on nutrient sensing and insulin-signaling in cells.

Action taken or to be taken

The NCI continues to support both intramural and extramural efforts directly investigating the molecular and cellular basis of TSC. Advances include the discoveries of new regulatory connections between the TSC proteins and two critical determinants of the cancer phenotype, Wnt and Tumor Growth Factor beta. To encourage basic and translational TSC research, the NCI is participating on the trans-NIH initiative, Understanding and Treating Tuberous Sclerosis Complex, PAS-05-085, and has used this mechanism to fund a new investigator to study the relationship between regulatory inhibitors of the TSC protein such as the kinase Akt and potential cancer therapies. 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 for renal angiomyolipomas (AML). 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 and the Tuberous Sclerosis Alliance in this effort to design clinical trials that could also assess the cognitive effects of candidate cancer therapies. The NCI participated in a preclinical trial that showed that rapamycin is effective against tumors in a mouse model for Kaposi's sarcoma.

In May 2006, the NCI sponsored, with National Institute of Diabetes & Digestive & Kidney Diseases and the NIH Office of Rare Diseases, a workshop entitled, “Nutrient Sensing, Insulin Signaling and Hamartoma Syndromes” that brought together over 100 researchers to discuss new ideas about the regulation and function of the TSC proteins. NCI is interested in funding new research proposals involving collaborations established at this meeting, and will work with NIDDK and other members of the Trans NIH Working Group on Tuberous Sclerosis to maximize the number of outstanding grants NIH is able to support on this subject.

Item

Cancer Centers at Minority Institutions - 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 support 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.104)

Action taken or to be taken

Please refer to page 1 of this document for NCI’s response to this significant item regarding the Specialized Programs for Research Excellence

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. 107

Action taken or to be taken

Please refer to page 16 of this document for NCI’s response to this item on Nanosystems Biology.

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National Heart, Lung, and Blood Institute

House Significant Items

Item

Bone Marrow Diseases – The Committee encourages NHLBI and NCI to collaborate on a comprehensive study of the prevalence of bone marrow diseases in Asian countries. A better understanding of the disproportionate prevalence among Asians may lead to new scientific breakthroughs identifying the causes and cures for aplastic anemia and other bone marrow diseases. (p. 88)

Action taken or to be taken

Both NHLBI and NCI have had strong interests in various aspects of bone marrow disease in Asia. The largest epidemiologic study of aplastic anemia ever conducted was recently completed under NHLBI sponsorship in Thailand. It revealed a 2- to 3-fold higher incidence of aplastic anemia, especially in rural areas. The study also identified possible risk factors, including a number of unexpected environmental agents such as exposure to animals and contaminated water sources. At NCI, resources have been dedicated to the study of benzene effects on the bone marrow. Investigations have focused on threshold effects of benzene as they relate mainly to leukemia and secondarily to bone marrow failure.

NHLBI and NCI scientists will explore the possibility in the upcoming months of convening a small conference of experts to discuss how best to study whether genetic factors are may be responsible for differences in incidence of blood diseases among various ethnic populations and differences in susceptibility to environmental agents in various geographic areas.

Item

Cardiovascular Disease and Women – The Committee remains concerned that as the population ages, cardiovascular disease will reach pandemic proportions, and that women will continue to be affected at high rates. Therefore, the Committee encourages the institute to place a high priority on heart disease, stroke and other cardiovascular diseases in women by increasing resources to stimulate, strengthen, and intensify its investment in basic, clinical, translational, and trans-institute cardiovascular disease research through all available mechanisms. Despite new therapies, the Committee continues to believe that more research is needed to understand better the causes of these diseases in women, develop more effective treatments and cures, and prevent cardiovascular diseases. (p. 88/89)

Action taken or to be taken

The NHLBI continues to place high priority on improving the cardiovascular health of women by supporting fundamental and clinical research to: (1) elucidate the role of sex hormones in cardiovascular health, (2) identify and enhance healthy behaviors, and (3) develop methods and practices for prevention, diagnosis, and treatment. As a result of studies in women supported by NHLBI, significant advances have been reported on the

influence of lifestyle, menopause, chest pain, hypertension, diabetes, drug treatment (including hormone therapy), and improved diagnostic tests and treatment guidelines for women. In particular, the Women's Health Initiative (WHI) and the Women's Ischemia Syndrome Evaluation (WISE) have provided invaluable scientific advances. The WHI continues to provide sex-specific data regarding women's cardiovascular health, cancer, and osteoporosis and is now more optimally restructured to make available its rich resources to seed new investigations that address women's health needs. The WISE program is nearing completion of its second project period and plans to compete for additional funding to test and validate novel diagnostic tools and further explore the pathophysiology of chest pain and non-obstructive coronary ischemia, a condition prevalent in women.

The Heart Truth, NHLBI's national awareness campaign for women about heart disease, continues to flourish, extending the reach of campaign messages and promotion of the Red Dress as the national symbol for women and heart disease awareness, to millions of women through the power of partnerships. More than 350 locally-sponsored *Heart Truth* events, and more than 1.3 billion media impressions have been achieved. First Lady Laura Bush participates in national and local events as *The Heart Truth's* ambassador. In 2005, *The Heart Truth* Road Show was designed to raise awareness about women and heart disease by helping participants learn about risk factors and by providing free health screenings and disseminating educational materials. In April 2006, the campaign launched the "*Heart Truth* Champions" program, to recruit health advocates and educators in local communities to increase awareness about women and heart disease. The NHLBI has disseminated more than 1.3 million campaign health education materials. Awareness of heart disease as the #1 killer of women has increased from 34 percent in 2000 to 55 percent in 2005; thirty-nine percent of women now recognize the "Red Dress" as the national symbol for women and heart disease awareness, up from 25 percent in 2005.

Despite substantial progress though, including declining death rates, heart disease remains the leading cause of death and disability for women. As NHLBI reviews and establishes a new strategic plan, women's heart health remains a key crosscutting issue in which NHLBI's leadership and support will not only direct traditional research, but will also address medical practice, public and provider awareness, and seek opportunities to partner with local communities and private, professional, philanthropic, and federal organizations to improve health outcomes for women.

Item

Cooley's Anemia - The Committee remains 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. The Committee believes that this network is just beginning to meet its promise and encourages NHLBI to continue supporting this research. In addition, the Committee commends NHLBI for convening a meeting with regard to gene therapy and encourages the institute to move much more aggressively in pursuing a research agenda that will lead to a cure at the earliest possible time. (p. 89)

Action taken or to be taken

The NHLBI is pleased to report that the Thalassemia Clinical Research Network has been renewed for another five years, 2005-2010. The network currently comprises five clinical centers in Boston, New York, Philadelphia, Toronto, and Oakland and a data coordinating center (DCC) at the New England Research Institute in Watertown, Massachusetts. Major satellites to the clinical centers and the DCC include Chicago, Los Angeles, and London (UK). Now in the second year of its renewal, the network has four active clinical studies. One trial is assessing the ability of combination drug therapy to improve heart function in thalassemia major patients suffering from iron overload in the heart. Another will evaluate several methods of measuring iron burden in the body to determine the most accurate and informative procedure. We also will continue to follow patients who were previously entered into our registry to assess the natural history of the disease. Finally, the network is embarking on a new protocol to study the usefulness of decitabine in raising hemoglobin F levels in patients with thalassemia intermedia. It is anticipated that this treatment will ameliorate disease symptoms.

At present, the only cure for thalassemia and other hemoglobinopathies is bone marrow transplantation, a procedure that carries some risk of morbidity and mortality and is often available only to a select few patients who can identify a histocompatible donor match. Gene therapy is a promising new procedure that is still in its developmental stage. The NHLBI currently supports several program project grants that are working to improve viral vectors to make them more effective and safe. The NHLBI and other NIH components look forward to supporting a clinical gene therapy program once investigators feel confident about the prospects for clinical success.

Item

Cystic Fibrosis – The Committee encourages NHLBI to increase support for research aimed at understanding the precise mechanisms by which small molecules correct protein misfolding and mistrafficking relevant to lung diseases. Understanding the mechanisms of correction of protein folding and trafficking may contribute to NIH-supported efforts to identify additional ways to affect positively these cellular processes. Also, such investigator-initiated grant proposals could augment current efforts by NIDDK to use screening methods to identify promising molecules to address protein misfolding. The Committee also encourages the NHLBI to continue to explore opportunities to support clinical research networks to accelerate therapeutic development. (p. 89)

Action taken or to be taken

Building on the recommendations of two workshops co-sponsored by NHLBI and the NIH Office of Rare Diseases, NHLBI issued a program announcement (PA) in November 2005 titled “Protein Interactions Governing Membrane Transport in Pulmonary Health and Disease.” Seven applications had been received as of November 2006. The NHLBI is also participating in an NIH-sponsored exploratory/developmental research grant PA initiated in May 2006. Programs such as these have a good track record of effectively stimulating meritorious, innovative research. Examples of investigator-initiated research supported through PA solicitations include development of high-throughput screening

assays for identification and use of small-molecule inhibitors/correctors for probing biological processes involved in protein folding and trafficking and correction of folding defects, development of small-molecule “correctors” of defective functioning of mutant cystic fibrosis transmembrane conductance regulator (CFTR), and use of RNA interference to silence an overactive protein contributing to CFTR’s destruction and thereby to return the lung cells to normal.

The NHLBI is pursuing various avenues to support clinical research networks to accelerate therapeutic development. In 2004, NHLBI, with co-support from NIDDK, partnered with the Cystic Fibrosis Foundation (CFF) to support the data coordinating center of the CFF Therapeutics Development Network in conducting the Early Pseudomonas Infection Control (EPIC) trial. The trial will determine the best treatment for initial Pseudomonas infection to delay or prevent the development of chronic infections that lead to progressive lung destruction and premature death in CF patients. The NHLBI also supports the NIH Rare Diseases Clinical Research Network launched in 2003 to test therapies or drugs in a variety of diseases including CF. In September 2006 NHLBI initiated a Specialized Center of Clinical Research focused on understanding the key structural and regulatory processes mediating mucus clearance and their dysfunction in CF and chronic obstructive pulmonary disease. The concepts emerging from this SCCOR are expected to stimulate development of new therapies to enable treatment early in the course of disease. As part of an ongoing DHHS-wide international research and development partnership between the United States, the Republic of Ireland, and Northern Ireland, the NHLBI, the NIDDK, and the CFF recently participated in a joint U.S.–Ireland workshop to explore research opportunities related to the etiology, pathogenesis, and treatment of CF. One of the major recommendations was to promote collaborations in translational research to enhance the availability of CF patients for clinical studies.

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 understands that very recent scientific findings have presented new treatment approaches for clinical testing, and that experimental trials with the drug sirolimus have begun. The Committee encourages the NHLBI to explore opportunities for funding clinical treatment trials through both intramural and extramural means and 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. (p. 89)

Action taken or to be taken

NHLBI-supported basic research into the origins and growth of LAM cells is providing insights that may someday help control the disease. Investigators have identified proteins that promote the growth and movement of LAM cells and that also suggest an explanation for how LAM cells can metastasize among different organs, including the lung, kidney, and lymphatics. More is being learned about the role of estrogen and why LAM affects women almost exclusively.

NHLBI-funded scientists exploring the cellular pathways affected by genetic abnormalities in tuberous sclerosis complex (TSC) and LAM cells found that an essential protein for controlling cell size and growth was missing or misshaped. This finding led quickly to a potential target for treatment of LAM when it was discovered that sirolimus (rapamycin) mimics the function of the missing protein. A promising pilot study of sirolimus as a possible treatment for TSC and LAM, sponsored by NCI through the Quick Trial Initiative, provided a basis for development of a larger and more definitive multicenter trial under the auspices of the Rare Lung Diseases Consortium supported by the Office of Rare Diseases and the National Center for Research Resources. The protocol is currently in the final stages of approval. Additional therapeutic approaches will most likely be needed, however, because LAM cell lines derived from different individuals appear to vary in their sensitivity to sirolimus. This observation, and the evolving concept that LAM behaves like a neoplasm, suggests that multiple drug therapy will be the key to controlling the disease.

NHLBI intramural investigators have been able to isolate LAM cells from blood and other body fluids, thereby facilitating genetic diagnosis of the disease. LAM cells in the lungs and in culture have markers on their surface similar to those found in breast cancer and melanoma. These markers may cause LAM cells to target different organs in the body.

Researchers studying lung tissue from LAM patients have found increased production of proteins that cause the destruction of the lung. These and associated proteins are similar to those found in breast and other cancers. A collaborative extramural–intramural clinical trial is being planned to test whether these proteins can be safely inhibited and whether such inhibition improves lung function in patients with LAM.

The NHLBI intramural program continues to support the collection, processing, and distribution of LAM tissue. The Institute also continues to co-fund the annual scientific conference organized by the LAM Foundation. Information on LAM research is exchanged and discussed at trans-NIH TSC working group meetings, organized by NINDS.

Item

National COPD Education and Prevention Program – The Committee is pleased that NHLBI held a preliminary workshop to formulate strategies towards implementing a National Chronic Obstructive Pulmonary Disease (COPD) Education and Prevention Program. Since COPD is the fourth leading cause of death in the United States, the Committee encourages NHLBI to continue its education efforts to bring advances in medical care to the public. Early identification of those at-risk for or who have COPD is essential in the effort to stem the growth of the population with COPD. The Committee encourages NHLBI to continue its efforts in this area, working with national lung organizations to develop a national education campaign for providers and the public about COPD. (p. 90)

Action taken or to be taken

The NHLBI has completed the initial year of a 3-year COPD Awareness and Education Campaign, an undertaking that addresses the leading recommendation from a 2004 COPD strategy development workshop. The campaign aims to raise awareness about COPD among people who have the disease or are at risk of developing it and among health-care providers, with the goal of encouraging early diagnosis. During fiscal year 2006, the campaign mapped out specific plans and developed educational materials, including a Web site, for patients and health-care providers. In fiscal year 2007, NHLBI will launch the public-education component of the campaign, using media outreach as well as grassroots efforts through the many interested stakeholders. The NHLBI has initiated several partnerships with national organizations, including the American Academy of Family Physicians (AAFP), the American Lung Association (ALA), the American Thoracic Society, and the U.S. COPD Coalition. Through a partnership with AAFP for its 2007 Annual Clinical Focus on the Management of Chronic Illness, the campaign reached nearly 5,000 family physicians attending the annual scientific assembly through public service announcements in meeting materials, an exhibit, and two lectures on COPD. The ALA will employ its network of state-based chapters to conduct outreach to patients and health care providers.

Coordinated with the educational effort, NHLBI continues to disseminate new advances in COPD research so that they are applied rapidly by health-care providers, patients, and people at risk of developing 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 nontuberculous mycobacteria [NTM] pulmonary infections in women, particularly involving rapidly growing mycobacteria, an inherently resistant subspecies. The Committee encourages NHLBI to collaborate with NIAID and other institutes on research that will lead to a better understanding of NTM and enhanced diagnostics and treatment and promoting appropriate education of health care providers. (p. 90)

Action taken or to be taken

NHLBI scientists maintain an ongoing collaboration with NIAID intramural and extramural staff regarding NTM research. The NHLBI participated with NIAID in a meeting with the president of NTM Information and Research, Inc., and investigators from the tuberculosis and pulmonary communities who have research interests in NTM to discuss issues associated with NTM research. In addition, NHLBI recently held the workshop "Research Needs in Bronchiectasis" in which NIAID intramural and extramural staff participated. The meeting brought together experts in the fields of pulmonology, mycobacterial infections and other infectious diseases, immunology, and basic sciences to summarize the state of the field and identify research needs and priorities. Representatives from the NTM Information and Research, Inc., and the Alpha One Foundation attended.

NHLBI staff also serve as liaisons to the Rare Diseases Clinical Research Network program (supported by NCCR and ORD). The focus of one of the Rare Lung Disease Consortia is ciliary dyskinesia – a condition that predisposes to bronchiectasis associated with NTM and other chronic bacterial infections.

Item

Outcomes Research in Cardiovascular Diseases – The Committee commends NHLBI for convening a Working Group on Outcomes Research in Cardiovascular Disease and for subsequently publishing a report identifying priority areas for research, including developing national surveillance of cardiovascular care and outcomes, promoting patient-centered care, translating best practice into clinical practice, involving patients in care, and placing the cost of interventions in the context of their real-world effectiveness. The Committee encourages the institute to fund the priority areas highlighted in the report to enhance the prevention and treatment of heart disease, stroke and other cardiovascular diseases. (p 90)

Action taken or to be taken

The results of the 2002 NHLBI Working Group were published in 2005 in the widely read medical journal *Circulation*. The group identified the following priority areas: national surveillance projects for high-prevalence cardiovascular conditions, promotion of patient-centered care, translation of the best science into clinical practice (including definition of best practices), and studies placing the cost of interventions in the context of their real-world effectiveness. The group also called for better use of existing databases. In the aftermath of these recommendations, NHLBI released two requests for applications (RFAs). One RFA resulted in 5 funded grants that are evaluating clinically feasible interventions to effect changes in medical care delivery to improve hypertension control rates in African American patients. The second RFA resulted in 3 funded grants that will test the effectiveness in routine clinical practice of interventions for weight loss in obese patients who have other cardiovascular risk factors such as hypertension, unhealthy blood cholesterol levels, and diabetes. Several relevant investigator-initiated studies have also been funded. In December 2006 NHLBI released an RFA for a Cardiovascular Research Network in Community-Based Care. This project will take advantage of existing electronic data systems within large, geographically diverse health-care organizations. A major goal will be to augment outcomes research on cardiovascular diseases addressing risk factors, prevention, detection, diagnosis, treatment, and prognosis in the context of community-based health-care delivery.

Item

Preventing Weight Gain in Young Adults – The Committee is concerned about the ever increasing obesity rates and resulting chronic disease burden. Given the typical increase in weight throughout adulthood, evidence suggests that reducing the obesity epidemic will require significant attention to preventing progressive weight gain starting in early adulthood. Yet, little is known about the best methods to achieve weight management in this population. The Committee encourages NHLBI to develop and test innovative practical, cost-effective ways for preventing weight gain in young adults to reduce heart disease, stroke and other cardiovascular diseases. (p. 90)

Action taken or to be taken

The NHLBI held a Working Group on Preventing Weight Gain in Young Adults in August 2005, which concluded that innovative approaches to weight control in that age group should be identified and tested. (See <http://www.nhlbi.nih.gov/meetings/workshops/wgt-gain.htm>). Based on the working group's recommendations, NHLBI staff are developing and assessing an initiative to support the design and evaluation of promising intervention approaches for preventing weight gain in young adults and thereby reducing cardiovascular disease risk.

Item

Pulmonary Hypertension – The Committee continues to view pulmonary hypertension research as a high priority and encourages NHLBI to support three to four Specialized Centers of Clinically Orientated Research (SCCOR) in pulmonary hypertension in fiscal year 2007. (p. 90/91)

Action taken or to be taken

During fiscal year 2006, NHLBI supported a portfolio of more than 80 projects on pulmonary hypertension (PH). They included studies of the basic cell and molecular biology of PH, identification of genes and gene mutations that predispose a person to develop PH, and multi-disciplinary program projects combining basic and patient-oriented research. A new clinical trial has begun that will evaluate use of simvastatin (a drug used to lower cholesterol), with or without aspirin, as a new treatment for PH. The intramural program of the Institute also supports two clinical trials that are examining the underlying mechanisms of PH that occurs secondary to sickle cell anemia.

In response to a new program announced in 2005, two SCCOR in Pulmonary Vascular Disease centers will be funded in FY 2007. They are cooperative research projects, integrating basic research to study mechanisms and clinical research to evaluate diagnostic methods and treatment regimens for adult and pediatric PH.

The Institute will continue to encourage submission of new applications in both basic and clinical research for PH and to collaborate with the Pulmonary Hypertension Association in supporting new clinical investigators pursuing research in PH.

Item

Sleep Disorders – The Committee is pleased that public and professional awareness on sleep will be a component of NHLBI's strategic planning process and encourages the institute to engage voluntary organizations throughout this process. The Committee continues to encourage the National Center on Sleep Disorders Research to partner with other federal agencies, such as the Centers for Disease Control and Prevention, as well as voluntary health organizations to implement a sleep education and public awareness initiative using the roundtable model that has been successful for other institutes and Public Health Service agencies. (p. 91)

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR) has engaged in partnerships with the Centers for Disease Control and Prevention (CDC) and other federal agencies since its establishment in 1993. During fiscal year 2006, NHLBI sponsored a national assessment of sleep, sleep disorders, and sleep-related quality of life as part of the CDC's National Health and Nutrition Examination Survey. The initial data release is scheduled for 2008. The NCSDR also funds research grants that are analyzing sleep-related data collected by CDC, the Bureau of Labor Statistics, and the Centers for Medicare and Medicaid Services. These studies will identify leading health risks associated with lifestyles characterized by short sleep duration and untreated sleep disorders.

As recommended by an NCSDR-organized public National Sleep Conference held in 2004, NCSDR, voluntary health organizations, and CDC established the National Sleep Association Roundtable. In addition, an advisory committee to NCSDR consisting of representations from CDC, eight other federal agencies, and 12 public entities meets twice each year to make recommendations regarding sleep research and community education opportunities. A new NHLBI initiative in fiscal year 2007 will encourage organizations with appropriate sleep medicine and educational expertise to translate recent advances into educational programs to increase awareness among researchers, physicians, and health care providers about sleep disorders and the role of sleep, along with diet and exercise, in establishing and maintaining a healthy lifestyle.

Senate Significant Items

Item

Advanced Imaging Technology for Heart Disease and Stroke B 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. 109)

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

also been significantly improved, and they may reduce reliance on invasive coronary artery catheterization to evaluate the extent of 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. 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 NHLBI.

Item

Chronic Obstructive Pulmonary Disease [COPD] – The Committee understands that COPD may be a predictor of future onset of lung cancer. With 24 million people having decreased lung function, and in the face of an ever-aging population, the need to develop better treatment and prevention strategies to address this linkage will only increase over the coming decade. The Committee encourages NHLBI to collaborate more fully with NCI to develop appropriate research initiatives that can be undertaken cooperatively, and encourages NHLBI to sponsor a workshop on COPD as it relates to lung cancer with input from the lung community to address these issues. (p. 109)

Action taken or to be taken

The NHLBI is promoting research in this area, guided by the outcomes of two working groups: “COPD and Lung Cancer” and “Clinical Research in Chronic Obstructive Pulmonary Disease.” In response to the groups’ recommendations, the NHLBI established the Lung Tissue Research Consortium, which is obtaining lung tissue specimens for research from patients with varying degrees of COPD severity, with and without lung cancer. Molecular and histopathological studies of these tissues are expected to clarify the pathogenetic relationship between these diseases. In addition, staff of NHLBI and NCI are engaged in ongoing discussions regarding the value and feasibility of cooperative clinical studies of both diseases, especially chemoprevention trials. Updated guidance on these issues will be sought through a working group of experts titled “The Role of COPD in the Development of Lung Cancer” that NHLBI plans to convene in the spring of 2007.

Item

Congenital Heart Disease – The Committee commends the 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 the NHLBI to work with the CDC, the Adult Congenital Heart Association, and others to develop outreach efforts to reach the many CHD survivors currently “lost” to cardiac care and to create a national adult congenital heart disease registry and research network. (p. 109)

Action taken or to be taken

The successes of research and therapy, funded in large part by NHLBI, have resulted in survival into adulthood of a large number of individuals with congenital heart disease. These individuals face unique medical and personal challenges, and NHLBI considers this a high priority area for study. Thus the Institute convened a working group on research in adult congenital heart disease in 2004, in which senior CDC staff participated, and provided funding to the Adult Congenital Heart Association through a conference grant to publicize these issues. The NHLBI is committed to helping researchers obtain suitable training and funding to undertake the research necessary to provide an evidence-based approach to the care of adults with congenital heart disease.

Item

Cooley's Anemia – The Committee remains strongly supportive of the focused research effort that is being undertaken by the Thalassemia Clinical Research Network, which is composed of the leading research institutions in the field of thalassemia, or Cooley's anemia. The Committee believes that this network is just beginning to meet its promise, and it urges the Institute to continue to support the research projects undertaken by it. In addition, the Committee commends NHLBI for convening a meeting with regard to gene therapy and urges the Institute to move much more aggressively in pursuing a research agenda that will lead to a cure at the earliest possible time. (p. 110)

Action taken or to be taken

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

Item

Hematology - The Committee recognizes the strategic planning process underway at NHLBI and encourages the Institute to continue to place a high priority on hematology research. Further research efforts in vascular biology and thrombosis, immunobiology, and blood progenitor/stem cells will provide a better understanding of hematologic diseases and allow for the development of improved treatments and targeted therapies to combat heart attacks, stroke, and chronic malignant and non-malignant blood disorders. The Committee encourages NHLBI to work with experts in the field of hematology in developing its strategic plan. (p. 110)

Action taken or to be taken

The NHLBI is developing a strategic plan that will provide a scientific blueprint for research over the next decade. The multi-stage process has involved close interaction with experts from many scientific disciplines, including the field of hematology. Five strategic planning meetings of particular relevance to hematology were held in the summer of 2006: (1) Critical Role of Inflammation in Ischemic Disorders, (2) Diagnosis and Treatment of Thrombotic Disorders, (3) Cellular Therapeutics, (4) Global Blood Safety and Availability, and (5) Acquired and Inherited Blood Diseases. The recommendations from these and other thematic panels were discussed and further developed at a meeting convened in October 2006 with broad representation from the hematologic, cardiovascular, and pulmonary communities. Comments on the resulting

draft report have been solicited from numerous stakeholders, including professional organizations such as the American Society of Hematology and patient advocacy groups. The final report reflecting this input will be published in the spring of 2007.

Item

Hereditary Hemorrhagic Telangiectasia [HHT] – The Committee is aware that HHT is a rare, multi-system genetic disorder of the blood vessels that can result in stroke, hemorrhage, and death. The Committee encourages the NIH to explore opportunities for additional clinical and basic research on HHT. (p. 110)

Action taken or to be taken

The NHLBI has been funding research on HHT for many years, and this work has resulted in important contributions to understanding the underlying disease process. In June 2006, the Institute participated in the NIH Workshop “Hereditary Hemorrhagic Telangiectasia: Vascular biology and pathophysiology.” About 100 scientists and physicians attended this meeting, which featured presentations on the state of the art and expert subgroup discussions on promising research opportunities in HHT, major obstacles to progress, approaches to advance HHT research. A grant-writing and training workshop was also offered, primarily to assist young investigators in obtaining independent NIH support for HHT research. In addition, NHLBI staff met with the leaders of the HHT community and the executive secretary of the HHT Foundation to continue discussion about research opportunities in HHT.

Item

Juvenile Diabetes – Cardiovascular disease is the major cause of mortality for individuals with diabetes. It is also a major contributor to morbidity and direct and indirect costs of diabetes. The Committee urges NHLBI to support research to investigate the epidemic of cardiovascular disease in patients with type 1 diabetes. (p. 110)

Action taken or to be taken

Understanding why there has been a recent increase in cardiovascular disease (CVD) in patients with type 1 diabetes (previously called juvenile onset) has proved elusive to date. The NHLBI is making a concerted effort, with its NIH and private sector partners, to address this at both basic and clinical research levels, and in the many programs listed below.

In June 2006, NHLBI convened a working group, which included representatives from the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation (JDRF), to identify opportunities and make recommendations for research needs in this field. These recommendations included diabetes research in a number of conditions, such as hypertension, atherosclerosis, and peripheral vascular disease. The panel also highlighted the need for using pre-clinical animal models of diabetic complications. The NHLBI will be implementing some of these recommendations, in collaboration with other NIH institutes and agencies.

In December 2003, NHLBI initiated a program, “Progression of Cardiovascular Disease in Type 1 Diabetes”, to investigate the effects of inflammation, hyperglycemia, insulin resistance, hypertension and unhealthy blood cholesterol levels, on the early development and rate of progression of cardiovascular disease in patients with type 1 diabetes. In 2007, NHLBI will convene a meeting with program investigators to report on their research and promote scientific collaboration.

The Diabetes Mellitus Interagency Coordinating Committee (DMICC), chaired by NIDDK, recently published, “*Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*”. As part of this collaborative effort, NHLBI participated in the executive committee as well as a working group on “Research to Prevent or Reduce Complications of Type 1 Diabetes”. The NHLBI is currently considering the DMICC recommendations.

In 2006, NHLBI initiated funding for a five-year study on cardiovascular disease in type 1 diabetes. A multi-disciplinary team of experimental biologists, biochemist, clinicians and geneticists is studying progression of cardiovascular disease and potential therapies in three unique, well-characterized, groups of patients (numbering about 5,000 in total) who have type 1 diabetes.

The new *Future Revascularization in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM)* trial is evaluating whether drug-eluting stents will be more or less effective than coronary artery bypass surgery in 2,400 patients with type 1 or 2 diabetes who have confirmed multi-vessel CAD. Recruitment will continue until 2008 and follow-up until 2010.

The NHLBI continues to work with NIDDK on developing new programs to stimulate research on the cardiovascular complications of type 1 diabetes. In the past year, NHLBI made grant awards in the following joint initiatives: “Animal Models of Diabetes Complications Consortium”, “Mouse Metabolic Phenotyping Centers”, and “Administrative Supplements for a Drug Screening Program for Diabetic Complications”. The NHLBI also participated in NIDDK initiatives: “Biomarker Development for Diabetic Complications”, “High-Density Genotyping of Diabetes and Diabetic Complications Sample Collections” and “Ancillary Studies to Major Ongoing NIDDK and NHLBI Clinical Research Studies”.

Item

Lymphangiomyomatosis [LAM] – The Committee remains very interested in efforts to find a cure for LAM. 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 encourages continuation of the intramural research protocol and further urges the NHLBI to explore opportunities for funding clinical treatment trials through both intramural and extramural means and to use all available mechanisms as appropriate, including support of state-of-the-science symposia, request for applications, and the facilitation of access to human tissues, to stimulate a broad range of clinical and basic LAM research. (p. 110)

Action taken or to be taken

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

Item

Lymphatic Research and Lymphatic Diseases – 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. 111)

Action taken or to be taken

The NHLBI Division of Lung Diseases continues to support a research program in lymphatic biology, including the study of molecular signaling mechanisms that control lymphatic growth. The Division is actively involved in preparation of an NHLBI-wide program announcement on the Biology of Lymphatic and Venous Disease. One area of emphasis is abnormal lymphatic vessel development, postnatal vessel remodeling, and subsequent pathologic responses.

Item

Marfan Syndrome – The Committee commends NIAMS for its support of research opportunities to study this life-threatening, degenerative genetic disorder. The Committee also commends the NHLBI Pediatric Heart Network for its support of a clinical trial of a potential new drug therapy. The Committee urges the Institute to continue to support the major advances made in this area through all available mechanisms, as deemed appropriate. (p. 111)

Action taken or to be taken

The NHLBI, the NIAMS, the National Marfan Foundation and an NHLBI-convened working group recently met to review the current status of Marfan syndrome and related conditions. Attendees agreed that establishing a Marfan registry was critical to stimulate research in this area. In September 2006, NHLBI awarded a contract to establish and maintain such a national registry, which will contain information about patients, care providers, hospitals, and clinical interventions; collect blood and tissue specimens; and maintain a repository of tissue and blood, family pedigrees, and data on extra-cardiac complications. The NHLBI will collaborate with NIAMS, NEI, NIDCR, and NHGRI in monitoring the work of the registry and enable development of standardized reporting of patient characteristics, indications for surgical intervention and other treatments, and adverse events. This approach is expected to facilitate clinical evaluation and patient management. The resulting resource should also enhance future research to improve fundamental understanding, treatment, and management of genetic aortic aneurysms and other cardiac and extra-cardiac complications.

The NHLBI's Pediatric Heart Network (a multi-center, collaborative, clinical research group; www.PediatricHeartNetwork.com) is launching a clinical trial to compare the effects of losartan and atenolol on the rate of aortic root enlargement in individuals 6 months to 25 years of age. This trial will begin enrolling patients in early 2007. The Network has entered into a unique collaboration with the National Marfan Foundation

and the FDA's Orphan Drug Program in this endeavor. The National Marfan Foundation will support investigator and patient travel, and one or more ancillary studies for this trial that will use joint scientific review. The FDA's Orphan Drug Program is providing grant support for the trial. This trial also represents a singular opportunity to translate basic science work that NHLBI partially funded into public health advances for individuals with this rare, but potentially lethal, disease.

Item

Outcomes Research in Cardiovascular Diseases – The Committee commends the NHLBI for convening a Working Group on Outcomes Research in Cardiovascular Disease and for subsequently publishing a report identifying priority areas for research, including developing national surveillance of cardiovascular care and outcomes, promoting patient-centered care, translating best practice into clinical practice, involving patients in care, and placing the cost of interventions in the context of their real-world effectiveness. The Committee encourages the Institute to fund the priority areas highlighted in the report to enhance the prevention and treatment of heart disease, stroke and other cardiovascular diseases. (p. 111)

Action taken or to be taken

Please refer to page 29 of this document for NHLBI's response to this item on Outcomes Research in Cardiovascular Diseases.

Item

Preventing Weight Gain in Young Adults – Evidence suggests that reducing the obesity epidemic will require significant attention to preventing progressive weight gain starting in early adulthood. Yet, little is known about the best methods to achieve weight management in this population. The Committee urges the NHLBI to initiate a project to prevent and test innovative practical, cost-effective ways to prevent weight gain in young adults, with the goal of reducing heart disease, stroke and other cardiovascular diseases. (p. 111)

Action taken or to be taken

Please refer to page 29 of this document for NHLBI's response to this item on Preventing Weight Gain in Young Adults.

Item

Pulmonary Fibrosis – The Committee previously has expressed concern regarding the need to expand public health strategies to combat lung disease, particularly pulmonary fibrosis. Many individuals are diagnosed too late to initiate treatment regimens that could reduce morbidity and mortality. The committee urges the NHLBI to increase funding for lung research, particularly in the area of pulmonary fibrosis. The committee further urges the NHLBI to convene a consensus conference of experts in the area of lung disease and other stakeholders to lay the groundwork for a formal Pulmonary Fibrosis Disease Action Plan for prevention and control of this deadly disease. (p. 111)

Action taken or to be taken

NHLBI support for basic and clinical research in lung fibrosis has continued to increase from \$7.2 million in FY03 to \$14.0 million in FY05. An NHLBI-sponsored workshop to assess future research directions in idiopathic pulmonary fibrosis (IPF) provided a plan for future research (Crystal, RG et al, Am J Respir Crit Care Med 2002, 166:236-246). Two major programs were implemented as a result of this workshop. The first is supporting six grants to discover and validate new molecular targets that would interfere with fibrogenesis in IPF. It is hoped that the targets will form the basis for therapeutic agents that could attenuate, halt, or reverse the fibrotic process. The second program established a clinical research network to treat patients with newly diagnosed IPF, using combinations of drugs that might attack the fibrotic process at multiple points and thereby stabilize or improve the disease. The network includes 11 clinical centers, a data coordinating center, and a clinical research skills development core. Two protocols have been developed, with recruitment to begin in January 2007.

Item

Pulmonary Hypertension – Pulmonary hypertension [PH] is a rare, progressive and fatal disease which causes deadly deterioration of the heart and lungs. The Committee continues to view research in this area as a high priority and commends NHLBI for its plans to establish Specialized Centers of Clinically Orientated Research [SCCOR] in pulmonary hypertension. The Committee encourages NHLBI to prioritize support for 3-4 SCCORs this year and continue efforts to expand basic and translational research on PH in partnership with the pulmonary hypertension community. (p. 111/112)

Action taken or to be taken

Please refer to page 30 of this document for NHLBI's response to this item on Pulmonary Hypertension.

Item

Sleep Disorders - The Committee is pleased that public and professional awareness on sleep will be a component of NHLBI's strategic planning process and encourages the institute to engage voluntary organizations throughout this process. The Committee continues to urge the National Center on Sleep Disorders Research to partner with other Federal agencies, such as the Centers for Disease Control and Prevention, as well as voluntary health organizations, such as the National Sleep Foundation, to implement a sleep education and public awareness initiative using the roundtable model that has been successful for other institutes and Public Health Service agencies. (p. 112)

Action taken or to be taken

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

Item

Tuberous Sclerosis Complex – Research has demonstrated a link between TSC and lymphangioliomyomatosis (LAM), a lung disorder that primarily affects women. The

Committee urges NHLBI to support clinical trials on individuals suffering from both LAM and TSC. (p. 112)

Action taken or to be taken

NHLBI-funded scientists elucidated the cellular pathways affected by genetic abnormalities in tuberous sclerosis complex (TSC) and LAM cells and found that a protein needed to control cell size and growth was missing or misshaped. This finding quickly resulted in a potential target for the treatment of TSC and LAM when it was discovered that sirolimus (rapamycin) mimics the function of the missing protein. A pilot study of sirolimus as a possible treatment for TSC, with and without LAM, was sponsored by NCI through the Quick Trial Initiative. Based on its promising results, a larger and more definitive multicenter trial for LAM and TSC patients was developed under the auspices of the Rare Lung Diseases Consortium supported by the NIH Office of Rare Diseases and NCCR. The protocol is currently in the final stages of approval.

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National Institute of Dental and Craniofacial Research

House Significant Items

Item

Saliva – The Committee is aware that research on saliva has progressed rapidly and holds the potential to be an inexpensive non-invasive diagnostic tool for early detection of breast cancer, osteoporosis, hepatitis, HIV, and Sjögren’s disease. The Committee encourages NIDCR to work cooperatively with NCI and other appropriate institutes in pursuing research initiatives on the development of saliva as a diagnostic tool. (p. 92)

Action taken or to be taken

The NIDCR has stood for several years at the forefront of efforts to develop state-of-the-art diagnostic technologies based on the use of saliva as a diagnostic medium. Several Institute grantees are now working to develop the various constituent parts required to assemble a small, automated device that can simultaneously measure levels of the various antibodies, antigens, and nucleic acids present in saliva, all of which may be correlated with a disease state or condition. In the first four years of the program, known as Phase I, investigators have developed saliva collection protocols and perfected and fabricated analyzer platforms that include various sensors. These platforms are disposable, low-cost, and miniaturized and can detect proteins such as C-reactive protein a well-documented marker for future cardiovascular risk, nucleic acids of virus such as HIV and oral cancers. In the next five years of the project, known as Phase II, grantees will develop an easy-to-use diagnostic prototype with wireless communication systems that has the potential to attract commercial development. Specifically, the fabricated platforms will be integrated with existing front-end technologies to create a fully functional hand held salivary diagnostic test that can be used in different settings (e.g., home, remote areas, hospitals).

The Human Salivary Proteome program, which complements the Salivary-Based Diagnostic Technologies program, continues to make substantial progress towards deciphering the entire spectrum of salivary proteins. Intense efforts are now ongoing towards the comprehensive identification of all proteins in parotid and submandibular/sublingual saliva. As of November 2006, there are 1594 proteins identified in parotid secretions, 1397 proteins in submandibular/sublingual secretions. Overall there are 2085 proteins in the combined parotid and SM/SL proteomes. The first draft of the Human Salivary Proteome is expected to be published in early in 2007.

The human salivary proteome will present for the first time, a complete “alphabet” for the translational and clinical utility of saliva as a diagnostic fluid. This toolbox will contain the entire “alphabet” necessary for scientists to harness from saliva the proteomic elements that will mark clinical diseases, local and systemic, such as caries, Sjögren’s syndrome, and oral cancer. NCI and NIDCR are collaborating on the validation of oral cancer biomarkers discovered by one of NIDCR’s grantees.

Moreover, the NIDCR has further expanded its efforts to develop a multi-ethnicity, multi-national research registry for Sjögren's syndrome, an autoimmune disease manifested in the salivary glands. This clinical resource of well-characterized biological specimens, including saliva, from patients and healthy controls is of paramount importance in determining the feasibility of the new diagnostic technologies for Sjögren's syndrome.

Senate Significant Items

Item

Dental Disease – Dental Diseases is the single most common chronic childhood illness and the most prevalent unmet need 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 caries. The Committee commends the NIDCR for its current efforts in this area and urges NIDCR to strongly support additional research to determine the most effective method for preventing, controlling, and treating early childhood caries. (p.112)

Action taken or to be taken

The NIDCR is making substantial progress in developing effective 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 complex environmental, social, behavioral, and biological factors underlying the high rates of early childhood caries (ECC) in minority and underserved populations. Seven ECC studies are currently ongoing in these *Centers*. These studies involve children from a variety of populations (inner city African Americans, rural and urban dwelling Hispanics, Asian and Pacific Islanders and families receiving health care in Community Health Centers). One recently completed clinical trial tested whether fluoride varnish applications reduced caries in high-risk children. The study compared three approaches to reduce ECC and found that children who had fluoride varnish applied to their teeth were about 2-4 times less likely to develop dental caries than children who did not receive the fluoride varnish.

NIDCR is also encouraging studies to establish the foundation for conducting large multi-center trials for prevention and control of ECC. One such planned trial would determine if applying fluoride varnish to toddlers' baby teeth during well-child visits to pediatric clinics will reduce 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.

Several behavioral studies are evaluating how having caries influences children's daily life. In one study, the presence of dental pain and the ability to chew foods were compared between children with and without dental caries. Responses differed dramatically for the caries-free children and those with caries. Almost 40% of children with caries reported that their teeth hurt and 68% indicated they were unhappy with their teeth or smile. Moreover, following dental care, both children and their parents reported immediate improvements in the child's oral function and quality of life. In a

separate study, children with and without caries were videotaped to evaluate their smile while watching a cartoon. Children without caries rated their own smiles more positively, showed more teeth when smiling, and received more positive parent evaluations on their smiles than children with caries. These findings clearly indicate that poor oral health in childhood can negatively influence self-perception and how children are perceived by others.

Recognizing the critical role of early oral infection in the caries process, NIDCR recently issued a Request for Applications titled “Health Promotion Research Directed to Improving the Oral Health of Women and their Children (R21) (RFA-DE-07-008). This initiative encourages research on health promotion to improve the oral health 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 to reducing this all too common debilitating disease in infants and young children.

Item

Genetic Disorders – The Committee commends the NIDCR for its participation in efforts to create a strain of mice which has the same genetic characteristics as that of humans, and urges that research in this area be continued. (p.112)

Action taken or to be taken

In FY 2002, NIDCR, in collaboration with NINDS, initiated a research project to create a mouse model with a defective gene to mimic the human disease, mucopolysaccharidosis IV (ML-IV). In FY 2006, in collaboration with NINDS researchers, NIDCR intramural researchers made significant progress by successfully generating mouse lines with a targeted defect in the ML-IV genetic locus. However, extensive analysis did not reveal any gross abnormalities in these mice, suggesting that the function of the targeted gene was not completely eliminated. Production of a mouse model of ML-IV continues to be pursued by NINDS.

Item

Temporomandibular Joint [TMJ] Disorders – The Committee commends the NIDCR for its efforts to increase funding for TMJ research and stimulate interest in young investigators in TMJ research. Because the multifaceted nature of TMJ disorders requires an approach that coordinates the work of many interested parties at NIH, the Committee expects the NIDCR to continue to collaborate and coordinate research and awareness activities with NINDS, ORWH and all other relevant ICs. The Committee also urges the NIDCR to consult regularly with patient advocacy groups in the planning of research initiatives. (p112)

Action Taken or to be Taken

Recognizing the complex nature of temporomandibular joint and muscle disorders (TMJD), the National Institute of Dental and Craniofacial Research (NIDCR) along with the Office of Research on Women’s Health (ORWH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute on Deafness and Other

Communication Disorders (NINDS), National Institute on Drug Abuse (NIDA), National Institute of Neurological Disorders and Stroke (NINDS) co-sponsored a two day scientific meeting organized by the TMJ Association this past year. The focus of this meeting was to explore the possibility of using a systems approach to research in gaining an understanding of TMJD as a complex disease. The NIDCR, through the TMJD Interagency Working Group (TMJDIWG), and working closely with the TMJ Association leadership, sponsored a one-half day scientific meeting in May 2004. The purpose of this meeting was to address the possible underlying physiological mechanism(s) that link TMJDs to other co-morbid conditions. Following from that meeting, the TMJDIWG developed an initiative to encourage research on the pathophysiological mechanisms that link TMJDs with other conditions such as chronic fatigue syndrome, irritable bowel syndrome, multiple chemical sensitivity, cardiovascular disorders, sleep disorders, hearing problems, and a host of other conditions. Consequently a program announcement, titled *Temporomandibular Joint and Muscle Disorders: Pathophysiological Mechanisms Linking Co-Morbid Conditions*, was issued on March 1, 2006 with the first receipt date for applications set as October 1, 2006. Additionally, it became apparent that traditional approaches to research on TMJDs, while useful, do not address the entire picture faced by TMJD patients. In order to do so, it is necessary to adopt an entire systems approach to research that includes interdisciplinary research teams.

The NIDCR continues to value the input from patients on a variety of issues relevant to the mission of the Institute and sponsors an annual meeting with the leadership of all patient advocacy groups whose members may benefit from the research activities of the Institute. In addition, leaders of the two TMJD patient advocacy groups are included in the meetings of the TMJDIWG. Also, as indicated in our response last year, patient advocates continue to provide input into ongoing research projects and the President of the TMJ Association serves on the steering committee of the jaw implant registry funded by the NIDCR at the University of Minnesota.

National Institute of Diabetes and Digestive and Kidney Diseases

House Significant Items

Item

Action Plan for Liver Disease Research.—The Committee is pleased that the NIH Director approved a trans-NIH action plan for liver disease research in December 2005. The Committee applauds the NIDDK-led efforts to evaluate and critique progress being made in each of the sixteen research areas identified by the plan. The Committee looks forward to being kept informed as to the progress being made to implement the goals of the plan and continuing efforts by NIH to establish priorities within the framework of each individual research area and among the sixteen areas as a whole. (p. 92)

Action taken or to be taken

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

Since the Action Plan's release in December 2004 (<http://liverplan.niddk.nih.gov>), the Subcommittee has taken an active and collaborative approach to its implementation. In Spring 2006, the Liver Disease Subcommittee developed a "Progress Review for 2005 (Year One Analysis): *Action Plan for Liver Disease Research*" based on input from experts who participated in the Action Plan's development. The Progress Review is available for public input on the *Action Plan*'s website. Additionally, the NIDDK prepared a congressionally requested report on "Activities and Future Plans for Implementing the *Action Plan for Liver Disease Research*," which was transmitted to the Congress in July 2006.

The NIDDK will continue its leadership and support for the Liver Disease Subcommittee's active monitoring of research progress and implementation of research activities addressing the Action Plan's goals. Planned activities include regular Liver Disease Subcommittee meetings and annual Progress Reviews with input from researchers external to the NIH. At the 5-year and 10-year marks, larger meetings are planned to encourage public participation and input for realizing the Action Plan's goals.

Item

Acute Liver Failure.—The Committee applauds the leadership of NIDDK to convene a meeting in December 2006 to address the important issue of acute liver failure. The Committee encourages that attendance at the December 2006 meeting be broad enough to

determine what improvements can be made in the U.S. based on best practices in other countries. (p. 92)

Action taken or to be taken

The NIDDK co-sponsored a meeting on “Acute Liver Failure” on December 4-5, 2006, in Bethesda, Maryland, together with the U.S. Food and Drug Administration, the NIH Office of Rare Diseases, and the National Institute of Biomedical Imaging and Bioengineering. The purpose of this meeting was to assess current knowledge about acute liver failure, including its causes, incidence, natural history, management, and prevention. The meeting will lead to recommendations for future research to further advance understanding and control of this condition in the U.S., with a summary to be submitted for publication.

Participation in the meeting included broad representation by investigators from across the U.S., as well as experts on international practices related to management of acute liver failure from the United Kingdom and countries such as Germany and Denmark. Many participants shared their experiences as principal investigators associated with the NIDDK-supported Adult Acute Liver Failure Study Group and Pediatric Acute Liver Failure Study Group. These groups collect data for research that will yield insights into the natural history, causes, and outcomes of acute liver failure. The groups are currently conducting clinical trials to test whether the drug N-acetylcysteine improves survival of patients with acute liver failure.

Item

Biliary Atresia.—The Committee is pleased that the number of Biliary Atresia Research Network Centers has increased from 9 to 10 and that NIDDK, in conjunction with HRSA, will conduct a newborn screening conference in September 2006. This conference will permit a review and evaluation of best practices in other countries around the world. The Committee looks forward to being informed as to the results of the conference. (p.92)

Action taken or to be taken

The NIDDK is pleased to inform the Committee of the results of a meeting held on September 11-12, 2006, in Bethesda, Maryland, on “Screening and Outcomes in Biliary Atresia.” This meeting was sponsored by the NIDDK, the Health Resources and Services Administration, the NIH Office of Rare Diseases, the Children’s Liver Association for Support Services, and the American Liver Foundation. The purpose of this meeting was to assess current knowledge of the pathogenesis, natural history, surgery and outcomes of biliary atresia in the U.S. and internationally. A major focus of the meeting was to determine the role of newborn screening and means of early detection in biliary atresia, as well as to consider the effectiveness and medical outcomes associated with available screening methods. Speakers and attendees included American investigators - some of whom are associated with the NIDDK’s Biliary Atresia Research Consortium (BARC) - and health care providers, patient advocates, international investigators, and practitioners from countries in which pilot or full-scale national screening programs have been implemented to rapidly diagnose and treat infants born with biliary atresia. Discussions addressed such important issues as optimal diagnostic tests and public health approaches

to screening for biliary atresia; improving outcomes of treatments such as surgery (the “Kasai procedure”) or liver transplantation; and approaches to patients’ unique nutritional and developmental needs. The participants’ diverse perspectives enabled the experts assembled to determine the current state of knowledge concerning biliary atresia and to reach some conclusions about ways to approach screening and optimize outcomes for affected infants in the U.S. The NIDDK plans to work with the other meeting sponsors and participants to crystallize discussions at this meeting into recommendations for future research. A summary of the meeting and its recommendations will be submitted for publication, in order to share them with the wider research/health care community.

Item

Cooley’s Anemia.—The Committee continues to support the high quality research being conducted by NIDDK on such issues as iron chelation, non-invasive iron measurement, fetal hemoglobin, and other topics critical to improving the lives of Cooley’s anemia patients. 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. (p. 92)

Action taken or to be taken

In efforts to improve the lives of patients with Cooley’s anemia, the NIDDK is pursuing research to develop less burdensome therapies for removing toxic iron levels that result from the chronic blood transfusions needed for survival. A specific research focus is the development of effective and more easily administered iron chelators. The NIDDK is seeking alternatives to the injected drug, desferrioxamine, whose administration regimen is difficult and painful for patients. Another chelator (HBED) has entered an industry-supported clinical trial; while this chelator must also be injected, the procedure is much less onerous than conventional therapy and patients are expected to be much more compliant with this drug regimen. NIDDK-supported studies have also resulted in successful preclinical evaluation of a re-engineered version of the oral chelator, desferrithiocin. This new compound is currently being tested in an industry-supported clinical study. The NIDDK is supporting additional studies on other chelators, and has emphasized the importance of this area by providing an expedited “MERIT” award to an investigator in the field. Two new chelators have entered the NIDDK toxicology contract program for preclinical toxicity testing. Finally, through studies supported by the NIDDK, researchers have a better understanding of how the different iron chelating drugs remove iron from body tissues. Researchers are now testing whether “smart” combinations of chelators may both maximize iron removal and enable use of lower doses of the drugs; early results are encouraging.

The NIDDK and NIBIB are collaborating in support of projects that may improve the utility of magnetic resonance imaging (MRI) for assessing the toxic iron overload that can result from the repeated blood transfusions needed by patients with diseases such as Cooley’s anemia. The NIDDK and the NIBIB have hosted two meetings of investigators to enhance the utility of MRI as a method for quantitative determinations of tissue iron, especially in the liver, heart, and brain. Several groups reported progress regarding the ability to obtain clinically-useful information via MRI technology, and to advise patients

concerning their iron burden. The next steps will involve refining the MRI technology, and using this information to tailor treatment to the needs of individual patients.

Item

Digestive Diseases.—Diseases of the digestive system continue to affect more than 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 continues to encourage NIDDK to expand this important program with an increased emphasis on irritable bowel syndrome. (p. 92/93)

Action taken or to be taken

The NIDDK continues to support multifaceted research programs, such as the Digestive Diseases Research Centers Program, to combat the wide spectrum of digestive diseases. The objective of this program is to bring together clinical and basic science investigators in a manner that will enhance and extend the effectiveness of research related to digestive and liver diseases and their complications. In May 2006, the NIDDK issued a Request for Applications for Digestive Diseases Research Centers Programs to advance understanding in areas such as inflammatory bowel disease, functional bowel disorders (including irritable bowel syndrome), pancreatic disease, liver disease, and pediatric gastrointestinal disease. Following a rigorous two-tier, independent review process, meritorious applications will be selected for funding in 2007.

Item

Drug Induced Liver Injury.—The Committee is aware of increased incidence of drug induced liver injury and encourages additional research focused on identifying the cause of this drug induced morbidity and recommendations for prevention. (p. 93)

Action taken or to be taken

In view of the increase in cases of drug-induced liver toxicity in the U.S. and its consequences for the individual (morbidity and mortality) and society (withdrawal of drugs from the market), the NIDDK established the Drug-Induced Liver Injury Network (DILIN) in 2003. This Network represents a consortium among the NIDDK, five clinical centers, and a data coordinating center.

Since its establishment, the Network has developed protocols to study liver toxicity due to both prescription drugs and complementary and alternative medicines (CAM), as well as collected detailed clinical and epidemiological information and samples from 287 patients who experienced drug- or CAM-induced liver toxicity. The information and samples collected enable epidemiological, clinical, and laboratory studies, including those focusing on genomics, proteomics, and metabolomics, that may provide the diagnostic tools needed for risk assessment of the causes and, ultimately, means of prevention of drug-induced liver injury. This information will also be useful in helping

to develop simple causality assessment criteria to determine the likelihood that a case of liver injury is truly the result of exposure to a drug or CAM. The Network is also developing partnerships with the pharmaceutical industry to collaborate in the identification of cases of drug-induced liver injury and application of genome-wide screening techniques, which can aid in assessing the role of genetic variability in such injury.

Item

End Stage Renal Disease (ESRD) — The Committee is concerned about the significant differences among minority groups in the incidence and prevalence of patients suffering from ESRD. The U.S. Renal Data System (USRDS) reports that incidence rates for African-Americans for hemodialysis are more than quadruple that for white Americans, and rates for Native Americans and Hispanic-Americans are more than double those for white Americans; while transplant rates are highest in non-Hispanics. The Committee encourages NIDDK to take steps to ensure adequate inclusion of minority ESRD patients in the Comprehensive Dialysis Study and other relevant research so that such trends can be understood for their impact on these populations. (p. 93)

Action taken or to be taken

The NIDDK actively seeks adequate inclusion of racial and ethnic minorities in its clinical studies. An excellent example of this is the Comprehensive Dialysis Study (CDS), which is sponsored by NIDDK and the Centers for Medicare and Medicaid Services. CDS is designed to fully represent all end-stage renal disease (ESRD) patients in terms of age, gender, and race. However, due to different consent rates among sub-groups, the final sample may vary slightly from the overall population. The trial will collect clinical information from approximately 3,000 volunteers, who will be selected for an evaluation of self-reported health status and physical function. Among patients recruited thus far, twenty-five percent are African American and one percent are Native American—values that are very close to the incidence rates seen in the overall ESRD population.

Item

Fatty Liver Disease – The Committee notes that there is an emerging, obesity-related chronic liver disease that 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 is pleased that NIDDK is funding a fatty liver disease clinical trial that includes both adult and pediatric populations, and that NIH has generated a significant increase in highly competitive science and research focused on fatty liver disease. (p. 93)

Action taken or to be taken

The NIDDK continues to vigorously support research on fatty liver disease, which occurs in two forms: alcoholic and non-alcoholic. Non-alcoholic liver disease--when

accompanied by liver injury, liver cell death, inflammation, and scarring--is referred to as non-alcoholic steatohepatitis (NASH). The clinical research highlighted by the Committee is the NASH Clinical Research Network, a collaborative group of eight adult and pediatric clinical research centers, plus a data coordinating center focusing on causes, natural history, complications, and therapy of NASH. The Network's efforts include establishment of a long-term database and two clinical trials of promising therapies of NASH, one in adults and one in children. The Institute also funds a research program to develop a model to identify patients with more severe grades of non-alcoholic fatty liver disease--which can lead to NASH--and to better define the biological basis of its progression.

In addition, the NIDDK—together with the National Institute on Alcohol Abuse and Alcoholism and the NIH Office of Dietary Supplements—is actively encouraging competitive research applications to understand the molecular and biochemical mechanisms of both alcoholic and non-alcoholic forms of fatty liver disease through a recent initiative. The NIDDK also provides leadership in implementing the ten-year, trans-NIH “Action Plan for Liver Disease Research,” released in December 2004 (<http://liverplan.niddk.nih.gov>). Important goals include: (1) to more accurately determine the number of Americans are affected by NASH, (2) to more fully characterize the clinical, metabolic, and molecular abnormalities during disease progression, and (3) to test existing treatments and find new potential therapies for fatty liver disease. A recent Progress Review indicates that strides are already being made toward achieving several of these research goals.

Item

Hemodialysis and Peritoneal Dialysis — The Committee also is aware of wide geographic and ethnic variances in rates of hemodialysis, both center-based and home hemodialysis, as well as peritoneal dialysis, for patients suffering from End Stage Renal Disease (ESRD). The Committee understands that a large clinical trial involving hemodialysis is underway and encourages NIDDK to expand its research in this area to include peritoneal dialysis, or to develop a similar review for peritoneal dialysis that examines medical outcomes, quality of life, and clinical improvements for ESRD patients who choose this important and well-established therapy. (p. 93)

Action taken or to be taken

The NIDDK has supported studies of both hemodialysis and peritoneal dialysis. The large clinical trial involving hemodialysis referenced by the Committee is the Frequent Hemodialysis Network (FHN). The trial is comparing hemodialysis conducted six-times-per-week with conventional thrice-weekly hemodialysis. It was designed after another NIDDK-supported clinical trial showed that increased dose levels and/or the use of high-flux membranes did not improve patient outcomes in a three-times-per-week dialysis regimen. Because over 90 percent of all dialysis patients are on hemodialysis, increasing the frequency of dialysis is a very promising therapeutic option.

Insights into the use of peritoneal dialysis are being gleaned from the NIDDK-supported United States Renal Data System (USRDS), which tracks patients who are undergoing

peritoneal dialysis in terms of the prevalence of this form of treatment and all outcomes, including mortality, morbidity, and costs.

Item

Hemophilia and Hepatitis C (HCV).—The Committee understands that hepatitis C continues to have a devastating impact on the hemophilia population, with nearly half of all persons with hemophilia having contracted HCV, and many of these individuals co-infected with HIV. The Committee encourages NIDDK to convene a panel of experts and develop a research agenda that would address issues related to co-infection and the progression of liver disease in this population. (p. 93-94)

Action taken or to be taken

The recently published trans-NIH *Action Plan for Liver Disease Research* is responsive to the Committee's request for a research agenda to address issues of co-infection with HCV and HIV, and the progression of liver disease in patients with hemophilia. The *Action Plan* includes goals to define: (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. A one-year review of progress toward realizing the goals of the *Action Plan* was recently conducted (http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/Progress_reviews.htm).

Consistent with the *Action Plan*, the NIDDK, along with other NIH Institutes, will continue to support research on liver disease associated with HCV infection, with or without HIV co-infection, in highly affected patient populations, such as those with hemophilia who were infected by contaminated blood transfusions prior to screening programs for these pathogens in donor blood. For example, the NIDDK recently helped to 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 Multicenter Hemophilia Cohort Study sponsored by the NCI and NHLBI.

Item

Hepatitis B —The Committee is aware that there are currently 1.25 million Americans chronically infected with hepatitis B, a disease that disproportionately affects Asian Americans. The Committee applauds the leadership of NIDDK in conducting an experts' conference in April 2006, and is aware that a significant number of new research opportunities have been identified. The Committee encourages continued research for hepatitis B. The Committee also encourages that a focus be placed on identifying best practices for treatment of hepatitis B and supports efforts to reduce the disproportionately high annual treatment costs. Additionally, the Committee encourages NIDDK to collaborate with CDC to develop a document to reach at-risk populations for intensive public health screening, outreach and testing campaigns. (p. 94)

Action Taken or To Be Taken

The NIH recently reported to the Committee on scientific needs and opportunities in hepatitis B research, and will continue to support investigations in this area. An effective and safe preventive vaccine against the hepatitis B virus has been available for many years. Still, a most pressing need is to determine how best to treat individuals who become newly infected or have had the infection for a long period of time. Although the disease can be controlled temporarily with one year of treatment with currently-available drugs, it often recurs after medication is stopped. Control of infection often requires long-term—perhaps lifelong—therapy, which is costly and can be limited by antiviral drug resistance. Moreover, there are not clear guidelines as to who should be treated; with which agent or agents; at what stage of the disease, for how long, with what expected outcome, and what measure(s) of success. To help resolve these important medical questions, the NIDDK convened a workshop in 2006 to address the issue of hepatitis B management and to outline needs for future research. A summary of the meeting is being prepared. As a research agency, the NIH is focused on expanding the scientific knowledge base on which more medically- and cost-effective treatments can be developed.

Populations at risk for hepatitis B infection would benefit from public health screening, outreach, and testing programs. Most people with chronic hepatitis B are unaware they have it. Notwithstanding the hepatitis B management challenges described previously, therapies are sufficiently effective that they should be used more widely. The problem lies in screening of high risk individuals—sexually active young adults; recent immigrants from regions in which the disease is endemic, such as Asian Americans; drug abusers; dialysis patients; and family members of persons with hepatitis B. The NIDDK and the Centers for Disease Control and Prevention (CDC) have many publications on hepatitis B prevention (vaccination), control, and education—including several focused on immigrant, adolescent, and other at-risk populations. NIDDK staff also review CDC materials to ensure that NIDDK documents for at-risk individuals and others are consistent with and complementary to those of the CDC. In 2007, NIDDK staff will be collaborating with the CDC through participation in an expert advisory meeting being held by the CDC on the issue of screening for hepatitis B. The CDC will also be collaborating with the NIDDK on the planning of a future consensus development or state of the science conference on hepatitis B.

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 increase funding for 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.”

The Committee also encourages 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.

Finally, the Committee is aware that IBD manifests itself differently in children than it does in adults, highlighting the importance of pediatric-focused research if improved diagnostic and treatment tools are to be available. The scientific priorities identified by patients, physicians and professional societies include growth failure and bone disease; identification of the genes responsible for early onset IBD; and the relationship between children's immune system and IBD onset and treatment. As a next step, the Committee encourages NIDDK to conduct focused conferences on these priorities and develop research initiatives that will lead to a better understanding of the unique issues in pediatric IBD. (p. 94)

Action taken or to be taken

The NIDDK remains committed to working closely with the scientific community in developing a robust IBD research portfolio. The NIDDK will sustain support for the Digestive Diseases Centers, which play an important role in the IBD research program, providing collaborative state-of-the-art technology to advance research. For example, one center produces monoclonal antibodies used to identify the roles of proteins responsible for IBD; maintains IBD blood sample and tissue repositories; and developed and characterized genetic mouse models of IBD. Notably, a new mouse model was recently used to demonstrate the critical role of a distinct population of immune cells, known as regulatory T cells, in the development and severity of mouse colitis.

The NIDDK is aware of the important, unique questions related to pediatric IBD. In developing a long-range research plan for digestive diseases, the National Commission on Digestive Diseases is bringing together members of the scientific community to identify key research opportunities for addressing important research topics such as those noted by the Committee. The Commission's deliberations will also provide an opportunity for the NIDDK to continue to strengthen its ties with the IBD community. Expertise in IBD is included in the Commission's membership, and the Commission is seeking input from the digestive research professional and patient-advocacy communities, including the IBD community. The NIDDK supports a vital pediatric IBD research portfolio that includes several clinical trials in children with IBD. A recent study has shown these children to have significant bone and associated muscle deficits. The NIDDK is supporting a Phase III clinical trial to evaluate a novel bone treatment for children with Crohn's Disease (CD), low-magnitude mechanical stimuli (LMMS).

Item

Interstitial Cystitis (IC) — Research on interstitial cystitis is still in its infancy and while there has been important progress in this area in the last decade, there is still very little known about the etiology and pathogenesis of the disease. The Committee encourages NIDDK to place emphasis on IC-specific funding in order to focus on the basic science of IC and to attract and sustain research in the field. The Committee is concerned about the lack of clarity surrounding the definition of IC. While the Committee recognizes that

this is a complex challenge, NIDDK is encouraged to develop a research definition of IC to clarify the investigative questions and ensure that the research results are comparable and therefore, more meaningful. The Committee is concerned that studies of interstitial cystitis epidemiology are hamstrung by a lack of clarity and leadership in this area. The Committee is pleased that NIDDK worked closely with the IC Community to sponsor an international scientific symposium on IC. The Committee is also encouraged by NIDDK's efforts to elevate awareness of IC among providers and encourages NIDDK to work more closely with the interstitial cystitis patient community and CDC to utilize its resources and expertise effectively. (p. 94/95)

Action Taken or To Be Taken

The NIDDK is pursuing multiple efforts to combat IC, including clinical, epidemiological, genetic, and basic science research to help further understanding of underlying causes and symptoms and thus speed new interventions. To help bolster basic research in IC, the NIDDK issued a Program Announcement in FY 2006 that encourages basic research on the bladder and lower urinary tract. Active through March 2009, this initiative incorporates recommendations from investigators funded through the highly successful 2003 Request for Applications, "Basic Research in Interstitial Cystitis." On October 25, 2006, the NIDDK hosted a meeting of these IC basic research grantees that also reached out to scientists in related fields of interest, promoting cross-fertilization of ideas. The meeting outcomes will be incorporated into future planning for basic research on IC. Finally, the NIDDK has initiated a project to test and validate promising candidate "biomarkers" for IC, such as anti-proliferative factor (APF). Identification of a validated biomarker would significantly advance IC basic, clinical, and epidemiological research studies.

As this work moves forward, the NIDDK also continues to promote interactions among practitioners, from urologists to urogynecologists, neurologists, pain specialists and primary care physicians, to help develop research definitions for IC. For example, a working definition for clinical research studies was discussed at the NIDDK-sponsored international symposium on IC and painful bladder syndrome (PBS), October 26-27, 2006, which was developed in collaboration with the IC research and patient advocacy communities. Fundamental questions about potential causes, risk factors, and prevalence of IC are being addressed through several large studies, including the Rand IC Epidemiology study, the Boston Area Community Health study, and an IC Genetics Consortium, and the NIDDK is carefully monitoring their progress. The Institute will continue to translate results from these multifaceted research efforts into messages for the public and health care providers, with input from the external scientific and lay community. An NIDDK-led women's urologic health outreach program currently under development will include IC and painful bladder syndrome. The NIDDK also continues to contribute expertise to a CDC-sponsored information campaign on IC for patients and the public.

Item

Irritable Bowel Syndrome.—The Committee is pleased that NIDDK is formulating an action plan for digestive diseases through the National Commission on Digestive

Diseases and that irritable bowel syndrome or IBS will be included. The Committee encourages NIDDK to expedite this plan. (p. 95)

Action taken or to be taken

In order to identify promising future research directions for digestive diseases, such as irritable bowel syndrome and related motility disorders, the NIH has established a National Commission on Digestive Diseases, which is charged with developing a Long-Range Research Plan for the field. The ultimate goal of the Plan is to improve the Nation's health through advancing digestive diseases research. The Commission will conduct an overview of the state-of-the-science in the field of digestive diseases research and make specific recommendations to improve approaches to diagnosis, treatment, and prevention. Convened for their first meeting in June 2006, the Commission identified 13 compelling research topic areas for chapters of the Research Plan including "Functional Gastrointestinal Disorders and Motility Disorders." The Commission reconvened on November 6, 2006 to hear progress reports from members chairing the 13 Working Groups assigned to the research topic areas. A third Commission meeting is planned for June 2007.

Item

Pediatric Kidney Disease.—Kidney disease is a major cause of illness and death in infants, children and adolescents. The increasing awareness that many diseases like diabetes and hypertension that lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) in adults begin in childhood, demands that strategies to prevent kidney disease must begin early in life. The Committee recognizes the urgent need to better understand the pathogenesis of these conditions, and encourages NIDDK to continue to support research focused on the identification and study of genes and gene mutations that cause and increase the risk of progressive kidney disease. In addition, translational research aimed at clarifying the mechanisms underlying the genesis and evolution of kidney injury will help create targeted interventions to prevent, identify, and treat kidney disease in children. Specifically, the Committee recommends that emphasis be placed on research to determine how obesity, type 2 diabetes, and hypertension contribute to the evolution of CKD, and what interventions may limit cardiovascular morbidity in patients with these diseases. (p. 95/96)

Action taken or to be taken

The newly-launched Prospective Study of Chronic Kidney Disease in Children (C-KiD) is expected to provide insights into the ways that obesity, type 2 diabetes, and hypertension contribute to the progression of chronic kidney disease and to provide a foundation for future studies of interventions to limit kidney damage. C-KiD is a longitudinal, observational study of 540 children, ages 1-16, who have mildly to moderately impaired kidney function. The goals of the study are to determine risk factors for progression of pediatric chronic kidney disease and to examine the impact of CKD on neurocognitive development, risk factors for cardiovascular disease, and growth. As part of the study, researchers will measure blood pressure, growth and nutritional/metabolic status, and protein in the urine. Researchers will thus be able to explore the associated cardiovascular morbidity and mortality, and a number of risk factors for worsening

kidney disease, including those mentioned by the Committee. Data analyses thus far are already yielding important knowledge about this disease in the pediatric population, including natural history and outcome measures for use in future intervention and prevention trials.

Senate Significant Items

Item

Action Plan for Liver Disease Research —The Committee is pleased that the NIH Director approved a trans-NIH action plan for liver disease research in December 2005. The Committee applauds the NIDDK-led efforts to evaluate and critique progress being made in each of the 16 research areas identified by the plan. The Committee looks forward to being kept informed as to the progress being made to implement the goals of the plan and continuing efforts by NIH to establish priorities within the framework of each individual research area and among the 16 research areas. (p. 113)

Action taken or to be taken

Please refer to page 45 of this document for NIDDK's response to this item on progress in implementation of the *Action Plan for Liver Disease Research*.

Item

Acute Liver Failure —The Committee applauds the leadership of the NIDDK to convene a meeting in December 2006 to address the important issue of acute liver failure. The Committee urges that the attendance at the meeting will be broad enough to determine what improvements can be made in the U.S. market based on best practices in other countries. (p. 113)

Action taken or to be taken

Please refer to page 45 of this document for NIDDK's response to this item on a meeting on acute liver failure.

Item

Behavioral Research on Diabetes — The Committee commends the Institute for its continuing commitment to behavioral research on adherence to diet and exercise regimens to prevent or slow the progression of Type II diabetes. The Committee is concerned, however, that the strategic plan for research to combat Type I diabetes includes almost no behavioral research. NIDDK is encouraged to examine the impact of diet and exercise interventions on the health and glucose control of Type I diabetics. (p. 113)

Actions taken or to be taken

The final published Type 1 Diabetes Research Strategic Plan includes behavioral research in several chapters. In response to input submitted during the public comment period on the draft Strategic Plan, the NIDDK solicited feedback from numerous experts in behavioral research, health services research, and diabetes education about ways to enhance the Plan with respect to behavioral research. The external experts provided

written comments or participated in a conference call to provide input regarding recent scientific advances and future research objectives. The NIDDK revised the Plan and shared it with the group for final comment before publication. The final Strategic Plan is on the NIDDK website: www.T1Diabetes.nih.gov/plan.

The NIDDK continues its strong commitment to supporting behavioral research in type 1 diabetes because of its importance in improving the health and well being of patients. Behavioral researchers have been significantly involved in major research consortia studying type 1 diabetes, to provide expertise in areas such as recruitment and retention; examining factors that influence patients' choices to enter trials; and examining the effects of participation in trials on individuals' psychological well-being (e.g., how do people react when they are told that they are at increased risk for or have developed signs of the disease?). These and other key questions are being addressed by behavioral researchers and will inform future type 1 diabetes clinical trials.

Research has also shown that close control of blood glucose levels, in both forms of diabetes, can prevent or delay development of life-threatening complications. However, achieving close control is difficult (e.g., finger sticks, insulin administration), and it could result in episodes of hypoglycemia (low blood sugar). Behavioral research is identifying ways to help patients and their families cope with this burden and achieve the close control that is so important for their health. One example of a practical result that is helping patients and parents avoid nighttime hypoglycemia stems from research conducted by the Diabetes Research in Children Network, which is supported by NICHD and NIDDK. Investigators found that exercising in the late afternoon nearly tripled adolescents' risk for nighttime hypoglycemia relative to exercise-free days. This finding suggests the importance of bedtime snacks on days when children with diabetes are particularly physically active.

The NIDDK is also continuing its vigorous research efforts with respect to behavioral research and type 2 diabetes. Jointly with the NIMH, the NIDDK will be examining issues related to weight gain and predisposition to type 2 diabetes in people taking certain, highly prescribed anti-psychotic medications. The National Diabetes Education Program, a partnership of the NIDDK, CDC, and many private partners, launched a gestational diabetes (GDM) educational campaign in 2006. The campaign offers materials to help women with a history of GDM take steps to delay or prevent development of type 2 diabetes, and help their children lower their risk for the disease.

Item

Biliary Atresia — The Committee is pleased that the number of Biliary Atresia Research Network Centers has increased from 9 to 10 and that NIDDK, and in conjunction with HRSA, will conduct a newborn screening conference in September 2006. This conference will permit a review and evaluation of best practices in other countries around the world. The Committee looks forward to being informed as to the results of the conference. (p. 113)

Action taken or to be taken

Please refer to page 46 of this document for NIDDK's response to this item on the results of a conference on biliary atresia.

Item

Bone Marrow Diseases — The Committee commends the NIDDK's focus on finding effective treatment for iron overload that threatens the lives of transfusion-dependent bone marrow patients. The NIDDK is urged to collaborate with the NIBIB to expand research that will enable patients suffering from aplastic anemia, myelodysplastic syndromes, and paroxysmal nocturnal hemoglobinuria to obtain efficient iron measurement and chelation. (p. 113)

Action taken or to be taken

The NIDDK and NIBIB are collaborating in support of projects that may improve the utility of magnetic resonance imaging (MRI) for assessing the toxic iron overload that can result from the repeated blood transfusions needed by patients with serious forms of bone marrow diseases. MRI potentially provides a useful and widely available technique for monitoring excess iron in the body in some conditions of iron overload, such as found in Cooley's anemia and sickle cell disease patients. In October 2005, the NIDDK and the NIBIB hosted a second meeting for investigators funded under an FY 2003 Request for Applications (RFA) to enhance the utility of MRI as a method for quantitative determinations of tissue iron, especially in the liver, heart, and brain. Several groups reported progress regarding the ability to obtain clinically-useful information via MRI technology, and to advise patients concerning their iron burden. The next steps will involve refining the MRI technology, and using this information to tailor treatment to the needs of individual patients.

Removal of excess iron is currently achieved through infusion of "iron chelators," drugs that bind to excess iron and allow it to be excreted. Through studies supported by NIDDK, researchers have a better understanding of how the different iron chelating drugs remove iron from body tissues. Researchers are now testing whether "smart" combinations of chelators may both maximize iron removal and enable use of lower doses of the drugs; early results are encouraging.

Item

Cooley's Anemia — The Committee continues to support the high quality research being conducted by the NIDDK on such issues as iron chelation, non-invasive iron measurement, fetal hemoglobin, and other topics critical to improving the lives of Cooley's anemia patients. 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 the NIBIB to develop and perfect non-invasive means of measuring iron. (p. 114)

Action taken or to be taken

Please refer to page 47 of this document for NIDDK's response to this item on "Cooley's anemia."

Item

Crohn's 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 the NIDDK for its strong leadership in this area and continues to encourage the Institute to increase funding for research focused on the cellular, molecular and genetic structure of IBD; identification of the genes that determine susceptibility or resistance to IBD in various patient subgroups; and 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. 114)

Action taken or to be taken

The NIDDK supports a robust IBD research program. This program is based on scientific opportunities and guided by principles for advancing scientific research with potential for increasing understanding of the underlying mechanisms of IBD and developing new therapies and a cure for this disease. The strategies used in designing and expanding NIDDK's IBD program complement the scientific research plan, "Challenges in Inflammatory Bowel Disease," developed by the Crohn's and Colitis Foundation of America (CCFA), with significant input from the NIDDK. The NIDDK continues to work closely with the scientific community in its fight against IBD. A notice has recently been published requesting applications for a second 5 year period for centers in the IBD Genetics Consortium.

The NIDDK will sustain support for its Silvio O. Conte Digestive Diseases Research Core Centers, which play an important role in NIDDK's IBD program. The centers provide collaborative state-of-the-art technology to advance research in defining the cellular, molecular, and genetic structure of IBD; identifying genes contributing to IBD; and translating basic research findings into clinical trials. For example, centers produce monoclonal antibodies used to isolate and identify the roles of proteins responsible for the inappropriate inflammatory response that causes IBD. A collaboration of a center with an outside research group provides a joint cell-sorting facility, giving center researchers access to this important technology for less than a third of the cost available to non-center investigators. Repositories containing tissue and blood samples from patients enrolled in IBD clinical studies are maintained and made available to researchers characterizing genes and proteins associate with IBD. Animal models are considered to be one of the most valuable tools for scientific researchers in their quest to understand disease and in testing the effectiveness of potential therapies. The Centers program has made major contributions to advancing IBD research by developing and characterizing new genetic mouse models of IBD. Notably, a new mouse model was used recently in an important study that demonstrated the critical role of a distinct population of immune cells known as regulatory T cells (CD4+25+) in the development and severity of mouse colitis, thus providing new insights into the mechanisms underlying the development of

colitis and highlighting new opportunities for understanding the control of inflammation.

Item

Diamond-Blackfan Anemia — The Committee strongly encourages NIDDK to develop grant opportunities and increase research to support DBA. (p. 114)

Action taken or to be taken

To further research into Diamond-Blackfan Anemia, the NIDDK hosted a scientific workshop on Diamond Blackfan Anemia and other inherited bone marrow failure syndromes in the Spring of 2006. The workshop focused on a number of scientific research areas within the NIDDK mission that are critical for making progress regarding the causes and treatment of these conditions. The NIDDK and the NIH Office of Rare Diseases convened a follow-up meeting in January 2007 to establish consensus views on definable inherited bone marrow failure syndromes and the diagnostic criteria for categorization of these conditions. Common agreement on the definitions and diagnostic criteria for these disorders will facilitate the establishment of patient registries and future clinical research.

Item

Digestive Diseases —Diseases of the digestive system continue to affect more than 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 continues to encourage NIDDK to expand this important program with an increased emphasis on irritable bowel syndrome. (p. 114)

Action taken or to be taken

Please refer to page 48 of this document for NIDDK's response to this item on Digestive Diseases.

Item

Drug-Induced Liver Injury —The Committee is aware of increased incidence of drug-induced liver injury and urges additional research focused on identifying the cause of this drug-induced morbidity and recommendations for prevention. This research is particularly important because the unintended and episodic liver injury creates an impediment to people using highly beneficial pharmaceuticals to address other indications. (p. 114)

Action taken or to be taken

Please refer to page 48 of this document for NIDDK's response to this item on research on drug-induced liver injury.

Item

End Stage Renal Disease (ESRD) — The Committee is concerned about the significant differences among minority groups in the incidence and prevalence of patients suffering from end-stage renal disease (ESRD). The Committee urges NIDDK to take steps to ensure adequate inclusion of minority ESRD patients in the Comprehensive Dialysis Study and other relevant research so that such trends can be understood for their impact on these populations. The Committee also is aware of wide geographic and ethnic variances in rates of hemodialysis, both center-based and home hemodialysis, as well as peritoneal dialysis, for patients suffering from ESRD. The Committee understands that a large clinical trial involving hemodialysis is underway and urges the NIDDK to expand its research in this area to include peritoneal dialysis, or to develop a similar review for peritoneal dialysis that examines medical outcomes, quality of life, and clinical improvements for ESRD patients who choose this important and well-established therapy. (p. 114/115)

Action taken or to be taken

Please refer to page 49 of this document for NIDDK's response to this item, which incorporates information contained in the responses to the House items entitled "End-stage renal disease (ESRD)" and "Hemodialysis and Peritoneal Dialysis."

Item

Fragile X — The symptoms of Fragile X syndrome include digestive difficulties. Some affected individuals also show hyperphagia and obesity. Understanding this disorder may help researchers develop treatments to relieve disease symptoms and to better understand disorders with similar symptoms. 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 NIMH, NINDS, NICHD and the Fogarty International Center. (p. 115)

Action Taken or to be Taken

In Fragile X syndrome, extra DNA in a regulatory region near the FMR1 gene effectively reduces expression of this important gene, which can result in mental retardation and other problems. NIDDK scientists are studying this effect, and the biology of FMR1. The NIDDK also supports four Molecular Therapy Core Centers that are pursuing the goal of gene therapy, which could be of potential benefit to patients with Fragile X, as well as to those with other genetic diseases. Because Fragile X is a genetic, developmental disorder that most dramatically affects the central nervous system, other components of the NIH—NICHD, NIMH and NINDS—are primarily responsible for research on this disease. The NIH Office of Rare Diseases serves to coordinate research on disorders like Fragile X by the Institutes and Centers.

Item

Genetics of Type 1 Diabetes.—The NIDDK is asked to accelerate its efforts to ensure the research community's access to biosamples and data collected by the Type 1 Diabetes Genetics Consortium and the Genetics of Kidneys in Diabetes [GoKinD] Study. Efforts to share resources and support innovative research will assist researchers in developing

new methods of measuring an individual's risk for Type 1 diabetes or its complications. (p. 115)

Actions taken or to be taken

The NIDDK is committed to maximizing the usefulness of biosamples and data collected by research consortia studying the genetics of Type 1 diabetes and its complications by making them available to the broad scientific community. The Type 1 Diabetes Genetics Consortium (T1DGC), led by the NIDDK in collaboration with NIAID, NHGRI, and the Juvenile Diabetes Research Foundation (JDRF), is repositing samples and data in all three NIDDK Central Repositories (Biosample, Genetics, and Data Repositories). Samples stored in NIDDK repositories will be made available to scientists worldwide for application of the latest genetic technology to study DNA from this large and well-characterized set of affected families. T1DGC investigators are also planning to conduct a whole genome association study; the data from that study will also be placed into the NIDDK Repository so that the scientific community will have an opportunity to analyze it. The T1DGC also maintains a comprehensive public website (www.t1dgc.org) with information for researchers on available samples and data.

The Genetics of Kidneys in Diabetes (GoKinD) Study, led by the CDC and the JDRF, is storing blood plasma, blood serum, and urine samples in a CDC repository for use by any investigator in the diabetes research community based on a competitive review process. Plans are also being made to send samples to the NIDDK Central Repositories. Furthermore, a recent initiative sponsored by the NIDDK, NHLBI, and NIAID funded three investigators to carry out high-density genotyping of genetic samples from GoKinD and the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. The studies will be analyzing either GoKinD samples exclusively or in combination with EDIC samples. The GoKinD and EDIC genotyping data will be made publicly available after the investigators have an opportunity to perform initial analyses. In addition, the Genetic Association Information Network (GAIN), which is a public-private partnership created to encourage whole genome association studies of common diseases, will be including GoKinD as one of its six studies to analyze. Data from this effort will be deposited into a central database maintained by NCBI and made available for broad research use. Collectively, these efforts are ensuring the broadest possible access to genetic data from this valuable collection.

Item

Glomerular Disease Research — The Committee continues to be pleased with the work of NIDDK in the area of glomerular disease research, particularly as it relates to focal segmental glomerulosclerosis. The Committee commends NIDDK for conducting the recent Glomerular Disease Workshop in January 2005, and urges NIDDK to issue a specific program announcement or other appropriate mechanism to ensure the initiation of grant proposals, training positions, and other activities to expand the NIDDK portfolio in this important area of research. The Committee requests a progress report during the fiscal year 2008 hearings. (p. 115)

Action taken or to be taken

The NIDDK has used the Program Announcement mechanism to solicit applications on important clinical research areas such as: “Pilot and Feasibility Clinical Research Grants in Kidney or Urologic Diseases,” “Ancillary Studies to Major Ongoing NIDDK and NHLBI Clinical Research Studies,” “Development of Disease Biomarkers,” and “Ancillary Studies of Kidney Disease Accessing Information from Clinical Trials, Epidemiological Studies, and Databases.” The NIDDK’s program development efforts are guided by the opportunities identified in the January 2005 Glomerular Disease Workshop and by two scientific meetings that focused on new observations related to membranoproliferative glomerulonephritis type II. The proceedings of the January 2005 Workshop have been published in the *Journal of the American Society of Nephrology* (*J Am Soc Nephrol* 16: 3472–3476, 2005).

The NIDDK’s research solicitations complement the Institute’s ongoing research program in glomerular diseases, which is diverse and robust. The portfolio includes studies of the mechanisms of disease progression and potential therapeutic interventions. Clinical projects include a large study of focal segmental glomerulosclerosis (FSGS) in children and young adults, as well as several smaller clinical studies of FSGS. The Chronic Renal Insufficiency Cohort study is investigating disease progression in patients with chronic glomerular disease. The NIDDK also supports the USRDS, a large database that provides epidemiologic data on the development of end-stage renal disease, including that resulting from glomerular disease, within the United States. Other ongoing clinical glomerular disease projects involve studies of membranous nephropathy, lupus nephritis, HIV-associated nephropathy, and renal vasculitis. In addition to these extramural projects, the NIDDK intramural program is conducting several clinical trials that focus on patients with glomerular disease, particularly those with FSGS and membranous nephropathy.

Item

Hepatitis B — The Committee urges a continuing priority on increased research for hepatitis B. The Committee applauds the leadership of the NIDDK in conducting an experts’ conference on this disease in April 2006 and is aware that a significant number of new research opportunities have been identified. The Committee urges that a focus be placed on identifying best practices of the treatment of hepatitis B and supports efforts to reduce the disproportionately high annual treatment costs for hepatitis B. Additionally, the Committee urges the NIDDK to collaborate with the CDC to develop a document to reach at-risk populations for intensive public health screening, outreach and testing campaigns. (p. 116)

Action Taken or To Be Taken

Please refer to page 51 of this document for NIDDK’s response to this item on “Hepatitis B.”

Item

Incontinence — Many otherwise healthy, active individuals suffer from incontinence. Fecal incontinence, also called bowel incontinence, affects people of all ages and is

associated with a wide variety of causes. The Committee is pleased that NIDDK is collaborating with NICHD and the Office of Medical Applications of Research on the incontinence state-of-the-science conference and urges the institute to prioritize implementation of this conference. (p. 116)

Action taken or to be taken

The NIDDK's co-sponsorship of a state-of-the-science conference on "Prevention and Treatment of Fecal and Urinary Incontinence" reflects the Institute's continuing efforts to seek guidance from external experts to inform the direction of future research in this area. The NIH Office of Medical Applications of Research (OMAR) is planning and coordinating the conference which will be held on December 7-10, 2007, on the NIH campus in Bethesda, Maryland, with co-sponsorship by the NIDDK and the NICHD. Six questions will be presented to the conferees addressing the burgeoning incidence of incontinence in the United States as more members of the U.S. population reach the age of 65, putting them at risk for this condition. What are the prevalence, incidence, and natural history of fecal and urinary incontinence? What is the burden of illness and impact of fecal and urinary incontinence on the individual and society? What are the risk factors? What can be done to prevent fecal and urinary incontinence? What are the strategies to improve the identification of persons at risk and patients who have fecal and urinary incontinence? What are the research priorities in reducing the burden of illness in these conditions? The answers to these questions and the recommendations emanating from the conference, will serve as a scientific guidepost to the NIH in pursuing future research on fecal and urinary incontinence.

Item

Inflammatory Bowel Disease [IBD] in Children — The Committee has learned that research into adult disease is of limited assistance in managing younger patients because the condition manifests itself in very different ways in pediatric cases. Consumer and physician organizations have identified priority areas for basic research in pediatric IBD. These are growth failure and bone disease; identification of the genes responsible for early onset IBD; and the relationship between children's immune systems and IBD onset and response to treatment. The Committee encourages NIDDK to conduct focused conferences on these priorities to develop research initiatives that will lead to better diagnosis and more effective treatment of pediatric IBD, as well as to determine potential ways that the condition may be prevented. (p. 116)

Action taken or to be taken

The NIDDK is aware of the important, unique questions related to pediatric IBD. Through the process of developing a long-range research plan for digestive diseases, the NIH National Commission on Digestive Diseases, chaired by the Director of the Division of Digestive Diseases and Nutrition, NIDDK, is bringing together members of the scientific community with expertise in specific disease areas to identify key research opportunities for addressing important research topics, such as those noted by the Committee. In recognition of the very different ways that IBD manifests itself in children, the NIDDK supports a vital pediatric IBD portfolio that includes several new clinical trials on treating children with IBD. Children with Crohn's disease (CD), a type

of IBD, have numerous risk factors for impaired bone accumulation including poor growth, delayed puberty, and inflammation, as well as the side effects of steroid therapy. A recent study has shown that these children have significant bone and associated muscle deficits. However, no trials have been conducted to evaluate therapies designed to build bone or prevent bone breakdown in these young patients. A new NIDDK-supported Phase III clinical trial will be conducted to evaluate a novel bone treatment for children with CD, low magnitude mechanical stimuli (LMMS). For this study, 160 children, ages 8- to 18-years-old, will be treated with LMMS and compared to those receiving a placebo treatment to determine if LMMS increases bone and muscle in pediatric CD patients.

The steroid drug, prednisone, is widely used for many pediatric disorders including nephritic syndrome (NS) and CD. Children with NS usually respond favorably to treatment with this drug without experiencing bone loss or decreases in bone formation. In contrast, studies have shown that treating pediatric CD patients with prednisone induces low bone density. Because of these differences, the NIDDK is supporting a new clinical trial, with an enrollment of approximately 550 children, to distinguish between the drug-related and disease-related effects on bone in children treated for CD and those who are treated for NS.

In another new trial, the NIDDK-funded researchers are investigating infectious agents involved in Crohn's disease in children from ages six months to 18 years to improve methods of biopsy collection, determine if there are specific agents that are more common in children with CD, and investigate whether factors such as race or geographical location increase a child's risk for CD.

Item

Interstitial Cystitis (IC) — Research on interstitial cystitis is still in its infancy. While there has been important progress in this area in the last decade, there is still very little known about the etiology and pathogenesis of the disease. The Committee urges the NIDDK to set aside IC-specific funding in order to focus on the basic science of IC and to attract and sustain research in the field. The Committee was pleased that the NIDDK worked closely with the Interstitial Cystitis Association to put on an international scientific symposium on IC. The Committee was also encouraged by the NIDDK's efforts to elevate awareness of IC among providers and would like to see the NIDDK continue to work more closely with the interstitial cystitis patient community and the CDC to utilize its resources and expertise effectively. (p. 116)

Action Taken or To Be Taken

Please refer to page 53 of this document for NIDDK's response to this item on "interstitial cystitis."

Item

Irritable Bowel Syndrome — The Committee is pleased that NIDDK is formulating an action plan for digestive diseases through the National Commission on Digestive Diseases and that irritable bowel syndrome [IBS] will be included. The Committee continues to direct NIDDK to expedite this plan and ensure that IBS be given sufficient

attention in order to increase the functional gastrointestinal and IBS research portfolio at NIDDK. The Committee also encourages 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. 116-117)

Action taken or to be taken

Please refer to page 54 of this document for NIDDK's response to the section of this significant item regarding irritable bowel syndrome. Please refer to page 59 of this document for NIDDK's response to the section of this significant item regarding IBD (Crohn's Disease).

Item

Living Donor Transplantation — The Committee recognizes that the transplantation of organs, tissues, and cells is a powerful mode of treatment for dozens of life-threatening diseases affecting millions of Americans. From this perspective, the Committee urges NIDDK's basic and clinical research programs in transplantation to focus efforts on the study of living donor transplantation, to enhance success rates by reducing morbidity and mortality. Additionally, the Committee would like to be informed on the Institute's plans to initiate a cohort study to assess the health outcomes of living donors not only following the period immediately after the donation but for the quality of life implications for decades post donation. (p. 117)

Action taken or to be taken

Consistent with the Committee's interest in living donor transplantation, since 2002, the NIDDK has supported the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL), with assistance from the American Society of Transplant Surgeons and the Health Resources and Services Administration. The primary goal of this large, multi-center, prospective and retrospective study is to provide valuable information on the outcomes of this type of transplantation for both liver donors and recipients, with the goal of reducing donor morbidity and recipient morbidity and mortality. One major focus of the study is to assess the health and quality of life of liver donors up to 5 years after transplantation, comparing people who donated to those who offered to donate but were found to be ineligible or whose donations were not accepted. Long-term follow up is also planned on recipients. Although this study is scheduled to continue enrolling patients and collecting data through 2008, investigators are already analyzing data and publishing results.

The NIDDK also supports the Studies of Pediatric Liver Transplantation (SPLIT)—a cooperative research effort of transplant centers in the U.S. and Canada to improve outcomes, including those in children who received a living donor liver transplant. Researchers aim to assess factors that predict both short- and long-term (5 years or more) survival, as well as to study long-term consequences of liver transplantation and immune suppression in children who receive liver transplants. In addition, the NIDDK plans to sponsor a clinical research workshop on "Improving Long Term Outcomes for Pediatric Liver Transplantation" on February 12, 2007 in Washington, D.C. This workshop will bring together experts in pediatric liver transplantation to consider how to improve long-

term outcomes, including quality-of-life and health issues associated with long-term survival following liver transplantation. A summary of the meeting and resulting research recommendations will be submitted for publication.

Item

Lymphatic Research and Lymphatic Diseases — The lymphatic system plays an important role in the transport and digestion of fats. The NIDDK is urged to study the metabolic link between lymphatic function and obesity, dyslipidemia and diabetes. In addition, the Committee strongly urges NIDDK to study protein losing enteropathy, a life-threatening complication associated with numerous syndromes involving congenital lymphatic malformations. (p. 117)

Action taken or to be taken

Some recent research has suggested that, under certain conditions, the lymphatic vascular system can influence the behavior of fat tissue by promoting fat accumulation. The NIDDK has a major ongoing effort to understand the lifecycle of adipocytes (fat cells), as well as the cellular makeup and signaling characteristics of various fat depots. Included in this research program are tissue culture and rodent studies of the commitment of progenitor cells to the adipocyte lineage, regulation of adipocyte differentiation, and fat tissue turnover and remodeling. Examples of areas include: transcription factors that regulate adipocyte commitment and differentiation; consequences of insulin action on adipocyte physiology; growth factors, lipids, and extracellular matrix components that influence the metabolic or proliferative states of cells in a particular fat depot; and regulation of adipokine and cytokine secretion by adipocytes. The NIDDK anticipates that new data on the potential role of the lymphatic system in this regard will generate investigator-initiated studies to confirm or extend these observations.

Protein-losing enteropathy is not a single disease, but a manifestation of many inflammatory diseases including inflammatory bowel disease, for which the NIDDK has a significant research portfolio. This condition is also associated with many other inflammatory disorders, which fall under the missions of other ICs, such as systemic lupus erythematosus and sarcoidosis, which affect the immune system--as well as lymphoma and cancer of the lymphoid system.

Item

Pediatric Kidney Disease — Kidney disease is a major cause of illness and death in infants, children and adolescents. In addition, many diseases like diabetes and hypertension that lead to chronic kidney disease [CKD] and end-stage renal disease [ESRD] in adults begin in childhood; therefore, strategies to prevent kidney disease must begin early in life. The Committee recognizes the urgent need to better understand the pathogenesis of these conditions, and it urges the NIDDK to continue to support research focused on the identification and study of genes and gene mutations that cause and increase the risk of progressive kidney disease. In addition, translational research aimed at clarifying the mechanisms underlying the genesis and evolution of kidney injury will help create targeted interventions to prevent, identify, and treat kidney disease in children. Specifically, the Committee recommends that emphasis be placed on research to

determine how obesity, type 2 diabetes, and hypertension contribute to the evolution of CKD, and what interventions may limit cardiovascular morbidity in patients with these diseases. (p. 117)

Action Taken or To Be Taken

Please refer to page 55 of this document for NIDDK's response to this item on "pediatric kidney disease."

Item

Polycystic Kidney Disease [PKD]— The Committee is pleased to learn that NIH-supported PKD research, in partnership with private organizations, has rapidly led to multiple clinical drug trials in humans and to interdisciplinary blood pressure and heart studies to validate the advantages of slowing PKD progression. The Committee is encouraged that with additional support and resources for these trials, the establishment of core facilities, gene registries and research on the interrelationship of PDK with tuberous sclerosis complex, new innovative therapies may soon be developed to slow or reverse the progression of PKD for more than 600,000 Americans who suffer from the disease. The Committee also acknowledges the recent publication of data from the CRISP study, which makes available a much better measure of disease progression and which dramatically reduces the number of patients needed to obtain valid results from clinical trials, thus greatly accelerating the pace and accuracy of clinical PKD research and reducing its cost. The Committee recognizes the significant benefits emanating from the PKD Centers of Excellence in promoting interdisciplinary scientific research and developing alternative animal models; therefore, the Committee encourages the NIDDK to support the efforts of the PKD Centers to the maximum extent possible. Given the momentum and therapeutic opportunities in PKD science, the Committee also strongly urges the NIDDK to pursue fulfillment of the PKD Strategic Plan, facilitate PKD clinical trials and multidisciplinary research, and expand studies of pathophysiology and cellular pathobiology. (p. 117-118)

Action taken or to be taken

The NIDDK is committed to research that will capitalize on opportunities to combat polycystic kidney disease (PKD)—a serious, burdensome, and costly disease. The Institute supports four Interdisciplinary Centers for Polycystic Kidney Disease Research. The Centers represent an integrated program to promote multidisciplinary interactions and to provide shared resources needed to address complex disease processes at the cellular and molecular level.

The Institute also has two important clinical research projects related to PKD. The PKD Clinical Trials Network, co-funded by the PKD Foundation, is testing whether optimum blood pressure management, in combination with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, will slow the progression of PKD in patients with either early or advanced disease. Patient enrollment began in March 2006 and will continue through March 2008. A partnership with industry has been negotiated to provide medications. New insights are also emerging from the CRISP study, which suggests that changes in kidney size detected over time may be a reliable method of

monitoring disease progression (*New Engl J Med* 354:2122-2130, 2006). In order to verify these important observations for non-invasively monitoring of PKD, the NIDDK initiated a second phase in 2006 to provide longer follow-up. All of these efforts address the goals outlined in the PKD Strategic Research Plan, which guides research toward improving the quality and length of life for patients with PKD.

Item

Prostatitis — The Committee encourages the Institute to provide more diverse medical specialties to supplement and build upon the insufficient treatment options and the background of basic information now available for prostatitis. (p. 118)

Action Taken or To Be Taken

The NIDDK seeks to expand treatment options and information available about prostatitis by engaging investigators in clinical research, the results of which can be translated into medical practice. Through the Chronic Prostatitis Collaborative Research Network (CPCRN) and related research and strategic planning efforts, the NIDDK is bringing multiple disciplines to bear upon the understanding and treatment of chronic prostatitis (CP). Currently, two clinical trials are being implemented by the Network--one focused on treating patients early in the course of disease, the other focused on a novel approach to treat symptomatic men who have not responded to conventional therapies. Numerous consultants with a variety of clinical expertise, from immunology to neurology and chronic pain, have been involved in the design and implementation of these new Network trials. The Network also has a rigorous ancillary research program that encourages scientists and clinicians from related specialties to apply their knowledge and expertise to further the understanding of this condition. In related work, researchers are utilizing clinical data and tissue samples from a completed major clinical trial supported by NIDDK (Medical Treatment of Prostate Symptoms study) as they explore numerous scientific hypotheses related to chronic prostate inflammation and symptoms suggestive of CP. As it works to advance research on chronic prostatitis, the NIDDK is also being guided by topics and issues discussed at a major NIDDK-sponsored scientific workshop held in October 2005. This workshop brought together experts in a variety of fields important to understanding and treating CP and other chronic pelvic pain syndromes, including experts in pain and pain management, depression, neurology, interstitial cystitis, inflammation, and microbial infection. Finally, the NIDDK is initiating the development of a strategic plan for prostate disease research. Basic and clinical experts will be convened in 2007 to discuss the current state of knowledge about the benign (non-cancerous) diseases of the prostate, including chronic prostatitis. It is anticipated that a long range plan for research, including identification of disciplines that can contribute to this field, would be the product of this meeting.

Item

Tuberous Sclerosis Complex — Tuberous sclerosis complex, or 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 collaborate with the NCI to conduct

research on the needs identified in a recent conference on nutrient sensing and insulin-signaling in cells. The Committee also encourages the NIDDK to expand research on the link between PKD and TSC. (p. 118)

Action taken or to be taken

In May 2006, the NIDDK—in collaboration with the NCI and the NIH Office of Rare Diseases—co-sponsored a meeting entitled: “Nutrient Sensing, Insulin Signaling, and Hamartoma Syndromes.” Participants discussed clinical and basic studies on Hamartoma Syndromes—including tuberous sclerosis, Peutz-Jeghers syndrome, and Cowden’s syndrome—insulin signaling, mammalian target of rapamycin (mTOR), and nutrient sensing. The research opportunities identified through this conference will serve as a scientific guidepost for future program development efforts by the NIH.

The NIDDK supports a number of research projects to address the molecular and cellular mechanisms underlying TSC that may illuminate possible links between TSC and PKD. These efforts include investigator-initiated basic science studies designed to elucidate the genetic factors that lead to TSC, as well as preclinical studies in mouse models. Projects include studies of the TSC signaling pathway and nutrient sensing that span the interest of both NIDDK and NCI, as well as a study of the role of the TSC genes in the formation of kidney tumors in TSC and PKD. The NIDDK will also continue to participate in the inter-Institute TSC Research Coordination Committee, which works to implement the NIH Tuberous Sclerosis Research Agenda.

Item

Urological Research — The Committee strongly urges the NIDDK to establish a Urological Disease Research Branch within the Division of Kidney, Urologic, and Hematologic Diseases [DKUH]. Despite significant increases in funding for the Institute, the Committee remains concerned that the research portfolio in urology has not kept pace with the impact of these diseases on women, men and children. The Committee believes a Urological Disease Research Branch will better focus and accelerate research on urology disease in the NIDDK and help coordinate and stimulate urology-related research across the NIH and within other Federal agencies. (p. 118)

Action Taken or To Be Taken

The current organizational structure of the NIDDK enables the Institute to foster and accelerate research on urologic diseases. Between fiscal years (FY) 2002 and 2004, the NIDDK increased its funding of urologic diseases research by nearly 47 percent. In order to highlight urology research, the NIDDK recruited the assistance of a senior urologist from the University of Virginia to advise on oversight of urology programs. Responding to the disproportionate burden of urologic diseases in women, the Institute recently recruited an urologist to assume leadership of this portfolio and develop a women’s urologic health outreach program. Beyond the Institute, the NIDDK provides leadership and coordination for trans-NIH urologic diseases research through its chairmanship of the statutory Kidney, Urologic, and Hematologic Diseases Interagency Coordinating Committee, which has a specific subcommittee for urology. A recent effort to enhance research training opportunities for urologic surgeons, in which NIDDK was joined by the

National Cancer Institute, is just one example of efforts that have stemmed from coordinating committee discussions to advance urology research. The NIDDK has also enhanced research training opportunities for urologists through a recent agreement with the American Urological Association for joint sponsorship of candidates. Finally, the Institute continues to plan strategically to address current and future needs and opportunities in urology research. Recent efforts include the Bladder Research Progress Review Group (BRPRG), an expert group convened by the NIDDK that provided a 2002 strategic plan for research. This Plan has been pivotal in scientifically guiding the NIDDK's short- and long-term program development in urology research, including several recent research solicitations for basic and clinical urology research studies and clinical trials. The NIDDK also completed a strategic plan for pediatric urology research in February 2006, and is taking steps to develop a prostate disease research strategic plan. These examples of recent program enhancements in urology research studies, strategic planning, and research training demonstrate the NIDDK's continuing commitment to effectively bolstering support for research that can help reduce the burden of urologic diseases on men, women, and children in the United States.

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National Institute of Neurological Disorders and Stroke

House Significant Items

Item

Alzheimer's Disease – Research supported by NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. In a study supported jointly by NINDS, NIA and the Alzheimer's Association, scientists found that administering lithium to genetically engineered mice reduced the accumulation of an abnormal protein that contributes to the degeneration of neurons in Alzheimer's disease. Further research will determine whether lithium could also reduce neuronal degeneration if administered before any significant structural abnormalities occur in neurons. The Committee encourages NINDS to continue to assign a high priority to its Alzheimer's research portfolio, and to continue to work closely with NIA and other institutes. (p.96)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to invest in basic research directed at the biological mechanisms underlying the development of AD and strategies that can be used to prevent or treat the disease. As an example, the NINDS has funded several new grants in a number of basic research areas that may ultimately contribute to the development of therapeutics, including the links between cholesterol processing, neuroinflammation, and AD; and the study of novel enzyme inhibitors that may prevent the accumulation of amyloid-beta (a cellular hallmark of AD) in affected neurons. The NINDS has also funded a translational project that involves the screening of small molecules that may prevent mutant proteins linked to inherited forms of AD from assuming their abnormal structure and contributing to detrimental cellular changes.

With respect to collaboration, the NINDS participates in regular meetings of the trans-NIH Alzheimer's Disease Coordinating Committee, which includes the National Institute on Aging (NIA) and several other NIH Institutes and Centers (ICs). As just one example of the type of collaborations the Committee facilitates, the NINDS co-sponsored a large planning meeting for AD, led by the NIA, which took place in October 2006. The NINDS also co-funds many scientific advances with the NIA and other ICs. In one recent example, the NINDS and NIA both provided support for the discovery of an enzyme that may protect against the nerve cell deterioration caused by abnormal changes to the tau protein – both in AD and several other neurodegenerative conditions. Both Institutes also supported another recent therapeutic advance suggesting that increasing levels of an enzyme called cathepsin B can effectively reduce amyloid deposits in a mouse model of AD. Both enzymes serve as potential therapeutic targets for future research studies. In addition to co-funding such research teams, both the NINDS and the NIA also collaborate regularly on the release of grant solicitations. For example, in March 2006, the NINDS joined the NIA and the National Institute of Mental Health in a solicitation for exploratory research projects focused on AD drug discovery. This Program Announcement with Set-aside funding will support the discovery, development, and preclinical testing in cellular, tissue, and animal models of novel compounds for the

prevention and treatment of the cognitive impairment and behavioral symptoms associated with AD.

Item

Down Syndrome - As a follow-up to its successful Down syndrome workshop to address research priorities relating to the synaptic structure and function of neuronal circuits, NINDS is encouraged to issue program announcements related to its workshop findings. Specifically, the Committee encourages NINDS to support investigations relating to the genetic and cellular basis for abnormalities in the structure and function of neuronal circuits in both developing and mature nervous systems. NINDS is also encouraged to work with the Office of the Director, OPASI, and other institutes to develop a strategic plan for Down syndrome research and to coordinate all Down syndrome research within NIH. In anticipation of future clinical trials that will seek to measure accurately cognitive improvement in individuals with Down syndrome, the Committee further encourages NINDS to develop better measurement standards and a common data base that can be used generally for such trials. (p.96-97)

Action taken or to be taken

In February 2005, NINDS, together with the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), and the National Institute of Mental Health (NIMH), sponsored a workshop entitled: “Down Syndrome: Toward Optimal Synaptic Function and Cognition.” Recommendations from this workshop are being discussed as part of a larger effort by the NIH Down Syndrome Working Group to develop a plan for Down Syndrome research. This working group, made up of representatives from NIH Institutes and Centers (including NINDS) with an interest in Down syndrome research, will assess the current research across NIH on Down Syndrome, and will identify gaps in the field and areas for additional research. The group will work closely with OPASI in developing the final plan. In addition, scientists with expertise in Down syndrome research and related areas as well as members of the Down syndrome voluntary disease community will have the opportunity to provide input into the final plan.

NINDS funds research on cellular and molecular mechanisms that may contribute to Down Syndrome. One study is determining the expression and regulation of proteins from different brain regions in a mouse model of Down Syndrome, with the goal of identifying critical proteins and cellular processes that are altered in Down Syndrome. A recently awarded grant focuses on the underlying cellular and molecular basis for degeneration of a certain class of neurons –the basal forebrain cholinergic neurons - seen in Down Syndrome and how this degeneration contributes to cognitive dysfunction. Interestingly, there is strong evidence that degeneration of basal forebrain cholinergic neurons plays a role in certain forms of Alzheimer’s disease, which is found in a high proportion of individuals with Down Syndrome.

NIH has recognized the need to develop better measures of behavioral and neurological function for use in clinical studies. As part of the NIH Blueprint for Neuroscience Research, a trans- NIH effort designed to enhance collaboration among the NIH institutes

and centers that support research on the nervous system, NIH has recently awarded a contract for the development of the “NIH Toolbox for Assessment of Neurological and Behavioral Function.” This contract will develop a set of measurements appropriate for a variety of project types, including clinical intervention trials. The Toolbox could be applicable to studies on a wide range of conditions, including Down syndrome.

Item

Duchenne Muscular Dystrophy (DMD) - The Committee encourages NINDS to partner with NIAMS and NHLBI to provide the funding needed to adequately support the research agenda at each of the six Wellstone Muscular Dystrophy Cooperative Research Centers. (p.97)

Action taken or to be taken

NIH currently funds six Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (referred to here as “Wellstone Centers”). The National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and National Institute of Child Health and Human Development (NICHD) each fund two Centers, as follows: University of Rochester (NINDS), University of Iowa (NINDS), University of Pittsburgh (NIAMS), University of Pennsylvania/Johns Hopkins University (NIAMS), University of Washington (NICHD), and Children’s National Medical Center (NICHD).

In addition to direct costs (\$1 million per center per year for five years), there are currently other funds available to enhance the ongoing research activities at the Wellstone Centers. The Wellstone Centers program has built-in set-aside funds to promote new collaborations, and several projects have been approved for funding using these collaborative funds. To further enhance ongoing and collaborative activities, the Wellstone Centers may apply for supplemental funds through two NIH-sponsored programs. The first, the “Senator Paul D. Wellstone Muscular Dystrophy Research Fellowships,” are supplements to support senior postdoctoral fellows or non-tenure track investigators affiliated with the Centers. The second, support for Muscular Dystrophy Workshops and Research Conferences, encourages the Directors of the Wellstone Centers, in collaboration with other muscular dystrophy researchers and/or representatives from voluntary health organizations, to apply for supplements to support small workshops or conferences focused on specific topics in muscular dystrophy research. One workshop, *High Throughput Drug Screening for the Muscular Dystrophies*, which took place at Children’s National Medical Center on April 17-18, 2006, has been funded through this program. Wellstone Center directors are currently considering new workshop proposal ideas for 2007.

The NINDS, NIAMS, and NICHD partner with the National Heart, Lung, and Blood Institute (NHLBI) on a number of activities related to muscular dystrophy. For example, NHLBI, together with these other institutes, participated in the reissue of the initiative, “Muscular Dystrophy: Pathogenesis and Therapies.” In addition, an NHLBI representative regularly attends meetings of the Muscular Dystrophy Coordinating

Committee (MDCC), and participates in activities relevant to the committee and the implementation of the MDCC's Action Plan for the Muscular Dystrophies.

The NHLBI recognizes that the Wellstone Centers are a valuable resource to foster research on muscular dystrophy, including research on the effects of muscular dystrophy - in particular Duchenne muscular dystrophy (DMD) - on the cardiopulmonary system. The Wellstone Fellowship program described above is particularly attractive to NHLBI given the current emphasis by the NHLBI and the NIH on fostering junior investigators. The NHLBI would be interested to consider support for a cardiac or pulmonary researcher through the Wellstone Fellows program.

Item

Epilepsy - Epilepsy remains a major, unsolved public health problem affecting the lives of millions of Americans and their families. The Committee encourages intensified efforts by the Institute to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the "Curing Epilepsy: Focus on the Future" conference held in March, 2000 and encourages the institute to address important research issues raised at the "Living Well with Epilepsy II" conference held in July, 2003. The Committee further encourages NINDS to continue to carry out its benchmark priorities, to develop plans and goals for the antiepileptic drug development program, and to report to the Committee on its activities to further these important areas of research. (p. 97/98)

Action taken or to be taken

The NINDS continues to make epilepsy research a high priority. The NINDS Anticonvulsant Screening Program (ASP) is a public-private partnership program to evaluate the potential efficacy and toxicity of pre-clinical candidate compounds in validated epilepsy model systems. In 2006, the ASP screened several hundred molecules for potential activity against epilepsy and related disorders. The Program has participated in the evaluation and development of eight currently marketed antiepileptic drugs, and nine new ASP compounds are currently in clinical testing.

Over the past year, the NINDS held several targeted workshops to stimulate progress and collaboration in a number of areas of epilepsy research. In several cases, these workshops were followed by larger sessions at the annual American Epilepsy Society meeting, which brought the topics to the attention of a larger number of epilepsy researchers. Workshop topics included strategies to accurately predict seizure onset, to identify individuals at higher risk for epilepsy after injury, and to develop or improve animal models of the epilepsies.

The Institute will also sponsor a major conference, "Curing Epilepsy 2007: Translating Discoveries into Therapies" in March 2007 as a follow-up to the March 2000 "Curing Epilepsy: Focus on the Future" conference. Ten different professional and patient voluntary organizations are partnering with NINDS to support this effort, and the Centers for Disease Control and Prevention (CDC) is a Federal partner. The goals of the

conference are to highlight important areas of progress in epilepsy research, to examine areas that remain the greatest challenges, and to develop epilepsy research benchmarks for the next several years.

The Curing Epilepsy 2007 conference includes a session called “Beyond Seizures: Cognitive and Psychological Issues in Epilepsy” that will address research on common co-morbidities like cognitive problems and depression. This session, in particular, complements the research issues raised at the CDC-led “Living Well with Epilepsy II” conference. The NINDS also participates in the Living Well II Task Force. Most recently, the Task Force has been developing an implementation update to review progress made on the Living Well II priorities since 2003; this paper was published in the November issue of *Epilepsy and Behavior*.

Item

Hypoglycemia - Hypoglycemia or extremely low blood sugar is especially difficult to manage in young children with type 1 diabetes but can quickly result in serious consequences such as cognitive impairment, nerve damage, seizure, coma, or death. NINDS is encouraged to foster research on understanding the biology of the brain and nervous system under conditions of low glucose, devising better glucose management technologies that reduce the risk of hypoglycemia, and develop new agents to protect patients from hypoglycemia-related nerve damage. (p.98)

Action taken or to be taken

Hypoglycemia occurs when blood glucose (blood sugar) levels drop too low to provide enough energy for the body's activities. This may be caused by excessive treatment with insulin in patients with type 1 diabetes. Furthermore, in individuals with type 1 diabetes, hypoglycemia warning signals are often not triggered, and the body cannot correct for the low blood sugar. Young children are especially vulnerable to this state of “hypoglycemia unawareness,” particularly when they are asleep.

The National Institute of Neurological Disorders and Stroke (NINDS) supports research aimed at understanding the relationship between impaired glucose metabolism and the effects on the brain and nervous system. For example, NINDS supports a project to study the mechanisms by which the brain detects low blood sugar concentrations and the compensatory mechanisms the brain uses, including utilizing glycogen (an alternative source of “fuel” for the body) stores and altering glucose transport across the blood-brain barrier (a membrane that controls the passage of substances from the blood into the central nervous system). Another grant focuses on defining the effects of both recurrent hypoglycemia and chronic hyperglycemia (excessively high blood sugar levels) on brain glucose transport and metabolism. Understanding how the brain regulates glucose balance will help patients with glycemic control and long-term diabetes management.

As a member of the Diabetes Mellitus Interagency Coordinating Committee, NINDS participated in the development of the strategic plan, “Advances and Emerging Opportunities in Type 1 Diabetes Research,” which was released in July 2006. One of the goals in the plan is to prevent or reduce hypoglycemia in type 1 diabetes, including

understanding brain and peripheral nervous system mechanisms of hypoglycemia and developing clinical interventions for the condition.

As one way of addressing this goal, NINDS, the National Institute of Child Health and Human Development (NICHD) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), released a request for applications (RFA) for a “Cooperative Multicenter Diabetes Network for Hypoglycemia Prevention.” The purpose of the RFA is to invite applications from investigators willing to participate in a research network designed to reduce the incidence of hypoglycemia in children and young adults. The network will use new tools to evaluate factors contributing to hypoglycemia and will set up clinical trials to test novel therapies, intervention strategies and devices for hypoglycemia prevention for individuals with type 1 diabetes. A wide range of studies may be undertaken as part of the network, including studies to understand and prevent nighttime hypoglycemia.

Item

Neurofibromatosis (NF) - Advances in NF research have linked NF to cancer, brain tumors, learning disabilities, memory loss and heart disease. The Committee encourages NINDS to expand its NF clinical, pre-clinical and basic research portfolios and to continue its efforts to accelerate the process of translational research. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other institutes and government agencies engaged in NF research. The Committee encourages 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 encourages NINDS to continue to coordinate its efforts with other appropriate institutes at NIH as well as other government agencies. (p.98)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research to better understand, treat, and eventually prevent the debilitating effects of neurofibromatosis. The NINDS continues to lead the Trans-NIH Neurofibromatosis Working Group, which includes representatives from the National Cancer Institute, the National Heart, Lung and Blood Institute, the National Institute of Deafness and Other Communication Disorders, the National Human Genome Research Institute, the National Eye Institute, the National Institute of Child Health and Human Development, the National Institute of Mental Health, the NIH Office of Rare Diseases, and the Department of Defense’s Congressionally Directed Medical Research Program (CDMRP). The group and voluntary representatives meet once per year to share information about their respective neurofibromatosis research portfolios and to identify ways to better coordinate programmatic activities and expand research opportunities. For example, the NINDS Program Director for neurofibromatosis is a member of the CDMRP’s Neurofibromatosis Integration Panel, which prioritizes and recommends the funding of grant applications.

In fiscal year 2004, the NINDS and the NIDCD issued a Program Announcement with special Review (PAR) to invite grant applications for National Centers for Neurofibromatosis Research. The PAR is active until February 2007. The purpose of the announcement is to encourage the formation of multi disciplinary research centers that will accelerate basic, translational, and clinical research progress on the neurofibromatoses. The first Center has made remarkable progress in its first year, establishing new mouse models of neurofibromatosis that are designed to better predict the safety and efficacy of new therapeutics.

The NINDS neurofibromatosis research portfolio also includes studies of basic mechanisms of neurological dysfunction, the relationship between gene mutation and disease expression, and translational projects to identify and evaluate new brain tumor therapies. In addition, the NINDS is sponsoring a clinical trial to address one of the most common quality of life issues for children with neurofibromatosis, reading disabilities. The trial will investigate which interventional methods are most effective for treating reading disabilities in children with neurofibromatosis.

Item

[Clinical Neuroprotection Trials -Parkinson's disease] – The Committee supports the innovative multidisciplinary research and training concerning Parkinson's disease provided by the Morris K. Udall Parkinson's Disease Research Centers of Excellence. The Committee encourages NINDS to require that the Udall Centers include a significant clinical/translational component, in addition to ongoing basic research. The Committee encourages the Director to provide funding expeditiously at the conclusion of the neuroprotection trials (NET-PD) for phase III clinical trials of all the neuroprotection compounds that survive futility testing. The Committee requests that the Director report on funding for phase III trials three-months after the conclusion of each of the NET-PD trials. The Committee recognizes that continuation of promising research is an integral part of the strategic plan for future investments in Parkinson's research. (p. 98)

Action taken or to be taken:

The National Institute of Neurological Disorders and Stroke (NINDS) plans to continue the Morris K. Udall Centers for Parkinson's Disease (PD) Research program. With respect to clinical research, the NINDS continues to actively support the expansion of clinical studies across the program. The November 2005 solicitation for Udall Centers included language emphasizing the need to move basic science findings toward the development of therapies, and in July 2003, NINDS increased the funding limit of \$1 million in direct costs for solicited, specialized research centers engaged in clinical projects to \$1.5 million. Many Udall Centers have benefited from this new policy, and are engaged in clinical projects that include the study of PD genetics in at-risk families; the collection, banking, and distribution of postmortem PD brain tissue; the study of the relationship of abnormal cellular structures believed to be causal in PD to clinical symptoms of disease; the collection of data on responses to therapy among patients; and the characterization of protein expression profiles in postmortem PD tissues. In addition, many Udall Centers are already engaged in translational research, from the screening of potential therapeutics in preclinical test systems to the exploration and testing of

treatment strategies in non-human primate models of PD. The NINDS is completing a formal evaluation of the Udall centers program which will provide valuable insights into the collaborations and productivity of each Center in basic, translational and clinical PD research. The Institute anticipates delivery of the final report on the evaluation to the National Advisory Neurological Disorders and Stroke Council in September 2007, and subsequently, it can utilize these data to determine if further emphasis in any of these research areas is warranted.

Investigators involved in the Neuroprotection Exploratory Trials in PD (NET-PD) studies published the findings from the first two drugs evaluated, minocycline and creatine, in March 2006. Based on the results of this study, NINDS is planning a large Phase III trial of the antioxidant creatine. As requested by the Committee, the Institute will also submit formal reports to the Committee, through the regular Congressional Appropriations Committee Report process, within three months after the NET-PD research team publishes its data on additional futility studies.

Item

Traumatic Brain Injury (TBI)- The Committee encourages NINDS to build upon basic and translational research in brain injury rehabilitation at the National Center on Medical Rehabilitation and Research (NCMRR). NCMRR has awarded grants to eight bench science research centers and a data center to establish the cooperative multi-center traumatic brain injury clinical trials network. The Committee encourages NINDS to participate in supporting these centers and to support training grants for TBI researchers. (p.99)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) leads NIH traumatic brain injury (TBI) research and works closely with the NCMRR to ensure that NINDS and NCMRR efforts against TBI complement one another. To enhance communication and coordination throughout the federal government, in 2006 the NINDS convened a meeting of representatives from numerous Federal Agencies, including the NCMRR, that support research on TBI. This group will continue to work together in the coming year. The high rate of TBI among U.S. military personnel in Iraq was a major stimulus to this meeting, and NINDS Intramural investigators have played an important role in investigating the long term consequences of TBI among military personnel.

The extensive NINDS TBI extramural research program supports research to understand the mechanisms of TBI, translate these insights to practical treatments, and test interventions in clinical trials. The TBI program currently supports grants and contracts to individual investigators and multi-disciplinary research teams, including scientists at most of the institutions in the NCMRR TBI network. The NINDS co-funds with NCMRR infrastructure centers that bring together experts in neuroscience and rehabilitation and provide cross-disciplinary training. The NINDS and the NCMRR also co-sponsor scientific workshops that address issues in TBI. To expedite the development of emergency treatments for brain injuries and other neurological disorders, the NINDS in 2006 awarded contracts to establish the Neurological Emergency Treatment Trials

(NETT) network that brings together scientists and physicians from emergency medicine, neurology, neurosurgery, and other disciplines. In addition to supporting the NETT network and the NCMRR infrastructure centers, NINDS also provides support to the National Heart, Lung, and Blood Institute (NHLBI) for their Resuscitation Outcomes Consortium (ROC). ROC projects include a multi-center clinical trial that includes a cohort of patients with TBI.

Training of TBI investigators is also a major priority of NINDS TBI programs. The majority of NINDS research grants on TBI also support the training of graduate students and post-doctoral fellows. In addition, the Institute supports training of future researchers in TBI through individual and institutional training programs tailored to the needs of M.D.'s, M.D.-Ph.D.'s, and Ph.D.'s. in basic and clinical research. These include pre- and post-doctoral fellowships and career development awards to individual trainees, as well as institutional training grants.

Senate Significant Items

Item

Alzheimer's Disease – Research supported by the NINDS continues to play an integral role in widening the scientific base of knowledge about Alzheimer's disease. In a study supported jointly by the NINDS, the NIA and the Alzheimer's Association, scientists found that administering lithium to genetically engineered mice reduced the accumulation of an abnormal protein, called tau, that contributes to the degeneration of neurons in Alzheimer's disease. Further research will determine whether lithium could also reduce neuronal degeneration if administered before any significant structural abnormalities occur in neurons. The Committee encourages the NINDS to continue to assign a high priority to its Alzheimer's research portfolio, and to continue to work closely with the NIA and other Institutes. The Committee further urges the NINDS, in collaboration with the NIA and NIMH, to 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. (p. 119)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to invest in basic research directed at the biological mechanisms underlying the development of Alzheimer's disease (AD) and strategies that can be used to prevent or treat the disease. With respect to collaboration, the NINDS participates in regular meetings of the trans-NIH AD Coordinating Committee, which includes the National Institute on Aging (NIA) and several other NIH Institutes and Centers (ICs). As just one example of the type of collaborations the Committee facilitates, the NINDS co-sponsored a large planning meeting for AD, led by the NIA, which took place in October 2006. The NINDS also co-funds many scientific advances with the NIA and other ICs, such as the discovery of an enzyme that may protect against the nerve cell deterioration caused by abnormal changes to the tau protein – both in AD and several other neurodegenerative conditions. This enzyme serves as a potential therapeutic target for future research studies. In addition to co-funding research teams, both the NINDS and the NIA collaborate regularly on the

release of grant solicitations. For example, in March 2006, the NINDS joined the NIA and the National Institute of Mental Health in a solicitation for exploratory research projects focused on AD drug discovery.

Both the NINDS and the NIA support imaging studies that might provide earlier diagnosis of AD, permit earlier intervention, and monitor progression in disease trials. For example, both Institutes fund researchers to study the use of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to examine plaques and tangles, the cellular hallmarks of AD, in individuals with a genetic predisposition to the disorder. NINDS-funded researchers have also contributed to recent advances in the use of PET for identifying which nerve chemical receptors to target to improve brain function in people with AD. Lastly, the NINDS and the NIA supported the discovery that Pittsburgh Compound-B, a PET imaging tag that binds to amyloid-beta plaques, may be sufficiently sensitive to use as an early predictor of AD in people with no detectable cognitive impairment.

The NINDS and the NIA will continue to explore opportunities to encourage investigator-initiated applications for novel use or development of imaging techniques aimed at early diagnosis. The results of any such studies or those described above would be published in a peer-reviewed medical journal and available to the Centers for Medicare and Medicaid Services.

Item

Amyotrophic Lateral Sclerosis [ALS] – The Committee is gratified by the increased capacity in the past 2 years for drug discovery and patient care regarding ALS throughout the Nation’s major academic centers and community clinics. Collaborations between the NINDS and voluntary health associations, such as the coordination of the NIH National Center for Drug Discovery in Neurodegeneration with The ALS Association’s new clinical TREAT ALS program, provide an evolved nationwide infrastructure for accelerating programs in translational research. More patients now have access to more clinical trials through the increased prevalence of ALS centers, which not only define, establish and support a national standard of care in the management of ALS, but also interrelate with state-of-the art research. The Committee is also pleased with the continuing collaboration between NIH, the Department of Veterans Affairs and the Department of Defense to advance ALS research and identify treatments for this disease that afflicts veterans in disproportionate numbers. The Committee encourages NIH to continue collaborating with other relevant Federal agencies as well, including the Centers for Disease Control and Prevention. (p. 119)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) continues to collaborate with private organizations and government agencies to accelerate the discovery of new therapeutics for amyotrophic lateral sclerosis (ALS). As a recent example, NINDS staff met in June 2006 with representatives from the Department of Defense (DoD) and Department of Veterans Affairs (VA) to discuss how the three agencies could better align their ALS research and treatment programs. The outcome of

this meeting was a consensus to convene a panel of ALS experts to address the questions raised by the studies which suggest military personnel are at a higher relative risk for ALS, and to incorporate medical data, including exposure data, and DoD healthcare beneficiaries into more expansive research on ALS. The NINDS and VA agreed to cooperate on developing a list of invited experts and a preliminary agenda for the meeting. The NINDS does not currently engage in any formal collaborations with the Centers for Disease Control and Prevention on ALS, but is receptive to doing so on any future projects of mutual interest to both agencies.

Item

Batten Disease - The Committee strongly urges the Institute to increase funding for Batten disease research by actively soliciting grant applications and taking aggressive steps to ensure that a vigorous research program is established. The Committee expects to be informed of the steps taken to increase research on Batten disease. (p. 119)

Action taken or to be taken

Batten Disease is the juvenile form of a set of fatal hereditary neurodegenerative disorders known as the Neuronal Ceroid Lipofuscinoses (NCLs). Although each form of NCL is caused by mutation in a different gene, at the cellular level, all NCLs are characterized by abnormal accumulation of material in the lysosome, a cellular compartment that breaks down and recycles macromolecules. The National Institute of Neurological Disorders and Stroke (NINDS) supports several studies investigating the function of the different genes mutated in the NCLs and the underlying molecular pathways. Other NINDS-funded studies focus on the emergence of the disease in the brain. For example, one project is studying the recently identified possibility that the immune system mistakenly attacks certain nerve cells in Batten Disease. Another study has found that early on, nerve cells from a mouse model of infantile NCL contain significantly fewer neurotransmitter vesicles, which may be an early sign of degeneration and may lead to altered levels of neural activity. In addition, recent findings in a mouse model of infantile NCL have revealed that neurodegeneration starts and is most pronounced in the thalamus, a relay point in the brain, which may represent an important therapeutic target. Several other projects funded by NINDS are aimed at therapy development, including testing gene and stem cell therapies in animal models of the NCLs. Through its program in translational research, the NINDS recently awarded a large cooperative agreement to explore gene replacement therapy as a way to halt neurodegeneration in Batten Disease.

Because of the abnormal accumulation of material in the lysosome, Batten Disease and the NCLs are part of a larger class of diseases known as lysosomal storage disorders (LSDs). In conjunction with the NIH Office of Rare Disorders and the Lysosomal Storage Disease Research Consortium, the NINDS currently offers two program announcements with set-aside funds to encourage the development of therapies that target the neurological defects of LSDs, including Batten Disease. Several projects are currently being funded as a result of this effort including gene replacement approaches, the use of stem cells to replace dying nerve cells or produce lysosomal proteins, caloric restriction

to reduce the inflammation associated with LSDs, and strategies to improve the transport into the brain of proteins that can aid lysosomal breakdown.

The NINDS also stimulates new research ideas by supporting scientific conferences. In April 2006, the NINDS hosted a Workshop on Glycosphingolipids in Health and Disease. Glycosphingolipids are macromolecules that fail to be degraded in Batten Disease and other LSDs. In addition, the NINDS is sponsoring the 3rd Annual World Symposium of the Lysosomal Disease Network in December 2006 and the Joint 12th International NCL Congress and Batten Disease and Support Research Association (BDSRA) Meeting in July 2007.

Item

Brain Tumors - The Committee continues to believe that additional attention should be given by NINDS to identifying causes of and treatments for brain tumors and encourages NINDS to continue working with NCI to carry out the recommendations of the Report of the Brain Tumor Progress Review Group. (p. 119)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research to study the basic biology, diagnosis and improved treatment of brain tumors. The Brain Tumor Progress Review Group (PRG), sponsored by NINDS and the National Cancer Institute (NCI), identified many research, resource, and cross-cutting priorities for the field. Among these, the need to develop novel therapies and improve support for immunotherapy clinical trials remains a high priority, since current treatment options are limited and for most types of tumors, provide only modest benefits. The Surgical and Molecular Neuro-Oncology Unit within the NINDS Division of Intramural Research investigates brain tumor development and chemotherapy resistance to find new therapeutic strategies for malignant glioma treatment. The NINDS also funds a number of early Phase I and II trials through the Specialized Research Center on Primary and Metastatic Tumors of the Central Nervous System at Duke University, and through other mechanisms. For example, three NINDS-sponsored Phase I studies are investigating different ways to deliver therapies to brain tumors. A number of Phase I/II studies are evaluating safety and tolerability of different immunological therapies, including approaches that use an immunotoxin, a targeted vaccine therapy, monoclonal antibodies, or a combination of chemotherapy and immunotherapy. The NINDS also supports a Phase II trial to examine cognitive changes in pediatric brain tumor survivors.

The NINDS and NCI collaborated in issuing Program Announcements with set-aside funds (PAS) on “Understanding and Preventing Brain Tumor Dispersal.” This topic was identified as one of the PRG’s highest scientific priorities. The current PAS is active until July 2007. Some of the grants awarded through this PAS to date focus on targeting invasive tumor cells with chemical compounds, immune system strategies or stem cell therapy. Other grants focus on understanding tumor cell migration mechanisms and blood flow and oxygen changes that accompany rapid tumor progression. Additional studies focus on defining whether neural stem cells in the adult brain can cause tumor formation. One project will develop a model for glioma research in fruit flies, which will

allow sophisticated large-scale genetic studies to identify new genes (and thus, new therapeutic targets) involved in glioma invasion and progression.

To strengthen collaborative activities in the NIH brain tumor research portfolio, the NINDS and the NCI will form a Brain Tumor Working Group in Fiscal Year 2007.

Item

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) - The Committee recognizes that Chronic Inflammatory Demyelinating Polyneuropathy [CIDP] is a rare disorder of the peripheral nerves characterized by gradually increasing weakness of the legs and arms. The Committee urges the National Institute of Neurological Diseases and Stroke to support research to assist in the diagnosis and treatment of CIDP. (p.119)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad program of research on CIDP and other peripheral neuropathies. One project currently being funded by NINDS is exploring the role of a certain class of proteins (the sphingosine-1 phosphate (S1P) receptors) in CIDP. S1P receptors are expressed by myelin-producing Schwann cells as well as certain cells of the immune system. The study is investigating whether drugs that act on the S1P receptors can lessen the disease severity, using an animal model that mimicks CIDP. Other projects funded by NINDS are focused on understanding the process of myelination and its regulation and studying how abnormal or disrupted myelin formation causes diseases like CIDP.

In addition, research on other forms of peripheral neuropathy may contribute to our understanding of the causes of CIDP and help lead to the development of effective treatments for the disorder. NINDS-funded researchers are working to identify genetic mutations responsible for the different types of peripheral neuropathies. Identification of the genetic mutations that lead to disease will aid in molecular diagnosis and development of potential therapeutic targets for these conditions.

NINDS is also convening a workshop this October on the peripheral neuropathies. The workshop will bring together researchers from across the different types of neuropathy to share information and identify cross-cutting research objectives for the field as a whole. Prominent researchers in the neuropathies as well as representatives from patient voluntary groups have been invited to participate and discuss a range of issues in therapeutic development for the neuropathies, from identification of target mechanisms to the conduct of clinical trials.

Item

Down Syndrome - As a follow-up to its successful Down syndrome workshop to address research priorities relating to the synaptic structure and function of neuronal circuits, NINDS is strongly encouraged to issue special program announcements related to its workshop findings. Specifically, the Committee encourages NINDS to identify and fund investigations relating to the genetic and cellular basis for abnormalities in the structure and function of neuronal circuits in both the developing and mature nervous systems.

NINDS is also encouraged to work with the Office of the Director, OPASI, and the other institutes to develop a strategic plan for Down syndrome research and to coordinate all Down syndrome research within NIH. In anticipation of future clinical trials that will seek to accurately measure cognitive improvement in individuals with Down syndrome, the Committee further encourages NINDS to begin to develop better measurement standards and a common database that can be used generally for such trials. (p.120)

Action taken or to be taken

Please refer to page 74 of this document for NINDS's response to this item on Down Syndrome.

Item

Duchenne Muscular Dystrophy - The Committee further encourages NINDS to partner with NIAMS and NHLBI to provide the funding needed to adequately support the research agenda at each of the six Wellstone Muscular Dystrophy Cooperative Research Centers. (p.120)

Action taken or to be taken

Please refer to page 75 of this document for NINDS's response to this item on DMD.

Item

Epilepsy - The Committee encourages intensified efforts by the Institute to produce breakthroughs in the prevention, treatment, and eventual cure of epilepsy. The Committee applauds the development of benchmarks for epilepsy research resulting from the 'Curing Epilepsy: Focus on the Future' conference held in March 2000 and encourages the Institute to address important research issues raised at the 'Living Well with Epilepsy II' conference held in July 2003. The Committee encourages the NINDS to designate resources to implement its benchmark priorities, to develop plans and goals for the anti-epileptic drug development program, and to provide pertinent updates on these activities. (p.121)

Action taken or to be taken

Please refer to page 76 of this document for NINDS's response to this item on Epilepsy.

Item

Fragile X - Fragile X is a single-gene disorder, but both its symptoms and its cellular mechanisms suggest the involvement of multiple genes and specific brain pathways that are associated with other neurological disorders, such as autism and seizures. Recent research offers clear evidence of disruption of fundamental brain circuitry in Fragile X. Thus, Fragile X research has the potential to contribute to the understanding of multiple disorders, such as seizure disorders, developmental disorders and autism. The Committee urges the NINDS to intensify its research into these issues as they relate to Fragile X, and to coordinate this research with other Institutes working on Fragile X, including, but not limited to, NIMH and NICHD. (p. 121)

Action taken or to be taken

An extreme expansion mutation in a gene on the tip of the X chromosome has been shown to cause Fragile X Syndrome (FXS), one of the most common inherited forms of mental retardation. The mutation effectively abolishes expression of the Fragile X gene product, the Fragile X Mental Retardation Protein (FMRP). Researchers now believe that lack of FMRP has broad effects on the levels of many other proteins involved in various aspects of brain development and function. At the NIH, efforts on FXS are coordinated among the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the National Institute of Child Health and Human Development (NICHD). The NINDS supports research aimed at understanding the processes that lead to the FXS expansion mutation, as well as the roles of FMRP in protein expression and neuronal development and function. Mouse and fruit fly models of FXS have been developed and are being used by NINDS-funded investigators to identify potential drug targets and to tease-out the molecular and cellular pathways affected in FXS.

In about 15-30% of the cases, children with FXS have additional associated neurological or psychological conditions, such as epileptic seizures or autism. Identification of the networks of interacting proteins and cells affected in FXS may thus illuminate pathways and processes common to other disorders. To encourage research in this area, NINDS, NIMH, and NICHD have partnered with 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 called "Shared Neurobiology of Fragile X Syndrome and Autism." The announcement encourages research proposals aimed at understanding the nerve networks and molecular pathways involved in autistic behaviors and the defects in these that are common to both FXS and autism. In particular, the announcement encourages studies focusing on the discovery of new drug targets. The NINDS also supports a large portfolio of research on epilepsy, including studies to prevent the development of epilepsy in those at risk for the disease, which may be helpful in understanding and preventing seizures in children with Fragile X.

Item

Fragile X-Associated Tremor/Ataxia Syndrome [FXTAS] - Carriers of premutation [CGG] expansions of the Fragile X gene are generally thought to be spared most of the problems associated with the full mutation; however, a newly identified neurological disorder, involving progressively severe tremor and difficulty with walking and balance, appears to specifically affect some older premutation carriers, generally grandfathers of children with Fragile X syndrome. Although this neurological disorder occurs by a separate mechanism from Fragile X syndrome and affects different individuals, it is caused by the same gene, and therefore opens a new portal for understanding how the Fragile X gene works. The Committee encourages NINDS to use FXTAS as a gateway to understanding other adult/aging disorders including parkinsonism and dementia. The Institute is encouraged to work with the NIA to expand research on FXTAS. (p. 121)

Action taken or to be taken

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) was identified in 2001 by researchers funded through the National Institute of Neurological Disorders and Stroke (NINDS) and is the result of an expansion mutation in the same gene that causes Fragile X Syndrome (FXS). While extreme expansions (over 200 repeats) cause loss of expression of the Fragile X Mental Retardation Protein (FMRP) and lead to FXS, mid-size expansions known as “premutations” (55-200 repeats) may produce abnormal nerve cell deposits, neurodegeneration, and late-onset motor and cognitive decline in a subset of individuals.

The NINDS supports research to improve understanding of the disease mechanisms underlying FXTAS and to provide better tools for treatment and diagnosis. Several lines of research, funded in part by NINDS, suggest that increased levels of the expanded Fragile X messenger RNA, the molecule which is converted into FMRP, are responsible for the neurodegeneration observed in FXTAS. NINDS supported investigators are using cell and animal models of FXTAS to test the hypothesis of a toxic RNA species and to identify the proteins that mediate this toxicity. These studies may lead to the identification of drug targets for FXTAS. The NINDS also supports studies to define the clinical features and disease trajectories of FXTAS patients, and improve the timely diagnosis and treatment of movement disorders among older men. The NINDS shares support of research on FXTAS with the National Institute on Aging (NIA). The NIA supports a study characterizing the molecules that accumulate abnormally in the nerve cells of FXTAS patients using a neural cell culture model capable of recapitulating these cellular deposits. The identity of these molecules will inform the pathological mechanisms of FXTAS and give clues about the steps of disease progression. In addition, NINDS, NIA, the National Institute of Child Health and Human Development, and the National Institute of Mental Health all fund research on FXS and movement disorders, including ataxias, which may be relevant to the study and treatment of FXTAS.

Genetic expansion mutations, such as the one found in FXTAS, have also been observed in disorders such as Huntington’s and Spinocerebellar Ataxia. However, the conditions which make certain gene sequences unstable and prone to repeats are unknown. The NINDS supports research aimed at understanding the processes that lead to expansion mutations and sponsors scientific meetings to foster the sharing of discoveries across disease areas. For example, in 2007, NINDS will sponsor a Keystone Symposium focusing on the mechanisms by which repeat expansion diseases cause neurodegeneration.

Item

Healthy Brain Initiative - NINDS is commended for its cooperative efforts in producing a searchable database of studies and planning joint efforts to solicit research on enhancing healthy cognitive and emotional function. This initiative is a model of how institutes can work together on complex issues involving multiple disciplines and methodologies. Given the importance of maintaining and enhancing brain health at all stages of life, NINDS is encouraged to make this initiative a priority. (p.121)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Institute of Mental Health (NIMH), are part of the exciting trans-NIH initiative, *Cognitive and Emotional Health Project: The Healthy Brain*. The overall goal of the "Healthy Brain Project" is to assess the state of longitudinal and epidemiological research on determinants of cognitive and emotional health in aging adults and the ways in which cognitive and emotional health may influence each other. As a first step, a comprehensive review of measures that have been (or could be) used in epidemiologic research was undertaken, and summaries are posted on the project's website. In addition, to help NIH learn what epidemiological data exist on the cognitive and emotional health of adult populations in the United States, a questionnaire was used to poll investigators who are conducting large-scale longitudinal and epidemiological studies of cognitive and emotional health. A searchable database was created, and this invaluable tool is now available online.

As another component of the Healthy Brain Project, a Critical Evaluation Study Committee was formed to conduct an analysis of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health in the adult. A summary of the evaluation entitled, "The NIH Cognitive and Emotional Health Project: Report of the Critical Evaluation Study Committee" was published in *Alzheimer's & Dementia* 2006; 2:12 - 32. The report identifies factors contributing to poor mental health later in life, highlights the need to understand the relationship between cognitive decline and emotional stress, and emphasizes the importance of considering cognitive and emotional health simultaneously in future studies.

NINDS will continue to participate in the Healthy Brain Project, and is discussing new initiatives to expand the project. These include promoting the use of existing data sets to study the risk and protective factors for cognitive and emotional health and promoting the development of ancillary studies, particularly ones that would provide an opportunity to examine the pathways by which cognitive and emotional health influence each other.

Item

Human Herpes virus - The Committee requests the NINDS, in coordination with NIAID and other appropriate NIH Institutes, to engage in research into the possible role of human herpes viruses 6A and 6B in the onset and progression of multiple sclerosis, mesial temporal lobe epilepsy, status epilepticus, HIV/AIDS, chronic fatigue syndrome and other neurological, and immune system diseases. (p. 121-122)

Action taken or to be taken

Both the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID) support research studies on human herpes viruses, including HHV-6. For example, research projects in the NINDS Viral Immunology Section focus on the detection of HHV-6 from brain resections of patients with multiple sclerosis or mesial temporal lobe epilepsy, and from patients who experience neurological complications after receiving a bone marrow transplant. These researchers have developed novel immunological assays to detect antibodies to HHV-6 in

serum and cerebrospinal fluid. Intramural investigators from the NIAID and the NIH Clinical Center are pursuing a slightly different approach to develop and validate a method to detect HHV-6 DNA in cerebrospinal fluid. Such improved methods of detecting HHV-6 are critical tools to investigate potential relationships between HHV-6 infection and neurologic dysfunction.

The NINDS supports a number of clinical studies that are principally focused on HHV-6 and multiple sclerosis. These projects are investigating the possible role of HHV-6 in the etiology of multiple sclerosis in thousands of participants from the Nurses Health Study and the Nurses Health Study II, and from samples in the Department of Defense Serum Repository. Another project is designed to determine whether there is a relationship between specific environmental exposures, including HHV infection, and particular genetic subtypes in individuals who develop multiple sclerosis. Yet another clinical study is testing the hypothesis that, in children infected with HHV-6 or HHV-7, brain injuries caused by fever-induced seizures will be more frequent and severe than in children without HHV-infection.

The NINDS also supports basic research to specifically understand the effects of HHV-6 infection on brain glial cells, and to understand HHV infection, latency, and re-activation. NINDS-supported investigators have shown that HHV-6 infected glial cells respond differently to HHV-6 antiviral drugs compared to virus-infected immune cells, suggesting that different treatment strategies should be considered when trying to clear this virus from cells in the central nervous system.

Finally, the NINDS continues to participate with the NIAID, and several other NIH Institutes, in a Program Announcement on “Functional Links between the Immune System, Brain Function and Behavior.” The Program Announcement particularly encourages submission of applications to better understand the role of acute and chronic infections on brain function and behavior.

Item

Mucopolidosis Type IV [ML4] - The Committee encourages the Institute to expand research involving other organisms which bear genes resembling the one whose mutation in humans causes ML4. This research could be beneficial not only to those with ML4, but a number of other disorders involving TRP genes and other genetic disorders. (p. 122)

Action taken or to be taken

Researchers funded through the National Institute of Neurological Disorders and Stroke (NINDS) were among the first to identify that mutations in the gene which codes for mucolipin-1, which is a protein that conducts ions across membranes, were responsible for ML4. The NINDS currently supports projects aimed at generating a mouse model of ML4, characterizing the function of mucolipin-1 and associated proteins, and studying the role of mucolipin-1 ion channel activity in the degradation of molecules by the lysosome. Within its intramural research program, the NINDS is conducting a natural history study of ML4, aimed at improving the understanding of the clinical manifestations of the disease and at devising better ways of diagnosing ML4, and a study

on the progression of the retinal degeneration observed in the disease. The NINDS also supports scientific conferences that promote better understanding of ML4 and other LSDs and the communication of research findings. In April 2006, the NINDS hosted a Workshop on Glycosphingolipids in Health and Disease. Glycosphingolipids are macromolecules that fail to be degraded in ML4 and other LSDs. In addition, the NINDS is sponsoring the 3rd Annual World Symposium of the Lysosomal Disease Network in December 2006.

In conjunction with the NIH Office of Rare Disorders and the Lysosomal Storage Disease Research Consortium, the NINDS has also issued two program announcements with set-aside funds to promote the translation of basic science findings to new or improved therapies for the neurological defects associated with LSDs. The announcements will be active until the end of 2007. Several projects investigating therapies relevant to LSDs, including ML4, are currently being funded as a result of this effort. These projects include gene therapy approaches for LSDs, the use of stem cells to replace dying nerve cells or produce lysosomal proteins, therapies to prevent accumulation of material in the lysosome, caloric restriction to reduce inflammation, and investigations into strategies to improve the transport into the brain of proteins that can aid lysosomal breakdown.

Item

Neurofibromatosis (NF) - Advances in NF research have linked NF to cancer, brain tumors, learning disabilities, memory loss and heart disease. The Committee encourages NINDS to aggressively expand its NF clinical, pre-clinical and basic research portfolios and to continue its efforts to accelerate the process of translational research. The Committee commends NINDS for its leadership role in NF research and in coordinating efforts with other Institutes and government agencies engaged in NF research. The Committee encourages NINDS to continue its exemplary 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 calls upon NINDS to continue to coordinate its efforts with the other institutes at NIH as well as other government agencies. (p.122)

Action taken or to be taken

Please refer to page 78 of this document for NINDS's response to this item on Neurofibromatosis.

Item

Opsoclonus-Myoclonus Syndrome (OMS) - OMS is a rare, autoimmune, paraneoplastic disorder that targets the brain. In childhood, it is associated with neuroblastoma of the chest, abdomen, or pelvis. Besides the hallmark features of opsoclonus (involuntary saccadic eye movements), myoclonus (tremulousness, muscle jerks), and ataxia (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 urges the Institute to accelerate research

efforts to identify OMS susceptibility genes and biomarkers, and to develop innovative immunotherapeutic strategies. (p. 122)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research to better understand and treat autoimmune paraneoplastic neurological disorders such as opsoclonus-myoclonus syndrome (OMS).

The NINDS supports basic and translational research on interactions between the immune system and the nervous system, including the development of immune cells that attack self-tissues, the effects of inflammation on cells in the nervous system, and new strategies to protect the nervous system from immune-mediated damage or to repair damage once it has occurred. In addition, the NINDS supports basic studies on the function of Nova, a specific neuronal protein targeted by the immune system in OMS. The Institute sponsors observational and interventional clinical trials on autoimmune neurological disorders, including multiple sclerosis, myasthenia gravis, stiff-person syndrome, and autoimmune autonomic failure. Advances in understanding or treating these autoimmune disorders could provide insight into improved treatments for OMS.

In addition, the NINDS participates with several other NIH Institutes to support a Program Announcement (PA) on “Functional Links between the Immune System, Brain, and Behavior.” The purpose of this PA is to solicit research applications to better understand how immune cells and their mediators affect brain development, brain function, and behaviors related to cognition and mood. The NINDS considers grant applications to study the pathophysiology and behavioral outcomes in OMS to be highly responsive to this PA and encourages their submission.

Lastly, in July 2006, the NINDS sponsored the 2nd international “Rare Neuroimmunologic Disorders” symposium, which featured a presentation on paraneoplastic neurologic disorders. The goals of the symposium were to explore both common and unique features of these disorders, such as genetics and triggering mechanisms; the contribution of different types of immune cells to the development of autoimmunity, migration of immune cells, strategies for neuroprotection and remyelination, and emerging immunotherapies. A summary of the proceedings is being prepared for publication. The NINDS will work with other appropriate NIH partners to sponsor a workshop on the role of B cells in paraneoplastic neurological disorders, including OMS, with a goal of encouraging additional research and collaboration in this field.

Item

Parkinson’s Disease – The Committee supports the innovative multidisciplinary research and training concerning Parkinson’s disease provided by the Morris K. Udall Parkinson’s Disease Research Centers of Excellence. The Committee encourages the Director to create an additional Coordinating Udall Center to further focus and manage the interdisciplinary efforts of the Udall Centers. The Committee further encourages NIH to require that the Udall Centers include a significant clinical component, in addition to their

ongoing basic research. In reviewing the Udall Center grants, the Committee also encourages the NIH to evaluate the applicants in a manner that recognizes the unique aspects of the clinical, coordination, and multidisciplinary components of the applicants, while continuing to preserve the integrity of the peer-review process. (p. 122)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) plans to continue the Morris K. Udall Centers for Parkinson's Disease (PD) Research program, and is eager to improve the coordination of research efforts across Centers. In a major step toward this goal, the Institute funded a PD Data Organizing Center (PD-DOC) at the University of Rochester in September 2004 to streamline the collection and distribution of clinical data across all the Udall and other PD research centers. In addition to data coordination, PD-DOC has also assumed the management of the annual meeting of Udall Center directors and staff, which is focused on the exchange of information between Centers and the development of collaborations. Regarding the need for additional coordination, the NINDS is completing a formal evaluation of the Udall centers program which will provide valuable insights into the collaborations and productivity of each Center in basic, translational and clinical PD research. The Institute anticipates delivery of the final report on the evaluation to the National Advisory Neurological Disorders and Stroke Council in September 2007, and subsequently, it can utilize these data to determine if further emphasis in any of these research areas is warranted.

With respect to clinical research, the NINDS continues to actively support the expansion of clinical studies across the Udall program. The November 2005 solicitation for Udall Centers included language emphasizing the need to move basic science findings toward the development of therapies, and in July 2003, NINDS increased the funding limit of \$1 million in direct costs for solicited, specialized research centers engaged in clinical projects to \$1.5 million. Many Udall Centers have expanded their clinical research programs under this new policy.

The reviews of the individual Udall Center applications continue to be carried out by a special emphasis panel of reviewers that is managed by the NINDS. The NINDS instructs reviewers to use special requirements described in the relevant Udall Program Announcements to guide their assessments; these requirements take into account the unique clinical, coordination, and multidisciplinary components of this program.

Item

Neuroprotection Trials - Parkinson's Disease Report – The Committee has urged the Director to expeditiously provide funding at the conclusion of the neuroprotection trials [NET-PD] for phase III clinical trials of all the neuroprotection compounds found to be not futile, including combinations of them. The Committee requests the Director to report to the Committee the current status of the NET-PD after the conclusion of each of the futility studies. (pp. 122-123)

Action taken or to be taken

Investigators involved in the Neuroprotection Exploratory Trials in PD (NET-PD) studies published the findings from the first two drugs evaluated, minocycline and creatine, in March 2006. The primary results of this study which used comparison data that were more than 15 years old (published in 1989) indicated that it would be reasonable to consider either drug for further clinical evaluation. However, additional comparisons of the minocycline group to controls that were just collected and are therefore more representative of the current PD patient population did not support pursuing minocycline in additional clinical studies. Based on these results, NINDS is planning a large Phase III trial of the antioxidant creatine. Trial investigators, along with NINDS staff are developing the clinical protocol and preparing to scale up the trial infrastructure to accommodate the increased enrollment that will be needed. The NINDS met with all of the trial site investigators in November 2006 to discuss multiple critical issues relevant to the Phase III trial, including the trial protocol, study timeline, recruitment goals and strategies, statistical analyses, site performance expectations, the use of electronic data capture, and minority recruitment.

The Institute will also submit formal reports to the Committee, through the regular Congressional Appropriations Committee Report clearance process, within three months after the NET-PD research team publishes its data on additional futility studies.

Item

Peripheral Neuropathy - This neurological disorder causes debilitating pain, weakness in the arms and legs, and difficulty walking. Although research is underway on diabetic neuropathy and HIV/AIDS-related neuropathy, the Committee strongly urges the NINDS to strengthen its research portfolio on other forms of neuropathy, and it notes with interest the upcoming workshop that the NINDS will convene to identify research goals. (p.123)

Action taken or to be taken

Peripheral neuropathy is a common neurological condition that is associated with a number of diseases, and the National Institute of Neurological Disorders and Stroke (NINDS) funds a wide range of research on the peripheral neuropathies. In addition to diabetic neuropathy and HIV/AIDS-related and other infectious neuropathies, NINDS also funds research on inherited neuropathies, such as Charcot-Marie Tooth disorder (CMT), inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), and rarer types of neuropathy such as familial amyloidotic polyneuropathy. Studies currently funded by NINDS focus on understanding the underlying genetic basis, molecular and cellular mechanisms, and natural history of these disorders.

Some of the neuropathies, including CIDP and some forms of CMT, are associated with disruptions in the myelin sheath, a covering of protein and fatty substances that insulates nerve fibers and prevents dissipation of the electrical signals. The NINDS supports a number of studies examining the process of myelination and its regulation, as well as the protein components that make up the myelin sheath. Other studies funded by NINDS

focus on identifying gene mutations responsible for certain forms of CMT and understanding the function and mechanism of action of these genetic defects. For example, NINDS-funded researchers have previously identified mutations in genes involved in some types of CMT. A number of these genes are important for basic cellular processes such as transport of cellular materials and the internalization and trafficking of proteins within the cell. Research funded by NINDS aims to further understand how disrupting these processes leads to disease. NINDS also supports studies focused on characterizing and understanding the underlying mechanisms of neuropathic pain, with the goal of developing treatments to alleviate the pain.

NINDS held a workshop on October 22-24, 2006 on the peripheral neuropathies. 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. Participants discussed a range of issues in therapeutic development for the neuropathies, from identification of target mechanisms to the conduct of clinical trials. Prominent researchers in the neuropathies as well as representatives from patient voluntary groups were represented. The Committee will be sent a summary of the workshop as part of the report to the Committee on Charcot-Marie Tooth-related research at NIH.

Item

Pick's Disease – The Committee urges the NINDS to initiate funding for drug discovery efforts that focus on specific targets relevant to treating the mechanisms underlying brain degeneration due to frontotemporal dementia [FTD]. The Committee further encourages the NINDS to conduct multicenter treatment trials for symptomatic management of Pick's disease and other FTDs. The Committee encourages the Institute to focus on methods for discovering the causes of this family of diseases, improving diagnostic accuracy, and providing longitudinal characterizations so that the success of intervention can be determined. (p. 123)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) grant portfolio on frontotemporal dementias (FTDs), including Pick's disease, is moving forward in exciting new clinical directions. In May 2006, the Institute funded a large translational research grant focused on the screening of drugs for FTDs. This research team expects to identify 1-2 optimal compounds for complete safety studies and to apply for an Investigational New Drug (IND) application to the Food and Drug Administration for human trials of the most promising drug.

Lithium, a drug used for many years to treat bipolar disorder in humans, is also emerging as a potentially promising approach to treat diseases that involve abnormal cellular accumulation of the tau protein (a component of the neuronal skeleton), including Pick's disease. In 2005, a group of investigators funded by the National Institute on Aging (NIA), the NINDS, and the Alzheimer's Association found that lithium treatment of mice exhibiting a form of neurodegeneration involving tau could reduce this degeneration if administered before significant structural abnormalities occurred in affected neurons. These data support further consideration of lithium as a treatment for neurodegenerative

diseases and dementias that involve abnormal tau accumulation. The NINDS is planning to provide support of a pilot clinical trial of lithium to treat progressive supranuclear palsy (another disease linked to abnormal tau which is more likely to respond to the lithium). The Institute hopes that any positive findings from this study may be useful in advancing lithium as a possible treatment for Pick's disease and other FTDs, as more is understood about their complex cellular causes.

Researchers funded by the National Institutes of Health are also making advances in understanding the fundamental causes of Pick's disease and other FTDs. NIA-supported laboratories have made two such recent discoveries: the identification of a new genetic mutation in families with FTD and an abnormal protein which may be present both in FTD and in amyotrophic lateral sclerosis (Lou Gehrig's disease). To capitalize on these discoveries and promote the discussion of the most timely research to pursue, the NINDS is partnering with the Association for Frontotemporal Dementias to support a meeting in January 2007 of leading researchers in FTD research. The sponsors will ask participants to identify priorities for basic, translational and clinical research.

Item

Rett Syndrome - The Committee remains concerned at the level of funding dedicated toward research into Rett Syndrome, an incurable and devastating childhood neurological disorder that is the leading cause of severe neurologic impairment in females and the only autism spectrum disorder with a known genetic cause. While once considered rare, increased diagnosis suggests that the prevalence of Rett Syndrome may be much greater than current estimates. Furthermore, Rett Syndrome is linked with autism, schizophrenia, bipolar disease and other mental disorders. The discovery in 1999 of the specific genetic cause of Rett Syndrome, a gene called MECP2, was a crucial breakthrough. The Committee encourages research aimed at understanding the pathogenesis of Rett Syndrome, the function of MECP2 in the developing and mature nervous system, and the identification of the targets of MECP2 and their role in disease. The development of outcome measures and new quantifiable assays to study Rett and related disorders are also needed to prepare for future interventional trials in patients. The Committee also encourages NIH to coordinate with private organizations supporting research initiatives in this area in order to ensure the most efficient use of resources. (p. 123)

Action taken or to be taken

The National Institute of Neurological Disorders and Strokes (NINDS) supports research to characterize the biochemical and neurophysiological basis of Rett syndrome. NINDS-supported studies are focusing on the regulation and function of MECP2, the gene mutated in Rett syndrome. The MECP2 protein is thought to modulate the expression of certain genes, including genes regulating brain growth. Deregulation of this process could lead to the abnormalities in brain development seen in Rett syndrome. Several ongoing NINDS-funded projects are identifying the targets of MECP2 and examining the mechanisms by which the MECP2 protein regulates gene expression. In addition, the MECP2 protein is itself regulated by nerve cell activity, suggesting that the MECP2 protein may play a key role in translating neuronal activity into changes in gene

expression. Two projects are characterizing the mechanisms by which nerve cell activity regulates MECP2 protein activity.

Several ongoing NINDS-funded projects are examining the mechanisms by which the MECP2 protein regulates gene expression and identifying the targets of the MECP2 protein and. Some of these genes regulate brain growth, and their deregulation could lead to the abnormalities in brain development seen in Rett syndrome. In addition, the MECP2 protein is itself regulated by nerve cell activity, suggesting that the MECP2 protein may play a key role in translating neuronal activity into changes in gene expression. Some NINDS-funded studies are characterizing the mechanisms by which nerve cell activity regulates MECP2 protein activity.

Several NINDS studies are examining some of the mechanisms common to Rett and other disorders such as autism, X-linked mental retardation. Since mutations in MECP2 cause a broad spectrum of disorders, a newly funded project is investigating the possibility that MECP2 loss in various subsets of neurons results in distinct behavioral changes. This research group will also characterize the downstream targets of MECP2 in the relevant brain areas in order to identify potential molecular targets for therapeutic intervention. Other NINDS-funded projects are focused on understanding the effects of the loss of MECP2 in brain areas involved in motor function or in learning and memory.

In addition, the NIH Blueprint for Neuroscience Research is addressing the need for better measures and assays for neurological function. The Blueprint is a collaboration among 15 Institutes and the Office of the Director aimed at facilitating neuroscience research by developing tools and resources. It recently awarded a contract for the development of an “NIH Toolbox for Assessment of Neurological and Behavioral Function.” This will consist of a comprehensive, easy-to-use assessment tool for cognitive, emotional, sensory and motor function. This tool will be useful for a variety of studies, including epidemiologic studies and clinical trials, and will be suitable for all neurological diseases, including Rett syndrome.

Finally, the NINDS has partnered with the National Institute on Mental Health (NIMH), and the National Institute on Child Health and Human Development (NICHD), the International Rett Syndrome Association (IRSA), and the Rett Syndrome Research Foundation (RSRF) to support a Program Announcement with Set-Aside Funds on Rett syndrome and MECP2. This initiative encourages applications on the pathogenesis of Rett syndrome, the function and regulation of MECP2, as well as therapy development and clinical studies.

Item

Stroke Rehabilitation – The Committee commends the Institute’s commitment to update the findings and recommendations of the Stroke Progress Review Report and urges that a special focus of the update be on the need to redouble efforts on rehabilitation science and the translation of rehabilitation discoveries into practice. The Committee notes that there is a growing body of evidence that stroke victims do not achieve the fullest possible recovery from rehabilitation because of limited awareness of research evidence for the

effectiveness of appropriate rehabilitation protocols and urges that this matter be addressed with additional research. Finally, the Committee urges the inclusion of rehabilitation scientists in NINDS - sponsored workshops, expert conferences and consensus conferences as appropriate. (p. 124)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is acutely aware of the importance of rehabilitation following stroke, and is already invested in research designed to expand our use of effective rehabilitation strategies and to develop new approaches for improving recovery across the patient population. For example, clinicians are increasingly using body-weight-supported locomotor training on a treadmill to facilitate recovery following stroke, however this use is not based on data from a well-designed clinical trial. To address this need, the NINDS is supporting the phase III Locomotor Experience Applied Post Stroke (LEAPS) trial, to determine if treadmill training facilitates the ability to walk in stroke survivors, compared with a rehabilitation regimen that involves non-specific, low intensity exercise. The NINDS has also co-funded the Extremity Constraint Induced Therapy Evaluation (EXCITE) study with the National Institute of Child Health and Human Development, which demonstrated that two weeks of constraint-induced therapy (a rehabilitation technique that involves forcing a patient to try to use a paralyzed limb) could provide clinically significant improvements in arm function that lasted for at least one year. Importantly, these findings serve as the first demonstration of effectiveness of a stroke rehabilitation approach in a large-scale, multicenter, randomized clinical trial.

The NINDS is also sponsoring clinical studies of constraint-induced therapy combined with behavioral therapy, and the use of transcranial magnetic stimulation (TMS) and other forms of brain stimulation to understand how brain circuitry reorganizes following a stroke and to treat any abnormal changes in these circuits.

Rehabilitation following stroke was one of 15 focus areas in the original Stroke Progress Review Group (SPRG) planning effort, initiated in 2001. That effort resulted in the identification of several research and resource goals for the National Institutes of Health and for the research community as a whole. In September 2006, the SPRG re-convened to assess progress made on all of the original SPRG goals and identify emerging research topics. The working group on stroke rehabilitation recommended the development of studies that examine critical parameters of conventional rehabilitation interventions (e.g., timing, dosing schedule); rehabilitation studies in animal models of stroke; develop interventions for chronically-impaired stroke survivors; and develop projects that focus on the links between neurologic impairment, disability and decreased social participation. The NINDS will continue to include representatives from the stroke rehabilitation research community in relevant future meetings as they are organized.

Item

Tuberous Sclerosis Complex - The Committee is encouraged that the NINDS has organized a Trans-NIH Tuberous Sclerosis Coordinating Committee, and it urges the Institute to continue to take a leadership role in convening meetings of this group. The

Committee believes that the scope of the Coordinating Committee should be broadened to include an international conference every 2 years. The Committee also encourages the NINDS to work with the NICHD and the NIMH to organize a conference focused on psychiatric issues and cognitive disabilities in TSC. (p. 124)

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 and the TS Alliance, a patient voluntary organization. The Working Group meets on an annual basis. At the most recent meeting in June 2006, the group shared information about the TSC research portfolios currently held by each of the member organizations and by the Department of Defense TSC Research Program. The group also discussed on-going clinical trials and preliminary plans for future trials, and the status of the five-year NIH Research Plan for Tuberous Sclerosis. The Working Group will discuss the best options available to support a trans-NIH international conference on TSC research. In addition, the NINDS will work with the NIMH and the NICHD to organize a workshop on psychiatric issues and cognitive disabilities in TSC.

A small case-report series published recently (*Annals of Neurology* 2006; 59:490-498) provides preliminary evidence that administering rapamycin to pediatric TSC patients with astrocytomas is well-tolerated and may lead to tumor regression. Although this small study is encouraging, a randomized, controlled trial is required to conclusively test whether rapamycin is safe and effective in treating TSC astrocytomas. Program staff from the NINDS and the National Cancer Institute are encouraging TSC clinical trial investigators to develop a grant application for a randomized, controlled trial to test the effect of rapamycin on astrocytomas.

In March 2007, the NINDS and partner organizations, including the TS Alliance, will sponsor a conference called “Curing Epilepsy 2007: Translating Discoveries into Therapies.” A presentation on rapamycin as a treatment for TSC will be featured during the session on medical treatment of cortical dysplasia. The conference also contains sessions on epileptogenesis and cognitive and psychological issues in individuals with epilepsy, which are also relevant to those with TSC who experience recurring seizures.

Item

Vulvodynia - NIH-supported research indicates that millions of women suffer from chronic pelvic and genitourinary pain conditions such as vulvodynia. Therefore, the Committee calls upon the NINDS, in coordination with the NICHD, ORWH, the NIH Pain Consortium and other ICs, to expand its support of research in this area, with a focus on etiology and multi-center therapeutic trials. The Committee also calls on NINDS to work with ORWH and other relevant ICs and government agencies, as well as patient and professional organizations, to implement an educational outreach campaign on vulvodynia. (p.124)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide range of research on understanding and treating chronic pain. Studies funded by NINDS aimed at deciphering the neurological basis of visceral and gynecologic pain have particular relevance to vulvodynia and other pelvic pain conditions. For example, studies funded by NINDS focus on understanding the nature and organization of the nerve supply to the uterine and vaginal tissues, how sensory neurons relay pain information back to the brain from these areas, and how the interplay between neurotransmitters (substances released by neurons), their receptors, and hormones contributes to pelvic pain. NINDS also supports a number of studies on the mechanisms and modulation of visceral pain, including studies on understanding the pain pathways between the brain and internal organs, as well as studying pain associated with conditions such as irritable bowel syndrome and pancreatitis. Understanding chronic pain in these conditions may help to shed light on other painful conditions such as vulvodynia.

NINDS is a member of the NIH Pain Consortium, which includes representation from National Institute of Child Health and Human Development (NICHD) and the Office of Research on Women's Health (ORWH) as well as numerous other NIH Institutes and Centers (ICs). In August 2006, a number of NIH ICs, representing the NIH Pain Consortium, released a Program Announcement, "Mechanisms, Models, Measurement, & Management in Pain Research," to inform the scientific community of the pain research interests of the various Institutes and Centers (ICs) at the NIH and to stimulate and foster a wide range of studies on pain as they relate to the missions of these ICs. As part of the announcement, the NIH solicits research on all conditions in which pain is a prominent feature, and encourages studies on a broad range of areas including the genetics of pain, the diagnosis and assessment of pain, pain management, and the epidemiology of pain. The initiative encourages research in basic, translational, and clinical research, and applications for multi-center therapeutic trials are welcome under the initiative.

NINDS will continue to partner with ORWH and other agencies and organizations, on both scientific efforts and outreach efforts, as appropriate, to advance research on chronic pain conditions such as vulvodynia.

National Institute of Allergy and Infectious Diseases

House Significant Items

Item

Asthma -- The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee encourages NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages NIAID to continue to support asthma prevention, treatment, and research activities. (p. 99)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to research to improve prevention and management of asthma, particularly related to pediatric populations. For example, the 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 members 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 NIAID also 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, ten trials are in development at four sites. In addition, the NIAID-supported Immune Tolerance Network is currently conducting two clinical trials and mechanistic studies in asthma.

To improve our asthma management efforts, especially as they relate to children, the NIAID opened a Pediatric Allergy Clinic at the NIH Clinical Center in FY 2005. This new clinic is now a focal point for translational research, physician training, and clinical trials of novel therapies. During FY 2006, there were over 250 patient care visits to the clinic. The clinic uses and evaluates child-friendly, non-invasive clinical tests to evaluate allergy symptoms.

In FY 2007, the NIAID will award the Immune Tolerance Network contract and establish the "Allergen and T-Cell Reagent Resources for the Study of Allergic Diseases" program to identify novel allergens and reagents to facilitate the development of therapeutic strategies to treat and prevent allergies. The NIAID is also seeking to initiate collaborative studies in pediatric allergic disease with other institutions and pharmaceutical companies. Studies will be directed toward elucidating the pathophysiology of allergic disease and providing resources for the discovery of novel therapeutic agents. The assessment and treatment of a large group of young patients will lead to a better understanding of asthma manifestations, treatment outcomes, and mechanisms of pediatric asthma and lay the groundwork for discovery of new therapies.

Item

Coinfection Research- The Committee is concerned that there is growing evidence of liver toxicity of highly active antiretroviral therapy (HAART) in those with decompensated liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients (HCV and/or HBV with HIV). The Committee encourages NIAID to initiate research initiatives in both of these areas. (p. 100)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains its commitment to the study of AIDS-associated opportunistic infections and co-infections, such as hepatitis B virus (HBV) and hepatitis C virus (HCV). Highly active antiretroviral therapy (HAART) has prolonged survival and reduced the incidence of opportunistic infections and co-infections in HIV-infected individuals; however, complications and side-effects associated with HAART have become an increasing concern for the medical management of HIV-infected individuals. In particular, individuals co-infected with HIV and hepatitis are experiencing therapy-related liver complications now being addressed by the scientific research community. For example, the NIAID is conducting the Solid Organ Transplant in HIV study to better understand the outcomes of kidney and liver transplants in HIV-infected subjects with viral suppression on HAART, many of whom are co-infected with HCV or HBV.

The NIAID is supporting research to improve understanding of the effects of HIV and HBV or HCV co-infection on liver disease. Currently, NIAID-supported research is investigating the impact of HIV proteins on HCV replication. This research will characterize the effect of HIV on HCV-regulated formation of fibrous tissue in the liver. This research also investigates the interaction of HIV and HCV in peripheral blood cells and the liver; the rate of HCV viral reproduction; and the prevalence, significance, and disease causing effect of an HCV viral load increase in individuals co-infected with HCV/HIV who are treated with antiretroviral therapy.

In FY 2006, the NIAID renewed support for the AIDS Clinical Trials Group (ACTG) through FY 2013. The ACTG will continue to include its Hepatitis Committee (HEP), which focuses on HIV/HCV and HIV/HBV co-infections as well as HCV and HBV monoinfections. The HEP aims to develop drugs and strategies for optimal timing and treatment of each virus and for the treatment of drug resistance for those individuals who do not respond to traditional treatment strategies; determine the natural history and effects of disease in all populations of HIV/HCV infected individuals; identify non-invasive markers of fibrosis; and assess the impact of HBV genetic characteristics on the natural history, drug response, and resistance. Currently, the ACTG is conducting several studies to evaluate the safety and efficacy of interferon-based therapies for HCV treatment, such as PEG-interferon, in persons co-infected with HIV and HCV.

Item

Hepatitis C Virus (HCV) Vaccine Development- The Committee is pleased to learn that phase I of a small hepatitis vaccine human trial has been successfully completed and that phase II regarding efficacy is underway. The Committee expects to be kept informed on progress regarding the development of this vaccine and its potential application for intervening in the development of chronic disease among the population currently infected with the hepatitis C virus. The Committee is concerned with preliminary information that this vaccine candidate may not be universally effective against all genotypes of hepatitis C and therefore encourages the simultaneous development of other vaccine candidates against hepatitis C vaccine. (p. 100)

Action taken or to be taken

Developing a safe and effective vaccine against hepatitis C virus (HCV) continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID plays a key role in trans-NIH hepatitis C research which includes development of an NIH-wide framework that incorporates the different missions of participating NIH Institutes and Centers into a cohesive global plan for hepatitis C research. In 2005, the NIAID cosponsored a workshop on Vaccines for Hepatitis C Virus which focused on the latest advances in HCV vaccine research and development.

The NIAID has completed a Phase I trial of a preventive HCV vaccine originally developed by one of our pharmaceutical industry partners. This vaccine candidate is focused on the HCV genotype that affects the majority of the U.S. population. The vaccine was administered with an adjuvant, a component added to improve the immune response to a vaccine. The trial results demonstrated that the vaccine is safe and elicits the anticipated immunological responses. In light of the successful completion of this trial, the company that originally developed the vaccine is planning a proof-of-concept Phase II field trial for efficacy. The NIAID has assisted in planning this study, which will be financed privately by the pharmaceutical manufacturer. The NIAID continues to conduct and support a broad range of research activities toward developing HCV vaccines.

Design of a protocol to study a therapeutic HCV vaccine candidate is currently being finalized. It is expected that this vaccine will be tested in two study groups: chronic HCV carrier patients who have failed standard treatment with interferon and ribavirin and chronic HCV carriers currently eligible for treatment but who have never been treated therapeutically.

The NIAID organized the Hepatitis Viruses and Drug Resistance meeting in April 2006 to discuss standardization of terms and assays for the assessment of antiviral resistance, and to build databases to catalogue and track mutations of hepatitis C virus and relevant clinical parameters. A panel of experts representing international agencies and government officials participated in a round table discussion. The panel anticipates publishing guidelines to address harmonization of nomenclature, definitions and clinical criteria early next calendar year.

Item

Implementation of the Transplantation Research Action Plan - The Committee is pleased that NIAID convened an expert conference and developed a five-year transplantation research action plan identifying the most urgently needed research to facilitate and increase in the success of organ transplantation. The Committee encourages an annual review of progress made in the various research areas identified by the plan with recommendations and appropriate follow up to enhance progress in promising, but low yielding areas of research specifically as they relate to organ donation, organ evaluation and organ transplantation. (p. 100)

Action taken or to be taken

Support for research to improve outcomes for transplantation continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). In September 2005, the NIAID convened an Expert Panel on Transplantation Research to develop the National Institutes of Health (NIH) Action Plan for Transplantation Research. Panelists participating in the development of the Action Plan included research scientists, clinicians and surgeons, and policymakers with expertise in solid organ and hematopoietic stem cell transplantation, immunology, immune tolerance, and organ preservation.

The development of the Action Plan was guided by three key principles: the importance of basic research in making fundamental advances in transplantation research; the bi-directional nature of translational research; and fostering multi-disciplinary research teams and maximizing trans-NIH transplantation research activities.

The Action Plan includes a set of goals and objectives intended to advance knowledge and clinical practice in the field of organ transplantation. The Action Plan also includes examples of ongoing research and a framework that has the potential, over the next five years and beyond, to yield scientific advances that may increase the success of organ transplantation. The NIAID will review the progress on the scientific activities outlined in the Plan on a periodic basis and will share scientific advances with the research community and the public.

Item

Inflammatory Bowel Disease- The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) entitled "Challenges in Inflammatory Bowel Disease (IBD)." This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to focus on: (1) the immunology of IBD and (2) the interaction of genetics and environmental factors in the development of the disease. (p. 100)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues its long standing commitment to research directed toward understanding and reducing 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, the NIAID seeks to translate this basic research into clinical trials of novel therapies for IBD.

On August 30, 2006, the NIAID sponsored the "Crohn's Disease and Intestinal Microbiota Workshop" for academic, industry and NIAID-supported researchers working on Crohn's disease. The workshop participants reviewed the current state of knowledge regarding intestinal microbial communities and Crohn's disease and identified research gaps and opportunities in this field. A summary of this meeting will be made publicly available on the NIAID website when finalized.

The NIAID will continue to participate in the Digestive Diseases Interagency Coordinating Committee, led by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The coordinating committee facilitates research on digestive diseases, including the immunology, genetics and role of the environment in IBD pathogenesis. Additionally, the NIAID serves as a member of the National Commission on Digestive Diseases, also led by NIDDK. The goal of this commission is to develop a long-range plan for digestive diseases research.

The NIAID will continue to support immunology-related research on inflammatory bowel disease through co-sponsorship of the Immune Tolerance Network (ITN); the Multiple Autoimmune Diseases Genetics Consortium (MADGC); 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

Living Donor Transplantation-- The Committee recognizes that the transplantation of organs, tissues, and cells is a powerful mode of treatment for dozens of life-threatening diseases affecting millions of Americans. The Committee encourages NIAID's basic and clinical research programs in transplantation to focus efforts on the study of living donor transplantation to enhance success rates by reducing morbidity and mortality. Additionally the Committee requests to be informed on the institute's plans to initiate a cohort study to assess the health outcomes of living donors not only following the period immediately after the donation but for the quality of life implications for decades post donation. (p. 100)

Action taken or to be taken

Improving the success rate of living donor transplantation continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). In FY 2006, the NIAID co-funded the "Outcomes of Live Organ Donors" initiative with the National Heart, Lung and Blood Institute and the Health Resources and Services Administration. This initiative established a research consortium to develop and implement a scientific

agenda to address issues relevant to living organ donors, including survival and health outcomes, risk assessment, and medical care needs.

The consortium is initiating retrospective and cross-sectional cohort studies to assess health outcomes of living donors of kidney and lung allografts. This assessment will include short-and long-term residual organ function, adverse medical events and quality of life of living organ donors. The data generated will characterize long-term health outcomes for living donors and provide best-evidence guidelines for future donors, recipients and transplant physicians. The consortium will also develop a database that aggregates existing registry cohorts of living donors at major transplant centers in the United States. These data include complete demographic, medical and where possible, immunological data for each donor subject.

In September 2005, the NIAID convened an Expert Panel on Transplantation Research to develop the National Institutes of Health (NIH) Action Plan for Transplantation Research. Panelists included research scientists, clinicians and surgeons, and policymakers with expertise in solid organ and hematopoietic stem cell transplantation, immunology, immune tolerance, and organ preservation. Panelists discussed the current state of the science and identified research issues related to live organ donation and reducing the morbidity and mortality of patients on waiting lists. Recommended areas of focus for NIH research identified by the panelists include research to increase organ availability and development of alternatives to organ transplantation and organ-assistive devices.

Additionally, the NIAID chairs the NIH Transplantation Research Coordinating Committee and represents the NIH on the Department of Health and Human Services Secretary's Advisory Committee on Organ Transplantation. The NIAID will continue to work with other NIH Institutes and Centers and with the Department to reduce the morbidity and mortality of living organ donors.

Item

Meningococcal Disease-Serogroup B Immunization Research – Although the Committee recognizes that meningococcal disease is vaccine-preventable in most cases, approximately 30 percent of the deaths and disabilities from this bacterial infection are attributed to serogroup B, which is not vaccine-preventable. The Committee encourages NIAID to increase specific research efforts to develop an effective, low-cost vaccine against serogroup B that will help protect infants and adolescents in the near term. (p. 100-101)

Action taken or to be taken

The bacterium *Neisseria meningitidis* (meningococcus) is a leading cause of bacterial meningitis, a disease that results in inflammation of the membranes covering the brain and spinal cord. There are two vaccines against meningococcus available in the United States. Both vaccines can prevent multiple types of meningococcal disease, but neither is effective against serogroup B infection.

The National Institute of Allergy and Infectious Diseases (NIAID) has supported basic research on meningococcal disease for many years. These efforts have included studies on microbial pathogenesis; studies designed to understand the molecular basis of the immune response to the serogroup B organism; and projects that have established an infant rat animal model for studying serogroup B meningococcal disease.

The specific immune properties of serogroup B meningococcus present challenges to vaccine development. The NIAID plans to sponsor a workshop in FY 2007 to identify and discuss strategies for the discovery and development of novel vaccines. Part of this workshop will focus on the difficulties involved with developing a vaccine against serogroup B meningococcus, and on alternative approaches to the problem. For example, the NIAID is supporting research that has shown that a combination of three monoclonal antibodies can recognize all serogroup B strains, thus presenting a potential vaccine approach.

The NIAID will continue to stimulate and support research that may lead to more effective prophylactic and therapeutic approaches for preventing and controlling respiratory infections, including the development of a vaccine against serogroup B meningococcus.

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. 127-128)

Action taken or to be taken

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 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 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

Primary Immunodeficiency Diseases (PI) - NIAID is the lead agency for research into bone marrow transplantation (BMT). Recently, the survival rate for severe combined immune deficiency (SCID) from related HLA-identical donors has resulted in a survival rate of over 90%. Unfortunately for most patients, there are no HLA identical donors. Alternative approaches using HLA-matched unrelated donors and HLA-mismatched related donors have produced very promising results. These new approaches have been designed to eliminate graft versus host disease, and other complications. The Committee encourages NIAID to develop therapeutic approaches to treating SCID patients who require BMT. Advancements in BMT will benefit not only children with SCID, but persons with many other diseases (such as cancer, lupus, and HIV/ AIDS) who rely on this therapy. (p. 101)

Action taken or to be taken

Research on the treatment of primary immunodeficiency diseases remains a priority for the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID, in collaboration with the National Heart Lung and Blood Institute, is developing safe and effective approaches to treat and cure patients with severe combined immunodeficiency (SCID) who require bone marrow transplants (BMT). Methods are being developed to minimize graft versus host disease (GVHD), improve GVHD therapies, and develop gene therapy for SCID.

First, to minimize the occurrence of GVHD, scientists are investigating a compound which reduces the inflammatory responses that initiate GVHD. Next, to improve therapies when GVHD does develop, NIAID scientists are studying the safety and efficacy of extracorporeal photopheresis for treating GVHD. In this procedure, a physician collects some of the cells that cause GVHD, treats them with a combination of drugs and light therapy, and returns them to the body. Finally, NIAID scientists have completed the first phase of a clinical trial of gene therapy as treatment for children with inadequate immune reconstitution despite prior bone marrow transplant from a parent. Results of this trial showed that the gene was inserted into the patients' cells. Follow-up

studies are being conducted to determine the long-term safety and efficacy of this approach.

In addition, the NIAID continues to support the Primary Immunodeficiency Diseases Consortium. The Consortium makes awards for pilot research projects, maintains a primary immunodeficiency diseases registry, and manages a repository of specimens from subjects with primary immunodeficiency diseases. The Consortium has funded 22 research proposals and continues to review new proposals every year. Advances made through this research may contribute to improvements in BMT and treatment of SCID. The NIAID also supports research on other potential therapies for SCID such as gene therapy, gene correction, and enzyme replacement.

Item

Tuberculosis - The Committee is pleased with NIAID's efforts to develop an effective TB vaccine, and encourages expansion of work on this important initiative. (p. 101)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to research to develop new and improved vaccines against tuberculosis. The currently available tuberculosis (TB) vaccine, known as bacillus Calmette-Guerin (BCG), is given right after birth and provides reasonable protection against complications of TB in children. However, the BCG vaccine does not reliably prevent the development of pulmonary TB, the most contagious form of the disease, in adults or adolescents. Furthermore, the deadly combination of HIV and TB and the increase in drug-resistant and extensively drug-resistant TB underscores the need for an effective preventive strategy.

Through the Tuberculosis Research Materials and Vaccine Testing contract, the NIAID provides TB research reagents for microbiological and genomic studies to qualified investigators around the world and conducts animal studies to help identify promising new vaccine candidates and approaches. More than 150 such studies have been conducted under this contract. One vaccine candidate developed using these resources has recently entered human clinical trials, and several other candidates are progressing through various stages of preclinical development.

The NIAID also is supporting the Millennium Vaccine Initiative – Novel Vaccines for Tuberculosis and Malaria. Under this contract, different delivery strategies for advanced vaccine candidates are being developed to maximize effectiveness of these candidates in later human trials.

In addition, the NIAID continues to support a Phase II clinical study of a candidate TB vaccine in HIV co-infected patients in Tanzania. The study seeks to prevent disseminated or pulmonary TB in this population.

Translational studies to better understand and improve upon the BCG vaccine are being conducted at the NIAID-supported Vaccine Treatment and Evaluation Unit (VTEU) in

St. Louis, Missouri. Beginning in FY 2007, this VTEU will conduct a Phase I clinical trial investigating the safety and immunogenicity of one versus two BCG vaccinations in healthy adults when the vaccine is delivered by intradermal injection, orally, or by combined routes of administration.

Senate Significant Items

Item

Antibiotic Resistance - NIAID should move aggressively to strengthen translational research efforts in the area of antibiotic research and development particularly with regard to multi-drug resistant gram negative bacterial infections for which few drugs are moving forward in the pharmaceutical pipeline as well as methicillin-resistant *Staphylococcus aureus* [MRSA] infections, which have become a silent epidemic in communities and hospitals across the country. NIAID also should accelerate its antibiotic resistance basic research efforts to more quickly advance our understanding of mechanisms of resistance and how resistant microbes impact human health. (p. 125)

Action taken or to be taken

Basic research on antibiotic resistance remains a high priority for the National Institute of Allergy and Infectious Diseases (NIAID). For example, the NIAID manages a portfolio of grants focused on antibiotic resistance among common bacteria responsible for hospital-acquired infections. These grants support research on the basic biology of resistant organisms; new diagnostic techniques, therapies, and preventive measures; and the mechanisms by which bacteria develop and share resistance genes.

Basic research efforts are underway at the NIAID to determine how *Staphylococcus aureus* resists the body's immune system. NIAID scientists hypothesize that the increase of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) disease is due to bacterial factors that alter immune system cells. Determining how the bacteria alter the immune system will further development of new therapeutic targets for MRSA infections.

The NIAID is also supporting the development of strategies to analyze surface proteins present in organisms such as *Staphylococcus aureus* strains that are resistant to the antibiotic vancomycin. These surface proteins play a role in virulence and survival in bacterial infections. This research holds promise for elucidating mechanisms of virulence and antibiotic resistance.

The NIAID supports the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA). The NARSA is a multidisciplinary international cadre of scientists conducting basic and clinical research focused on combating antimicrobial resistant *Staphylococcus aureus* and related bacterial infections. The Network maintains a repository of antibiotic-resistant staphylococcus strains that scientists can request for their research.

In addition, NIAID researchers are conducting a clinical study with patients suffering from extensively drug resistant tuberculosis (XDR-TB). This study is revealing important clues about the evolution and natural history of drug resistance in *Mycobacterium tuberculosis*.

In FY 2007, the NIAID plans to support two new initiatives to develop new or improved drug treatments for disease causing microbes such as *Clostridium difficile*, *Pseudomonas*, *Acinetobacter*, *Enterobacter*, *Klebsiella*, and *Staphylococcus aureus*.

Item

Antimicrobial Resistance - The Committee commends NCI, CDC and NIAID for their multi-agency efforts focused on reducing antimicrobial resistance to infectious diseases, improving the medical management of patients infected by hospital- and community-acquired *Staphylococcus aureus* and similar infections, and developing new therapeutics for treatment of these infections. However, the Committee notes that no FDA-licensed vaccines for prevention of hospital- and community-acquired multidrug-resistant *Staphylococcus aureus* and similar infections are currently available and views this as a critical gap in medicine and public health. The Committee is aware that new conjugate vaccine technologies currently exist and clinical studies of promising bacterial vaccine candidates have been conducted. The Committee urges NIAID to assist in supporting advanced development and clinical studies needed to make vaccines and immune therapeutics available for prevention and treatment of these life-threatening infections. (p. 125)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a robust research portfolio on *Staphylococcus aureus* and similar infections. This research has led to important discoveries that may lead to the development of vaccines and therapeutics for the treatment of life-threatening infections. Recently, NIAID-supported investigators created a vaccine that significantly protects mice from diverse strains of the *Staphylococcus aureus* bacterium that cause disease in humans. This vaccine represents a promising step toward identifying potential components to combine into a vaccine designed for people at high risk of invasive *Staphylococcus aureus* infection.

NIAID-supported researchers have identified the molecular structure formed between a particular *Staphylococcus aureus* protein and collagen, a protein present in human cells. Understanding the mechanism by which *Staphylococcus aureus* adheres to host structures will help to elucidate the infection process and could eventually lead to vaccines to thwart. Additional studies in mice have shown that immunization with *Staphylococcus aureus* clumping factor B reduces the bacteria that colonize the nasal passages. This basic research establishes the foundation for developing promising therapeutics which can advance to evaluation in clinical studies and ultimately advanced product development.

The NIAID will support an FY07 initiative entitled Clinical Trial for Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) Infections. This

initiative seeks to define the optimal outpatient treatment with skin and soft tissue infection in areas where prevalence of CA-MRSA is high.

Item

Asthma -- The Committee is very pleased with NIAID's leadership regarding asthma research and management. The Committee urges NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also urges the NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. (p. 125-126)

Action taken or to be taken

Please refer to page 101 of this document for the NIAID's response to this significant item regarding asthma.

Item

Atopic Dermatitis - The Committee was pleased to receive the February 2006 report on NIAID's research efforts related to atopic dermatitis (AD). The Atopic Dermatitis and Vaccinia Immunization Network and the Immune Tolerance Network are important initiatives. However, the Committee believes more needs to be done to encourage investigator-initiated research on AD, particularly in light of recently announced discoveries by NIH scientists regarding the relationship of ineffective skin barrier and immune system response to allergens. The Committee again encourages the NIAID to cooperate with NIAMS and other institutes to spearhead a multidisciplinary, multi-institute initiative to encourage investigator-initiated research projects on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. (p. 126)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to research to better understand the role of atopic dermatitis (AD) related to immunization against smallpox, as well as asthma and other allergic diseases. The NIAID remains committed to encouraging investigators conducting research related to AD. For example, in FY 2004, the NIAID, with expert advice from the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS), established the Atopic Dermatitis and Vaccinia Immunization Network (ADVNI) to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum and to protect individuals with AD from the adverse consequences of smallpox vaccine exposure.

Research supported by both the ADVNI and by the NIAMS provided the first clues about the pathogenesis of eczema vaccinatum. This research demonstrated that there is a defect in innate immune function in the skin of AD patients, that molecules characteristic of allergic inflammation are responsible for this defect, and that patients with AD and eczema herpeticum (EH) have a more profound innate immune defect than subjects with only AD.

The NIAID also supports clinical trials to evaluate strategies to reverse progression to asthma and other allergic diseases in patients who have atopic dermatitis. The NIAID-sponsored Immune Tolerance Network is currently conducting a clinical trial to determine whether oral administration of specific allergens will prevent the development of allergic diseases and asthma in children with atopic dermatitis and food allergy. A second clinical trial seeks to determine if feeding a peanut-containing snack to young children at risk of developing peanut allergy will prevent development of this allergy.

The NIAID has contracted with two pharmaceutical firms to conduct clinical trials of the next-generation smallpox vaccine, modified vaccinia Ankara (MVA); these trials are expected to be fully enrolled in FY 2007. MVA is anticipated to have fewer side effects than the traditional smallpox vaccine. One firm has completed an early trial in volunteers with atopic dermatitis with no adverse reactions. Both of these firms are also planning future clinical trials in volunteers with atopic dermatitis.

Item

Autoimmune Diseases - The Committee encourages NIAID to support communication between researchers studying different autoimmune diseases so that findings in one disease can quickly be applied to related conditions. As part of this effort, NIAID is urged to expand its interactions with the National Center for Biotechnology Information [NCBI] to establish a database where results of studies can be readily accessed by the research community. Congress commends the NIH Autoimmune Diseases Coordinating Committee [ADCC] for fostering collaborative, integrated multi-Institute research on issues affecting the genetically related family of autoimmune diseases. The ADCC should focus on the role of environmental and infectious agents in the initiation and/or exacerbation of autoimmune diseases. Additionally, the Committee encourages the ADCC to be proactive in identifying promising areas of autoimmune research where collaboration among the NIH institutes enhances the potential for major advances. (p. 126)

Action taken or to be taken

Research on autoimmune diseases continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). For example, the NIAID and the National Center for Biotechnology Information, a component of the National Library of Medicine, support a database which makes available to researchers information related to autoimmune diseases. The Major Histocompatibility Complex (MHC) database (dbMHC) supports information on DNA and clinical data for researchers investigating human leukocyte antigens. The dbMHC allows investigators to submit, edit, view, and exchange MHC research data. The dbMHC was launched in 2004. Currently, information on two types of autoimmune diseases, rheumatoid arthritis and type 1 diabetes, are included in the database.

The NIAID also supports the Multiple Autoimmune Diseases Genetics Consortium (MADGC) which maintains a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. The repository provides to qualified researchers well-

characterized material for use in research to identify genes involved in autoimmune diseases. The repository currently contains samples from 1,243 individuals diagnosed with an autoimmune disease and approximately 1,000 control subjects, all with associated clinical information.

The Autoimmune Disease Prevention Centers, co-sponsored by the NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the Office of Research on Women's Health, and the Juvenile Diabetes Research Foundation, conduct research on the development of new targets and approaches to prevent autoimmune diseases, including type 1 diabetes, Sjögren's syndrome, multiple sclerosis, and rheumatoid arthritis.

Item

Behavioral Research on Pandemic Flu -- The Committee encourages NIAID to work with OBSSR to identify and fund behavioral research on infectious diseases. In particular, behavioral research in areas such as risk perception, adherence to vaccination recommendations, and public health preparedness could enhance scientific research on preparation and response to pandemic influenza outbreaks. (p. 126)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases' (NIAID) infectious disease research portfolio is concentrated on basic research, applied research, and the development of vaccines and therapeutics to prevent and treat infectious diseases. The NIAID also conducts some ancillary studies to assess attitudes, beliefs, and behaviors related to vaccine research and the transmission of infectious diseases.

For example, the NIAID's HIV Vaccine Communications Campaign conducted a survey in 2003 to assess attitudes, knowledge and awareness of HIV vaccine research in U.S. adults. The survey found that awareness, knowledge, and attitudes toward HIV vaccine research vary by population and helped identify areas that need to be addressed in these populations in order to ensure an adequate number of volunteers for future HIV preventive vaccine clinical trials. In addition, the NIAID-sponsored HIV Prevention Trials Network (HPTN), which tests the safety and efficacy of non-vaccine interventions designed to prevent the transmission of HIV, sponsors research on behavioral interventions. The results of the study were published in the *Journal of Acquired Immune Deficiency Syndromes* in December 2005.

Another component of the National Institutes of Health, the National Institute of Mental Health (NIMH), also funds ongoing research centered on behavioral considerations in the development and dissemination of a vaccine for HIV/AIDS. One study examines how members of communities at-risk for HIV infection view the acceptability of hypothetical HIV/AIDS vaccines. The study will also determine whether perceived risk of infection and various socio-demographic factors, behavioral characteristics, and systemic barriers are predictors of vaccine acceptability and intentions. The study results will provide an empirical basis for the development of consumer-based public health education strategies

tailored to at-risk populations and will help guide public health agencies toward optimal dissemination of future vaccines. This study was started in 2004 and is anticipated to be completed in 2008.

Findings from these research efforts may inform future public health campaigns regarding dissemination of vaccines, not only for HIV/AIDS, but also for pandemic flu. The NIAID and the NIH Office of Behavioral and Social Sciences Research recognize that behavioral research related to the public's response to infectious disease outbreaks is increasingly important and welcome the possibility of working together on this issue should the appropriate opportunity arise.

Item

Coinfection Research -- The Committee is concerned that there is growing evidence of liver toxicity of highly active antiretroviral therapy [HAART] in those with decompensated liver disease awaiting liver transplantation. There also appears to be an emerging problem of liver cancer in co-infected patients [HCV and/or HBV with HIV]. The Committee encourages NIAID to initiate significant research initiatives in both of these areas. (p. 126)

Action taken or to be taken

Please refer to page 102 of this document for the NIAID's response to this significant item regarding coinfection research.

Item

Hepatitis- The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with voluntary health organizations to promote liver wellness, education, and prevention of hepatitis. (p.126)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to improving awareness of liver wellness, education and prevention of hepatitis through support for basic and clinical research, including product development and clinical trials. The NIAID strives to provide easily accessible information on these activities to the public. For example, the NIAID makes information on research related to hepatitis and disease management available through the Institute's website and provides links to publications posted on the National Institute for Digestive Diseases and Kidney website. Information on NIAID clinical trials related to prevention and treatment of hepatitis is included in the clinicaltrials.gov online database.

The NIAID's support for research related to hepatitis has included sponsoring two NIH Consensus Development Conferences focused on disease management of hepatitis C. The purpose of such conferences is to evaluate available scientific information and develop an NIH consensus or state-of-the-science statement to advance understanding about the current knowledge on a disease and inform patients and health providers. NIAID program staff participate in workshops and meetings geared toward scientific

audiences to discuss selected critical issues in basic hepatitis research and disease management.

The NIAID plans to continue research related to hepatitis through investigator-initiated grant awards and applied research and development efforts through partnerships with academic and corporate scientists. Additionally, the NIAID will continue to work to enhance efforts of the NIH to promote awareness and education related to hepatitis and liver wellness.

Item

Hepatitis C Virus [HCV] Vaccine Development -- The Committee is pleased to learn that phase I of a small hepatitis vaccine human trial has been successfully completed and that phase II regarding efficacy is underway. The Committee is concerned with preliminary information that this vaccine candidate may not be universally effective against all genotypes of hepatitis C and therefore urges the simultaneous development of other vaccine candidates against this disease. (p. 127)

Action taken or to be taken

Please refer to page 103 of this document for the NIAID's response to this significant item regarding Hepatitis C Vaccine Development.

Item

Immune Tolerance Network -The Committee commends the NIAID and NIDDK for their support of preclinical studies of new approaches to immune tolerance to prevent or treat type 1 diabetes. The Committee urges the NIAID to expedite the translation of promising results into early phase clinical trials within the Immune Tolerance Network. (p. 127)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad range of basic, translational, and clinical research on the underlying mechanisms of immune tolerance and the evaluation of tolerance induction strategies in animal models and clinical trials. The NIAID recognizes that advances in immune tolerance induction will provide valuable therapeutic strategies to treat type 1 diabetes and to eliminate the need for life-long, systemic immunosuppressive therapy for transplant patients.

An example of the Institute's research efforts in this area is the Immune Tolerance Network (ITN), an international, collaborative research consortium co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International. Researchers of the ITN evaluate novel tolerance induction strategies and their mechanisms of action in the treatment of autoimmune diseases, asthma, and allergic diseases, and in the prevention of rejection of transplanted organs, tissues, and cells.

Currently, the ITN is actively enrolling participants in eleven clinical research studies. These studies seek to improve understanding of the role of immune tolerance in treating

various diseases of the immune system. The ITN is also developing clinical research studies to analyze and monitor the safety of human insulin B chain peptide in subjects with type 1 diabetes and a Phase I/II trial to evaluate the safety and efficacy of islet transplantation in type 1 diabetics.

Results from a study conducted by the ITN related to the treatment of type 1 diabetes were published in the New England Journal of Medicine in September 2006. This study expanded on previous NIAID-supported research by showing that islet transplantation restores a patient's ability to produce insulin and greatly improves the ability to maintain more stable blood sugar levels for a time; however, insulin independence is not durable. Further studies to try to achieve longer periods of insulin independence are ongoing.

In FY 2007, the NIAID will award the ITN contract, which is being re-competed. In FY 2008, the Data Coordinating Center for the Immune Tolerance Network will be re-competed. Through continuing support of these programs, the NIAID will maintain its commitment to basic research on immune tolerance and the translational and clinical research that bring basic discoveries to the patient care arena.

Item

Implementation of the Transplantation Research Action Plan - The Committee is pleased that NIAID convened an experts conference and developed a 5-year Transplantation Research Action Plan identifying the most urgently needed research to facilitate and increase in the success of organ transplantation. The Committee urges an annual review of progress made in the various research areas identified by the plan with recommendations and appropriate follow-up to enhance progress in promising, but low-yielding areas of research specifically as they relate to organ donation, organ evaluation, and organ transplantation. (p. 127)

Action taken or to be taken

Please refer to page 104 of this document for the NIAID's response to this significant item regarding implementation of the Transplantation Research Action Plan.

Item

Inflammatory Bowel Disease -- The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) titled "Challenges in Inflammatory Bowel Disease [IBD]." This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to expand its research partnerships with the IBD community in FY 2007 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. (p. 127)

Action taken or to be taken

Please refer to page 104 of this document for the NIAID's response to this significant item regarding inflammatory bowel disease.

Item

Living Donor Transplantation -- The Committee recognizes that the transplantation of organs, tissues, and cells is a powerful mode of treatment for dozens of life-threatening diseases affecting millions of Americans. From this perspective, the Committee urges NIAID's basic and clinical research programs in transplantation to focus efforts on the study of living donor transplantation, to enhance success rates by reducing morbidity and mortality. Additionally, the Committee would like to be informed on the Institute's plans to initiate a cohort study to assess the health outcomes of living donors not only following the period immediately after the donation but for the quality of life implications for decades post donation. (p. 127)

Action taken or to be taken

Please refer to page 105 of this document for the NIAID's response to this significant item regarding living donor transplantation.

Item

Lupus - The Committee urges the NIAID to expand and intensify genetic, clinical and basic research and related activities with respect to lupus, with particular focus on identifying biomarkers and addressing the apparent health disparities associated with this disease. (p. 127)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to research related to lupus which will help to identify biomarkers and address the health disparities association with lupus. For example, the NIAID supports the Multiple Autoimmune Diseases Genetics Consortium (MADGC), a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides specimens and data for to scientists who identify genes involved in autoimmune diseases, including lupus. To date, samples from 1,243 affected individuals and approximately 1,000 control subjects are available to qualified researchers.

The NIAID sponsors research to treat lupus and other autoimmune diseases through the Autoimmunity Centers of Excellence (ACEs) and the Immune Tolerance Network (ITN). The ACEs are currently conducting or planning three clinical and pre-clinical trials of treatments for lupus nephritis. The NIAID also sponsors the Lupus Immunosuppressive/ Immunomodulatory Therapy or Stem Cell Transplant study to compare two potential treatments for lupus – immune system regulation and stem cell transplantation. This study is currently open to enrollment. In addition, the NIAID supports research on the development of new targets and approaches to prevent autoimmune diseases, including lupus, through the Autoimmune Disease Prevention Centers.

In FY 2007, the NIAID plans to support a new initiative, "Allogeneic Hematopoietic Stem Cell Transplantation for Autoimmune Diseases" to evaluate the effectiveness of transplantation of hematopoietic stem cells – which have the potential to become blood and immune cells – to halt progression, or even cure, patients with autoimmune diseases

such as lupus. The initiative will also provide data on the biological mechanisms that lead to autoimmune diseases.

The NIAID coordinates its lupus research activities with other NIH Institutes and Centers and with other Federal agencies through participation on the Lupus Federal Working Group and the Autoimmune Diseases Coordinating Committee, which the NIAID chairs.

Item

Primary Immunodeficiency Diseases - NIAID is the lead agency for research into bone marrow transplantation [BMT]. Recently, the survival rate for Severe Combined Immune Deficiency [SCID] from related HLA-identical donors has resulted in a survival rate of over 90 percent. Unfortunately, there are no HLA identical donors for most patients. Alternative approaches using HLA-matched unrelated donors and HLA-mismatched related donors have produced very promising results. These new approaches have been designed to eliminate graft versus host disease and other complications. Research and resources should be directed by NIAID to develop therapeutic approaches to “curing” SCID patients who require BMT. (p. 128)

Action taken or to be taken

Please refer to page 108 of this document for the NIAID’s response to this significant item regarding primary immunodeficiency diseases.

Item

Psoriasis - The Committee urges NIAID to support genetic, clinical, and basic research related to the understanding of the cellular and molecular mechanisms of psoriasis and psoriatic arthritis, chronic and immune-medicated diseases. (p. 128)

Action taken or to be taken

Improving understanding of psoriasis and other immune-mediated diseases continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). For example, the NIAID supports the Immune Tolerance Network (ITN) to evaluate novel tolerance-inducing therapies in autoimmune diseases, asthma, and allergic diseases and to prevent rejection of transplanted organs tissues and cells. Through the ITN, the NIAID has begun a clinical trial, “Treatment of Psoriatic Arthritis with hOKT3 γ 1 (Ala-Ala).” This study will determine the safety and efficacy of hOKT3 γ 1 (Ala-Ala), a humanized monoclonal antibody treatment strategy, in combination with other drugs that slow cell growth, in the treatment of psoriatic arthritis.

In addition, the NIAID supports a cooperative research group, “HLA Region Genetics in Immune-Mediated Diseases,” to define the association between human leukocyte antigen region genes or genetic markers and immune-mediated diseases such as psoriasis.

Finally, the NIAID is supporting a Phase II clinical trial of aminotrexate, a substance that blocks the activity of folic acid, for the treatment of psoriasis through the Small Business Innovation Research – Fast Track program. This trial is expected to begin enrolling patients in early 2007.

In FY 2007, the NIAID will award the Immune Tolerance Network contract. Autoimmune diseases, including psoriasis, will remain an important component of the NIAID's basic and clinical research portfolio. The Institute will continue to support research into psoriasis, the cellular and molecular mechanisms that underlie this disease, and possible treatments and prevention strategies.

Item

Tuberculosis - The World Health Organization [WHO] estimates that nearly one-third of the world's population will become infected with tuberculosis [TB], and by 2020, 70,000,000 people will die worldwide of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine and notes NIAID expansion of work on this important initiative. (p. 128)

Action taken or to be taken

Please refer to page 109 of this document for the NIAID's response to this significant item regarding tuberculosis.

Item

Xenotransplantation - The Committee commends the NIAID on developing a xenotransplantation initiative and encourages the Institute to foster collaborations and shared resources among investigators to reduce the waiting list of organ transplant recipients. Specifically, NIAID is encouraged to evaluate the benefits of using porcine pancreases, which could provide an unlimited supply of insulin-producing cells for transplantation to restore normal glucose control in diabetic patients. (p. 128)

Action taken or to be taken

In 2005, 28,108 organ transplants were performed in the United States, but more than 90,000 patients remained on the waiting list for an organ transplant. Although there has been a gradual increase in the number of donated organs, the number of patients on waiting lists greatly exceeds the supply of available organs. Xenotransplantation offers a potential solution to the severe shortage of human organs to treat patients with end-stage organ diseases. The swine is the primary species of interest as a potential source of donor organs, tissues, and cells due to its favorable reproductive capacity as well as anatomical and physiological similarities to humans.

Challenges of xenotransplantation to be addressed include the immune response of the recipient against the xenograft, the physiological limitations of organs or tissues functioning in a xenogeneic environment, and potential transmission of xenogeneic infectious agents from the graft to the recipient.

The National Institute of Allergy and Infectious Diseases (NIAID) continues to foster collaborations and shared resources among scientists studying xenotransplantation. In FY 2003, the NIAID established the National Swine Research and Resource Center, which maintains, preserves, and distributes swine models for biomedical research including xenotransplantation. In FY 2005, the NIAID established the Immunobiology

of Xenotransplantation Cooperative Research Program. This program is developing pre-clinical porcine to non-human primate models of xenotransplantation, including islet xenotransplantation. Efforts at the Research and Resource Center and in the Cooperative Research Program are ongoing.

The NIAID also serves as the NIH representative to the Secretary's Advisory Committee on Xenotransplantation. The NIAID will continue to support research on xenotransplantation, and to foster collaborations and shared resources among investigators to advance this field.

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National Institute of General Medical Sciences

House Significant Item

Item

Cystic Fibrosis (CF) – The Committee encourages NIGMS to support methods for the creation of tools and reagents and advances in techniques for precision monitoring of folding and trafficking events and to encourage sharing of resulting data, especially in area of protein folding or imaging. These tools will support ongoing research efforts by other NIH institutes to screen molecules that may affect improper protein folding and trafficking, as well as efforts to develop therapies to correct this defect for CF and other diseases. (p. 101)

Action taken or to be taken

Mutant proteins, over-abundant proteins, or proteins synthesized under stressful conditions in the cell may cause disease in several ways. Some, like the protein CFTR, responsible for cystic fibrosis, fold too slowly and are degraded prematurely, before they can assume their proper location and function. Others, like the proteins involved in Alzheimer's Disease and Parkinson's Disease, are dynamically unstable and can take on toxic forms before they complete their folding, leading to "plaques and tangles." Over the last twenty years traditional genetic and biochemical methods have made substantial progress toward understanding protein misfolding, the systems cells use to protect against it, and the ways it can lead to disease. Just recently, though, dramatic advances in biophysical techniques have begun to provide an entirely new window into the misfolding process and how it may be corrected or prevented.

Exciting new information is coming from instruments developed by NIGMS investigators that use lasers to produce snapshots of molecules like CFTR and the Alzheimer's amyloid protein in a millionth of a second or even less. Putting snapshots together makes a movie of the folding protein and allowed scientists to see, for the first time, the forms of the protein that occur before it is completely folded. These intermediate forms are often the true origin of the disease and present an entirely new target for potential therapeutics. Another new and rapidly expanding area of research is the use of computers to predict whether and how fast a protein may misfold, based on genetic information. Until recently misfolding was too complex a problem for such an approach. But with more powerful computers and more clever methods being developed, exciting progress is being made. One novel project, "folding@home," employs unused computer time on over one million computers throughout the world to speed up progress in understanding this important health problem. In addition, as part of the NIH Director's Pioneer Award program in which NIGMS plays a lead administrative role, two of the 13 new awardees for 2006 proposed developing new methods for examining protein folding processes inside living cells, an important step to understanding cystic fibrosis and many other diseases.

Senate Significant Item

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. (p. 128)

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 to prepare for research careers in the biomedical sciences, the MARC Branch focuses on undergraduate research training, supporting both institutional research training grants and grants for ancillary training activities. In FY 2006, the MARC institutional research training grants supported approximately 627 undergraduate students, many of whom attended historically black colleges and universities (HBCUs) or historically black health professions schools. 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 2006, the RISE program supported the research development of approximately 1055 underrepresented minority students, most of whom were 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 has 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.

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National Institute of Child Health and Human Development

House Significant Items

Item

National Children's Study. – The Committee is very disappointed to see that the proposed elimination of funding for the National Children's Study is mentioned only in passing under the 'Items of Significant Interest' section and nowhere else in the entirety of NIH's fiscal year 2007 justification material. The lack of discussion related to this significant termination, which has enjoyed bipartisan support in the House of Representatives, highlights a serious shortcoming in the justification materials – one the Committee expects will be remedied in the fiscal year 2008 submission and beyond. As a result, the Committee has included bill language directing NICHD to dedicate \$69,000,000 from within funds provided to continue the National Children's Study, including funding all Vanguard Centers and any other activities that were planned for fiscal year 2007. If NIH wishes to request that Congress discontinue the study in future fiscal years, the Committee directs that a complete justification of the reasons for terminating the study accompany the budget request, rather than one sentence tucked away in response to prior year report language. (p. 102)

Action taken or to be taken

The NIH acknowledges the House support for the National Children's Study. The FY 2007 President's budget requests no funding to support the study. As is described in the NICHD Congressional Justification, the FY 2008 President's budget request continues that policy.

Item

Autism Spectrum Disorders - The Committee is aware of research into the genetic basis of autism spectrum disorders and of NICHD's support for the High Risk Baby Sibling Autism Research Project (Baby SIBS) on the incidence of autism among children in the same families. Accordingly, the Committee encourages the Institute to enhance its support for the Baby SIBS project, and encourages the NICHD to enhance its work with and support for similar public-private partnerships. The Committee also encourages the Institute to enhance its autism research portfolio on gene-environment interactions. (p. 102)

Action taken or to be taken

The NICHD is continuing its public-private partnership with the Autism Speaks/National Alliance for Autism Research (NAAR) in support of the activities of the High Risk/Baby Siblings Research Consortium. The Consortium had significant accomplishments during FY 2006. First, collaborating investigators developed a primary project to examine recurrence rates of Autism Spectrum Disorders (ASD) and broader developmental outcomes in infant siblings of individuals with ASD, and to identify factors that may influence recurrence rates among infant siblings of individuals with ASD. Second, Consortium members published a paper, entitled "Studying the Emergence of Autism Spectrum Disorders in High-Risk Infants: Methodological and Practical Issues," in the

Journal of Autism and Developmental Disorders that addresses significant methodological, ethical, and practical issues such as the use of comparison groups in research and the developmental needs of infants suspected of showing early signs of ASD. Finally, the so-called “head circumference project,” which assesses head growth prospectively in high-risk infants, and correlates this data with diagnostic outcomes, is also making progress. Recruitment of sibling and comparison groups is on target. It is anticipated that the database development and data analysis will start in 2007.

The NICHD is also enhancing its partnership in another priority area of autism research. The NIH Autism Research Matrix lists enhanced brain acquisition as a priority area to allow for neuropathological investigators to characterize the morphological aspects of the pathophysiology of autism. Both NAAR and the NICHD have programs to collect, store, and distribute autism brain tissues. The NICHD is working in collaboration with the Autism Speaks/NAAR to enhance the acquisition of brains and other tissues and to improve the quality and consistency of such tissue.

As a member of the NIH Autism Coordinating Committee, the NICHD is fully aware of the need to elucidate the roles of gene and environment in the manifestation of autism spectrum disorders. Currently, the NIEHS is the lead NIH Institute focusing on environmental factors and autism. The NIEHS and US Environmental Protection Agency co-funded the CHARGE (Childhood Autism Risks from Genetics and the Environment) study that includes clinical evaluations, exposure histories assessment, and collection of biological sampling. The NICHD plans to participate in a new autism and the environment initiative that is under consideration by the NIEHS.

Item

Best Practices for Planned Vaginal Birth - The committee commends the NIH state-of-the-science panel for its work on cesarean section by maternal request, and notes that this panel called for ‘increased research devoted to strategies to predict and influence the likelihood of successful vaginal birth, particularly in the first pregnancy’ and for future studies to ‘determine whether there are modifiable factors in the management of labor that can decrease maternal and neonatal complications.’ Therefore the Committee encourages NICHD to develop a prospective study to compare optimal best practices for planned vaginal birth, measuring a broad range of physical and mental health outcomes appropriate to the sample size, including breastfeeding, attachment and other dimensions of the mother-baby relationship, secondary fertility, and the process and outcomes of subsequent pregnancies; and to support translational research to identify effective ways to bring best vaginal birth practices for healthy low-risk mothers into practice. The Committee further encourages NICHD to include the full range of health professionals involved with maternity care (midwives, obstetricians, family physicians, pediatricians, nurses, doulas) and social scientists in planning, implementation and reporting of this research. (pg. 102/103)

Action taken or to be taken

The NICHD is very interested in studies on optimizing vaginal delivery and understanding the potential short and long term risks and benefits to the mother and the

baby of vaginal delivery and cesarean delivery without medical indication. Manuscripts from the NIH's innovative State of the Science meeting on Cesarean Delivery on Maternal Request were published in the October 2006 issue of *Seminars in Perinatology* (Volume 30, Number 5). In making its recommendations, the conference panel took into account the hundreds of comments solicited from the entire maternal health community. In addition, the NICHD's Maternal Fetal Medicine Units Network is currently exploring the feasibility and costs of a clinical trial on planned vaginal delivery compared to elective cesarean delivery, and how such a trial might be designed. NICHD scientific staff has already met with several outside organizations, such as the American College of Obstetricians and Gynecologists and Childbirth Connection representing health professionals involved with maternity, to gather their feedback from the conference and get input on such a clinical trial. In the meantime, the NICHD is encouraging investigators to apply for research grants in this area and has received a number of applications for review.

Item

Mental Retardation/Developmental Disabilities Research Centers (MR/DDRC) - The Committee recognizes the outstanding contributions of MR/DDRCs 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 MR/DDRC 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 MR/DDRC Centers do not have sufficient resources to sustain the progress made in this critical area. The Committee encourages NICHD to provide sufficient resources to the MR/DDRCs to maintain the level of support available for the fourteen centers that were in the network during 2005. (pg. 104)

Action taken or to be taken

The NICHD has a number of activities to enhance the Mental Retardation/Developmental Disabilities Research Centers (MR/DDRC) and advance diagnosis, prevention, treatment, and amelioration of mental retardation and developmental disabilities (MRDD).

A Request for Applications invited Center Core Grant (P30) applications for FY 2006 funding. All applications covered the breadth and depth of MRDD, and attracted new investigators to the MRDD field and also New Program Development projects. In this RFA, the NICHD encouraged applicants to focus, among other topics, on translating basic research results into patient-oriented protocols. The ultimate aims are to validate the mechanistic basis of MRDD in humans and to develop new approaches for the prevention, diagnosis, and treatment of MRDD.

The applications proposed core centers providing infrastructure services such as use of animals and statistics and bioinformatics. The number of research projects planned to be supported per application varied from approximately 50 to over 120. The total number of

centers increased to fifteen with the funding provided through this solicitation. The Centers are also the home of three NICHD- funded Fragile X Syndrome Research Centers and their affiliated sites, two Rare Disease Cooperative Centers with their numerous affiliated sites, two Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers and several Autism Centers that are presently re-competing.

The NICHD is conducting a broad-based planning and evaluation effort to enhance the MR/DDRC Program in FY 2008. The planning process builds on the NICHD strategic plans and involves both, the scientific and patient communities. Building on extraordinary progress in understanding basic biological underpinnings of MRDD, the Centers will gradually evolve into a national network for translational and clinical research to ameliorate mental retardation and developmental disabilities.

Item

Near-Term Births - The Committee has learned that the preterm birth rate is now over 12 percent of all live births and of these 75 percent are near term births. It is estimated that this group encompasses 40 percent of neonatal ICU admissions. These infants are at risk for sepsis, pneumonia, feeding difficulties, white matter damage, seizures, apnea, and remain at risk for higher morbidities in early infancy. The Committee encourages NICHD to support research in this area. (pg. 104)

Action taken or to be taken

The NICHD has had a longstanding interest in research on the causes and outcomes of late preterm births (near term births) and organized a scientific workshop in 2005 to bring together a range of scientific experts in this area, called "*Optimizing Care and Long-term Outcome of Near-term Pregnancy and Near-term Newborn Infants*:"

http://www.nichd.nih.gov/about/meetings/2005/ppb_optimizing.cfm). Numerous scientific papers presented at the meeting have been published in professional journals, as well as a summary of the presentations. NICHD staff also are encouraging investigators to apply for funding in this area and are fielding questions about research opportunities concerning breastfeeding issues, growth and development, and lung disorders in late-preterm infants. In addition, NICHD staff have provided their expertise on the subject to the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics, as those groups are developing their clinical statements about optimizing care of women in late preterm pregnancies, and late preterm infants. In FY 2007, the NICHD expects to issue a program announcement to stimulate research in late-preterm pregnancy and late preterm infant care issues.

Item

Neurofibromatosis (NF). -- Learning disabilities occur with high frequency in children with NF and in approximately five percent of the entire world's population. The Committee encourages NICHD to expand its NF research portfolio through all suitable mechanisms, including RFAs and clinical trials. The Committee further encourages NICHD to coordinate its efforts with other NIH institutes and government agencies. (pg. 104)

Action taken or to be taken

The NICHD coordinates efforts to support NF-related research with other NIH institutes and other government agencies through its active participation in the Trans-NIH Neurofibromatosis Committee. The Committee is lead by NINDS and involves the NF Coalition of patient advocacy groups. For example, NICHD co-funds with NINDS two conference grants that support meetings relevant to NF research.

NICHD is expanding its NF research portfolio. NICHD's commitment to NF research is exemplified in several ways. NICHD-funded Mental Retardation and Developmental Disabilities Research Centers (MR/DDRCs) provide infrastructure to approximately nine NF projects at four Centers. One of the supported projects is the Phase I/II Clinical Trial at the Children's National Medical Center, Washington, DC. In addition, NICHD directly funds projects), which may be relevant to treating NF. The research of the projects has led to the synthesis of drugs that may act as tumor inhibitors in developing brain. These basic and clinical science projects are advancing our knowledge towards treating NF. They are leading the shift from genotype-phenotype studies to pre-clinical and clinical trials.

NICHD is also leading the effort to advance understanding and treatment of learning disabilities by supporting Learning Disability Research Centers (LRDCs). Specific clinical LD intervention trials in NF patients is not be scientifically justified. However, treating LD in animal models of NF1 has gained the interest of investigators as reflected in a recent workshop "Treating Learning Disabilities: Neurofibromatosis Type 1." NICHD program staff provided advice to the Children's Tumor Foundation about the organization of this meeting that gathered several leading NICHD-supported investigators, along with others, at UCLA. The MR/DDRC at UCLA assisted in the organization of the meeting. The conclusions of this meeting will be considered, when they become available, in light of a potential solicitation such as a program announcement.

Item

Obstetric Systematic Reviews - The Committee applauds NICHD's efforts supporting the Neonatal Cochrane Review Group since 1995 that not only provides a substantial scientific resource but also allows the community access to these reviews via the NICHD website. These reviews are a valuable resource, providing the most comprehensive and timely review of clinical topics. The Committee encourages NICHD to provide a similar service to the obstetrical community by supporting obstetric systematic reviews and providing them free of cost to the general public, a critical gap in the medical community. (pg. 104)

Action taken or to be taken

The Cochrane Collaboration is an internationally renowned group of scientists that has systematically evaluated the evidence for health care practices since 1992. These reviews are highly structured, with evidence included or excluded on the basis of explicit quality criteria to minimize bias. Data from numerous studies, which are too small individually

to produce reliable results, are often combined to increase the power of their findings. So far, the group has completed approximately 350 reviews, and will continue to provide new and updated reviews annually.

NICHD plans to support obstetric systematic reviews in FY 2007, beginning with identifying a group of obstetric experts to perform analyses of the data on specific obstetric topics, and updating them regularly. By providing these reviews free of cost to the general public, NICHD hopes to fill a critical gap in the medical community. Anyone who has access to the NICHD website, including practitioners, researchers and the public, will be able to obtain information on the most current medical advances and evidence-based medical practices in obstetrics without a subscription to a medical library.

Item

Spinal Muscular Atrophy (SMA) -- SMA is the leading genetic killer of infants and toddlers, and is the most prevalent genetic motor neuron disease. The severity of the disease, its relatively high incidence, and the possibility of imminent treatments led NINDS to initiate the innovative SMA project. The Committee encourages NICHD to continue to formulate a plan for expanding its work and funding for SMA research. Specifically, the Committee encourages NICHD to coordinate funding with NINDS to ensure increased participation of investigators in SMA and developmental neurobiology relevant to SMA. Further, the Committee encourages NICHD to take the lead on developing a cross- institute working group comprised of NICHD, NINDS and NIGMS to study broader questions of care and the role of exercise and nutrition on SMA and other neuromuscular disease. (pg. 105)

Action taken or to be taken

The NICHD is taking advantage of its participation in the Senator Paul D. Wellstone, MDCRC Steering Committee to take the lead on developing a cross- institute working group comprised of NICHD, NINDS and NIGMS to study broader questions of care and the role of exercise and nutrition on SMA and other neuromuscular disease. The NICHD will continue to seek and sponsor new and innovative research related to early identification and treatment of SMA.

The NICHD supports work on Spinal Muscular Atrophy (SMA) in the following domains: basic science, clinical applications and infrastructure support. Molecular genetic studies have revealed that mutations in the *Smn1* gene are responsible for this disease, and the SMN protein is involved in RNA processing. Despite these advances, little is known regarding the exact role of SMN in nervous system function, and the nature of the RNA processing defects that underlie SMA pathology have remained elusive. Recently, it was reported by several different groups that SMN is localized to the axon and the growth cone. Furthermore, in the absence of normal SMN, nerve cells have shorter axons and smaller growth cones. Reduced levels of normal SMN may influence other processes within nerve cells, which could be functionally important for the proper growth of motor nerve cell axons and maintenance of spinal motor nerve cells. NICHD funded a distinguished young investigator to characterize the relationship between these events in nerve cells and SMA disease.

Additional NICHD support went to two Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRC). At the Children's National Medical Center the grant is to advance the development of a SMA-specific quantitative muscle strength testing module. This will enable quantitative muscle testing (QMT) as a sensitive, specific and responsive outcome measure in pediatric and adult SMA clinical trials. This project coordinates with ongoing clinical work in SMA conducted in the NINDS pilot therapeutics network (NPTUNE), the American SMA Randomized Trials (AmSMART) and with the work of the Cooperative International Neuromuscular Research Group (CINRG).

Investigators at the Ohio State University funded by the NICHD through a University of Washington subcontract are evaluating whether effective molecular technology and other conditions exist that would warrant newborn screening, and are working to ultimately develop a newborn screening test for SMA.

All projects described above receive core support from the Mental Retardation and Developmental Disabilities Research Centers (MDDRCs) at the parent institutions. In addition, the MDDRCs at other institutions provide infrastructure for SMA-related projects funded by other NIH ICs.

Senate Significant Items

Item

Autism - The Committee is aware of research into the genetic basis of autism spectrum disorders and of NICHD's support for the High Risk Baby Sibling Autism Research Project (Baby SIBS) on the incidence of autism among children in the same families. Accordingly, the Committee encourages the Institute to enhance its support for the Baby SIBS project, and encourages the NICHD to enhance its work with and support for similar public-private partnerships. The Committee also encourages the Institute to enhance its autism research portfolio on gene-environment interactions. (p.129)

Action taken or to be taken

Please refer to page 127 of this document for the NICHD response to this significant item.

Item

Behavioral Science - The Committee emphasizes its strong support for the broad portfolio of behavioral research at NICHD and supports its efforts to determine the biological, behavioral, and social factors that affect cognitive, social, and personality development of children in a variety of settings. The Committee encourages the Institute to maintain its support for research and training in behavioral science as it engages in its priority-setting process. (pg. 129)

Action taken or to be taken

The NICHD supports the third largest behavioral and social sciences research portfolio at the NIH. The Institute is a leader in research that reaches across disciplinary lines to link psychological and behavioral processes in cognitive, social, and personality development with underlying biological processes, and to understand how features of the social and economic environment affect developmental outcomes.

The NICHD supports a broad research portfolio of investigator-initiated grants in the behavioral sciences, addressing topics such as health risk behaviors in childhood and adolescence; health promotion strategies and interventions for the prevention of unintentional injury, pregnancy, HIV, and obesity; learning, literacy, and school readiness; cognitive, social, and emotional development; prenatal health care and behaviors; parenting; and behaviors related to family formation and demographic change.

Several major Institute initiatives have drawn national attention, including: The Interagency School Readiness Consortium, which studies the effectiveness of early childhood programs or interventions in promoting school readiness; The Interagency Consortium On Outcomes Measurement, which is developing tools to measure important early childhood competencies, The Back to Sleep Campaign, which has reduced the prevalence of SIDS by more than half through modification of infant sleep position; and the National Longitudinal Study of Adolescent Health, which has expanded knowledge of the effects of family, peer, and community factors on adolescent development. An innovative new program, currently under development, will test the efficacy of workplace interventions for improving child health – and improving employee productivity - by reducing strains on working parents. A collaborative study involving NICHD, NINR, researchers, and community members is being designed to examine the social, behavioral and biological processes that produce health disparities in birth outcomes and early child development.

A new staff-level Consortium of the Behavioral and Social Sciences at NICHD is working towards further integration of behavioral, social, and biomedical research focused on child health and human development. The group's initial plans call for a conference that will explore the social environmental causes of rising childhood obesity using data from the United States and other countries.

NICHD recognizes the critical need to invest in innovative models of research and training to advance these areas of science, including training in both the behavioral sciences and interdisciplinary fields. In recent years the NICHD Behavioral Research Branch has taken new steps to strengthen training and career opportunities, expanding the Mentored Research Scientist program and encourage strong disciplinary and interdisciplinary science training.

Item

Childhood Obesity - The Committee encourages additional clinical trials that focus on the effectiveness of behavioral interventions in settings beyond primary care, including the home, school, community, and other environments that influence physical activity and health behaviors. The Committee recognizes the critical importance of prevention

efforts in this area and supports continued initiatives to promote healthy behaviors in children and adolescents, particularly for ethnic minority populations. (p. 129)

Action taken or to be taken

The NICHD recognizes that there is an urgent need for effective interventions in a wide range of settings that could influence children's physical activity and health behaviors. To this aim, the NICHD is funding intervention trials in schools, the home, and the community to tackle the obesity problem among children and adolescents. The NICHD is the lead Institute on a program announcement entitled *School-Based Interventions to Prevent Obesity*.

Several school-based interventions are currently funded: Testing the effect of school breakfast on health and learning among children of diverse ethnic background; promoting fruit and vegetable consumption at schools as a means to improve the dietary quality of children; evaluating an after-school program designed to promote physical activity among minority girls from low-income families, in response to the decline in physical activity during adolescence; testing the efficacy of environment versus behavior modification to prevent obesity in Los Angeles schools. The NICHD plans to support a new study that aims to translate two evidence-based drug use prevention models into an obesity prevention program among school children in Orange County, CA. This study will focus on strengthening executive functioning, the ability to receive and organize information and then make decisions and plans based on that information, and social competence among school children as a means to counteract an obesity-predisposing environment. This intervention will also be able to examine potential ethnic differences in the adoption and efficacy of such a program.

The home has also been a center of interventions. Researchers at the University of Buffalo have been comparing an intensive family-based intervention program with an innovative program based on behavioral economics, in which children are rewarded for healthy behaviors. These researchers are now examining the mechanisms by which the reduction of sedentary activity may lead to improved physical activity and dietary patterns among children. The NICHD is also funding an innovative intervention in which healthful food is delivered to the homes of participating families in order to prevent childhood obesity.

Most of the studies of obesity treatment and prevention in primary care settings include family-based or community-based components. These studies draw upon resources from the larger community and utilize the primary care setting as a point of dissemination of the intervention. These interventions involve both children and their parents to improve the health behaviors of these children. These studies include a diverse range of at-risk populations, including African American and Mexican American children.

Item

Demographic Research - The Committee commends the NICHD for supporting demographic research, which is essential for understanding the health, socioeconomic, and geographic implications of the rapidly changing U.S. population. The Committee

encourages the Institute to invest in its demographic training programs to prepare the next generation of social scientists. Further, the Committee urges the Institute, in a partnership with other Federal agencies, to continue supporting critical, accessible databases, such as the National Longitudinal Study of Adolescent Health. (pg. 129)

Action Taken or to be Taken

Improving the nation's health depends on understanding the characteristics of our population and how they are changing. Demographic research provides scientific information on topics such as our nation's increasing diversity, fertility and marriage patterns, health disparities, and immigrant adaptation. Such research analyzes the causes of population change and its consequences for the health and well-being of children and families, and provides unbiased information that can be used by policy makers and program planners responsible for addressing public health needs. Information garnered from demographic research on poverty, family structure, residential segregation, and community change provides essential underpinnings for studies that attempt to understand the complex causes of disease – and differences in disease risk – that originate in the environment.

NICHD's investments in scientific studies that are representative of the nation's population provide a critical foundation for this research. During 2006, NICHD has renewed three ground-breaking studies. The Fragile Families and Child Well-Being Study will continue to follow children born to unmarried parents to assess how economic resources, involvement of fathers, and parenting practices affect children's development. The National Longitudinal Study of Adolescent Health will field an exciting fourth wave of data collection integrating biomedical, behavioral, and social science to discover the pathways that lead to health and/or chronic disease in adulthood. The New Immigrant Survey will follow up the first nationally representative sample of legal immigrants to the United States. Each of these studies has made significant contributions to scientific research and to informing public policy. Their funding relies on extensive collaboration with other NIH Institutes and federal agencies.

The future of demographic research depends critically on the training of new generations of scientists, particularly as the ability to interact across disciplines becomes increasingly necessary to conducting cross-cutting research. NICHD funds 16 institutional training grant programs across the United States, as well as individual fellowships for pre-doctoral and post-doctoral study. In addition, the Institute supports junior investigators through a Mentored Research Scientist Development Award program in population research.

Item

Down Syndrome - NICHD is encouraged to partner with 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 also encourages NICHD to work with the Office of the Director, OPASI and the other Institutes to develop a strategic plan for Down syndrome research and to coordinate its research within NIH. (pg. 130)

Action taken or to be taken

Mouse models developed with NICHD funding have made possible work on the region of the human chromosome 21, known as Down Syndrome Critical Region, including potential therapeutic interventions and a better understanding of the molecular commonalities between Down syndrome and Alzheimer disease. NICHD currently supports a contract with the Jackson Laboratories to provide investigators around the world with mouse models for research related to Down syndrome. In addition, a number of individual investigators have successfully applied for NICHD funding to conduct studies on and continue the creation of mouse models. Continued support for the production of the mouse stock, along with verification that the stock provided meets consistently high genetic and behavioral criteria, has ensured that the demands of researchers can be met.

To facilitate this and other issues related to research on Down syndrome across the NIH, the NIH Down Syndrome Working Group was established in early 2006, comprising those institutes and centers with an interest in some aspect of Down syndrome research. NICHD leads the effort, along with NINDS and NIA. The group is currently developing a draft research plan, based on recent scientific meetings on Down syndrome, its genetics, its developmental consequences, and its impact on cognition and synaptic function. Input on this plan will be sought from national constituency organizations and scientific experts to define further and address clearly strategies for basic and clinical research in this area.

Item

Family Formation - The Committee is pleased that the NICHD is working with other Institutes and agencies to assess the state of the science and research needs related to children exposed to domestic and community violence, war, and terrorism. 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. The Institute is encouraged to include research related to family, community and cultural factors that serve as risk or protective factors and promote resilience from exposure to violence in the home, communities, and schools. (p. 130)

Action taken or to be taken

Over the last half-century, NICHD research has documented dramatic changes in the American family. The proportion of children born out-of-wedlock continues to increase and many children grow up in unstable families. These trends in family formation have contributed to high rates of child poverty and father absence, circumstances strongly linked to poor cognitive development and behavior problems. It is important to understand why these changes have occurred, and what might be done to strengthen families and support them in raising healthy children.

NICHD has a strong commitment to research informing these questions. NICHD-sponsored research has provided the scientific basis for efforts to encourage and strengthen marriage among parts of our population that have low marriage rates by documenting the importance of economic opportunities, public policies, and cultural

values that influence marriage. NICHD-supported research is exploring ways to strengthen couple relationships and improve the stability of marriage in vulnerable populations. Research on fatherhood has demonstrated mechanisms through which fathers' involvement with their children in both intact and non-intact families contributes to their children's health and development. New research also shows that having a chronically ill or disabled child undermines parents' ability to work, increases welfare dependency, and contributes to family instability.

NICHD's investment in research on the implications of violence for healthy child development continues to expand. A recent study linked a mother's exposure to domestic violence during pregnancy to a two-fold increase in the risk of infant death in the perinatal or neonatal period. Ongoing studies have demonstrated that exposure to violence in childhood and adolescence has serious developmental effects, including the ability to form long-lasting family relationships as an adult. NICHD collaborated with other institutes and agencies to issue a Program Announcement calling for research on the incidence and prevalence of children exposed to domestic or community violence, the impact on children's development, and the efficacy of parent skills training interventions for children exposed to violence. The Institute has funded nine grants to date as a result of this announcement, and has held workshops dedicated to disseminating existing knowledge. NICHD also supports career development and research training in the fields of child abuse and neglect.

Item

Fragile X - The Committee notes the impressive progress made by Fragile X researchers in understanding the basic neural defects that cause this developmental disorder. The success of these translational research efforts has made treatment of Fragile X a near-term possibility. However, collaborative efforts between industry, academia and NIH Institutes are likely to be necessary to develop promising therapies. The Committee further notes that while Fragile X is a relatively common genetic disease, the treatments being developed for Fragile X may also be effective for a much larger number of people with related autism spectrum disorders. Research has shown many possible treatment strategies which merit human Fragile X clinical trials, including, but not limited to, mGluR5 antagonists, Ampakines, aripiprazole, and lithium. The Committee strongly urges the Director to facilitate and fund public/private partnerships that will enable these vital studies to proceed. The Committee also urges the Director to take an active role in coordinating Fragile X research at NIH, by organizing regular intramural meetings of program directors from all institutes sponsoring Fragile X research projects. (p. 130)

Action taken or to be taken

The NICHD is the lead NIH institute in funding Fragile X (FX) research. It funded the initial discovery of the genetic basis for FX and the most likely first target of drug therapy. In FY 2005, NICHD funded about 30 research grants and other awards that support FX research. This portfolio is continually updated with new applications and investigators, ensuring the quality of the FX research effort. The NICHD works with other NIH I/Cs that fund FX research, such as NIMH and NINDS, and FX advocacy groups. A common initiative was the jointly solicited Program Announcement "Shared

Neurobiology of Fragile X Syndrome and Autism” that attracted 17 new applications. The NICHD organizes regular trans-NIH meetings of FX research program directors, which jointly issued an RFA to re-compete the FX Research Centers in FY 2008, encourages the submission of applications on high priority topics, and fosters cooperation among institutions, funding agencies, and advocacy constituencies in creating a coherent national translational research infrastructure for FX studies.

The NICHD leads NIH’s implementation of the Best Pharmaceuticals for Children Act. In July 2006 NICHD sponsored a workshop on approaches to new pharmacological approaches in treatment of FX. Attendees including scientific experts and representatives of FX advocacy groups, who assessed the state of interventions research in FX, particularly interventions for children, and identified key areas for future emphasis. The workshop pointed to the need for physicians experienced in clinical trials to enter the field of FX research. NICHD, NIMH, and NINDS are exploring ways to jointly support the public/private testing of new pharmaceuticals for the treatment of FX.

The NICHD-funded Pediatric Pharmacology Research Network is poised to facilitate testing of therapeutic agents after pre-clinical tests evaluate their safety and potential to ameliorate FX. Already NICHD has received a high quality application to screen potential drugs for FX. NICHD is also collaborating with investigators to develop and test new methods for screening newborn infants for FX, an important part of NICHD’s broader initiative on newborn screening for genetic disorders.

Item

Fragile X - related Premature Ovarian Function[POF] - POF is a condition in which the ovaries stop functioning normally in a woman younger than age 40. Studies show that women who have POF of unknown cause have a 1 in 50 chance of being a pre-mutation carrier of the FMR1 gene, the gene that causes Fragile X syndrome. Women with POF and a family history of female relatives with POF have a 1 in 15 chance of carrying this pre-mutation. The Committee recognizes that there is a need for a focused approach to investigating POF due to the FMR1 pre-mutation. While the intramural research program of NICHD has been doing work for nearly two decades in this area, there remains much to be learned about the mechanism causing POF, abnormal ovarian function as it relates to FMR1, and mental health effects on young women who get the double diagnosis of premature ovarian failure and the FMR1 pre-mutation. The Committee encourages the NICHD to commit additional resources and expand research into POF. (p. 131)

Action taken or to be taken

Premature ovarian failure (POF) is a condition of infertility caused by an earlier than normal depletion of ovarian egg follicles. POF occurs in one percent of all women and 0.1% of women before the age of 30. It is estimated that 10-20% of POF cases are linked genetically (hereditary); about 15-20% of women with a pre-mutation of the FMR1 gene, a gene responsible for Fragile X syndrome, develop POF. NICHD has long supported this important area of research, both intramurally and through extramural grants. The Specialized Cooperative Centers Program in Reproduction Research convened a focus group meeting on Fragile X and POF in 2001. This meeting resulted in support of a collaborative clinical study involving NICHD-supported investigators at

several center sites across the country and the NICHD intramural research program. NICHD's Reproductive Sciences Branch also issued a Program Announcement (PA) in 2001 entitled, *Reproductive Genetics and Epigenetics*, which encouraged the field to submit grant applications on the genetic causes of POF in addition to other topic areas. Only one application was submitted in response to the PA *Reproductive Genetics and Epigenetics*. Nevertheless, given the high incidence of POF in Fragile X pre-mutation carriers, the NICHD is committed to encouraging additional research in this area. The Institute intends to issue a PA in FY 2008 specifically focused on the Fragile X pre-mutation and ovarian function in order to stimulate research in this highly important, but under-researched area. The goal of the PA is to support studies that 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 specifically and ovarian function generally.

Item

Learning and School Readiness - The Committee continues to support NICHD's commitment to research in reading, learning disabilities and math and science cognition. The Committee is encouraged that NICHD has made progress on developing comprehensive, culturally neutral and developmentally appropriate assessments and instruments to measure cognitive, social and emotional skills for pre-school aged children that are necessary for school readiness. (p. 131)

Action taken or to be taken

In FY 2006, the NICHD, with co-funding from the Administration for Children and Families (ACF), and the Office of Special Education and Rehabilitation Services (OSERS) in the U.S. Department of Education, provided \$2.4 million for the Interagency Preschool Measurement Consortium. This consortium comprises grant awards to support six projects to develop and test cognitive and socio-emotional outcome measures that assess critical school readiness developmental domains, especially for children who are at risk for later school difficulties. These measures include assessments of children's school readiness across the multiple domains of socio-emotional development and cognitive development (executive functioning, mathematical abilities, bilingual phonological development), and teacher ratings of socio-emotional functioning in the classroom. These projects are in the second year of their five year grant cycle. Results to date suggest that these projects are developing promising measures of both the cognitive and socio-emotional development of children. Once fully developed and empirically validated, these measures will be usable across a diverse range of early childhood settings to monitor child progress in acquiring important school readiness skills, provide feedback on program performance, and in some cases, directly inform instructional strategies for young children.

Item

National Center for Medical Rehabilitation Research - The Committee is pleased with the continuing effort of NCMRR to coordinate rehabilitation research initiatives among the several relevant Institutes including NINDS, NICHD, NIA, and NIMH. The Committee is concerned, however, that the contribution of rehabilitation sciences to the

fullest possible recovery of individuals who experience functional limitations or have chronic disabilities does not meet its potential. Therefore, the Committee urges that NCMRR redouble its trans-NIH efforts to expand rehabilitation research in the portfolio of the several Institutes and help insure the translation of this research into practice. (p. 131)

Action taken or to be taken

A large number of NIH Institutes, including NIA, NIAMS, NCI, NIDCD, NINDS, NINR, actively participate in the NCMRR advisory council providing valuable perspective on their Institute's rehabilitation research priorities. The NICHD actively collaborates with NINDS and NIBIB in promoting and funding research on robotics and advanced prosthetic designs and is meeting with staff from the Centers for Medicare and Medicaid Services to develop collaborations between NIH and CMS on rehabilitation research.

The NCMRR chairs the trans-NIH Rehabilitation Coordinating Committee and co-chairs the Medical Subcommittee of the Interagency Committee on Disability Research (ICDR). The trans-NIH committee participated in the review of the trans-NIH Program Announcement on Research Partnerships to Promote Functional Improvements, and recommends a re-issue of the announcement. The Medical Subcommittee of the ICDR has collaborated with NCMRR in developing meetings to inform the members of the ICDR on longitudinal studies and opportunities for promoting rehabilitation research in allied health professional schools.

Item

National Longitudinal Study of Adolescent Health - The Committee is pleased that the NICHD funded another round of the Add Health Study, which has provided a rich resource on the effects of home, family, and school environment on behaviors that promote health or could contribute to adverse health outcomes. By collecting data on biological, behavioral and social factors, researchers are discovering at which points during development significant increases in some risk behaviors, such as smoking, alcohol use and physical activity, are most likely to occur. As these risk behaviors offer early predictors of future chronic diseases such as cardiovascular disease and diabetes, the study provides valuable information to inform public health prevention efforts. Given the important findings of this nationally representative study, the Committee encourages NICHD to ensure that the next wave is provided adequate funding. (p. 131)

Action taken or to be taken

Recent findings from the third wave of the National Longitudinal Study of Adolescent Health (Add Health) revealed disturbing facts about health trends among the nation's young people. The study showed that, between adolescence (ages 12-18) and very early adulthood (ages 18-24), youth experienced deteriorating health behaviors (e.g., smoking, drug use, physical activity and diet); increased health problems such as obesity, asthma, and sexually transmitted diseases; and poorer access to health care. Further, disparities across racial and ethnic groups in these health indicators widened. Wave IV of Add Health will follow up on these disturbing findings by studying how adult chronic disease emerges in early adulthood, and how behavioral patterns established in adolescence lay

the foundation for adult health. The study will integrate rich information on the health, behaviors, and environments of young people collected during adolescence and very early adulthood with new data on health, behavior, and environment at ages 24-30. Study investigators have established partnerships with biomedical scientists with expertise in cardiovascular disease and obesity.

NICHD has given high priority to ensuring that this exciting new phase of Add Health achieves its full potential. In collaboration with the NIH Office of Behavioral and Social Sciences Research (OBSSR) and the NIH Office of Research on Women's Health (ORWH), NICHD has established the "NIH Executive Roundtable for Add Health," representing 15 NIH Institutes and Offices and four other DHHS entities. The Roundtable provides a mechanism for sharing information about the study and linking the study investigators to expertise available within DHHS. Funding for Add Health Wave IV is a collaborative effort between NICHD and twelve other NIH Institutes and Centers joining NICHD in funding the study: the National Cancer Institute, the National Center for Minority Health and Health Disparities, the National Institute of Allergy and Infectious Diseases, the National Institute on Deafness and Other Communication Disorders, the National Institute of Nursing Research, the National Institute on Aging, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Drug Abuse, the Office of AIDS Research, NIH, OBSSR and ORWH, NIH, and the Office of the Assistant Secretary for Planning and Evaluation, DHHS. Support for the National Longitudinal Study of Adolescent Health currently involves partnership with ASPE and eleven other NIH institutes and offices. Support for the National Survey of Family Growth involves partnership with CDC, ASPE, the DHHS Office of Population Affairs, and the Administration of Children and Families. Support for the National Longitudinal Surveys of Youth involves partnership with the Department of Labor. Support for the New Immigrant Survey involves partnership with the Department of Homeland Security.

Item

Near-term Births -- The preterm birth rate is now over 12 percent of all live births; of these, 75 percent are near-term births. It is estimated that this group encompasses 40 percent of neonatal ICU admissions. These infants are at risk for sepsis, pneumonia, feeding difficulties, white matter damage, seizures, and apnea and remain at risk for higher morbidities in early infancy. The Committee understands that this group of infants has not been well studied and may account for a portion of the increase in adverse long-term outcomes such as autism, attention deficit disorders, and neuron-developmental disorders. The NICHD is encouraged to facilitate the critical need for research in this area. (p. 132)

Action taken or to be taken

Please refer to page 130 of this document for the NICHD response to this significant item.

Item

Neurofibromatosis – Learning disabilities occur with high frequency (30-65 percent) in children with NF and in approximately 5 percent of the entire world’s population. Enormous advances have been made in the past few years in the successful treatment and curing of learning disabilities in pre-clinical NF animal models. Therefore, the Committee encourages 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. 132)

Action taken or to be taken

Please refer to page 130 of this document for NICHD’s response to this significant item.

Item

Obstetric Systematic Reviews -- The Committee applauds the NICHD's efforts supporting the Neonatal Cochrane Review Group, which not only provides a substantial scientific resource but also allows the community access to these reviews via the NICHD website. These reviews are an invaluable resource, providing the most comprehensive and timely review of clinical topics. The Committee strongly encourages NICHD to provide a similar service to the obstetrical community by supporting obstetric systematic reviews and providing them free of cost to the general public. (pg. 132)

Action taken or to be taken

Please refer to page 131 of this document for the NICHD response to this significant item.

Item

Physician Scientists and Researchers - The Committee commends the NICHD for responding to the scientific community's need for enhanced training programs to provide a solid framework for the development of physician scientists and researchers. A substantial investment has been made in traineeships, fellowships, and research career awards. The NICHD is encouraged to identify funding opportunities for NIH-trained investigators who have demonstrated a commitment to a research career. (p. 132)

Actions taken or to be taken

Each year, NICHD supports the training and career development of over 1,200 students and young doctors who show the greatest promise of developing into physician scientists and researchers. Through more than ten different mechanisms, the NICHD supports over 800 individuals with traineeships and fellowships and over 400 individuals with research career awards every year. These awards enable our most promising young investigators to obtain the knowledge and skills they need to become successful scientists. They subsequently apply for and receive research grants at a very high rate. The NICHD ensures the future success of NIH-trained investigators who are committed to a research career by holding numerous workshops for young investigators to provide overviews of the NIH and how we support research careers, and teach them how to apply for and obtain research grants.

The NICHD was instrumental in devising the new Pathway to Independence Award (K99/R00), which is designed to help NIH-trained investigators obtain research grants and participates in Loan Repayment Programs that enable young physician scientists to enter research careers in the fields that we support, including the field of pediatric research.

The NICHD strategic funding plans include using the Small Research Grant (R03) and the Exploratory / Developmental Research Grant (R21) programs in ways that makes them attractive funding opportunities for young investigators and giving special consideration to new investigators who apply for research grants.

Item

Prader-Willi Syndrome - Prader-Willi Syndrome is the most common known genetic cause of life threatening obesity in children. The Committee strongly encourages the NICHD to place a high priority on Prader-Willi Syndrome research to study childhood obesity. Furthermore, the NICHD is urged to incorporate Prader-Willi Syndrome into the planning process for The National Children's Study. (p. 132)

Action taken or to be taken

The NICHD agrees with the Committee that a high priority should be placed on Prader-Willi Syndrome (PWS) research. When the metabolic testing area of the Obesity Clinical Research Center [OCRC] opens at the NIH Clinical Center early next year, NICHD investigators plan to emphasize studies of children with PWS as part of a protocol on biochemical genetic defects in children. The investigators will admit children with PWS to the OCRC in order to document modifications of genes that are involved in the pathogenesis of PWS. They will also study how the hypothalamic dysfunction often seen in cases of PWS affects the endocrine status of these children. Nutritional therapy for affected children and genetic counseling for the parents will also be included in this protocol.

Genetic studies of children and families with PWS focus on correlating the characteristic symptoms of PWS, such as compulsive overeating, obesity and hypothalamic dysfunction, with genetic subtypes of PWS. Other genetic studies focus on improving our understanding of the malfunction of the small portion of Chromosome 15 that appears to be involved in the genesis of PWS. These studies in humans and related studies in mouse models focus on how altered gene expression during development correlates with characteristic symptoms of PWS. These studies should elucidate the genetic origins of PWS and also provide information on how genes on Chromosome 15 may be involved in more commonly encountered forms of childhood obesity.

The staff of both the intramural and the extramural research programs of the NICHD have close ties with the members of the Prader-Willi Syndrome Association-USA. As soon as research advances in our understanding of the behavioral, endocrine and genetic aspects of PWS are discovered, they are communicated to the leadership of the PWSA-USA. The NICHD also supports a Rare Disease Clinical Research Consortium at Baylor

College of Medicine in Houston TX that focuses on Angelman, Prader-Willi and Rett syndromes. This consortium maintains a website that includes information for patients with these disorders and their families, as well as for practicing clinicians and investigators.

Item

Preterm Birth - The Committee applauds NICHD's efforts in supporting research to understand, prevent and treat preterm birth, including workshops on major gaps in knowledge areas. Despite these efforts, however, the rate of preterm births continues to rise. The Committee therefore strongly urges the NICHD to fully support the Maternal Fetal Medicine Units Network so that it can continue to address issues pertaining to preterm births and low birth-weight deliveries, and to fully support the new Genomic and Proteomic Network, which will hasten a better understanding behind the pathophysiology of premature birth, discover novel diagnostic biomarkers, and ultimately aid in formulating more effective interventional strategies to prevent premature birth. (p. 132)

Action taken or to be taken

The NICHD is very interested in improving the understanding of preterm birth, including prevention and prediction of preterm birth. The NICHD supports this research through investigator initiated grants and networks of research institutions such as the Maternal Fetal Medicine Units (MFMU) Network and the Genomics and Proteomics Network. The MFMU Network is composed of 14 sites across the US and a data center. Ongoing clinical trials include several specifically related to preterm birth prevention and management including one known as the Beneficial Effects of Antenatal Magnesium Sulfate (the "BEAM" trial) testing whether cerebral palsy can be prevented if this substance is provided to women in late pregnancy. This trial is currently finishing the two year follow-up of the infants. Results are now being analyzed from another trial that will help to determine whether a progesterone therapy, "17-P", prevents preterm birth in twins or triplets, and should be available in early 2007. Researchers are also testing whether 17-P can prevent preterm birth when used in conjunction with Omega-3 fatty acid supplements. A third study being conducted through this network attempts 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. The results will be presented at a professional meeting in February 2007. Further, 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 related data to the scientific community. The research will advance by designing and implementing hypothesis-driven studies, and providing a public, web-based, database to make the data readily available to the research community. The Network includes three clinical sites (University of Alabama at Birmingham, University of Utah, University of Texas Medical Branch at Galveston), an analytic core (University of Pennsylvania) and a datacenter (Yale University).

Item

Primary Immunodeficiency Diseases - The Committee commends the NICHD for continuing to dedicate financial and personnel resources to the physician education and public awareness program conducted by the Jeffrey Modell Foundation regarding this class of about 140 diseases. The Committee is strongly encouraged by the Institute's commitment to develop newborn screening procedures for PI, particularly various forms of severe combined immune deficiency, utilizing microarray technologies. The Committee believes that the NICHD should move ahead aggressively with this initiative, in partnership with the Foundation, other NIH Institutes and private industry, and dedicate financial and personnel resources to newborn screening. (p. 133)

Action taken or to be taken

The NICHD continues to have an active interest in promoting research on primary immunodeficiency diseases as well as raising awareness among physicians with regard to identifying and diagnosing these conditions. The NICHD's program in developmental immunobiology covers basic, applied, and clinical studies in developmental genetics and the ontogeny [the origin and development] of the immune system. This program looks at both normal development of the immune system and abnormalities in developmental processes that result in these birth defects of the immune system. Through this program, new findings are continually providing new information on the mutations associated with such primary immunodeficiency diseases as severe combined immunodeficiency disease (SCID).

In addition, the NICHD coordinates with the National Institute on Allergy and Infectious Diseases (NIAID) to more efficiently approach research and training in primary immunodeficiency diseases. The major collaboration between the two Institutes is the Primary Immunodeficiency Research Consortium. The Consortium is a coalition of the world's most prominent investigators in the field of primary immunodeficiency diseases, and is charged with helping to prioritize and coordinate research directions and to develop new resources to study these rare disorders. In addition, the NICHD and the NIAID have collaborated to provide support for scientific and training conferences that help to provide the latest information on research and clinical findings to the field related to primary immunodeficiency diseases.

The NICHD has taken a leadership role in promoting and encouraging more research in the area of newborn screening. In 2006, the NICHD has issued two funding opportunities that specifically highlight interest in primary immunodeficiency diseases, in particular severe combined immunodeficiency. Three funding opportunity announcements entitled "Innovative Therapies and Clinical Studies for Screenable Disorders," which can include SCID, Duchenne muscular dystrophy, and spinal muscular atrophy, were released and will be active until November 2009. The NICHD also released a Request for Proposals which sought to award contracts to develop a technology prototype for newborn screening. Two contracts were awarded in FY 2006. The NICHD is currently planning to develop a translational newborn screening research network to create a system which can potentially translate the outcomes from these initiatives into clinical practice.

Item

Pulmonary Rehabilitation – Pulmonary rehabilitation has been increasingly recognized as an important treatment option for the many patients with disabling chronic lung diseases, like COPD. The Committee encourages the National Center for Medical Rehabilitation Research to expand research opportunities in this area. (p. 133)

Action taken or to be taken

Pulmonary rehabilitation is a particularly active area of research in the Pediatric Critical Care and Rehabilitation Program in the National Center for Medical Rehabilitation Research, NICHD. In 2002, a Request for Applications was published to signal the Institute's interest in funding clinical trials for the prevention and treatment of respiratory failure in children. Projects funded under that announcement include research aimed at improving ventilatory techniques in home care for children with cystic fibrosis, and another project to improve ventilator care for infants. Other current projects include research to help understand and prevent lung injuries. The Institute's new Pediatric Critical Care Research Network also is planning a study to improve care for pediatric asthma, one of our nation's children's most pressing and common chronic health issues. These research projects are the concrete result of longstanding efforts to reach out to the scientific field encouraging interested investigators to submit applications that build on NICHD-sponsored meetings on home mechanical ventilation, and building on earlier meetings sponsored by NICHD on home mechanical ventilation and related topics.

Item

Spinal Muscular Atrophy (SMA) - SMA is the leading genetic killer of infants and toddlers, and is the most prevalent genetic motor neuron disease. The severity of the disease, its relatively high incidence, and the possibility of imminent treatments led NINDS to initiate the innovative SMA project. The Committee encourages NICHD to continue to formulate a plan for expanding its work and funding for SMA research. Specifically, the Committee encourages NICHD to coordinate funding with NINDS to ensure increased participation of investigators in SMA and developmental neurobiology relevant to SMA. Further, the Committee encourages NICHD to take the lead on developing a cross-institute working group comprised of NICHD, NINDS and NIGMS to study broader questions of care and the role of exercise and nutrition on SMA and other neuromuscular disease. (pg. 105)

Action taken or to be taken

Please refer to page 132 of this document for the NICHD response to this significant item.

Item

Stillbirth - The Committee applauds the 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 initiated a pilot study, with the overall study using a standard protocol planned to start this year. The Committee strongly encourages the NICHD to fully fund this effort. (p. 133)

Action taken or to be taken

Established in 2003, the NICHD's Stillbirth Collaborative Research Network includes five clinical centers (Brown University, University of Texas Medical Branch in Galveston, University of Texas at San Antonio, Emory University, University of Utah) and a data coordinating center (Research Triangle International, North Carolina). The specific aims of this five-year study are: to obtain a geographic population-based determination of the incidence of stillbirth defined as fetal death at 20 weeks gestation or greater, to determine the causes of stillbirth using a standard stillbirth postmortem protocol (including review of clinical history, protocols for autopsies and pathologic examinations of the fetus and placenta, and other postmortem tests to illuminate genetic, maternal, and other environmental influences), and to elucidate the risk factors for stillbirth. The main study protocol has IRB approval and all study sites (including over 50 hospitals) are now recruiting and enrolling cases and controls. Enrollment began in February 2006 with all sites enrolling by May 2008.

Item

Tuberous Sclerosis Complex -- The Committee urges the NICHD to explore the links between autism and TSC, and to conduct epidemiology studies on the prevalence of mental illness in TSC patients. The Committee suggests that the NICHD collaborate with the NINDS and the NIMH to sponsor a conference focused on psychiatric issues and cognitive disabilities in TSC. (p. 133)

Action taken or to be taken

The NICHD sponsors research on tuberous sclerosis complex (TSC), including basic, behavioral and translational research. TSC is one of a number of genetic disorders in which signs and symptoms of autism are disproportionately more frequent. Because of the wide range of manifestations of TSC in affected persons, and the fact that many features are not present at birth, accurate epidemiologic data are sparse. NICHD is leading an NIH-wide initiative on new methods for newborn screening and new treatments for screenable disorders. TSC is one of the conditions for which new DNA-based newborn screening technologies will allow for the collection of more information on the frequency of such mutations at birth. This will facilitate the type of studies recommended by the committee. Currently, the NICHD is exploring a collaboration with NINDS and NIMH to sponsor a conference on psychiatric issues and cognitive disabilities in TSC.

Item

Type 1 Diabetes Information Access and Integration - The Trial to Reduce the Incidence of Diabetes in the Genetically-At-Risk [TRIGR] is a multi-year clinical trial testing the potential influence of cow's milk on the development of type 1 diabetes in young children. The Committee urges the NICHD and NIDDK to ensure that TRIGR bio-samples and data are made available to the research community. The Institutes are encouraged to integrate TRIGR with other relevant clinical studies, such as the Type 1 Diabetes Genetics Consortium. (p. 133/134)

Action taken or to be taken

The NICHD agrees with the Committee that the data and the bio-samples generated by TRIGR on approximately 5000 children at high risk of type 1 diabetes constitute a rare and valuable resource. The investigators associated with TRIGR had planned from the outset to share TRIGR data and bio-samples with other relevant clinical studies such as the Type 1 Diabetes Genetics Consortium [T1DGC]. Sharing of data and bio-samples will be facilitated by having investigators associated with both TRIGR and T1DGC at several common sites, including Columbia University, the University of California at Los Angeles, and the University of Pittsburgh, as well as at 15 other sites in Canada, Australia and Europe. Collaborations and data sharing are also planned with another large study of the origins of type 1 diabetes called The Environmental Determinants of Diabetes in Youth [TEDDY].

Representatives from TRIGR, T1DGC, TEDDY and other type 1 diabetes research consortia and networks met in Boston in May, 2005, to plan further collaboration and to develop guidelines for sharing data and bio-samples. It was decided then that the samples obtained from each of these large studies can be combined to create a larger common database. Because several of the same investigators are involved with both TRIGR and TEDDY, it has been possible to implement similar standards in data collection, entry, quality control and analysis. This standardization, in turn, will permit direct comparisons between results obtained in each study.

The current policy established by the lead TRIGR investigators and agreed to by investigators associated with other type 1 diabetes research consortia is that TRIGR bio-samples and data will remain in the TRIGR storage system until the endpoints of the study have been reached, i.e., within six years for the autoantibody results and within 10 years for the onset of clinical diabetes. However, other studies or consortia that require TRIGR data or bio-samples prior to the advent of these structured endpoints would have access to TRIGR data or bio-samples as part of an ancillary study approved by the TRIGR Ancillary Study Committee.

Item

Type 1 Diabetes Research in Children Network - The Committee commends the NICHD for excellent progress made through the Diabetes Research in Children Network (DirecNet) which supports research to optimize the complex management of type 1 diabetes in children. The Committee urges the Institute to continue its strong support of DirecNet and to pursue robust translation of the research into clinical practice to improve the health of diabetic children. (p. 134)

Action taken or to be taken

The NICHD agrees with the Committee and plans to continue its strong support of DirecNet. DirecNet's is a network of investigators who are dedicated to improving the management of type 1 diabetes in children afflicted with this serious metabolic disorder. The NICHD, in conjunction with the NIDDK and the NINDS, recently issued a request for applications to continue support of DirecNet for another five years. During DirecNet first five years of existence the network's investigators published 21 articles in peer-

reviewed journals. In their efforts to translate the new discoveries from DirecNet into clinical practice, DirecNet investigators presented their findings annually at national meetings of the American Diabetes Association and the Society for Pediatric Research.

These exceptionally productive investigators have provided important insights into glucose monitoring and have developed practical guidelines for diabetic children to avoid attacks of low blood sugar that occur in the middle of the night, known as nocturnal hypoglycemia. Because these well-publicized advances are so necessary in the care of diabetic children, they are immediately translated into clinical practice by diabetologists and pediatricians who are responsible for their care.

DirecNet investigators are currently involved in three major studies: (1) Assessing the effect of altering insulin infusion rates during periods of exercise on the development of hypoglycemia in diabetic children wearing insulin pumps. The major finding of this study is that decreasing the infusion rate of insulin during exercise has a striking beneficial effect in reducing the incidence and severity of hypoglycemic attacks. (2) Evaluating the efficacy of the *Navigator*--- a new sensor that monitors glucose levels continuously--- in the management of type 1 diabetes in children. This study will form the basis for a larger protocol that will be implemented within the next several months. (3) Documenting the release of hormones such as adrenalin, growth hormone, and glucagon that work to increase levels of blood sugar in response to attacks of hypoglycemia. These hormones are known as counter-regulatory hormones. This protocol will assess the counter-regulatory responses to hypoglycemia in diabetic children who are three-to-six years old in comparison to those of diabetic adolescents who are 12-to-17 years old. Typically hypoglycemic attacks are more severe and more threatening in younger children, in part because their counter-regulatory hormone response to hypoglycemia is not yet mature. An important component of this study will be an assessment of the accuracy of new continuous glucose monitoring systems during periods of hypoglycemia and rebound hyperglycemia resulting from counter-regulatory hormone release.

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 recommends that a request for applications be issued. The Committee strongly urges NICHD to increase the number of awards for vulvodynia studies, with a particular emphasis on etiology and multi-center therapeutic trials. Finally, the Committee calls upon NICHD to work with ORWH and other relevant ICs and Government agencies, as well as patient and professional organizations, to implement an educational outreach campaign on vulvodynia. (p. 134)

Action taken or to be taken

The NICHD anticipates additional investigator-initiated applications in response to our recently reissued Program Announcement entitled *Vulvodynia – Systematic Epidemiologic, Etiologic or Therapeutic Studies*. This program announcement continues NICHD’s longstanding effort to stimulate research in this underserved area and supports

the overall strategy of augmenting and strengthening multidisciplinary approaches for treating this distressing condition. Investigators funded through previous vulvodynia initiatives are focusing on the prevalence, etiology, and potential treatment regimens through a series of clinical trials. The NICHD is excited about the increase of new and established investigators in vulvodynia research, and we are pleased to report that more junior and mid-career clinical scientists are entering this field and focusing on optimal treatment strategies. One of the investigators supported by NICHD hosted an international consensus conference and is currently disseminating the findings to the public and scientific communities. The proceedings of this 2004 research conference entitled *Vulvodynia: A State-of-the-Art Consensus on Definitions, Diagnosis and Management*, were just published (Journal of Reproductive Medicine 2006; 51:447-56). The NICHD also has held several meetings with the Office of Research on Women's Health at NIH to discuss the potential for an expanded and collaborative educational outreach campaign into the causes and treatments of vulvodynia, and plans to reach out to other relevant institutes and Government agencies, as well as patient and professional organizations, as plans progress for implementing this program. The NICHD has coordinated with the ORWH and contributed information to the NIH web site on vulvodynia. The overall goal of these activities is to build a substantive scientific knowledge base, as well as provide the public with information related to this debilitating condition.

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National Eye Institute House Significant Items

Item

Diabetic Eye Disease – The Committee applauds NEI for the collaborative efforts of the Diabetic Retinopathy Clinical Research Network to test innovative treatment 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 reverse or prevent diabetic retinopathy. (p.105/106)

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network dedicated to facilitating multicenter clinical research to improve the treatment of diabetic retinopathy, diabetic macular edema, and associated conditions. DRCR.net currently includes more than 150 participating sites with more than 500 clinicians throughout the country.

DRCR.net welcomes input from the diverse array of individuals interested in diabetes ophthalmic trials including those from academic, community, foundation, corporate and other groups. DRCR.net studies currently recruiting patients include: an evaluation of clinical and functional outcomes associated with the surgical removal of the jelly-like vitreous from within the eyes of individuals with swelling of the macula (the area of the retina responsible for sharp central vision) caused by diabetes; a study of the effects of laser photocoagulation surgery for diabetic retinopathy on the subsequent development of macular swelling; and, a study of the incidence and progression of subclinical diabetic macular edema that will also include an evaluation of predictive factors and risk factors for progression of the condition. These studies will continue for an additional one to two years. Additional clinical studies are planned for 2007 and beyond, and include: Evaluation of Laser Photocoagulation and Adjunct Therapy for the Treatment of Diabetic Macular Edema, expected to begin recruitment in early 2007; Phase 3 Evaluation of Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema, also expected to begin recruitment in early 2007, which will evaluate the use of inhibitors of growth factors that stimulate the abnormal growth of blood vessels and swelling of the macula; and, a study of cataract surgery and diabetic macular edema that is expected to begin recruitment in the fall, 2007.

Senate Significant Items

Item

Age-related Macular Degeneration – The Committee was pleased to hear of the recent discovery of a second gene which can increase the risk of developing age-related macular degeneration. The identification of these genes creates the opportunity to predict and preempt the disease, thus preserving independence and mobility for millions of Americans. These gene discoveries also validate a new approach to identify the subtle genetic risk factors underlying common, complex diseases. The Committee notes that

Genome wide association studies allow scientists to scan the entire genome of patients with common diseases and compare their DNA to controls without disease. The Committee urges the Institute to move on an expedited basis to translate this finding into treatment for those suffering from this condition. (p. 135)

Action taken or to be taken

NEI recently released genetic data from the Age-Related Eye Disease Study (AREDS) in a new NIH database that provides access to an unprecedented level of detail on the association between study participants' genetic makeup and their clinical outcomes. AREDS, a key study on age-related macular degeneration, is the first set of data to be included in the new public NIH database, called dbGaP, or database of Genotype and Phenotype. This database was developed and will be managed by the National Center for Biotechnology Information, a component of the National Library of Medicine. Whole genome association studies explore the connection between specific genes and genetic variations (genotype information) and observable traits, such as blood pressure and weight, or the presence or absence of a disease or condition (phenotype information). Having this information widely available will help researchers better understand gene-based eye diseases, such as age-related macular degeneration, and will help accelerate development of effective therapies and preventive measures.

National Institute of Environmental Health Sciences

House Significant Items

Item

Asthma – Given the link between environmental factors and the onset of asthma, COPD, and pulmonary fibrosis, the Committee encourages 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. 106)

Action taken or to be taken

Since 1966, the National Institute of Environmental Health Sciences (NIEHS) has supported important research on environmental links to respiratory disease, including research resulting in major findings, such as the role of asbestos in causing mesothelioma, a cancer of the lining of the lung.

NIEHS scientists are working to identify genes that mediate host response to a number of environmental toxins and allergens. One project, involving the genetics of environmental asthma, seeks to identify genes that are involved in the development of airflow obstruction and airway inflammation in asthmatics, and to determine whether gene variations (polymorphisms) in these differentially expressed genes predispose individuals to develop asthma. Another research project seeks to identify genetic determinants of innate immunity and host defense. A third project seeks to uncover the genetic determinants of interstitial lung disease.

Partnering with the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics, NIEHS added an allergy/asthma component to the 2005-2006 National Health and Nutrition Examination Survey. The final dataset for analyses will be available by the end of calendar year 2007. The significance of this research is that it will provide surveillance of allergen exposure, sensitization, and disease; shed light on processes that may lead to interventions; allow for investigation of why asthma is disproportionately distributed among African-American and inner-city children and adults; and provide data for evaluating national goals for asthma, among others.

NIEHS recently awarded special grants through the NIEHS Outstanding New Environmental Scientist (ONES) Awards program. These grants, awarded to some of the brightest rising talents in environmental sciences, will address such issues as: the relationship between exposure to airborne chemicals from vehicle exhaust and industrial sources and increased susceptibility to respiratory illnesses such as emphysema and chronic obstructive pulmonary disease; the relationship between ozone and the incidence of respiratory disease and death in exposed populations; and the effects of fine particle exposure on blood flow and heart disease risk.

Item

Autism Spectrum Disorders - The Committee is aware of the important research into the genetic and environmental basis of autism spectrum disorders. Accordingly, the Committee encourages the Institute to expand its support and funding for gene-

environment interaction research in autism, and encourages the institute to expand its work with and support for similar public-private partnerships. (p. 106)

Action taken or to be taken

NIEHS partners with the U.S. Environmental Protection Agency to invest in the Centers for Children's Environmental Health and Disease Prevention. In 2006, a five-year grant was awarded to the Center at the University of California at Davis to extend previous work to elucidate the environmental basis of autism. A pilot study at the Center targets younger siblings of children with autism, a high risk group for developing autism, to collect data on environmental exposures and other risk factors beginning in pregnancy and continuing through early postnatal development.

Other interdisciplinary projects also supported through the Children's Centers, range from epidemiologic and clinical studies to studies in animal and cellular models. For example, using biological specimens collected previously as part of the large case-control epidemiologic study, investigators are focusing on identifying environmental and genetic markers of autism risk.

In addition, NIEHS continues to encourage investigator-initiated applications in this area. A notable success of these efforts was the award of an exploratory grant to Johns Hopkins University in 2006 to develop a methodology to measure individual susceptibility to mercury toxicity and to conduct a pilot study to compare susceptibility in individuals from families with autism with those from unaffected families.

Also, as a member of the NIH Autism Coordinating Committee (ACC), which coordinates NIH efforts to find a cure for autism, NIEHS co-funded the Studies to Advance Autism Research and Treatment (STAART) Centers and the National Database for Autism Research (NDAR).

As a member of the Interagency Autism Coordinating Committee (IACC), which provides federal-wide coordination of autism research, NIEHS co-sponsored three broad program announcements developed to solicit applications for small (R03), exploratory/developmental (R21) and traditional (R01) grants. The announcements encourage grant applications focused on environmental aspects of autism. The IACC has undertaken an evaluation of the Autism Research Matrix, initially adopted in 2003. The Matrix is used as a guide for NIH and other federal research efforts. The role of the environment is incorporated in several elements of the Matrix and progress toward these specific goals will be determined as part of the Matrix evaluation. NIEHS will consider carefully the results of this evaluation in planning future activities in this area.

Item

Mercury - In order to properly research gaps in the area of mercury exposure and brain chemistry, and given recent hearings on mercury exposure and relationships between autism and Alzheimer's disease and mercury exposure, NIEHS is encouraged to pursue studies of how inorganic mercury and organic mercury compounds (including ethyl, methyl, and other forms of mercury from all sources) are processed in the bodies of

children and adults. NIEHS is also encouraged to support studies of the toxic effects of inorganic mercury and organic mercury compounds on the nervous systems of young children, adults, and the elderly and methods of properly removing mercury and mercury-containing compounds from the brains of affected humans. (p. 106)

Action taken or to be taken

NIEHS supports a broad array of research aimed at gaining a more complete understanding of the impact of mercury on the developing brain. One study examined the fate of organic mercury compounds in the brain of nonhuman primates. The study found that not only is less ethylmercury taken up by the brain following ethylmercury exposure compared to methylmercury, the ethylmercury that is taken up is broken down faster than methylmercury. A comparable study examined the distribution of mercury, comparing the route of exposure and form of mercury, and found less mercury in the brain following ethylmercury administration (compared to methylmercury) and also significantly less mercury in the brain following an intramuscular injection as compared to oral intake.

Other studies funded by NIEHS examine the central nervous system targets of the alkyl and inorganic mercury forms, and most importantly, the relative toxicity of these mercury species in brain development. Some of these studies use invertebrate embryo models to establish relevant systems that are highly conserved across species before examining them in mammalian models. Most of the studies indicate that methylmercury is more toxic to the developing brain than inorganic mercury, but one study has shown that neural inflammation occurs only in the brain area where there is inorganic mercury.

Another study examines the effect of mercury exposure and speciation across the life-span. One approach, using rodent models, examines the effect of early methylmercury exposure on the aging brain by looking at cognitive and locomotive effects.

Other ongoing research on prenatal exposure to mercury in children indicates that when the source of exposure is fish, there may be nutritional benefits that mitigate the effects of exposure. Further studies will continue to explore this issue, as well as the possible effect of prenatal exposure to elemental mercury from maternal caries on neurodevelopment.

Item

Toxic Exposure and Brain Development - Notwithstanding the Institute of Medicine May 2004 report on autism, the Committee believes it is important to develop a more complete understanding of the impact that toxic exposures may have on brain development. There is a convergence of findings from tissue culture studies, animal models, and clinical studies of immune dysfunction in children with autism and other neurodevelopmental disorders (NDDs) that suggests a biological link between genetic sensitivity and damage to developing brains from certain toxins. It is important that NIH continue this research to better understand the impact that exposures to mercury (including thimerosal) and other toxins have on brain development. A more complete understanding of the impact of these exposures through research, including animal models, will help to develop more effective interventions. (p. 107)

Action taken or to be taken

To develop a greater understanding of the effects of toxic exposures on the developing brain, NIEHS supports studies of organophosphates on the developing brain in rodent models, as well as in children, from pre- and postnatal exposure. These studies include research on the effect of pesticides and polychlorinated biphenyls (PCBs). From the epidemiology studies conducted by the Children's Environmental Health Centers, evidence shows that PCB exposure contributes to the development of attention deficit hyperactivity disorder (ADHD) in children.

Other exposures of concern in the developing nervous system are heavy metals, such as mercury and lead. Research on lead has been extensively supported and has resulted in a vast amount of data that has contributed to the realization that there is no safe level of lead for the developing brain. The oral chelator (succimer) that NIEHS helped develop, while shown to be safe and simple to administer, cannot repair prior damage to the developing brain.

Senate Significant Items

Item

Autism - The Committee is aware of the important research into the genetic and environmental basis of autism spectrum disorders. Accordingly, the Committee encourages the Institute to expand its support and funding for gene-environment interaction research in autism, and encourages the Institute to expand its work with and support for similar public-private partnerships. (p. 135)

Action taken or to be taken

Please refer to page 153 of this document for NIEHS' response to this item on Autism.

Item

Behavioral Research in Strategic Plan - NIEHS is requested to report to the Committee during the fiscal year 2008 hearings on plans to extend its research on obesity and the built environment, and other areas in which behavioral research is to be involved in its research portfolio in the coming years. Individual and group behavior with regard to diet, exercise, work, recreation, family, and neighborhood interaction, are critically important areas to investigate, to build knowledge about how people's environments shape their health. (p. 135)

Action taken or to be taken

NIEHS has historically supported innovative projects that involve behavioral research, and recently those that involve the examination of the built environment and obesity. In August 2004 NIEHS/NIH/DHHS released a Request for Applications (RFA), Obesity and the Built Environment, to begin building a program of R01 and R21 research projects in two specific areas related to the built environment and obesity: understanding the role of the built environment in causing/exacerbating obesity and related co-morbidities; and developing, implementing, and evaluating prevention/intervention strategies that

influence parameters of the built environment in order to reduce the prevalence of overweight, obesity and co-morbidities. The Office for Behavioral and Social Science Research (OBSSR), the NICHD and CDC are also participating in the program. In September 2005, \$2 million from NIEHS and \$1 million from the NIH Director's Discretionary Fund were used to fund five R01 projects (with up to five years of funding) and three R21 projects (two years of funding). In addition, NIEHS oversees three CDC-funded R21 projects. All are part of this initiative.

The purpose of the R01 studies is to provide solutions for alleviating the burden of obesity and overweight in the U.S. by providing insights into treatment mechanisms or developing models for prevention. The R21 studies are focused on developing and validating built environment measures and methods of data collection. Applications funded include longitudinal, cross-sectional and intervention studies in rural, urban and suburban areas and were chosen to create a diverse, balanced portfolio. These awards create a fully integrated research program to better understand how the environment contributes to obesity and how environmental interventions can prevent or treat this condition.

In August 2006, a successful First Annual Meeting of the Obesity and the Built Environment Program grantees was held in Research Triangle Park, NC. The Principal Investigator and/or Co-Investigator from each project presented the purpose and goals of their project and progress made during the first year of funding.

Other NIEHS behavioral research includes the Genes and Environment Initiative (GEI), the Environmental Justice: Partnerships for Communication program, Community-based Participatory Research and Centers for Population Health and Health Disparities.

Item

Genes and the Environment - The Committee commends the NIEHS for its partnership with NHGRI in the Genes and Environment Initiative [GEI] which supports studies in genetic analysis and environmental technology development to understand the causes of common diseases such as Parkinson's, asthma, stroke, cancer, and heart disease. NIEHS's role in developing new technology to monitor personal environmental exposures, dietary intake, and physical activity will greatly enhance our ability to understand how they interact with genetic variations and result in human disease. The NIEHS is encouraged to take a closer look at environmental interactions with genes, and to involve expert behavioral and social scientists in the initiative to enhance the success and applicability of this important research. (p. 135)

Action taken or to be taken

The GEI, a NIH-wide initiative, seeks to investigate the interactions between genetic and environmental factors that underlie complex human diseases. The Exposure Biology Program (EBP) of the GEI focuses on the development of innovative technologies to measure environmental exposures, diet, physical activity, psychosocial stress, and addictive substances. The EBP will support development of environmental sensors, development of "fingerprints" (markers) of biological response, integration of biological

responses with the development of biosensors, and application of these biomarkers to genome-wide association (GWA) studies of gene-environment interaction.

New initiatives for the development of environmental sensors include:

- RFA on new technologies for measuring dietary/supplement intake and measures of physical activity using sensor technologies simultaneously with physiologic indicators of response (heart rate, respiration).
- RFA on new technologies for measuring exposure to psychosocial stress and addictive substances using hand-held devices for automated self-report and recall, innovative software, wireless technology, or other technology.
- RFA on new technologies for measuring human contact exposure and internal dose to priority environmental chemical/biological agents (e.g., airborne particulates, reactive gases, microbial toxins, solvents, pesticides, and mold/microbial toxins).

New initiatives for biological response include:

- RFA on the development of biological response indicators reflecting components of key physiologic and pathogenic processes, such as oxidative stress, immune response and inflammation, and DNA damage.
- RFA to support the development of centers that integrate biological response indicators with the development of field deployable biosensors to track exposures from point of contact to biological response.

NIEHS, in partnership with NIDA and OBSSR, is participating in an initiative aimed at developing improved sensors or biomarkers of stress, which includes a GEI-related RFA entitled “Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and to Addictive Substances for Studies of Health and Disease.” A number of social and behavioral scientists attended the Exposure Biology Program meeting in May 2006 to help inform the initiatives in this area of the GEI.

Item

National Toxicology Program Interagency Center for the Evaluation of Alternative Methods/Interagency Coordinating Committee on the Validation of Alternative Methods [NICEATM/ICCVAM] - The Committee encourages the NICEATM/ICCVAM, in partnership with the relevant Federal agencies to build on the NTP Roadmap to create a 5-year plan to research, develop, translate and validate new and revised non-animal and other alternative assays for integration of relevant and reliable methods into the Federal agency testing programs. The Committee encourages the Federal agency program offices to identify areas of high priority for new and revised non-animal and alternative assays for the replacement, reduction and refinement of animal tests. The Committee further encourages relevant agencies to include the public when developing this plan. The Committee further requests a status report during the fiscal year 2008 budget hearings. (p. 135)

Action taken or to be taken

NIEHS, NICEATM, and ICCVAM have begun the process of creating a 5-year plan for research, development, translation, and validation of new and revised non-animal and other alternative assays that can be integrated into federal agency testing programs. The report will identify planned activities by NICEATM, ICCVAM, and federal agencies relevant to areas of high priority for assays that will provide for replacement, reduction, and refinement of animal tests. NIEHS will form a workgroup to direct and coordinate plan development. A *Federal Register* notice was published to request input from the public that can be considered during preparation of the plan. This notice was also widely distributed via ICCVAM and NTP listservs to interested stakeholders. The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) and ICCVAM will identify areas of high priority for new and revised non-animal and alternative assays for replacement, reduction, and refinement of animal tests, as well as research, development, translation, and validation activities for non-animal and other alternative assays. NIEHS, in coordination with NICEATM and ICCVAM, will consider and incorporate information provided by the public, SACATM, and federal agencies into the draft 5-year plan. The Director of NTP/NIEHS will finalize and publish the plan. The plan will be widely distributed, published on the ICCVAM-NICEATM public website, and its availability announced in the *Federal Register*.

Item

Volcanic Emissions - The Committee continues to have concerns about the public health impacts of volcanic emissions in Hawaii. Such emissions contribute to the exacerbation of a myriad of pre-existing health conditions in many island residents, especially children. The acute and long-term impact that these emissions have on both the healthy and pre-disposed residents warrants further study. The Committee strongly advises the NIH to embrace a multi-disciplinary approach in studying the short- and long-term health effects of volcanic emissions, and to consider the establishment of a center dedicated to such research. (p. 136)

Action taken or to be taken

NIEHS has been concerned about the respiratory health effects of volcanic emissions for some time and to that end has provided continuous support to Dr. Elizabeth Tam's research at the University of Hawaii at Manoa from 2001 to 2007. This research engages residents of the Big Island of Hawaii to explore the effects of volcanic air pollution ("vog") on their respiratory health. Scientists and community researchers have been working together to explore the hypothesis that children who have been exposed to volcanic pollution during most of their lives suffer significantly more respiratory symptoms, decreased lung function, or diminished lung growth than children who reside in areas of low vog. The overall goals of this work are to: (1) develop a community research infrastructure that promotes collaboration between research institutions, community leaders and participants and that builds capacity in the community to address environmental research questions; (2) compile and analyze available air monitoring data, historical volcanic activity and weather patterns to estimate the concentrations of vog to which children have been exposed since 1990; (3) monitor concentrations of particulate matter, acid aerosols, and SO₂ in residential areas that are predicted to differ in vog

concentration; (4) characterize and compare in a cross-sectional study the respiratory symptoms and function of children in these areas; and (5) compare the rates of lung growth in these children in a 3-year follow-up study. Dr. Tam collaborates with scientists from the NIEHS Environmental Health Sciences Center at Harvard School of Public Health on this important project.

National Institute on Aging

House Significant Items

Item

Alzheimer's Disease – The Committee continues to regard Alzheimer's disease as a high research priority for the Institute, which is encouraged to enhance its investment in Alzheimer's disease research, placing special emphasis on expediting the translation of research findings into effective treatments and prevention strategies for at-risk individuals. (p. 107)

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, the NIA launched a Translational and Drug Discovery Initiative. This ongoing initiative includes an R21 Early Drug Discovery Program (PAS-06-261) and a U01 Preclinical Drug Development Program (PAR-05-148).

NIA-supported investigators involved in drug discovery and drug development can utilize 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.

NIA staff will convene the First Annual Investigators Meeting for Translational Research in the summer of 2007 to include grantees of the above programs and investigators that use the Toxicology Contract services, program staff from the NIA and the NINDS, a representative of the AD Drug Discovery Foundation, FDA experts, and several experts on drug discovery for AD from academia and/or industry as advisors. These advisors will provide immediate feedback and guidance to the investigators and in doing so increase the likelihood of success of these translational projects. NIA plans to convene ~20 investigators and about half a dozen expert advisors, together with NIH program staff.

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.

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, including exercise and mechanisms of biomineralization. However, little is understood as to how these properties assist in the maintenance of bone strength. The Committee encourages NIA, in collaboration with NIAMS, NIBIB, NICHD, and NHLBI to support research that will achieve identification of these parameters and lead to better prediction for prevention and treatment of bone diseases such as osteoporosis,

osteogenesis imperfecta, bone loss due to kidney disease, and heart attacks due to hardening of the arteries. (p. 108)

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 2006 include:

- NIA renewed two cooperative agreements for the Osteoporotic Fractures in Men (MrOS), co-sponsored by NIAMS, to quantify the determinants of fracture in men. The study follows 5,995 men, 65 years and older, in six diverse U.S. communities. In addition to measurements of bone density, the study conducts quantitative computed tomography skeletal assessments to further characterize bone geometry changes and quantify femoral strength to better understand the finite characteristics of bone by using an imaging technique called densitometry, which measures transmitted light through an object, and biomechanical risk factors underlying skeletal fragility and hip fracture.
- NIA continues to support trans-NIH program announcements, including PA-06-242, Aging Musculoskeletal and Skin Extracellular Matrix, with NIAMS, under which an NIA study is investigating whether age-related bone loss is due in part to aberrant musculoskeletal behavior caused by alteration of the material produced and secreted by cells of the bone marrow and the biology of the material that is produced and secreted by cells in the joint space; and PA-03-147, Age-Related Changes in Tissue Function: Underlying Biological Mechanisms, co-sponsored by NCI, NIDCD, NIDCR, and NIDDK, under which an NIA investigator is studying ways to identify common mechanisms underlying age-related changes in cell function as it relates to muscle and bone loss.
- Under RFA-AG-06-003, The Adipogenic Phenotype in Aging Musculoskeletal Tissues, NIA seeks to 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.

Item

Demographic and Economic Research – The Committee commends NIA for supporting exceptional demographic and economic research on the implications of population aging. The Committee encourages the Institute to continue supporting the Health and Retirement Study (HRS)--an important resource policymakers rely on to help inform potential changes to the Social Security and Medicare programs. The Committee applauds the Institute for proactively reviewing its data collection activities and looks forward to learning more about the outcome of this review and how the future of major surveys, such as the HRS and the National Long-Term Care Survey, may be affected. (p. 108)

Action taken or to be taken

NIA renewed its cooperative agreement with the University of Michigan in FY 2006 to continue the Health and Retirement Study (HRS), the nation's leading resource for data on the combined health and economic conditions of Americans over age 50.

The HRS will include additional key constructs in cognitive aging, such as executive functioning, reasoning, and speed of processing. An HRS sub-study, the Aging, Demographics, and Memory Study (ADAMS), will provide the first estimates of cognitive impairment and dementia based on nationally representative data, as well as "gold standard validation" of survey measures (first publication of results expected in 2007). A supplement provides support for HRS staff to supply information on sample design, questionnaire design, computer-assisted interview programming, interviewer performance, and data dissemination. This stands to improve the quality of data collected and provides an incentive for international partners to follow a harmonized design that will maximize the potential for cross-national behavioral and social research on aging.

The HRS, now in its 14th year, follows more than 20,000 people at two-year intervals, providing data from pre-retirement to advanced age. A major goal of the study is to help address the scientific and policy challenges posed by the nation's aging population. The renewal will provide approximately \$70 million in funding over the next six years to continue the study. The U.S. Social Security Administration also will provide funding for such activities as collecting and developing data on pensions and consumption.

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. The Committee 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 further encouraged to consider how studies of the Down syndrome population might enhance the ability to understand, diagnose and treat Alzheimer's disease. (p. 108)

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 is currently recruiting 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.

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

Edward R. Roybal Research Centers on Applied Gerontology – The Committee supports the Edward R. Roybal Research Centers on Applied Gerontology, which are designed to move promising social and behavioral basic research findings out of the laboratory and into programs, practices, and policies that will improve the lives of older people and the capacity of society to adapt to societal aging. The Committee encourages NIA to expand the numbers of centers, to develop new topics for research especially in the area of diversity and ethnic and minority communities, and to provide opportunities for collaborative, interdisciplinary research between the Roybal Centers and other program initiatives such as the Resource Centers for Minority Aging Research (RCMAR) and the Demographic Centers. (p. 108)

Action taken or to be taken

There are currently ten Roybal Centers. In pursuit of their objectives, collaborative, interdisciplinary research between the Roybal Centers and other program initiatives is highly encouraged. For example, the Resource Centers for Minority Aging Research (RCMARs) partner with the Roybal and other NIA-supported Centers to develop and implement strategies to improve recruitment and retention of minorities in clinical research. A 2006 review of NIA clinical trial recruitment activities concluded that the Institute's strategies, which include partnership activities between the RCMARs and other Centers, including Roybals, are making a significant difference in terms of methods and practices used in the recruitment and retention of minority elders in aging research.

An evaluation in early 2007 has been planned to help the NIA chart future directions for the program, including potential changes to program scope, goals, and objectives. Results from the evaluation will also be used in developing the content and scope of the research solicitation.

Item

Epilepsy – Epidemiologic studies now show that the incidence of epilepsy increases in old age, often in association with stroke, cardiovascular disease, brain tumors and Alzheimer's disease. The Committee encourages NIA, working with NINDS, to carry out research to better understand why epilepsy frequently develops in association with diseases of the elderly and to develop therapies to prevent the occurrence of epilepsy in the elderly and diminish its consequences. The Committee also encourages NIA to actively participate in NINDS 2007 "Curing Epilepsy" conference to further develop a research agenda related to epilepsy and the elderly. (p. 108/109)

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 association of certain polymorphisms in the IL-1 cytokine gene with inflammatory processes and neuropathological changes in tissues from patients with Alzheimer's disease, Down syndrome, head injury, and epilepsy; another study explores aging as a risk factor for seizure-induced cell death in an animal model.

With NINDS, in 2006 the NIA released 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 NINDS sponsored workshops on "Model Development in Epileptogenesis" and "Models of Geriatric Epilepsy" in 2006, and NIA will participate in the NINDS conference on "Curing Epilepsy 2007: Translating Discoveries into Therapies" to be held in March, 2007. 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.

Senate Significant Items

Item

Alzheimer's Disease – More than one in 10 Americans over age 65 and nearly half of those over 85 suffer from Alzheimer's disease. As the Baby Boom generation enters the age of highest risk, between 11 million to 16 million will be stricken with Alzheimer's. Their complex health and long-term care needs will continue to take an enormous toll on family caregivers, and place an even greater strain on Federal and State healthcare programs. Total Medicare spending for beneficiaries with Alzheimer's will double in the next decade – rising from \$91,000,000,000 in 2005 to \$189,000,000,000 in 2015; over

the same period, Medicaid spending on nursing home care alone will increase from \$21,000,000,000 to \$27,000,000,000. As a result of past investments in research recommended by the Committee, drugs now are available for treating the symptoms of Alzheimer's, and clinical trials are underway to test other promising compounds. The NIA has launched a public/private imaging initiative that should accelerate the development of new, more effective treatments; and a genetics initiative that will make it possible to target new treatments on those who stand the best chance of benefiting. In light of its enormous human and financial toll this disease exacts, the Committee regards Alzheimer's disease as a high priority for the Institute. NIA is urged to expand its investment in Alzheimer's disease research, placing special emphasis on expediting the translation of research findings into effective treatments and prevention strategies for at-risk individuals. (p. 137)

Action taken or to be taken

Please refer to page 163 of this document for NIA's response to this item on Alzheimer's disease.

Item

Bone Strength – Although bone mineral density has been a useful predictor of susceptibility to fracture, other properties of the skeleton contribute to bone strength, including exercise and mechanisms of biomineralization. However, little is understood as to how these properties assist in the maintenance of bone strength. The Committee urges the NIA, in collaboration with the NIAMS, NIBIB, NICHD, and NHLBI, to support research that is aimed at identifying these parameters and will lead to prevention and treatment of bone diseases such as osteoporosis, osteogenesis imperfecta, bone loss due to kidney disease, and heart attacks due to hardening of the arteries. (p. 137)

Action taken or to be taken

Please refer to page 163 of this document for NIA's response to this item on Bone Strength.

Item

Behavioral and Social Research on Work and Retirement – The Committee encourages NIA to maintain its commitment to research on patterns and cycles of work in aging populations. Research on how jobs may be “retrofitted” for an aging workforce, or how workplaces can better accommodate aging workers, is encouraged. Research on how older workers plan for and experience retirement is also timely and encouraged. (p. 137)

Action taken or to be taken

Retirement research has evolved considerably over the course of the last twenty years, with improvement in retirement research infrastructure and a number of substantive analyses examining key factors related to the retirement decision. Improvements in computer technology coupled with successful long-term investments by NIA in longitudinal data files have greatly improved retirement research possibilities.

The Health and Retirement Study, the Panel Study of Income Dynamics, and internationally comparable retirement and health studies have greatly improved access to comprehensive longitudinal data. RFA-AG-07-007, “Developing Integrated Economic Models of Health and Retirement,” seeks to stimulate studies to develop comprehensive econometric models of retirement from the labor force. The objectives of this research initiative are to comprehensively integrate health and disability, wealth, and family factors into a single retirement modeling framework.

Two areas of increasing interest to the general public and targeted for development within the NIA are 1) technology adaptation for general living, health and work; and 2) the older worker. The CREATE Technology Center was established and two new studies on health of the older worker have begun.

National workshops and meetings are planned to address the issues of technological adaptivity and the components of technology, cognitive intervention, and motivation that will maintain the health and productivity of an older work force.

Item

Demographic and Economic Research – The Committee commends the NIA for supporting demographic and economic research on the implications of population aging. With the number of Americans over the age of 65 expected to double over the next 25 years, the Institute is well poised to inform the public and policymakers about the implications of this anticipated trend and the macroeconomic and global aspects of aging. In particular, the Committee urges the Institute to continue supporting the Health and Retirement Study [HRS], which can help inform policymakers about potential changes to the Social Security and Medicare programs. (p. 137)

Action taken or to be taken

Please refer to page 164 of this document for NIA’s response to this item on Demographic and Economic Research.

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 coordinate its research with NICHD, NINDS, NIMH and other institutes. (p. 138)

Action taken or to be taken

Please refer to page 165 of this document for NIA’s response to this item on Down Syndrome.

Item

Fragile X-associated Tremor/Ataxia Syndrome [FXTAS]- The Committee applauds the NIA for working alongside the NINDS to fund research on FXTAS. It encourages the NIA to expand its research into this newly identified neurological disorder, which involves progressively severe tremors and difficulty with walking and balance that appears to specifically affect some older premutation carriers, generally grandfathers of children with Fragile X syndrome. (p. 138)

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. Other NIA-supported research focuses on epigenetic changes (DNA modifications that are not the result of a change in the coding sequence of genes). Although not directly focused on FXTAS, these basic studies have the potential to provide insight into the etiology and pathological mechanisms underlying the disease. For example, the NIA supports research on DNA methylation, a type of chemical modification of the DNA that can, under certain conditions, cause several debilitating health conditions, including FXTAS.

Item

Healthy Brain Initiative – NIA is commended for its cooperative efforts in producing a searchable database of studies and planning joint efforts to solicit research on enhancing healthy cognitive and emotional function. This initiative is a model of how institutes can work together on complex issues involving multiple disciplines and methodologies. Given the importance of maintaining and enhancing brain health as the population ages, NIA is encouraged to make this initiative a priority. (p. 138)

Action taken or to be taken

The Cognitive and Emotional Health Project (CEHP), a joint venture of the NIA, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke, remains a priority for the NIA. The goals of this initiative are to assess the state of longitudinal and epidemiological research on demographic, social, and biologic determinants of cognitive and emotional health in aging adults and the pathways by which cognitive and emotional health may reciprocally influence each other.

A searchable database of studies of cognitive and emotional health is now available at <http://trans.nih.gov/CEHP/hbq/search.asp>. Other recent activities include:

- An in-depth critical review of longitudinal and epidemiological studies targeting factors involved in maintenance of cognitive and/or emotional health. In this review, a variety of risk factors were consistently identified with cognitive and emotional outcomes. Findings from the review suggested several opportunities to advance knowledge in this area, including the use of secondary data analytic studies to exploit the rich datasets that currently exist.

- Initiation of the development of a cognitive and emotional function assessment tool for use in large cohort studies. Once developed and validated, this instrument will serve as a national resource for the scientific community and across the NIH.

In late 2007, the NIA is planning to host 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.

Item

Hematology – The Committee looks forward to learning more about NIA’s collaborative efforts with the American Society of Hematology and NHLBI to identify research priorities in venous and arterial thrombosis, blood clots that can lead to death and serious morbidity, including pulmonary embolism, lower extremity phlebitis, heart attacks, strokes and chronic respiratory dysfunction. In light of research findings showing that age is one of the most important risk factors for thrombosis, the Committee urges NIA and NHLBI to develop a research agenda in this area to learn more about the underlying causes of thrombosis and its impact on the elderly. (p. 138)

Action taken or to be taken

Advanced age is associated with a dramatic increase in venous and arterial thrombosis (the development of dangerous blood clots in the veins and arteries), and research on thrombosis is an area for ongoing collaborative development between the NIA and the National Heart, Lung, and Blood Institute (NHLBI). To explore the implications for venous thrombosis and thromboembolism in older patients, the American Society of Hematology (ASH), in collaboration with NIA and the NHLBI, sponsored a workshop of national and international experts in this field in June 2006. The goal of the workshop was to identify knowledge gaps and research opportunities in this area, and to stimulate research addressing this clinical problem in older patients.

Following this workshop, 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. The RFAs are an initial activity in this area that NIA hopes will stimulate interest and lead to further collaborative activities on this topic. NIA is already seeing special sessions on this topic at the ASH annual scientific meeting.

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

House Significant Items

Item

Burden of Skin Diseases - The Committee notes the relationship between the recent Burden of Skin Diseases report and the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. The committee continues to encourage NIAMS to expand the research portfolio on skin disease and develop partnerships with the skin disease research community to address the recognized challenges and future research endeavors. (p. 109)

Action taken or to be taken

NIAMS awarded a contract in May 2004 to examine existing data sets containing information on the burden of skin disease, including available epidemiological data, quality-of-life measures, and economic data. The researchers were also asked to identify available instruments used for the collection of data relating to disease in general, skin disease as a whole, and specific skin diseases. The final report from this contract was recently submitted to NIAMS for review and consideration. Results included in the report will be shared with the relevant research communities, as appropriate. Additionally, NIAMS will continue to work with researchers to make the most of existing databases, including new information from the Center for Disease Control and Prevention's National Health and Nutrition Examination Survey.

NIAMS-supported researchers have recently reported improvements to an established measure of skin disease. By paring down an existing measurement tool, researchers have been able to create a shorter instrument that may be easier to administer in large-scale data collection exercises. Additional work needs to be completed to further validate these findings; however, this study indicates the progress being made in addressing the concerns related to gathering information from both adult and pediatric patients, particularly in younger children where the parents will have to provide the data.

Other researchers have identified a gene called PSORS1 that plays a role in determining who gets psoriasis, and autoimmune skin disease. The researchers, along with colleagues from around the country and in Germany, looked closely at genetic samples from 678 families in which some of the family members had early-onset psoriasis, and they identified a specific alternate form of a gene as the one that confers susceptibility to this form of the disease. Support for this work was provided by the NIAMS, the National Center for Research Resources, the National Psoriasis Foundation, and others.

Additionally, NIAMS has signed a memorandum of understanding with the American Skin Association to support fellows funded by NIAMS under the Individual Postdoctoral National Research Service Awards (NRSA) program in epidemiology, clinical trials research, and outcomes research in skin diseases. NIAMS is committed to offering training support for current and future basic and clinical researchers focused on core components of its mission. The NRSA mechanisms help to ensure the development of a

diverse and highly trained workforce that is available to assume leadership roles related to the Nation's biomedical and behavioral research agenda.

Item

Congenital and Genetic Disease of Bone - The Committee is aware that thousands of children and adolescents nationwide suffer from musculoskeletal disorders and malformations. Diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, 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 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.

(p. 109)

Action taken or to be taken

Bones are living tissues, which are regularly broken down by cells called osteoclasts and rebuilt by cells called osteoblasts. Normally, this process is kept in balance; however, several different genetic diseases can affect this process, leading to disease. For example, osteogenesis imperfecta (OI), a disorder characterized by bones that break easily, 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. Fibrous dysplasia of bone is a developmental disorder characterized by expanding fibrous lesions of bone-forming tissue that result in pain, fracture, and/or deformity. Osteopetrosis is a group of genetic bone diseases that are characterized by an increase in skeletal mass resulting from inadequate bone breakdown. In osteopetrosis, osteoclasts usually are either fewer in number or are ineffective in breaking down bone, leading to dense but fragile bones. Finally, Paget's disease of bone is characterized by bones that grow too large and weak, also raising the risk of fracture due to poor bone quality.

NIAMS supports a broad portfolio of research in genetic diseases of bone including novel gene- and cell-based therapeutic approaches; the molecular and cellular mechanisms of disease; and the genetic and environmental risk factors that cause disease. For example, NIAMS-supported researchers recently discovered a potential approach to treating OI. The most common cause of OI is a defect in the gene that controls the production of Type 1 collagen proteins. In severe cases, this results in both the production of insufficient amounts of collagen and the production of defective collagen. The defective collagen interacts with other proteins, magnifying the defect's harmful effects. The challenge is to find a way to reduce or eliminate the production of the defective protein without affecting the same cells' production of normal collagen. In this study, specially designed ribozymes, acting as molecular scissors, were used to break the chemical links that held together the carriers of genetic information, thus cutting off communication between the defective gene and collagen-producing cells. The findings thus far have been limited to cultured cells and mice; much work remains to be done before ribozymes can be tested in people. But the success in targeting collagen production in bone clearly shows that the

ribozyme approach has significant potential for treating not only OI, but many other genetic conditions involving atypical proteins.

NIAMS actively works with the bone research community at the NIH and beyond to develop a multi-faceted, collaborative approach in order to address both common and rare diseases of bone. For example, NIAMS – in conjunction with other NIH components, the Food and Drug Administration, and industry partners – is exploring a public-private collaboration on bone strength. The main goals of the initiative are to provide data supporting the use of new bone strength markers as surrogate endpoints for fractures in clinical trials, and to find measurements that predict risk of fracture more accurately than does bone density. This would facilitate the continued development and approval of new treatment alternatives to prevent fractures through the support of clinical trials that are smaller, shorter, and less expensive than current studies. This initiative has the potential to provide valuable information to researchers studying a variety of bone diseases.

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 imperative that a sustained effort be made to translate these research advances into clinically relevant treatments. The Committee encourages the Institute to develop focused programs designed to move research advances beyond the laboratory. (p. 109)

Action taken or to be taken

NIAMS has recently developed a new funding mechanism specifically designed to bring together basic and clinical research in a way that helps translate basic discoveries into new drugs, treatments and diagnostics. The Centers of Research Translation (CORT) program requires participating centers to encompass at least three projects, including one clinical and one basic research study. Lupus is the focus of one of the first CORT awards. Researchers will study the role of different cell types in lupus pathogenesis, develop markers of disease activity and severity, and look for new targets for treatment. The multifaceted approach promoted through the CORT mechanism will likely yield some of the most significant advances in understanding and treating lupus.

People with lupus often develop renal (kidney) disease, which may sometimes lead to end-stage renal disease (ESRD). Currently, the only way to tell if a patient has renal disease is by taking a biopsy of the kidney. Frequently, repeated biopsies are needed to determine the exact kind of disease and the most effective treatment. NIAMS-supported researchers have recently identified a potential new method to obtaining this information that does not involve using an invasive procedure such as a biopsy.

Researchers studied urine samples collected from 20 patients immediately before they underwent kidney biopsy. Using a process known as two-dimensional gel

electrophoresis, they looked for proteins in the urine samples that could be biomarkers for lupus-related kidney disease. These results were then compared with the findings from the kidney biopsies. The researchers were able to identify a list of proteins in the urine of people with renal disease caused by lupus. These biomarkers can be used to indicate the type and severity of renal disease in these patients, as well as the extent of damage to the kidney. Such biomarkers could form the basis of clinical tests that could help doctors to establish an effective treatment plan for these patients without putting them through repeated kidney biopsies. Further studies are needed to determine whether urine protein analysis could replace the use of biopsies to assess kidney damage in lupus.

Item

Marfan Syndrome - The Committee commends NIAMS and its collaborative efforts with other institutes to provide vital research on Marfan syndrome, a life-threatening, progressive and degenerative genetic disorder which is characterized by aortic aneurysms, orthopedic disabilities and ocular manifestations. Management of the syndrome by complicated aortic surgery is extending the life span of many. However, it has introduced a new generation of people with debilitating painful orthopedic issues such as early-onset arthritis, back pain and headaches due to dural ectasia and joint, leg and foot pain. Basic, translational and clinical research including the natural history of skeletal problems in this area is needed to investigate the underlying causes of these manifestations and to investigate therapeutic choices. This research is essential to improve the quality of life of those suffering from Marfan syndrome. The Committee encourages NIAMS to support research in this area through all available mechanisms, as appropriate. (p. 109)

Action taken or to be taken

Caused by a mutation in the gene that encodes for fibrillin-1 (a protein component of connective tissue), Marfan syndrome can affect the bones, skin, eyes, heart and blood vessels, nervous system and lungs. The syndrome can prove fatal if it weakens the aorta (the largest artery of the body) to the point of rupture. Traditionally, scientists have believed that fibrillin-1 played primarily a structural role in connective tissue disease, and that the only way to prevent aortic aneurysm or rupture in Marfan patients was to surgically replace the aorta. But, recent findings about the role of fibrillin have not only offered new insight into the cause of aortic rupture in Marfan syndrome, but also have offered clues to simpler, less invasive ways to prevent it.

Previous research has indicated that fibrillin-1 regulates the growth factor, transforming growth factor-beta (TGF- β), and that this growth factor is in excess in Marfan syndrome patients. Looking for an easier way to slow down the activity of TGF- β , NIAMS-supported researchers decided to try the drug losartan, which is known to suppress TGF- β in animal models of other conditions. Researchers found that when animals with established aortic aneurysm were treated with losartan, the architecture of the aortic wall was restored and aortic rupture was prevented. In follow-up to this study, the National Heart, Lung, and Blood Institute now supports a natural drug therapy clinical trial in this area as part of the Pediatric Heart Network. The results of both studies have exciting implications for treating the serious complications of Marfan syndrome with a drug already in widespread clinical use.

Additionally, NIAMS-supported researchers are investigating the contribution of fibrillin to bone physiology in order to uncover the pathological underpinning of the skeletal manifestations of Marfan syndrome. Preliminary research has suggested that fibrillin-1 deficiencies affect bone formation and resorption by altering the signals that control the maintenance of bone mass. The current investigation aims to advance the understanding of fibrillin function in the skeleton and shed new light on the relationship between bone formation, growth and turnover, and the role of the architectural matrix that contributes to bone strength. Results from this study will broaden the base of scientific knowledge which could lead to the design of new therapies for bone mineral replacement in patients affected with Marfan syndrome.

Item

Mucopolysaccharidosis (MPS) - The Committee encourages the NIAMS to support and work collaboratively with NIDDK in an effort to achieve a greater understanding of bone and joint lesions in MPS disorders. The committee supports meaningful NIAMS involvement with other institutes in research and specifically addresses the underlying pathophysiology of bone and joint lesions, the gene mutations and substrates that are stored, and potential therapeutic approaches to treating these debilitating aspects of MPS and related disorders. The Committee encourages NIAMS to work with participating NIH institutes and the MPS academic and patient advocate community to support and focus efforts in this area of study that can be particularly beneficial to patients. (p. 110)

Action taken or to be taken

The mucopolysaccharidoses (MPS) are caused by genetic defects in certain metabolic processes. The genetic defect is present in all cells in an affected individual, but the severity of the consequences varies from one cell type to another. In addition, different genetic defects yield different combinations of effects. The most serious problems usually occur in the central nervous system, heart, and airways. In some types of MPS, cells of the skeleton are significantly affected, most often resulting in deformed bones and swollen joints with limited movement.

The greatest potential for benefit to individuals with MPS lies in efforts to correct the underlying metabolic defect, which typically arises from deficiency of a specific enzyme. One approach to this goal is infusion of the missing enzyme directly into the blood. Alternatively, therapy can provide cells able to make the enzyme, either by transplantation of marrow cells from a normal donor, or by transferring the normal gene into cells of the affected individual. These therapeutic approaches are being pursued by the appropriate NIH components.

Because cells throughout the body can take up enzymes from the blood, approaches that provide enzymes only in the blood or only in cells of the marrow or liver can improve the skeletal outcomes for individuals with MPS. However, the cells of the skeleton are not efficiently replaced by marrow transplantation, and the cells of cartilage have little exposure to circulating blood. These difficulties also limit therapy of other skeletal disorders, including arthritis, osteogenesis imperfecta, and various chondrodystrophies.

The NIAMS supports a wide range of research aimed at improving the treatment of skeletal disorders. Included are efforts to reduce inflammation and cartilage erosion in arthritic joints, replace genetically defective skeletal cells by transplantation, target gene transfer to cells of the skeleton, and rebuild damaged skeletal tissues by tissue engineering. Advances in these areas are expected to benefit individuals with MPS, just as they benefit those with skeletal disorders arising from other causes.

Item

Osteoporosis - The Committee is aware that osteoporosis is becoming widespread in all ages of our population. The Committee encourages NIAMS to collaborate with other institutes to support research into the pathophysiology of bone loss in varied populations and in targeted therapies to improve bone density and bone quality according to the etiology of osteoporosis. Furthermore, the Committee encourages research to identify patients at risk for fracture who do not meet current criteria for osteoporosis, as well as to study the effects of available and developing osteoporosis treatments on the reduction of fracture risk in these patients. (p. 110)

Action taken or to be taken

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased risk of fractures. NIAMS continues to build on the base of previous research in osteoporosis by supporting a broad range of research aimed at developing new diagnostics and treatments for this disease. For example, NIAMS-supported researchers are examining the genetic and cellular mechanisms involved in bone build-up and breakdown in order to develop novel drug and gene therapies for bone diseases. Additionally, NIAMS supports research on the natural history of osteoporosis to better understand the genetic and environmental risk factors contributing to bone disease in both men and women.

In conjunction with other NIH components, the FDA, and industry partners, the NIAMS is exploring a public-private collaboration on bone strength. The main goals of this initiative are to provide data supporting the use of new bone strength markers as surrogate endpoints for fractures in clinical trials, and to find measurements that predict risk of fracture more accurately than does bone density. This would facilitate the continued development and approval of new treatment alternatives to prevent fractures through the support of clinical trials that are smaller, shorter, and less expensive than current studies.

Identifying dietary factors in building and maintaining bone quality is another important approach in NIAMS research. In partnership with the American Society for Bone and Mineral Research, NIAMS co-sponsored the “Contemporary Diagnosis and Treatment of Vitamin D-Related Disorders” scientific conference on December 4-5, 2006. Vitamin D plays a crucial role in the absorption of calcium and the mineralization of bone. This meeting convened scientists and clinicians from a wide range of disciplines to clarify recent advances and prioritize the key questions that researchers must address to improve the future diagnosis and treatment of diseases such as osteoporosis.

Osteoporosis can strike at any age and affects both men and women. In 2000, NIAMS launched a multi-center study of osteoporosis and fractures in older men known as Mr. OS. Nearly 6,000 men over the age of 65 have been recruited and data are being evaluated. Recently, researchers have identified specific lifestyle, medical and demographic characteristics that are associated with low bone mass and potentially fracture risk in older men. This information could be used in the clinic to facilitate the identification of men at high risk of fracture, to target interventions to these individuals, and to help understand the etiology of fracture in men.

Additionally, it is important to build bone mass across the lifespan. The rapid increase in bone mass that takes place during puberty is being studied by researchers supported by NIAMS. This period of life is critical for reaching peak bone mineral density. NIAMS-supported researchers are examining the hormonal, genetic, and dietary factors that can enhance maximum calcium absorption and bone development during puberty, with the goal of reducing the incidence of osteoporosis later in life.

Senate Significant Items

Item

Burden of Skin Diseases - The Committee notes the relationship between the recent Burden of Skin Diseases report and the September 2002 workshop on the burden of skin diseases sponsored by NIAMS. The Committee continues to urge NIAMS to expand the research portfolio on skin disease and develop partnerships with the skin disease research community to address the recognized challenges and future research endeavors. (p. 138)

Action taken or to be taken

Please refer to page 173 of this document for IC's response to this significant item regarding the burden of skin diseases.

Item

Congenital and Genetic Disease of Bone - The Committee is aware that thousands of children and adolescents nationwide suffer from musculoskeletal disorders and malformations. Diseases such as osteogenesis imperfecta, fibrous dysplasia, osteopetrosis, 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 urges 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. (p. 139)

Action taken or to be taken

Please refer to page 174 of this document for IC's response to this significant item regarding congenital and genetic disease of bone.

Item

Genetics of Rare Disorders - The Committee urges NIAMS to collaborate with NICHD, NIDCR, and NIDDK to expand research on the genetics for the rare disorders fibrous dysplasia and osteopetrosis, and to expand research on mechanisms of these diseases in humans. (p. 139)

Action taken or to be taken

Genetic influences on the skeleton are complex, potentially reflecting the contributions of many different genes. For example, fibrous dysplasia is a developmental disorder characterized by expanding fibrous lesions of bone-forming tissue that results in pain, fracture, and/or deformity. While mutations leading to the activation of gene-regulating signaling pathways in bone have been identified in patients, the mechanism leading to fibrous dysplasia is not clear. In osteopetrosis, the cells that break down bone (osteoclasts) usually are either fewer in number or are ineffective in breaking down bone, leading to dense but fragile bones. To date, the precise genetic control of osteoclast function remains inadequately understood. Several NIAMS-supported researchers are working to identify the gene-regulating signaling pathways in bone cells that control bone formation and break down. Advances in locating these pathways would provide researchers with additional clues to facilitate the development of potential therapeutic and prevention strategies for these and other diseases of bone.

In addition to ongoing research efforts in these areas, NIAMS has recently released a long-range plan that outlines scientific opportunities, research needs and gaps that we currently envision, including research in the developmental biology of bone, genetics of bone physiology, molecular and cellular biology of bone diseases, and gene therapies for bone diseases. The purpose of this long-range plan is to serve as a broad scientific outline for the NIAMS, and for the investigative and lay communities, by identifying compelling research opportunities. NIAMS has shared this plan with colleagues in the bone research community in order to identify potential areas for collaboration within the NIH and with relevant professional and patient advocacy organizations.

Additionally, the NIAMS leads the Federal Working Group on Bone Diseases, an interagency committee focusing on both common and rare bone disorders. The working group offers a forum for sharing information and facilitating the development, early in the planning stages, of collaborative research activities based on each agency's mission. Several other NIH components including the National Institute of Child Health and Human Development, the National Institute on Aging, the National Institute of Diabetes, Digestive, and Kidney Disorders, the National Institute of Dental and Craniofacial Research, the National Cancer Institute, and the National Center for Complementary and Alternative Medicine participate in working group activities. The most recent meeting of the working group was held in October 2006 and included an overview of opportunities available to bone researchers interested in genome-wide association studies, as well as research examining the influence of interactions between genes and the environment on disease development.

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 imperative that a sustained effort be made to translate these research advances into clinically relevant treatments. The Committee urges 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. 139)

Action taken or to be taken

Please refer to page 175 of this document for IC's response to this significant item regarding lupus.

Item

Marfan Syndrome - The Committee commends NIAMS for supporting research on Marfan syndrome and for collaborating with other Institutes to study this disease. Better management of cardiovascular issues associated with Marfan syndrome has extended the lives of many but has introduced an older generation of people who live with chronic pain because of orthopedic problems. Basic, translational and clinical research including the natural history of skeletal problems is required to understand the underlying early orthopedic deterioration in people with Marfan syndrome and to investigate possible therapeutic choices. The Committee urges NIAMS to support this effort through all available mechanisms, as deemed appropriate. (p. 139)

Action taken or to be taken

Please refer to page 176 of this document for IC's response to this significant item regarding Marfan syndrome.

Item

Musculoskeletal Trauma and Skeletal Pain - The Committee recognizes that more than half of all Americans who are injured each year incur injuries to the musculoskeletal system. Back pain is a major reason for lost time from work, and, in our military, bone trauma is now accounting for over 50 percent of all combat injuries. The Committee urges NIAMS, NIA, NIDCR, and NCCAM to study ways to better understand the epidemiology of back pain, improve on existing diagnostic techniques for back pain, as well as to develop new ones. The Committee also encourages the expansion of research to improve diagnostic and therapeutic approaches to lower the impact of musculoskeletal trauma. (p. 139)

Action taken or to be taken

At some point, back pain affects an estimated 8 out of 10 people. It is one of our society's most common medical problems. Additionally, accidental injury and chronic disease cause musculoskeletal pain that can be difficult to diagnose and treat. NIAMS is

committed to supporting research examining the causes of these conditions, as well as the development of new diagnostic and treatment options.

Most recently, NIAMS-supported researchers have published results from the Spine Patient Outcomes Research Trial (SPORT), the largest trial to date comparing surgical and non-surgical interventions for the treatment of low back and associated leg pain caused by lumbar intervertebral disk herniation. Patients receiving surgery underwent a lumbar discectomy, a procedure involving the removal, in part or whole, of an intervertebral disk. The non-surgical intervention consisted of physical therapy, education/counseling, home exercise instruction, and nonsteroidal anti-inflammatory drugs. After 2 years, improvements in levels of reported pain were seen in all patients regardless of their treatment protocol; however, patients receiving surgery reported having the highest level of improvement across both groups. The results of this study have broadened our understanding of the effectiveness of surgical versus non-surgical interventions for treating these common and often debilitating musculoskeletal conditions. Patients and their health care providers will be able to use the results of this study to help them select a treatment intervention based on their preferences.

The NIAMS, along with several other NIH components including the National Institute of Nursing Research, National Institute on Aging, National Institute of Dental and Craniofacial Research, and the National Center for Complementary and Alternative Medicine, recently released a Program Announcement entitled, "Mechanisms, Models, Measurement, and Management in Pain Research." Researchers were invited to submit proposals that sought to improve the understanding of the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two. Additionally, proposals that link such understandings to the development of better approaches to therapeutic interventions, including complementary and alternative medicine interventions, and management of acute and chronic pain were encouraged.

NIAMS has also developed a new funding mechanism for Centers of Research Translation (CORTs). One of the first funded CORTs will study the biological basis of fracture healing and the efficacy of a potential new treatment, teriparatide, for healing of fragility fractures in the elderly. CORT grants require centers to be highly translational and encompass at least three projects, including one clinical and one basic research study. The research being conducted at this particular CORT has the potential to provide new therapies for the types of injuries that occur in combat, automobile accidents, and other types of trauma involving bone.

Lastly, along with the American Academy of Orthopaedic Surgeons, NIAMS co-sponsored Extremity War Injuries: State-of-the-Art and Future Directions, a scientific symposium that took place in Washington, DC, January 24-27, 2006. The three-day event addressed wound management, antibiotics and infection, long-bone stabilization, management of segmental bone defects, and amputee care. Techniques and treatments developed and employed for wartime injuries can be used in managing civilian trauma and medical complications. Advances in the management of extremity injuries will lead

to quicker recovery times from blast injuries, better response rates to infection, and new advances in amputee care, benefiting both military and civilian patients.

Item

Osteoporosis - The Committee is aware that osteoporosis is becoming widespread in all ages of our population. NIAMS is urged to collaborate with other Institutes to support research into the pathophysiology of bone loss in varied populations and in targeted therapies to improve bone density and bone quality according to the etiology of osteoporosis. 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 available and developing osteoporosis treatments on the reduction of fracture risk in these patients. (p. 140)

Action taken or to be taken

Please refer to page 178 of this document for IC's response to this significant item regarding osteoporosis.

Item

Psoriasis - The Committee is disappointed that funding for psoriasis research has not grown significantly over the past decade. The Committee strongly urges NIAMS to expand and coordinate genetic, clinical, and basic psoriasis and psoriatic arthritis research and related activities, with emphasis on the cellular and molecular mechanisms of disease; genetics that lead to psoriasis susceptibility; the natural course and history of psoriasis before, during and after treatment with conventional therapies; the role of inflammation in skin and joints and co-morbidities such as obesity, depression and hypertension; the development of diagnostic tests for psoriatic arthritis; the unique challenges faced by children with psoriasis; and the use of certain types of antibodies to prevent relapse of psoriasis. (p. 140)

Action taken or to be taken

NIAMS funds a variety of research aimed at uncovering the cellular and molecular processes that contribute to the development of psoriasis and psoriatic arthritis, expanding our knowledge of genes that play a role in causing these diseases, and the creation of more effective treatments in order to help increase the quality of life for adults and children.

Skin cells usually grow deep in the epidermis of the skin, pushing the maturing cells slowly toward the surface where they perform the barrier function of the skin. Eventually, the outermost layer of cells gets sloughed off and is replaced by the cells below. With psoriasis, it can happen in just a few days because the cells divide too fast and pile up on the surface. NIAMS-supported researchers have recently reported findings on how cells of the epidermis go through the process of growing and differentiating. By understanding the normal mechanisms that control how stratified tissues such as the epidermis are able to maintain a balance between growth and differentiation and also repair themselves in response to injury, the scientists have gained a better understanding of how different disorders of the skin – including psoriasis – arise

when various aspects of these normal mechanisms become faulty. With this new understanding of the process, the scientists have also begun to use genetic studies in mice to try to identify which genes are necessary in the process.

Other genetic research supported by NIAMS has already led to the discovery of a gene called PSORS1 which plays a role in determining who gets psoriasis. Researchers looked closely at genetic samples from 678 families in which some of the family members had early-onset psoriasis, and they identified a specific gene allele (an alternate form of a gene) as the one that confers susceptibility to this form of the skin disease. Other researchers are continuing to build upon these discoveries to further understand how the PSORS1 and related genes increase susceptibility to psoriasis. The benefit to finding a gene that makes people susceptible to developing psoriasis is that scientists may be able to examine targeted therapies which could result in the prevention or improved treatment of the disease. Current treatments for psoriasis often suppress the entire immune system, leaving the person vulnerable to various infections. Ideally, treatments aimed at a particular gene would shut down only the process which causes the disease, providing relief, while still leaving a functioning immune system.

NIAMS-supported researchers have also demonstrated a connection between psoriasis and increased risk for other diseases, such as cardiovascular disease. The same inflammatory process that speeds up the growth cycle of skin cells in psoriasis is also involved in promoting blockages of arteries and ultimately causing ruptures of plaques, leading to heart attacks. The risk is nearly doubled in younger patients (30 to 40 years old) with severe psoriasis compared to those without the disease. This study demonstrates the importance for people with psoriasis to modify their cardiovascular risk factors as much as possible, by quitting smoking and controlling weight, blood pressure, cholesterol, and other factors that could increase the risk of heart disease.

Item

Tuberous Sclerosis Complex [TSC] - The Committee urges NIAMS to explore new strategies for the treatment of skin manifestations of TSC utilizing knowledge of basic mechanisms, such as mTOR inhibitors and angiogenesis inhibitors. (p.140)

Action taken or to be taken

Tuberous sclerosis complex (TSC) is a rare and genetic, neurological disorder primarily characterized by seizures, mental retardation, and skin and eye lesions. Small benign tumors may grow on the face and eyes, as well as in the brain, kidneys, and other organs. Individuals with TSC may experience none or all of the associated symptoms with varying degrees or severity.

NIAMS-supported researchers are currently examining the mechanisms of the development of TSC and associated angiogenesis (blood vessel development). TSC is caused by mutations in genes TSC1 or TSC2 whose protein products, hamartin and tuberin, respectively, normally function as a complex that regulates many cellular processes, including cell growth. NIAMS-supported researchers have created a mouse model with mutations in the tuberin gene that develops unique skin and brain tumors

similar to those in TSC patients. Investigators are exploring how molecular signals upstream and downstream of the hamartin/tuberin complex affect tumor development and growth. Knowledge of how the upstream and downstream events impact the development of TSC may lead to therapies that can prevent or improve the skin manifestations of the disease in humans.

TSC1 and TSC2 are part of the mTOR signaling pathway which is involved in the regulation of protein translation and cell growth. Several NIAMS-funded researchers are working on signaling in the mTOR pathway and its involvement in normal cellular processes and abnormal conditions and diseases. A better understanding of the mTOR pathway will provide additional targets for drug intervention in TSC, as well as a better understanding of how mutations in TSC1 and TSC2 lead to abnormalities in multiple organ systems.

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National Institute of Mental Health

House Significant Items

Item

Adolescent Depression and Suicide – Depressive disorders – one of the major risk factors for suicide--continue to be very common in adolescence. The Committee is pleased to note that NIMH, in partnership with NIDA and NIAAA, is supporting three research centers whose primary focus is on new trials to reduce adolescent suicide, which now accounts for 13 percent of all adolescent deaths and ranks third as a cause of death among teenagers. The Committee therefore encourages NIMH to continue this investment in finding ways to better identify the risk factors in children and adolescents, and examining the outcomes of actions taken to assist those found to be at risk. (p.113)

Action taken or to be taken

Three research centers in suicide prevention, funded by NIMH, NIDA, and NIAAA, continue to forge collaborative projects to advance understanding and prevention strategies for adolescent suicidality. The American Foundation for Suicide Prevention also intends to partner with the centers to support efforts to test the feasibility of registries of suicide attempters. This registry will facilitate understanding of the quality of care across services settings, as well as the longer-term outcomes of acute treatment of adolescent suicide attempters. Collaborative efforts have also expanded to other centers and independent investigators supported through NIH and other Federal agencies, such as the Centers for Disease Control and Prevention, the Indian Health Service, and Substance Abuse and Mental Health Services Administration.

Recent research supported by NIDA has focused on screening issues related to identifying high risk adolescents for prevention programs as well as heritability of risk factors for suicidality among adolescent twins. These studies address implications for prevention of drug abuse, mental disorders, and suicide risk. In addition to its center grant support, NIAAA-funded studies are examining the relationship between substance use disorders and depression. An important focus of the research is treatment of adolescent alcohol problems and comorbid depression and/or suicidality, as well as evaluation of long term outcomes of these high risk adolescents.

In FY06, NIMH funded five studies devoted to investigating the association between suicidality and antidepressants. Four of the five studies include youth, and one builds on efforts in the ongoing Treatment of Adolescent Suicide Attempters (TASA) study to test optimal strategies for monitoring antidepressant side effects. NIMH also supports research that examines the social, familial, and psychological processes that enhance risk for or protection against depression and suicide during adolescence. NIMH-funded researchers have recently identified the combination of depression and anxiety as a significant risk factor for suicidal behavior in youth. This information could be used to develop more targeted interventions for preventing suicide among adolescents. NIMH is also funding a pilot study to develop interventions for depressed adolescents who have attempted suicide.

Item

Alzheimer's Disease – NIMH continues to play an important part in efforts to develop effective treatment strategies for Alzheimer's disease. The Institute is currently supporting research examining various aspects of the pathophysiology and genetics of Alzheimer's disease, and studies examining behavioral, emotional and psychiatric symptoms associated with the disorder and their treatment. The Committee encourages NIMH to continue to assign a high priority to this research. (p. 113)

Action taken or to be taken

NIMH maintains an active research portfolio on Alzheimer's disease. This work encompasses all phases of research, from basic neuroscience studies to treatment and services research. In addition to supporting studies on genetics and pathophysiology, NIMH places major emphasis on the characterization and treatment of the psychiatric syndromes and behavioral and emotional symptoms associated with Alzheimer's disease. NIMH also supports research on other issues of clinical relevance in Alzheimer's disease, such as studies to identify biological markers and predictors of risk for developing the disease.

NIMH has funded a large practical clinical trial called the "Clinical Antipsychotic Trials in Intervention Effectiveness-Alzheimer's Disease" (CATIE-AD). This 42-site study examined the effectiveness of antipsychotic medications for treating agitation and other behavioral disturbances in Alzheimer's disease. Initial findings were recently reported in the *New England Journal of Medicine*. The researchers found that several of the atypical antipsychotic medications commonly used to treat Alzheimer's were no more effective than an inactive or "placebo" medication 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; those findings are expected to be published next year.

NIMH continues to participate in a trans-NIH workgroup on Alzheimer's disease and collaborates with other NIH institutes in Alzheimer's related research initiatives. For example, NIMH, in partnership with NIA, NINDS, NINR and NIBIB, held the "Conference on Alzheimer's Disease: Setting the Research Agenda a Century After Auguste D" in October 2006. The meeting focused on research issues that need to be addressed in order to improve diagnosis and treatments for patients and their families. Presenters covered a broad spectrum of research, ranging from the neurobiology of normal aging to the genetics and neuropsychological evaluation of Alzheimer's disease

Item

Disaster relief – The Committee encourages NIMH to consider supporting the Historically Black College and University (HBCU) mental health consortium to serve as a clearinghouse for responding to the mental health needs of the poor and underserved immediately following a disaster. (p. 113)

Action taken or to be taken

Under the guidance of NIMH, the Historically Black College and University (HBCU) Mental Health Research Consortium, based in Atlanta, Georgia, has expanded to five schools: Meharry Medical College, Morehouse School of Medicine, Florida A&M University, Texas Southern University, and Jackson State University. In 2006, the Minority Health Professions Foundation (MHPF) and the consortium submitted a concept paper to NIMH, proposing to establish a national center for disaster response for the poor and underserved. NIMH staff provided extensive feedback on the paper, and the NIMH Office for Special Populations will continue to provide technical assistance to the MHPF/HBCU Mental Health Research Consortium to develop a research grant application for establishing a national center for disaster response.

Item

Down Syndrome – The Committee encourages NIMH to develop new strategies for cataloging, understanding, 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. 114)

Action taken or to be taken

NIMH continues to work collaboratively with other NIH Institutes to advance research on the best ways to identify, prevent, and treat common psychiatric disorders in individuals with Down syndrome. In particular, two Program Announcements (“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. In addition to these Program Announcements, NIMH is participating in a trans-NIH working group to plan joint activities for research related to Down syndrome.

Item

Epilepsy – The Committee applauds the NIMH for its recent RFA on the etiology and treatment of comorbid mental and neurologic disorders. Studies looking at the connections between epilepsy and depression as well as the cognitive burden of epilepsy are of particular importance and relevance to this initiative. The Committee encourages NIMH to actively participate in the NINDS 2007 “Curing Epilepsy” conference and to continue to advance research related to epilepsy and mental health. (p. 114)

Action taken or to be taken

NIMH continues to support basic and clinical research dedicated to understanding the pathophysiology of depression and its treatment, including studies of how seizure induction (i.e., electroconvulsive therapy) modifies depression and how anti-seizure medications exert mood-stabilizing effects in patients with bipolar disorder. In collaboration with NINDS, NIMH issued a Request for Applications (RFA) entitled “Collaborative Research on Mental and Neurological Disorders” in September 2005.

One study funded from this RFA examines the relationship between seizures and emotional dysfunction.

NIMH staff will be well represented at the NINDS-sponsored meeting scheduled for late March 2007, "Curing Epilepsy 2007: Translating Discoveries into Therapies." Scientists, health care providers, and leaders of voluntary health organizations will convene to discuss potential targets and technologies for new therapies with the goal of advancing the field toward a cure. Cognitive and psychological issues relating to epilepsy will be discussed at the meeting.

Item

Mental Health for Older Americans – The Committee is aware that demographics will demand a greatly increased focus on mental disorders in older persons and commends NIMH for recently recognizing the need to place higher priority on the mental health needs of that population. The Committee encourages the Institute to follow through on the 2004 recommendations promulgated by the NIMH Aging Research Workgroup and the restructuring of the Adult and Geriatric Treatment and Preventive Intervention Research Branch. However, the Committee believes it is critical that studies related to the elderly keep pace with the rapid growth of this cohort. Despite the recent internal reorganization to focus intervention efforts on the aging population, the Committee encourages NIMH to continue to emphasize research on adults over age 65 to reflect the growth in numbers of this population, particularly in light of the public health consequences of an inadequate knowledge base about late-life mental illness. A correlating issue is the need for greater numbers of investigators focused on late-life mental health research. Therefore, the Committee encourages NIMH to expand research in this area, including issues relating to neurodegenerative disorders, and to provide adequate resources to advance the geriatric mental health research agenda. The Committee encourages NIMH to continue its commitment to research on late-life mental illness as a means to act as a catalyst for investigators to focus on this critical area of research. (p. 114)

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. Through the NIMH Geriatrics Research Branch and other funding programs, the Institute supports numerous 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. The Geriatrics Research Branch oversees research on mood and anxiety disorders and psychosis in older adults, spanning diverse clinical settings and health care delivery systems. A number of these studies examine interactions between mental disorders and neurodegenerative disease processes, such as research aimed at identifying potential predictors of future cognitive decline and central nervous system dysfunction in older adults with major depressive disorder.

In FY 2006, NIMH issued two Program Announcements encouraging research grant applications that address high priority issues on the mental health of older Americans. The first, entitled “Clinical Research in Mental Illnesses in Older Adults,” invites research applications covering the range of mental disorders seen in old age, highlighting the need for research on the safety of antipsychotic medications for older adults and the examination of health disparities across different racial/ethnic groups. The purpose and goals of the second program announcement, “Pathophysiology and Treatment Response in Late-Life Mood and Anxiety Disorders,” were based on priorities developed out of an NIMH workshop held in FY 2005. This announcement encourages increased use of structural and functional brain imaging, genetic analyses, and other neuroscience methods to advance understanding of the neurobiological basis of geriatric depression and anxiety disorders. In addition, the announcement fosters the development of disease biomarkers and predictors of treatment response that will enhance clinical care for older adults with these disorders.

NIMH continues to support training programs and career development awards that will expand the pipeline of future generations of scientists in the field of mental health and aging research. In addition, NIMH holds several annual technical assistance workshops to help junior investigators develop the essential grant-writing and research implementation skills necessary to establish successful research careers in this field.

Item

Minority Training – The Committee is disappointed to learn that NIMH intends to reduce its commitment to training minority scientists through the Minority Fellowship Program and the Career Opportunities in Research Program. Both of these programs have demonstrated success in training biomedical and behavioral scientists who are addressing critical ethnic minority mental health issues. The Minority Fellowship Program in particular has been an important national program that has provided access to training to all, without regional or university-specific restrictions. The Committee encourages NIMH to continue to fund programs to meet the demands for research on disparities in mental disorders. (p. 114)

Action taken or to be taken

The Minority Fellowship Program is supported under a Request for Applications (RFA) entitled “Institutional Research Training Programs: Increasing Diversity.” In FY 2006, NIMH issued an RFA of limited competition for competing renewal applications for institutional training grants funded in FY 2002 under the original RFA. Applications are currently pending review, and meritorious applications will be considered for possible funding in FY 2007. As with all programs, these awards will be made based on scientific merit as assessed by peer review and program balance.

The Career Opportunities in Research (COR) Program continues with a number of applications under consideration for possible award in FY 2007. The announcement for the COR Program will be reissued in FY 2007.

In addition to these two diversity programs, NIMH continues to support training of minority scientists through the Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships (F31) to Promote Diversity in Health-Related Research and the Mental Health Dissertation Research Grants to Increase Diversity (R36). These programs focus on training individuals, under the guidance of established NIMH investigators, in research that addresses the priorities of the Institute. In addition, the Research Supplements to Promote Diversity in Health-Related Research program supports training from the undergraduate to faculty level.

NIMH also supports research to understand and reduce health disparities. The NIMH-funded Advanced Centers in Mental Health Disparities Research promote the enhancement of core research infrastructures and investigator-initiated research aimed at understanding and ameliorating mental health disparities. These centers provide valuable opportunities for junior investigators and trainees to study and learn state-of-the-art research methods in mental health disparities. Two centers are currently funded, and several applications are being considered for possible support in FY 2007. The Program Announcement for these centers will be reissued in 2007.

Item

Parkinson's Disease – The Committee encourages continued collaborations including additional intramural activities between NINDS, NIMH, and NIA to enhance understanding of the important psychiatric component of neurodegenerative diseases, particularly Parkinson's. (p. 114)

Action taken or to be taken

NIMH continues to be committed to research on Parkinson's disease by providing significant research support, participating in numerous trans-NIH activities, collaborating with advocacy groups, and providing information to patients and their family members. NIMH funds numerous projects in this area, including research on understanding relevant brain mechanisms; developing new animal models and diagnostic tools; and improving diagnosis and treatment of comorbid mood disorders. NIMH actively participates in the Interagency Parkinson's Disease Coordinating Committee, and with NINDS, co-leads the Parkinson's disease matrix activity, "Clinical Trials of Non-Motor Symptoms." NIMH contributed support to the first World Parkinson Congress held in February 2006 in Washington, D.C. In 2005, NIMH and NINDS solicited research grant applications on the neurobiological mechanisms of neurodegenerative diseases through a Request for Applications (RFA) entitled "Collaborative Research on Mental and Neurological Disorders." One study co-funded by NIMH and NINDS in response to this RFA specifically focuses on depression and Parkinson's disease.

The NIMH Division of Intramural Research Programs (DIRP) interacts closely with the intramural programs of other NIH institutes, particularly NINDS. These ties include the use of shared core facilities and ongoing formal and informal collaborations, especially involving the use of brain imaging technologies to understand brain function in psychiatric and neurological disorders, such as Parkinson's disease. In FY 2007, the NIMH DIRP will establish a new Laboratory of Molecular and Cellular Cognition, which

will use state-of-the-art molecular and cell biological techniques to probe the genes and molecules involved in higher cognitive processes. This group, in partnership with NINDS and NHGRI, will study patients who have neurological disorders with known genetic abnormalities to test specific hypotheses about cognition.

Item

Psoriasis – Psoriasis is associated with elevated rates of mental disability, depression and suicidal ideation. The Committee encourages NIMH to conduct research into the mental health aspects of psoriasis, especially as it relates to quality of life and burden of the disease. Furthermore, a 2005 study of 44 autoimmune diseases found that only psoriasis, when present in women around the time of pregnancy, was significantly associated with autism, doubling the risk of autism spectrum disorder in their children. The Committee encourages NIMH to support further study of the link between psoriasis and autism. (p. 115)

Action taken or to be taken

NIMH encourages applications on the mental health aspects of other physical disorders through the Program Announcement (PA) “Research on Co-Morbid Mental and Other Physical Disorders.” Applications proposing to investigate mental health aspects of psoriasis could fall under this PA. With regard to a possible association between psoriasis and autism, NIMH supports an investigation into the association between pregnancy and birth complications with autism and other severe mental disorders. Using the medical birth register and psychiatric case register of Denmark for births from 1973-1993, NIMH-funded investigators expect to identify over 1,000 cases of autism based on prevalence estimates in this population. The study will assess maternal health variables and other potential risk factors. NIMH also funds a study of potential biological markers for autism, in which investigators will retrospectively analyze biological samples (maternal sera and neonatal blood samples) that were drawn as part of a state-mandated prenatal screening program in California. This study could provide evidence of associations between maternal health during pregnancy and autism.

NIMH continues to solicit research on the causes of autism through several mechanisms. Since its creation in 2003, the Interagency Autism Coordinating Committee (IACC) Autism Research Matrix has been a resource for directing the expansion and intensification of autism research. The Matrix outlines research goals and activities in several areas, including research that will identify environmental factors (such as maternal health and other prenatal factors) contributing to autism. Furthermore, NIMH, NICHD, NINDS, NIDCD, and NIEHS will implement the new Autism Centers of Excellence (ACE) Research Program. The ACE Centers will focus on the causes of and best treatments for autism, as identified in the autism research matrix. NIMH also participates in a program announcement “Research on Autism and Autism Spectrum Disorders,” which encourages research on the causes and treatments of autism.

Senate Significant Items

Item

Adolescent Depression and Suicide – Depressive disorders, one of the major risk factors for suicide, continue to be very common in adolescence. The Committee is pleased to note that NIMH, in partnership with NIDA and NIAAA, is supporting three research centers whose primary focus is on new trials to reduce adolescent suicidality. Suicide now accounts for 13 percent of all adolescent deaths and ranks third as a cause of death among teenagers. The Committee therefore strongly encourages NIMH to continue this investment in finding ways to better identify the risk factors in children and adolescents, and examining the outcomes of actions taken to assist those found to be at risk. (p. 146)

Action taken or to be taken

Please refer to page 187 of this document for NIMH's response to this item on adolescent depression and suicide.

Item

Alzheimer's Disease – NIMH continues to play an important part in efforts to develop effective treatment strategies for Alzheimer's disease. The Institute is currently supporting research examining various aspects of the pathophysiology and genetics of Alzheimer's disease, and studies examining behavioral, emotional and psychiatric symptoms associated with the disorder and their treatment. The Committee encourages NIMH to continue to assign a high priority to this research. (p. 146)

Action taken or to be taken

Please refer to page 188 of this document for NIMH's response to this item on Alzheimer's disease.

Item

Basic Behavioral Science – The Committee urges the Institute to maintain its support for the research on the promotion of mental health and the study of psychological, social, and legal factors that influence behavior. In particular, the Institute is encouraged to continue its commitment to basic behavioral research that examines the basic psychological functions that promote mental health or become disturbed in mental disorders. (p. 146-147)

Action taken or to be taken

NIMH believes that support of basic science, including behavioral science, is essential for advancing the Institute's public health mission. The Institute's priorities for basic behavioral research are guided by a 2004 report from the National Advisory Mental Health Council (NAMHC). The report, titled "Setting Priorities for Basic Brain and Behavioral Science Research at NIMH," recommended strategies to sharpen the focus and impact of the basic science portfolio, including basic behavioral science, to better serve the mission of the Institute. NIMH strives to support basic research that 1) links brain, behavior, and experience and 2) informs, and is informed by, the understanding of

etiology, the need for diagnostics, and the quest for new interventions to prevent or treat mental and behavioral disorders.

Although most of the basic behavioral science research at NIMH is supported by the Behavioral Science and Integrative Neuroscience Research Branch (BSINRB) within the Division of Neuroscience and Basic Behavioral Science, behavioral science research is supported by each of the five extramural divisions and within the Division of Intramural Research Programs. For example, the BSINRB and the Adult Psychopathology and Psychosocial Intervention Research Branch (APPIRB) within the Division of Adult Translational Research and Treatment Development, are co-sponsoring a Request for Applications in the area of social neuroscience, which is designed to attract innovative studies on the brain-behavior determinants of complex social behavior. Disruption in social behavior is often a hallmark of mental disorders, such as autism and schizophrenia. Through investigating these brain-behavior determinants, more refined diagnostics and therapeutic targets and strategies may be able to be developed to better prevent and treat the often devastating social and behavioral components of mental disorders.

NIMH also supports behavioral science research in people with mental disorders examining the core psychological processes involved in a range of health behaviors. Included within this domain are studies to: improve the measurement of social, emotional, and cognitive functioning in order to better treat and assist those with mental disorders to resume productive lives; develop and test behavioral and social strategies to enhance adherence to treatments; and apply sociological and psychological principles and theories to develop more effective strategies for reducing mental health disparities and stigma.

Item

Down Syndrome – The Committee encourages 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 NIMH to coordinate its research on Down syndrome with NICHD, NINDS, NIA, and other institutes. (p. 147)

Action taken or to be taken

Please refer to page 189 of this document for NIMH's response to this item on Down syndrome.

Item

Fragile X – Fragile X is the most common single-gene neuropsychiatric disease known. It causes cognitive impairment, mental disorders such as obsessive-compulsive disorder, and extreme anxiety. The Committee commends the NIMH for spearheading three focused research meetings devoted to identifying critical research needs, in November 2001, January 2003, and July 2004. The Committee notes that many of these needs remain to be addressed, and it again urges the NIMH to pursue them. 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 urges the NIMH to work with industry and academia to test available medications and bring new treatments to market. (p. 147)

Action taken or to be taken

In May 2005, NIMH issued a Program Announcement (PA) entitled “Shared Neurobiology of Fragile X Syndrome and Autism.” This PA represents a public-private partnership between NIMH, two other NIH institutes (NINDS and NICHD), 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. Applications submitted in response to this PA are expected to focus on topics related to understanding neural pathways, circuits, systems, and molecules that play a role in the etiology or pathophysiology of Fragile X and may be implicated in autism (including other autism spectrum disorders such as Rett syndrome). Studies to identify drug targets for new medications to treat Fragile X and autism 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 of any age with intellectual disabilities, including Fragile X.

NIMH-funded research on Fragile X includes preclinical studies of cognitive processes disrupted in Fragile X and possible biological mechanisms by which these disruptions occur. NIMH supports a multi-site magnetic resonance imaging (MRI) study that is following a cohort of toddlers for two years in order to examine the relationships between the Fragile X mental retardation 1 gene (FMR1), brain abnormalities, and behavior throughout development. Another longitudinal study is examining 120 school-age children with Fragile X and their families to assess the biological and environmental factors contributing to clinical outcomes. NIMH continues to support an active training program at the University of Colorado School of Medicine, which has for the past 22 years been a source of postdoctoral training for clinician researchers with an interest in developmental disabilities, including Fragile X. Additionally, NIMH supports two postdoctoral fellowships that focus on understanding the regulation and activation of the FMR1 gene.

Item

Frontier Mental Health Needs - The Committee commends NIMH on its outreach efforts to determine the differences in mental health needs which may exist in remote frontier communities, including Alaska. The Committee encourages NIMH to expand its research efforts into these communities, which are often ignored in research projects, but

which continue to suffer from high incidences of mental health problems including depression, suicide and co-occurring disorders with substance abuse. (p. 147)

Action taken or to be taken

In 2006, 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 convened technical assistance workshops at the annual conference of the National Association of Rural Mental Health Research as well as workshops in Mississippi to enable community mental health workers to cope with the after-effects of hurricanes. In 2007, ORMHR plans to conduct technical assistance workshops in Anchorage, Alaska to further stimulate the quantity and quality of research grants that address mental health issues in frontier areas. These workshops will provide frontier mental health investigators with technical assistance on preparing concept papers concerning the delivery of mental health care to frontier populations. Similarly, ORMHR plans to hold a technical assistance workshop in Wyoming or North Dakota that will aid investigators who reside in states with the highest number of counties designated as frontier by the Frontier Education Center—a nonprofit organization that raises awareness about frontier communities. More than 800 of the 3,190 counties in the United States have been designated as frontier.

Item

Historically Black College and University [HBCU] Mental Health Consortium – The Committee recommends that NIMH consider support for the Historically Black College and University [HBCU] mental health consortium to serve as a clearinghouse for responding to the mental health needs of the poor and underserved immediately following a disaster. (p. 147-148)

Action taken or to be taken

Under the guidance of NIMH, the Historically Black College and University (HBCU) Mental Health Research Consortium, based in Atlanta, Georgia, has expanded to five schools: Meharry Medical College, Morehouse School of Medicine, Florida A&M University, Texas Southern University, and Jackson State University. In 2006, the Minority Health Professions Foundation (MHPF) and the consortium submitted a concept paper to NIMH, proposing to establish a national center for disaster response for the poor and underserved. NIMH staff provided extensive feedback on the paper, and the NIMH Office for Special Populations will continue to provide technical assistance to the MHPF/HBCU Mental Health Research Consortium to develop a research grant application for establishing a national center for disaster response.

Item

Mental Health and Older Adults – The Committee is pleased that NIMH recognizes the importance and interrelatedness of cognitive, emotional health and mental health function in older adults and is collaborating with other institutes on efforts such as the Cognitive and Emotion Health Project. Given the increasing older adult population, it is critical to explore scientific opportunities to maintain cognitive functioning and mental health to prevent mental disorders like depression in older adults. NIMH is encouraged to

continue its pivotal role as the primary institute for mental health and aging research by expanding its research on older adults to include large-scale, multi-site trials of behaviorally based treatments of depression, anxiety, and for managing behaviors associated with cognitive impairments as well as increasing opportunities for training future behavioral scientists focused on older adults. (p. 148)

Action taken or to be taken

During FY 2006, NIH issued a request for proposals (RFP) and awarded a contract for development of an “NIH Toolbox for Assessment of Neurological and Behavioral Function.” This RFP was one outcome of the Cognitive and Emotional Health Project led by NIMH, NIA, and NINDS. The purpose of developing this Toolbox is to provide investigators with a brief, but comprehensive, measurement tool for assessing the cognitive, emotional, sensory, and motor function of participants in large cohort studies, such as epidemiological studies, longitudinal clinical studies, or clinical trials. This effort is related to the NIH Blueprint for Neuroscience Research, a trans-NIH partnership to accelerate neuroscience research by increasing collaboration and information-sharing among 16 NIH Institutes and Centers that conduct or support research on the brain and nervous system.

The NIMH Geriatrics Research Branch recently held a workshop entitled “Current Issues in Psychosocial Intervention Research in Late-Life Mental Disorders.” Expert investigators discussed current research priorities and needs, assisting NIMH staff in defining new directions for studying behavioral approaches to alleviate or prevent mental disorders in old age. Large-scale, multi-site intervention and prevention trials were among the topics considered. A report on the workshop proceedings will be issued in FY 2007.

NIMH is also collaborating with the Center for Medicare and Medicaid Services, the Agency for Healthcare Research and Quality, and other Department of Health and Human Services agencies in a broad-based initiative to develop and test electronic decision-support tools that will serve as a guide for treating depression in older adult residents in nursing homes. Once developed, the tools will be evaluated in a large-scale demonstration project for their impact on improving the quality of care of depressed individuals in nursing homes.

NIMH continues to support training programs and career development awards that will expand the pipeline of future generations of scientists in the mental health and aging research field. In addition, NIMH holds several annual technical assistance workshops to help junior investigators to develop the essential grant-writing and research implementation skills necessary to establish successful research careers in this field.

Item

Minority Training – The Committee is disappointed to learn that the NIMH intends to reduce its commitment to training minority scientists through the Minority Fellowship Program and the Career Opportunities in Research Program. Both programs have demonstrated success in training biomedical and behavioral scientists who are addressing

critical ethnic minority mental health issues. The Minority Fellowship Program in particular has been an important national program that has provided access to training to all, without regional or university-specific restrictions. Reducing these programs will have a disproportionate impact on minority mental health training when the focus should be on reducing health disparities for vulnerable and underserved populations. (p. 148)

Action taken or to be taken

Please refer to page 191 of this document for NIMH's response to this item on minority training.

Item

Parkinson's Disease – The Committee encourages continued collaborations including additional intramural activities between NINDS, NIMH, and NIA to enhance understanding of the important psychiatric component of neurodegenerative diseases, particularly Parkinson's. (p. 148)

Action taken or to be taken

Please refer to page 192 of this document for NIMH's response to this item on Parkinson's disease.

Item

Prader-Willi Syndrome – The Committee commends the NIMH for its efforts to further the understanding and description of the mental health components of Prader-Willi syndrome. The Committee recommends that NIMH expand its programs to develop practical treatment protocols, including pharmaceutical options, for the severe anxiety, obsessive-compulsive disorder, oppositional-defiant disorder and psychotic mental illness aspects of Prader-Willi Syndrome. (p. 148)

Action taken or to be taken

NIMH continues its efforts to expand research on treatments of common psychiatric disorders in developmental conditions that involve intellectual disabilities. The NIMH-sponsored Program Announcement, "Research on Psychopathology in Intellectual Disabilities," encourages new grant applications for research on the psychiatric aspects of various behavioral developmental disorders and conditions, including Prader-Willi Syndrome. In addition, this Program Announcement will support the development of practical diagnostic techniques and procedures; the comparison of the relative effectiveness of behavioral, psychosocial, and pharmacological treatment programs; and the utilization of neuroimaging techniques to assess treatment outcomes.

Item

Psychological Impacts of Trauma – The Committee is pleased that NIMH is working with the Department of Veterans Affairs to ensure that psychosocial and pharmacological interventions are available to returning soldiers, veterans and their families. The Committee supports NIMH research related to the psychological impact of both acute and chronic exposure to threats of violence, including terrorism, war, natural disasters, and domestic and community violence. Within the area of trauma, particular emphasis should

also be placed on vulnerable populations, such as trauma survivors, children and older adults. The Committee encourages NIMH to expand its research portfolio to include research related to psychosocial factors that promote detection or prediction, prevention, and post-exposure recovery and resilience. (p. 148)

Action taken or to be taken

NIMH continues to actively support research on the psychobiological impact of acute and chronic exposure to violence and threats of violence, such as war, terrorism, interpersonal violence, community violence, disasters, and major accidents. The NIMH research program includes a primary focus on multi-level (e.g., behavioral, neural, social, hormonal) modeling of risk and resilience factors over time for developing highly predictive markers of disorder in order to: better target interventions; improve the translation of risk and resilience factors into preventive interventions; and develop more effective treatments. Populations of concern include child, adolescent, and adult trauma survivors. In FY 2007, NIMH will re-issue four Program Announcements to stimulate the full spectrum of research needed on the mental health consequences of violence and trauma, including an emphasis on vulnerable populations.

NIMH supports prospective longitudinal studies to improve identification of those most likely to suffer chronic psychological effects of trauma, including studies to understand the interaction of environmental events, individual/biological factors, social factors, and developmental influences. For example, NIMH-supported researchers at the Rand Corporation are analyzing data from several prior trauma studies (e.g., veterans of the first Gulf War, motor vehicle accident survivors, community violence survivors, victims of traumatic injuries, and victims of intimate partner violence) to develop clinically meaningful screening tools that can predict who will recover from trauma and who will develop chronic conditions.

In addition, NIMH supports cutting-edge early intervention and prevention trials of medications and psychosocial therapies to advance prevention and post-exposure recovery. One notable study in Israel is screening thousands of trauma victims (of terrorism, accidents, interpersonal violence) at a hospital emergency room and is tracking the development of PTSD and depression while studying the effectiveness of early intervention. Another set of studies is testing the delivery of psychotherapy through novel approaches such as virtual reality, the Internet, and the telephone. Other researchers are exploring the added benefit of certain medications used in conjunction with cognitive behavioral therapy for trauma survivors.

In response to the recommendations of the Institute of Medicine report “Preparing for the Psychological Consequences of Terrorism – A Public Health Strategy” and the U.S. Department of Health and Human Services’ “Strategic Plan to Combat Bioterrorism and Other Public Health Emergencies,” NIMH has developed an annual action plan for mass trauma mental health research. The objectives of this interdisciplinary plan and program are to coordinate research within and between agencies, improve epidemiology and surveillance, and improve interventions for acute and chronic trauma related conditions.

Item

Tuberous Sclerosis Complex – Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body. The Committee urges NIMH to explore the links between autism and TSC, and conduct epidemiology studies on the prevalence of mental illness in TSC patients. The Committee suggests that NIMH collaborate with NINDS and NICHD to sponsor a conference focused on psychiatric issues and cognitive disabilities in TSC. (p. 149)

Action taken or to be taken

NIMH, NINDS, NCI, NIAMS and NIDDK currently support an active Program Announcement with set aside funds (PAS), “Understanding and Treating Tuberous Sclerosis Complex,” for projects addressing new and/or exploratory research in TSC. These projects could include studies of the links between autism and TSC, assessment and treatment of TSC-associated cognitive and behavioral problems (including pharmacological and non-pharmacological interventions), and neurodevelopmental and longitudinal studies of TSC patients that investigate the progression and inherent variability of the disease. Studies that will facilitate the future development of clinical trials are particularly encouraged.

In addition to this Program Announcement, NIMH has been working closely with other Institutes through a trans-NIH working group to increase awareness of TSC and TSC-related activities across NIH. This working group includes program staff representatives from NIMH, NINDS, NCI, NIDDK, NHLBI, NIAMS, NICHD, NIGMS, NHGRI and the Office of Rare Diseases, as well as representatives from the Tuberous Sclerosis Alliance. The working group meets regularly to review newly-funded research, identify gap areas in research portfolios, assess progress on existing initiatives, discuss potential collaborations, and plan joint activities. The group also regularly reviews the status of the trans-NIH Research Plan for Tuberous Sclerosis, which was developed in July 2003 as a ten-year strategic research plan to improve TSC detection and treatment. The working group plans to discuss options for supporting a trans-NIH conference that would concentrate on psychiatric illness and cognitive dysfunction in TSC.

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National Institute of Drug Abuse

House Significant Items

Item

Adolescent Brain Development – The Committee notes neuroimaging research by NIDA and others showing that the human brain does not fully develop until about age 25. This adds to the rationale for referring to addiction as a ‘developmental disease.’ 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. 84)

Action taken or to be taken

Research that expands understanding of the developing brain as well as specific effects of drug exposure on developmental trajectories, including the influence of environmental and genetic factors, is critical to developing new, research-based prevention and treatment approaches. Several active projects continue to investigate these areas as well as to evaluate prevention and treatment interventions. For example, ongoing studies are evaluating medical office brief interventions, school-based motivational interviewing for teens, and family therapy trials for adolescents with comorbid mental illness and substance abuse disorder.

NIDA will capitalize on its multiple longitudinal studies, a rich source of data on the health and development of children exposed to drugs in utero. Participants are followed from birth to young adulthood and examined at multiple points along the way for behavioral, cognitive, and health outcomes. Optimizing results of longitudinal data sets requires strengthening the data on what a normal developing brain looks like. One of several collaborative development studies in which NIDA participates—the NIH MRI Study of Normal Brain Development—is designed to do just that. A sample of about 500 children, infants to age 18, is imaged at interim points in their development, with cognitive, dexterity, and other tests given to examine brain and behavioral trajectories in parallel. The first wave of these data is due out soon.

Adolescents continue to be a priority group for study by NIDA, given their greater likelihood of engaging in risky behaviors, including abusing drugs. A recent study comparing reward processing in adolescents with that of adults and younger children using functional magnetic resonance imaging (fMRI) concluded 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, leaving them vulnerable to risky decision-making. A better understanding of these brain processes will help prevention specialists develop meaningful interventions for young people. In this vein, NIDA continues to sponsor and participate in scientific meetings examining brain development and drug exposure. A November 2006 conference featured a neurodevelopment theme to be explored by the NIH Blueprint.

Item

Drug Treatment in Criminal Justice Settings – The Committee is very concerned about the well-established connections between drug use and crime. Research continues to demonstrate that providing treatment to individuals involved in the criminal justice system decreases future drug use and criminal behavior, while improving social functioning. The Committee strongly supports NIDA’s efforts in this area, particularly the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS). (pp. 84-85)

Actions taken or to be taken

The connection between drug abuse and crime is well known, with the number of adults incarcerated in Federal, state, and local prisons and jails having risen to 6.9 million.¹ Many of those convicted have substance abuse problems; one study reported drug addiction rates of 44.3 percent for male inmates and 51.8 percent for female inmates.² However, in its 1997 survey, the Bureau of Justice Statistics reported that fewer than 15 percent of those in need of treatment services received them while incarcerated.³ Left untreated, drug-abusing offenders have high rates of relapse to drug abuse and to criminal behavior, re-arrest, and incarceration. This cycle jeopardizes public health and public safety and further taxes an already over-burdened criminal justice system. NIDA’s integrated public health-public safety response to counter this cycle includes an initiative to educate judges on the science of drug addiction to help them better understand the brain and behavioral effects of drugs and the role of rewards and sanctions in improving outcomes.

Building on this initiative, NIDA recently published the *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 the topics of what works and what does not work with regard to drug treatment services in criminal justice settings. Release of this NIDA publication garnered unprecedented media attention and promises to make a difference in the way society treats criminal justice populations for substance abuse.

Another effort to inform policy through research is NIDA’s ongoing National Criminal Justice Drug Abuse Treatment Studies (CJ-DATS), launched with several partners in 2002. The CJ-DATS research initiative is composed of rigorously designed, multisite collaborative studies that test well-articulated research hypotheses offering integrated approaches for treating offenders with drug abuse problems. At present, 13 studies are under way in the following areas: assessing offender problems, measuring progress in treatment and recovery, linking criminal justice and drug abuse treatment, adolescent interventions, HIV/hepatitis risk reduction, and understanding how treatment services are structured and delivered to drug-involved offenders in criminal justice and community

¹ Glaze, L.E. and Palia, S. *Probation and parole in the United States, 2003*. Washington, DC: U.S. Department of Justice, Office of Justice Programs, Bureau of Justice Statistics, 2004.

² Karberg J and James D, *Bureau of Justice Statistics Special Report: Substance Dependence, Abuse, and Treatment of jail Inmates, 2002*. Washington, DC: U.S. Department of justice: Office of Justice Programs, Bureau of justice Statistics, 2005.

³ Mumola, CJ, *Substance Abuse and Treatment: State and Federal prisoners, 1997*. Washington, DC: U.S. Department of justice: Office of Justice Programs, Bureau of Justice Statistics, 1999.

settings. NIDA's robust portfolio also includes studies examining ways to make quality treatment options available through the courts and improve outcomes.

Item

HIV/AIDS – The Committee understands that one of the most significant causes of HIV virus acquisition and transmission is drug-taking practices and related risk factors in different populations. Drug abuse prevention and treatment interventions have been shown to be effective in reducing HIV risk. The Committee congratulates NIDA on its “Drug Abuse and HIV—Learn the Link” public awareness campaign targeting young people, 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. 85)

Action taken or to be taken

Drug abuse continues to be a major avenue for the spread of HIV/AIDS in the United States, owing in large part to the connection between drug abuse and other risky behaviors. NIDA-supported research, from basic to clinical to health services science, has increased the understanding of this nexus and of the value of drug abuse treatment in preventing the spread of HIV. Notable findings include: drug abuse treatment increases adherence to HIV treatment, thereby improving health outcomes; methamphetamine abuse among HIV-infected individuals can lead to greater neuropsychological impairment and brain pathology; and genetics can contribute to a person's risk of becoming infected.

Beyond the dangers of infection associated with injection drug use, drugs are also linked to HIV through their effects on judgment and decision-making, which can prompt high-risk sexual practices—thus, NIDA's drug abuse prevention efforts also go toward HIV prevention. NIDA-supported modeling research has already contributed to broadening the CDC guidelines for providing HIV screening to populations at risk. Screening for HIV can lead to better outcomes and reduce the spread of the disease; therefore, NIDA plans to investigate rapid screening techniques within the National Drug Abuse Treatment Clinical Trials Network (CTN) and to identify obstacles to acceptance of HIV screening. A meeting to discuss these barriers and to help NIDA expand its role in HIV screening, particularly in vulnerable populations, was held in December 2006. Its goal was to solicit input from opinion leaders to inform and enhance NIDA's resulting research agenda.

Many people with HIV and substance abuse problems are involved in the criminal justice system, thus NIDA also intends to use the CJ-DATS research network to investigate the utility of HIV screening and to promote the adoption of medications that can prevent intravenous and other drug use. Depot naltrexone, a long acting opioid receptor antagonist, may be a useful treatment and is being investigated both within the US and internationally. Effective anti-addiction medications such as buprenorphine, have already led to a reduction in HIV prevalence among IDUs in countries experiencing dual epidemics of heroin use and HIV infection. Given the pandemic nature of HIV/AIDS, NIDA is continuing to work with international research institutions to establish stronger

collaborative relationships to discern how to provide the best infrastructure for translating science-based treatments and minimizing disease spread.

Finally, there is education. NIDA developed a public service announcement as part of its “Learn the Link” campaign to raise awareness of the linkages between drug abuse and resulting risky behaviors that can lead to HIV. A similar campaign designed specifically for the Latino community is currently being developed.

Item

Reducing Health Disparities – The Committee notes that the consequences of drug abuse disproportionately impact minorities, especially African American populations. The Committee is pleased to learn that NIDA is encouraging 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. 85)

Action taken or to be taken

As the Committee recognizes, HIV/AIDS and criminal justice involvement as a result of drug abuse disproportionately affects African Americans. In fact, HIV/AIDS is the leading cause of death in African American men and the second leading cause of death in African American women between the ages of 25 and 44. Although African Americans comprise 12-13 percent of the U.S. population, they account for the majority (over half) of new AIDS cases. Moreover, since the 1970s, African Americans have experienced one of the greatest increases in representation among prison and jail populations, with about 75 percent of this increase estimated to be drug-related.

In 2004, NIDA created an Institute-wide Health Disparities committee, which the following year convened a scientific meeting titled “Reducing HIV and Criminal Justice Involvement in African Americans as a Consequence of Drug Abuse.” There, experts discussed the current state of the science regarding these issues and developed a research agenda for the future. As a result of this meeting, a special issue of the *Journal of Health Care for the Poor and Underserved* was published in November 2005, highlighting this area of research.

To further address these issues, in FY06 NIDA invited applications to investigate HIV/AIDS and criminal justice involvement as a consequence of drug abuse among the African American population and has funded several in FY06. Topics addressed by these grants include understanding the role of drug abuse, violence, and insurance coverage in HIV/AIDS among African American women; addressing 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).

In FY06, NIDA also released a landmark report, “NIDA’s Principles of Drug Abuse Treatment for Criminal Justice Populations,” which outlines key proven components for successful treatment of drug abusers who have entered the criminal justice system. Given

the disproportionate involvement of African Americans in the criminal justice system, this publication will provide the tools necessary to lower rates of drug abuse and, as a result, criminal activity in this population (see *Drug Treatment in Criminal Justice Settings*, p. NIDA-2).

NIDA will continue to foster research to better understand and mitigate the devastating and disproportionate consequences of drug abuse for African Americans.

Item

Reducing Prescription Drug Abuse – The Committee notes the continued increases in the numbers of people, especially young people, who use prescription drugs for nonmedical purposes. The Committee is particularly concerned about the inappropriate use of opioid analgesics—very powerful pain medications. The Committee commends NIDA for its research focus in this area, and for the new Prescription Opioid Use and Abuse in the Treatment of Pain initiative. Research targeting a reduction in prescription drug abuse, particularly among our Nation's youth, should continue to be a priority for NIDA. (p. 85)

Action taken or to be taken

According to the 2006 Monitoring the Future Survey (MTF), nearly one in ten 12th graders reported past year non-medical use of the pain medicine Vicodin, making it among the most commonly abused drugs by high school seniors. And while past-year OxyContin abuse was down among 12th grade students—from 5.5% in 2005 to 4.3% in 2006—the rate doubled among 8th graders between 2002 and 2006—from 1.3% to 2.6%.

NIDA continues to sponsor research to elucidate these negative trends and develop effective counter strategies. For example, NIDA-sponsored research of large cohorts of secondary and college students is revealing different motivations for use, according to age and gender (e.g., adolescent girls tend to abuse prescription painkillers for perceived pain, physical and psychogenic, while boys tend to abuse them to get high and become part of a group). These motivations call for unique counter strategies to address these differing motivations.

A Program Announcement reissued in FY 2006 encouraging research on prescription drug abuse prevention, service delivery, and behavioral and pharmacotherapies has thus far funded half a dozen grants focusing on a range of issues. Because research is also needed to determine what makes pain patients more or less vulnerable to the addictive effects of prescription painkillers and how best to treat co-occurring pain and addiction, NIDA issued a 2006 RFA, “Prescription Opioid Abuse and Pain.” Funded grants will investigate these issues using basic and clinical research approaches. The goal is to develop the knowledge base for physicians and patients to ensure adequate treatment for pain while minimizing the risks for addiction. NIDA also continues to support research to develop alternative pain medications with reduced or no abuse potential and thus less addiction risk. Strategies include developing medications that work with natural receptors in the body and devising innovative medication delivery systems to lessen the likelihood of abuse.

NIDA is also continuing enrollment within its National Drug Abuse Clinical Trials Network (CTN) to determine effective regimens for treating people addicted to prescription painkillers, focusing on sublingual Buprenorphine/Naloxone (BUP/NX) and behavioral counseling.

To raise awareness of prescription drug abuse, in February 2006, Dr. Volkow addressed a briefing, “Prescription Drug Abuse—An Emerging Health Threat,” held by the Friends of NIDA coalition, in conjunction with the Congressional Caucus on Addiction. In July 2006, Dr. Volkow testified on the prescription drug abuse problem before the Subcommittee on Criminal Justice, Drug Policy, and Human Resources Committee on Government Reform.

Item

Translating Research to Communities – 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 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 its collaborative work with states to ensure the research findings are relevant and adaptable by state substance abuse systems. (p. 85)

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 to examine delivery of publicly supported drug abuse treatment or prevention services. Several grants received initial funding in FY 2006 to facilitate adoption of meritorious science-based policies and practices, including developing ways to measure and track program fidelity, promote adoption of research-based practices in addiction treatment, and streamline data collection and reporting requirements.

Other translation activities include the NIDA-SAMHSA Blending Initiative, designed to hasten the dissemination and adoption of recently tested, research-based treatment findings into mainstream drug abuse and addiction practice. Blending teams made up of practitioners and researchers continue to develop “products” based on NIDA research,

particularly research that was conducted with real-world community treatment programs in NIDA's CTN. CTN's use of community settings offers opportunities to address practical addiction treatment needs for diverse patient populations. The Blending initiative has produced five products to date—four are in active service in the field and one will be available by early 2007. They include training curricula, self-study programs, supervisory manuals, and distance-learning opportunities to give treatment providers the tools and training they need to implement proven protocols.

NIDA's successful history of collaboration with SSAs has been facilitated by the productive partnership with the National Association of State Alcohol and Drug Abuse Directors (NASADAD). NIDA continues to work with NASADAD and SAMHSA to fortify communication with the SSAs, NIDA's CTN, and Addiction Technology Transfer Center (ATTC) representatives. NIDA and SAMHSA have co-sponsored meetings to provide updates of Federal and state research-practice blending activities and to enhance the adoption of research-based practices by state-based systems, a strong NIDA commitment. This will continue to be a top priority at NIDA since it ensures that new scientific discoveries are translated into prevention and treatment interventions that are adopted by the community.

Senate Significant Items

Item

Adolescent Brain Development – The Committee notes neuroimaging research by NIDA and others showing that the human brain does not fully develop until about age 25. This adds to the rationale for referring to addiction as a “developmental disease.” 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. 143)

Action taken or to be taken

Please refer to page 203 of this document for NIDA's response to this item on Adolescent Brain Development.

Item

Collaboration with Single State Authorities [SSAs]- The Committee commends NIDA for its outreach and work with SAMHSA's Center for Substance Abuse Treatment (CSAT) and state substance abuse directors, also known as Single State Authorities (SSAs), 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 working with SAMHSA on a recent RFA designed to strengthen state substance abuse agencies' capacity to support and engage in research that will foster statewide adoption of meritorious science-based policies and practices. The Committee also encourages NIDA to continue its collaborative work with SSAs by working through the national association representing State substance abuse directors on its “blending activities” to ensure that research findings are relevant and adaptable by state substance abuse systems. (p. 143)

Action taken or to be taken

Please refer to page 208 of this document for NIDA's response to this item on Translating Research to Communities.

Item

Co-Occurring Disorders – The Committee recognizes that substance abuse is a disorder that can affect the course of other diseases, such as HIV/AIDS, mental illness, trauma, cancer, and cardiovascular disease. To adequately address co-occurring health problems, the committee encourages the Institute 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. 144)

Action to be taken

Many individuals simultaneously suffer from mental illness, alcohol and drug abuse, and other medical or physical disorders that exact not just huge individual costs but societal costs magnified well beyond those associated with substance use disorders alone. Substance abuse can also cause or affect the progression of diseases, which affect virtually every system in the body, as well as increase the risk of traumatic injuries.

Many people with a substance abuse disorder also have some other psychiatric disorder, with the reverse also being true. Thus, a continuing NIDA priority will be to unravel these intertwined conditions to learn more about what causes what and how to best use this information. To that end, the RFA "Enhancing Practice Improvement in Community-Based care for Prevention and Treatment of Drug Abuse or Co-Occurring Drug Abuse and Mental Disorders," co-issued with NIMH and SAMHSA in September 2005, has elicited more than 60 applications. In addition, NIDA's CTN has completed enrollment for its "Women's Treatment for Trauma and Substance Use Disorders" study. Currently in Phase III, the study's goal is to evaluate "Seeking Safety," a substance abuse treatment designed specifically for women with trauma who have a difficult time meeting their treatment goals because of their co-occurring abuse of drugs. This study is conducted in collaboration with the New York State Psychiatric Institute.

Another NIDA collaboration is aimed at developing the Federal Action Agenda, a living document undertaken with federal agency partners for a presidential initiative designed to transform the nation's mental health system. In addition, NIDA continues to engage the psychiatric community, keeping them informed about the bases, scope, and treatment relevance of co-occurring substance abuse and mental health disorders. NIDA also actively participates in the annual meetings of the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry, and offers training for psychiatrists in drug abuse research.

Because substance abuse is often linked to more than mental illness, NIDA has developed an extensive portfolio of basic research and outreach initiatives that target additional comorbid conditions. For example, studies are examining the cardiovascular effects of addictive drugs, such as nicotine, cocaine, morphine, and methamphetamine. Other studies are investigating similarities between the reinforcing properties of food and drugs, providing strong evidence of robust links between drug abuse and obesity and shedding light on the biology of eating disorders. NIDA's website also features a detailed section on medical consequences of drug abuse and addiction.

Item

Drug Abuse and HIV/AIDS – The Committee understands that one of the most significant causes of HIV virus acquisition and transmission is drug taking practices and related risk factors in different populations. Drug abuse prevention and treatment interventions have been shown to be effective in reducing HIV risk. The Committee congratulates NIDA on its “Drug Abuse and HIV—Learn the Link” public awareness campaign, targeting young people, 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. 144)

Action taken or to be taken

Please refer to page 205 of this document for NIDA's response to this item on HIV/AIDS.

Item

Drug Treatment in Criminal Justice Settings – The Committee is very concerned about the well-established connections between drug use and crime. Research continues to demonstrate that providing treatment to individuals involved in the criminal justice system decreases future drug use and criminal behavior, while improving social functioning. The Committee strongly supports NIDA's efforts in this area, particularly the Criminal Justice Drug Abuse Treatment Studies (CJ-DATS). (p. 144)

Action taken or to be taken

Please refer to page 204 of this document for NIDA's response to this item on Drug Treatment in Criminal Justice Settings.

Item

Emerging Drug Problems – The Committee recognizes that drug use patterns are constantly changing and is pleased with NIDA's efforts to monitor drug use trends and to rapidly inform the public of emerging drug problems. The Committee especially encourages NIDA to continue supporting research that provides reliable data on emerging drug trends, particularly among youth and in major cities across the country. (p. 144)

Action taken or to be taken

NIDA recognizes the need to disseminate information regarding the most recent drug abuse-related trends in a timely and effective manner. To this end NIDA has continued to invest a significant amount of resources in two major systems of data collection: 2006

Monitoring the Future (MTF) Survey and the Community Epidemiology Work Group (CEWG).

The CEWG is a unique epidemiology network of researchers that was established by NIDA in 1976 as a drug abuse surveillance system to identify and assess current and emerging drug abuse patterns, trends, and issues, using multiple information sources. The network is comprised of researchers from 21 major metropolitan areas of the United States, who meet semiannually to discuss current drug abuse epidemiology in their geographic regions, providing valuable insight into emerging drug abuse trends.

At the June 2006 CEWG meeting, representatives reported on current trends in drug abuse and focused attention on fentanyl—a powerful analgesic used in combination with other drugs usually before, during, or following surgery—whose abuse has emerged as a problem in several CEWG areas. Before the meeting, CEWG representatives reviewed available data and checked with local contacts (e.g., medical examiners, poison control centers, health departments) to receive updates on suspected or confirmed overdoses and deaths associated with fentanyl and fentanyl-laced mixtures of heroin or cocaine. Recent increases in fentanyl-related deaths were detected in seven CEWG areas. Findings were presented in the fall meeting reports.

Findings from NIDA’s MTF, which since 1975 has measured drug, alcohol, and cigarette use and related attitudes among adolescent students nationwide, show mixed results. Even though the MTF again reported declines in overall illicit drug use among 8th, 10th, and 12th graders combined—23 percent decrease in past month use since 2001, with cigarette use at its lowest level in the history of the survey—important areas continue to demand attention. These include the non-medical use of over-the-counter cough medicines by 12th graders (7% reporting past-year abuse to get high), and the continued high levels of prescription drug abuse, especially painkillers. In response to these findings, over the past year, NIDA has orchestrated a multi-pronged strategy aimed at better understanding the prescription drug phenomenon.

Finally, some indicators have emerged reflecting increases in problems with cocaine use that NIDA is poised to follow carefully to ensure that these indicators do not also reflect an increase in use. NIDA is also interested in assessing the value of mining the Web for information on drug abuse trends as expressed by various audiences there, and in developing standards for how to use this source as an indicator of changes in drug use patterns.

Item

Genetics and New Technological Advances to Curtail Addiction – The Committee recognizes that not everyone who takes drugs becomes addicted. Research has shown that genetics plays a critical role in addiction, and that the interplay between genetics and environment is crucial. The Institute is urged to further investigate this phenomenon. (p. 144)

Actions to be taken

It is estimated that about 50 percent of the risk for addiction is influenced by the action of specific genes and their interaction with environmental factors. Thus, NIDA maintains an active portfolio in this area, which includes projects that use epidemiologic approaches to study the role of genetic and environmental influences in the trajectory of abuse and addiction, as well as pharmacogenomic investigations to predict and enhance responses to medications.

Several initiatives are focusing on genetics. For example, NIDA, in collaboration with the National Institute of Mental Health, recently released a PA, “Molecular Genetics of Drug Addiction and Related Co-morbidities,” to solicit applications to identify genetic variations associated with increased or decreased vulnerability and/or treatment response for addiction to a variety of drugs of abuse, including nicotine. In fact, a recent NIDA-supported study has completed an unprecedented scan of the human genome that has identified genes that potentially increase a person’s risk of transitioning from occasional smoking to nicotine addiction.

NIDA has also recently released an RFA, “Genes, Environment, and Development Initiative,” or GEDI, to solicit research applications that investigate the interplay among genetic, environmental, and developmental factors underlying substance abuse and addiction. In part, the GEDI seeks to take advantage of ongoing studies by adding a genetics component to longitudinal datasets associated with drug abuse. NIDA’s particular interest in the impact of social environments led to a request for data collection instruments that are reliable and suitably sensitive and that can evaluate social variables dynamically in the life of an individual.

In addition, the RFA, “Epigenetics of Neurobiology and Addiction,” is designed to link epigenetic changes (i.e., modifications to DNA structure that result from exposure to drugs, which can exert long-lasting influences on gene function) to other biological changes related to addiction. Understanding how drugs of abuse effect epigenetic changes may help in developing interventions to counter or prevent such changes. Twenty-six projects are now being considered for the next cycle of funding.

Finally, two scientific events hosted by NIDA in 2005—“Translational Research on Drug Abuse: Linkages between Genetics and Prevention” and “Behavior Genetics of Drug Abuse in the Molecular genetics Era”—were instrumental for identifying critical focus areas for NIDA-sponsored research on the genetics of addictions.

Item

Health Disparities – The Committee notes that the consequences of drug abuse disproportionately impact minorities, especially African American populations. The Committee is pleased to learn that NIDA is encouraging 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. 144)

Action taken or to be taken

Please refer to page 206 of this document for NIDA's response to this item on Reducing Health Disparities.

Item

Inhalant Abuse – The Committee understands and is alarmed that inhalant use continues to be a significant problem among our youth. 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. 144)

Action taken or to be taken

Inhalants are often among the first drugs that young children abuse. According to the 2006 MTF, past-year inhalant abuse was reported by 9.1 percent of 8th graders, 6.5 percent of 10th graders, and 4.5 percent of 12th graders, with both past-year and past-month rates not significantly changed for any of the grades. 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's program, "Inhalant Abuse: Supporting Broad-Based Research Approaches," announced in May 2005, is designed to complement NIDA's existing portfolio in this area, as well as encourage research on all aspects of inhalant abuse. For example, one project is conducting an exploratory study of prefrontal cortex structure, function, and connectivity in inhalant abusers ages 18 to 23. Another recently published study showed that youth who used inhalants before age 14 were twice as likely to use opiates as those who never used inhalants.

NIDA is also supporting the development and testing of prevention programs targeting inhalant abuse. For example, NIDA is funding the development of a school-based program and a community trial to prevent inhalant use in Alaska. Because education is a primary vehicle for prevention, NIDA continues to enhance public awareness regarding this topic through the dissemination of its recently updated Community Drug Alert Bulletin and Research Report on inhalants.

Item

Marijuana Use – The Committee is concerned with the continuing widespread use of marijuana. The Committee urges NIDA to continue support for efforts to assess the long-term consequences of marijuana use on cognitive abilities, achievement, and mental and physical health, as well as work with the private sector to develop medications focusing on marijuana addiction. (p. 144/145)

Actions to be taken

Smoking marijuana (the most commonly abused illicit drug among teenagers in the U.S.) can produce adverse physical, mental, emotional, and behavioral changes, and—contrary to popular belief—it can be addictive. Scientists are still learning about the ways in which marijuana affects the brain and other organs. In general, the acute effects of marijuana abuse are better studied and understood than the consequences of chronic abuse; therefore, NIDA is committed to better understanding the long-term consequences of marijuana abuse, including its effects on cognition, mental performance, physical health, and behavior. 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 chronic marijuana abuse starts with animal studies showing the potential long-term effects on the immune, endocrine, reproductive, and cardiovascular systems, and extends to a growing number of human studies that indicate possible associations between heavy marijuana abuse and mental illness. Several ongoing NIDA grants are investigating the effects of chronic marijuana abuse, including neuroimaging studies that assess whether abuse causes measurable long-lasting changes in the brain.

NIDA-funded studies are also investigating marijuana's effects from the prenatal period to adulthood. One of these studies recently reported evidence of a negative impact of prenatal marijuana exposure on mid-gestational fetal growth, even when adjusting for maternal abuse of other substances known to impair fetal development. Of particular relevance to this item are two ongoing longitudinal studies: one showed that prenatal exposure to marijuana, in addition to other factors, is a significant predictor of marijuana abuse at age 14; the other is a follow-up (since birth) of children exposed prenatally to marijuana and tobacco, looking at long-term consequences of the exposure and at substance abuse rates in the sample (now 20-23 years old).

Please see the significant item on *Medications Development* (below) for an update on the medications NIDA is pursuing for cannabis addiction.

Item

Medications Development – The Committee applauds NIDA for over a decade of leadership in working with private industry to develop anti-addiction medications and is pleased this collaboration has resulted in a new medication for opiate addiction. The Committee encourages NIDA to continue its work with the private sector to develop anti-addiction medications, particularly for cocaine, methamphetamine, and marijuana. (p. 145)

Action taken or to be taken

NIDA continues its commitment to working with the private sector to develop medications for use with behavioral therapies to treat drug addiction. The current focus is on the development of medications for stimulant (cocaine and methamphetamine) and cannabis addiction. A secondary focus is on nicotine and opiates. Several medications show promise, and NIDA is interacting with multiple pharmaceutical companies at different levels to develop them.

For stimulant addiction, NIDA is particularly interested in drugs that ameliorate altered inhibitory and cognitive mechanisms in the brain. The latter could enhance learning and improve treatment outcomes for approaches such as cognitive behavioral therapy. Modafinil is one example of a medication currently marketed for narcolepsy that, in combination with behavioral treatment, reduced cocaine use in an initial phase II trial. NIDA is working with the pharmaceutical company Cephalon to follow up on these promising findings. NIDA is also funding studies for topiramate (TOPAMAX), tiagabine, and disulfiram (Antabuse), as potential medications for cocaine addiction. And, NIDA is working with Ortho-McNeil to test TOPAMAX and with Ovation Pharmaceuticals to evaluate vigabatrin, another anti-seizure medication like topiramate, for treating cocaine *and* methamphetamine addiction, with studies started in the fall 2006.

For methamphetamine abuse, NIDA researchers have recently shown that bupropion, the anti-depressant marketed as Wellbutrin, reduced the methamphetamine-induced “high” as well as drug cravings elicited by drug-related cues. A phase II study of bupropion in methamphetamine abusers has been recently completed; the results should be published shortly, and NIDA is also planning phase II studies of topiramate, and modafinil for treating methamphetamine addiction.

For cannabis, NIDA is funding both animal and human studies to evaluate compounds that can promote abstinence in former abusers. For opiate addiction, NIDA is conducting clinical trials with depot naltrexone, a long-acting antagonist, which has been shown to block the priming response in opioid-addicted patients—the catalyzing effect of a small dose in resumption of drug taking and thus relapse.

NIDA is also employing novel strategies for treating drug addiction. For example, rather than targeting the neural pathways/receptors involved in drug addiction, NIDA is targeting the drug itself using immunotherapy. Addiction immunotherapies would cause the body to generate antibodies that bind specific drugs while they’re still in the bloodstream, blocking their entry into the brain. Cocaine and nicotine vaccines are both under study, the former having completed a phase II trial and the latter being in a phase II trial that is expected to be completed early next year. A 2007 RFA seeks to develop a vaccine for methamphetamine addiction.

Item

Methamphetamine Abuse – The Committee is very concerned about the continued abuse of methamphetamine across the United States. The Committee notes the advances in understanding methamphetamine abuse and addiction, and is encouraged by growing

evidence of treatment effectiveness in these populations. The Committee urges NIDA to continue supporting research to address the broad medical consequences of methamphetamine abuse. (p. 145)

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 and increasing in several other areas throughout 2005-2006. NIDA recognizes the myriad problems posed by meth abuse and addiction and has been stepping up research efforts accordingly, almost 175 percent from 2000 to 2006.

NIDA supports a comprehensive research portfolio that includes initiatives to both prevent and treat methamphetamine abuse and addiction. In 2006, NIDA research demonstrated that prevention interventions designed to target all drugs of abuse can significantly reduce meth abuse. 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.

However, NIDA-supported research has also demonstrated that prolonged abstinence can reverse some of the brain changes associated with meth abuse. Therefore it is critical that those addicted to meth have access to effective treatments, which, as the Committee notes, do indeed exist. For example, a recent study conducted through NIDA's CTN showed that the behavioral treatment Motivational Incentives for Enhancing Drug Abuse Recovery (MIEDAR) is effective in achieving sustained abstinence. MIEDAR is currently being developed for dissemination to community treatment providers through NIDA's collaborative Blending Initiative with SAMHSA. NIDA is also invested in the development of medications for meth addiction (see *Medications Development*, p. NIDA-12). For example, NIDA researchers have recently shown that bupropion, the antidepressant marketed as Wellbutrin, reduced the meth-induced “high” as well as drug cravings elicited by drug-related cues. This medication and others are currently in clinical trials, while new compounds are being developed and studied in preclinical models.

Given the devastating consequences of meth abuse, NIDA will continue to support research not only on its medical consequences, but also on prevention and treatment interventions for methamphetamine abuse and addiction.

Item

Primary Care Settings and Youth – The Committee recognizes that primary care settings are potential key points of access to prevent and treat problem drug use among young people. The Committee encourages NIDA to support health services research on

effective ways to educate primary care providers about drug abuse and 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. 145)

Action taken or to be taken

Recommendations by a Blue Ribbon Task Force convened by NIDA to review its health services research portfolio call for boosting the relevance and use of drug abuse research in practice and policy. In response, NIDA has taken a number of steps to overcome barriers to delivering interventions, developing methods of blending science-based practices with community services and creating research tools that enable quality health services research on drug and alcohol abuse for young people.

In 2003, NIDA started the “Physician Outreach Initiative” to inspire strategies to enhance primary care physicians’ capacity to better serve drug-abusing patients through science-based screening and brief intervention approaches. The foundation for this work has already (1) established a physician work group composed of recognized experts invested in this project’s success, (2) developed a literature review that will be published in a peer-reviewed journal, and (3) completed formative evaluation activities specifying how physicians prefer to receive health information. Planning is under way to launch a comprehensive outreach communications campaign, developing materials for physicians and their patients, and implementing evaluation activities.

A workgroup formed from members of the Physicians Outreach Initiative sponsored a 1-day conference in January 2006, convening national leaders in primary care to guide NIDA’s physician outreach program to patients of all ages. Participants presented survey information from the American Academy of Pediatricians on screening youth for substance abuse disorders and on awareness of NIDA resources to assist and inform the medical community. NIDA, in conjunction with the American Medical Association, will sponsor four National Centers of Excellence in Physician Information to conduct research and develop messages and dissemination avenues for medical students, primary care, and family practice residents to raise their awareness of substance abuse issues and of NIDA as a resource.

The Physicians Outreach program also involves youth and primary care services, addressed at the 2006 Joint Meeting on Adolescent Treatment Effectiveness Conference in March. A panel session titled “Screening and Brief Intervention in Primary Care” addressed the growing interest of primary care providers in having efficient and effective screening tools to use with youth. New ways of coordinating primary care prevention, screening, and treatment services were also discussed. As part of this initiative, NIDA presented an informational session to the family practice residents at George Washington University on primary care and screening in all age groups for substance abuse.

Item

Reducing Prescription Drug Abuse – The Committee notes the continued increases in the numbers of people, especially young people, who use prescription drugs for nonmedical purposes. Particular concern revolves around the inappropriate use of opioid

analgesics—very powerful pain medications. The Committee commends NIDA for its research focus in this area, and for the new Prescription Opioid Use and Abuse in the Treatment of Pain initiative. Research targeting a reduction in prescription drug abuse, particularly among our Nation's youth, should continue to be a priority for NIDA. (pp. 151-152)

Action taken or to be taken

Please refer to page 207 of this document for NIDA's response to the significant item regarding Reducing Prescription Drug Abuse.

Item

Social Neuroscience – Research-based knowledge about the dynamic interactions of genes with the environment confirms addiction as a complex and chronic disease of the brain with many contributors to its expression in individuals. The committee applauds NIDA's involvement in the recently released "social neuroscience" request for applications, and 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. 145)

Action taken or to be taken

NIDA supports a broad basic neuroscience research portfolio on the causes and consequences of drug abuse and addiction, which undergirds the development and improvement of prevention efforts and treatment approaches based on science. Results from this research already provide important hints about how biological variables in drug abuse and addiction are influenced by social circumstances that can either harm or protect.

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, such as peer pressure, in the context of drug abuse or decision-making. Gaining a better understanding of the mechanisms underlying peer influences, and whether or not and how they might be reversed, will be important in terms of prevention in adolescents, and will go toward helping us ascertain which messages are most salient for the community.

NIDA's focus on the influence of social factors both in individual and group decision-making is critical not just for understanding drugs of abuse but other health behaviors as well, particularly when investigating adolescent populations. NIDA's recent "Social Neuroscience" RFA was designed to address this need by taking advantage of powerful new tools that allow researchers to see how genetics, epigenetics, and brain chemistry can change behavior and how behavior can change the brain. Several grants were funded in FY 2006 examining such topics as social approach behaviors and reward pathways in adolescent mice, peer effects on neural and behavioral markers of risk-taking, and the role of endocannabinoids in the behavioral consequences of social isolation.

NIDA is also committed to efforts to better describe the characteristics of social environments that integrate quantitative and dynamic environmental measures with

human genetic studies. NIDA plans to include strategies such as mapping community risk factors for drug use (e.g., education level, socio-economic status, crime, and drug availability) and using that data to drive research on neurobiological factors that mediate the impact on risk (or protection) for drug abuse. A better understanding on the neurobiology of social behaviors is relevant both for the treatment of drug addiction and for psychotherapeutic interventions for mental illness, which also involve social aspects of human behavior.

Item

Translational Research—Ensuring Research is Adaptable and Useable – The Committee commends NIDA for its broad and varied information dissemination programs. The Committee also understands that NIDA is focused on stimulating and supporting innovative research to determine the components necessary for adopting, delivering, and maintaining effective research-supported policies, programs, and practices. As evidence-based strategies are developed, the Committee urges NIDA to support research to determine how these practices can best be implemented at the community level. (p. 145)

Action taken or to be taken

Research supports the effectiveness of different approaches and interventions for preventing and treating drug abuse and addictive disorders. The translational process to go from research to practice is viewed as a complex multidirectional one that involves the interaction of multiple individual and systems-level factors aimed at continuous improvement. Therefore, NIDA has begun to focus increasingly on the change processes that occur within organizations in order to improve prevention and treatment services. For example, in 2006, NIDA issued three new PAs to examine health services research on practice improvement utilizing community treatment providers within the CTN.

To enhance the value of currently supported research, in November 2006, NIDA held a meeting for the seven funded grantees on the “Enhancing State Capacity to Foster Adoption of Science-based Practices” RFA to discuss their foundational research on which future services research by state agencies and their collaborators will build. New studies will enhance continuous practice improvement and foster implementation of innovative therapeutic and management policies and practices. Another RFA, issued in August 2005, sought to create capacity to conduct practice improvement research among community-based providers of drug abuse prevention and treatment services. Multiple grants were funded by NIDA, NIMH, and SAMHSA. The ultimate goal of this initiative is to foster implementation and sustained use of proven, innovative therapeutic and business policies and practices.

Additional efforts to narrow the distance between research findings and their implementation in community programs were reflected in several meetings of multiple stakeholders, including in the international arena. In April 2006, NIDA participated in a small international conference in Bulgaria entitled “Bridging the Gap between Science and Practice” and, in August, along with NIAAA, presented a program on “Substance Abuse Research and Clinical Practice” at the American Psychological Association

conference. In October 2006, NIDA hosted a well-attended “Blending Addiction Science and Practice: Bridges to the Future” conference in Seattle. NIDA continues its partnership with state directors and policy makers, convening an all-day meeting with members from the National Association of State Alcohol and Drug Abuse Directors (NASADAD) aimed at enhancing the States’ capacity to implement Evidence-Based Practices. And recently, NIDA created a “Blending Initiative Task Force,” composed of researchers and treatment providers to assist NIDA in future research dissemination activities.

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National Institute on Alcohol Abuse and Alcoholism

House Significant Items

Item

Underage Drinking– The Committee is aware of new NIAAA funded research findings suggesting that exposure to alcohol advertising increases the likelihood that young people will drink and drink heavily. The Committee encourages NIAAA to engage in additional study of alcohol advertising issues as an underage drinking prevention research priority, and encourages this research to include data on youth brand and beverage preferences. (p. 111/112)

Action taken or to be taken

As part of NIAAA's Initiative on Underage Drinking, the Institute is focused both on the consequences of underage drinking, especially on the developing brain, and on adolescent decision-making. Given the high prevalence of alcohol use and binge drinking by young people and the resulting negative consequences, it is important to understand why alcohol is so appealing to this age group. NIAAA needs to understand both adolescent decision-making in general as well as those factors specific to decisions about alcohol.

In the past few years, NIAAA funded a number of studies on the relationship of advertising and alcohol use by youth. One of these showed a small but statistically significant increase in drinking by youth who were exposed to local alcohol advertising over and above national alcohol advertising. Any study of the relationship between alcohol use and advertising is limited by the fact that virtually all youth are regularly exposed to at least some alcohol advertising making it difficult to discern the effects of particular additional exposures. Additional research has shown that for youth, their interpretation of messages may be as important as media exposure per se. Further, youthful decisions about alcohol are both logic-and affect-based and incorporate inputs from multiple sources, including parents and peers as well as the media. Given these complexities, a more complete picture of the factors that influence underage drinking can be obtained by studies of adolescent decision-making about alcohol as influenced by multiple factors, including alcohol advertising and the Institute would support meritorious studies using such a comprehensive approach. Investigations that attempt to focus on the study of a single factor, e.g., alcohol advertising, on whether underage youth drink or do not drink, would have less utility to the field because of confounding variables explained earlier in this response. Data on brand and beverage preferences by youth are best accrued through nationally representative surveys that collect information about youth drinking. Data on youth beverage preferences would be most useful if they also include information on the quantity and frequency of consumption of each of these beverages. NIAAA has discussed this issue with other relevant agencies of HHS for their consideration in design of the surveys they conduct or support.

Senate Significant Items

Item

Alaska Substance Abuse – The Committee is aware of serious problems with alcohol and substance abuse in Alaska, especially among its Alaska Native population, and of the need for translating research into clinical applications for this population. The Committee urges NIAAA to sponsor a Research to Practice Forum with the Substance Abuse and Mental Health Services Administration and universities to focus on bridging the gap between researchers and practitioners and translating scientific research into clinical applications, and encourages NIAAA to support the implementation of any recommendations developed at the forum. (p. 142)

Action taken or to be taken

NIAAA considers the translation of scientific research into clinical applications a priority. For example, the Institute is participating on the Technical Advisory Panel of the National Quality Forum to develop practice guidelines and performance indicators for providers. More specifically in regard to Alaska Natives, the Institute funded a medications trial in this population group. NIAAA is currently working with the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA) on the Science to Service Initiative to translate this research into practice. The goal of the initiative, which is a partnership between the National Institutes of Health (NIH) and SAMHSA, is to reduce the gap between the initial development and widespread implementation of new and effective treatments and services. This will facilitate more rapid delivery of research-based practices to the communities that provide services.

Item

Clinician's Guide – The Committee understands that NIAAA has recently revised its publication "Helping Patients Who Drink Too Much; A Clinician's Guide." The Committee applauds that the guide has been disseminated to thousands of primary care and mental health practitioners and organizations through an extensive program of direct mail and email announcements. The Committee encourages 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 inter-national organizations to further disseminate this important resource. (p. 142)

Action taken or to be taken

NIAAA is pleased with the enthusiastic response by health care providers to the revised Clinician's Guide. The Institute is working with the American Medical Association to ensure that the guide, which is available in both English and Spanish, is being extensively disseminated throughout the United States. This publication is also receiving attention internationally and was the topic of a presentation at the International Society on Addiction Medicine in September 2006. In addition, in cooperation with its Federal partners, NIAAA is developing a number of supplementary materials. For example, the guide is being updated for the fall of 2006 and will include tools to implement medication

management support counseling to be used with pharmacotherapy. The revised guide will also include a patient oriented handout. The Institute is also developing a handbook titled “Rethinking Drinking” that can be used by an individual to help assess his/her own drinking and provides advice on how to cut down on drinking.

To provide information for health care providers on how to best use the guide, online training is being developed. The ability for health care providers to obtain continuing education units (CEUs) will be an additional incentive for them to take the training. In addition, an animated Power Point presentation is available on the NIAAA web site <https://www.niaaa.nih.gov>. In collaboration with the Center for Substance Abuse Treatment (CSAT/SAMHSA) NIAAA is developing Treatment Improvement Protocols (TIPS) for pharmacotherapy for alcohol dependence. The Treatment Improvement Protocols (TIPS) are best practice guidelines for the treatment of substance abuse. In collaboration with Centers for Disease Control and Prevention (CDC), a trauma center guide is also under development.

Item

Epigenetic (Environmental) Effects Underlying Alcoholism – The Committee understands that alcoholism is a complex behavioral disorder and that the genetic composition of an individual contributes to over half of the risk for developing this behavior, while the individual's environmental interactions and influences also contribute significantly to this risk. Research supported by NIAAA has identified several candidate genes that increase an individual's risk for developing an alcohol use disorder once the person chooses to drink alcohol. The Committee encourages NIAAA to continue to fund research to determine the role of the environment and environmental factors in producing lasting and potentially life-altering changes in gene expression and gene function that contributes to the development of alcohol abuse and addiction with the ultimate goal of developing new medication for the treatment of alcohol use disorders. (p. 142)

Action taken or to be taken

NIAAA has been successful in supporting research that has identified candidate genes that increase risk for dependence as well as uncovering cellular pathways that may play a significant role in the tissue damage that can result from excessive alcohol consumption. In addition, NIAAA supports research investigating the metabolic and environmental factors, including alcohol that can influence the manner in which genes are expressed. This process of epigenetics allows an individual to adapt to his or her environment by modifying expression of specific genes at specific times or under specific conditions. However, it can also result in negative outcomes that may include tissue and organ damage and the development of alcohol dependence. By identifying epigenetic changes which do not alter the genetic sequence but do cause changes in gene expression we will better understand the process through which genes and the environment interact to produce disease and to find molecular targets for therapeutics. This line of research will be important in developing pharmaceuticals both to prevent tissue damage and to intervene in chronic behaviors such as relapse to drinking. It may also provide critical insights for the prevention and intervention for fetal alcohol syndrome disorders.

Item

Underage Drinking – The Committee commends the NIAAA for its team approach in developing and guiding its research programs to understand the many factors that contribute to the onset of drinking and abuse of alcohol by youth. The Committee is aware that the NIAAA has partnered with the Surgeon General in the preparation of "A Call to Action on Underage Drinking," which will provide guidance to the public on this topic. The Committee commends the NIAAA for providing the scientific foundation for this report through the research supported by its Underage Drinking Initiative and for continuing to work with the Office of the Surgeon General and other Federal agencies on this effort. (p. 142)

Action taken or to be taken

NIAAA was pleased to participate and welcomed the opportunity to provide knowledge accrued through scientific investigation for use by the Surgeon General to inform the American public about this important public health issue.

Item

Understanding Natural Recovery from Alcohol Dependence – Recent research has demonstrated that many individuals transition out of alcohol dependence without professional treatment. The Committee encourages NIAAA to investigate the mechanisms through which individuals alter their drinking behavior without professional treatment in order to design more effective treatments for alcohol use disorders. (p. 142)

Action taken or to be taken

Understanding natural recovery from alcohol dependence is an integral part of a larger NIAAA initiative focused on Mechanisms of Behavior Change. Recent analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) shows that many individuals will change their drinking behavior over time without treatment and not progress to a chronic disease state. This data has focused the Institute's attention on understanding this phenomenon and its implications for treating those individuals who do progress to a chronic disease state. NIAAA's strategic approach, which takes into account the impact of alcohol across the lifespan, has provided essential epidemiological data to address this issue. For example, data from NESARC indicates that while 18-24 year olds have the highest prevalence of alcohol dependence in the U.S. population, the prevalence for 30-49 year olds is much lower⁴. Even though this survey is performed at one point in time from people of various ages in the population, we can infer that many individuals change their drinking behavior over time.

People who resolve heavy drinking and its related problems without specialized treatment differ systematically from those who progress to a chronic disease state. Recovery outside of treatment is more likely in those with fewer symptoms of dependence, less comorbid psychiatric disorders, less pressure to quit drinking, and more social capital. Although these individuals resolve their alcohol use disorder, a more comprehensive

⁴ NIAAA National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) special analysis; Grant BF, Dawson DA, Stinson FS, Chou SP, Dufour MC, and Pickering RP. Drug and Alcohol Dependence 2004. 74: 223-234.

understanding of how the natural recovery occurs could inform development of interventions targeting individuals who would not normally seek treatment but who would benefit from accelerating the timeframe in which they change their drinking behavior so as to minimize consequences that result from it.

In addition, a better understanding of the characteristics, mediators, and environmental factors that motivate individuals to try to change their drinking behavior, either on their own or through professional alcoholism treatment, will greatly aid the search for improved prevention and treatment strategies.

Most individuals who seek treatment do so in the midlife period after they have experienced an aggregate of negative consequences as a result of their drinking behavior. Currently available treatments, which include behavioral therapies and those that employ medical management with newly available medications, help many such individuals recover from alcohol dependence. In general, treatments with very different conceptual frameworks and intervention techniques have approximately equivalent success rates. One explanation is that the mechanisms are specific to each technique but lead to a common outcome. An alternate hypothesis is that the motivation to seek treatment plays a major role in positive outcomes regardless of treatment modality. NIAAA will continue to fund research to gain a better understanding of the mechanisms of recovery at all stages of alcohol abuse and dependence to inform future interventions with the goal of accelerating natural recovery as well as improving treatment.

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National Institute of Nursing Research

House Significant Items

Item

Behavioral Research – The Committee recognizes the importance of behavioral research in preventing and treating disease. While understanding the biological basis of disease is essential, behavioral factors have a critical influence on the onset, course, and duration of disease and in the successful management of many disease conditions. The Committee encourages NINR to support behavioral research, including research that examines the interactions of biological and behavioral factors and their effect on treatment and prevention. (p. 141)

Action taken or to be taken

NINR recognizes the critical importance of behavioral research in preventing and treating disease. Projects that involve behavioral and social science research constitute a major portion of NINR's research portfolio, over 80% by funding in FY 2006. Consistent with the Institute's long-term commitment to this area of science, behavioral research, specifically biobehavioral research, is highlighted as a major research priority in NINR's new strategic plan. NINR-supported scientists examine the behaviors that underlie an individual's health choices (i.e. nutritional, physical), which are crucial to designing new ways of preventing disease. Other NINR investigators are designing new and innovative interventions that, for example, improve diabetics' adherence to treatment regimens, assist parents in managing the treatment of their sick children, teach women better awareness of the symptoms of a heart attack, and help family members cope with the stress of caring for a relative with dementia.

Biobehavioral research, which studies the interactions among biological, behavioral, and social factors and their effect on outcomes, is a central focus of many NINR-supported scientists. Certain behaviors, such as exercise, may have unforeseen effects on an individual's biological functioning. Conversely, biology can influence behavior, often through genetics, and determine how an individual will respond to a behavioral intervention. NINR-funded behavioral research often studies the socio-cultural contexts of disease and assesses the impact of cultural beliefs, values, and norms on research questions. For example, a behavioral dietary intervention that is sensitive to the traditional dietary habits of a certain ethnic group should prove more successful with people of that ethnicity than standard interventions. In addition, behavioral research often examines the decision-making processes of patients and family members in various situations. NINR-supported researchers, for example, study the decisions families make on behalf of their loved ones in end-of-life situations.

Item

Eliminating Health Disparities – Health disparities, whether in race, ethnicity, or socioeconomic status, continue to be of concern to the Committee. Reducing and ultimately eliminating health disparities is a critical priority for all areas of healthcare research. The Committee encourages NINR to fund research into the causes of health

disparities and into new ways to overcome such disparities. Developing new nurse scientists from underserved populations will prove valuable for encouraging new health disparities research. (p. 141)

Action taken or to be taken

NINR's focus on health promotion and disease prevention, along with its emphasis on behavioral and social sciences research, positions the Institute well for leadership in efforts to eliminate health disparities. The broad-ranging biobehavioral research sponsored by NINR not only has the opportunity to study the genetic and gender differences that underlie the biological causes of health disparities, but also the social and cultural experiences and behaviors that contribute to disparities. Consistent with the Institute's commitment to 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.

The elimination of health disparities is a cross-cutting area of health care science that is a part of every program of research funded by NINR. NINR investigators have made many notable advances in health disparities research over the twenty-year history of the Institute, and the Institute's commitment to such research will continue in the coming years. Current projects include studies: to prevent type-2 diabetes in low income, at-risk youth; to design a behavioral intervention aimed at improving asthma communication in minority families; and to increase access to HIV-related clinical trials for rural minorities. NINR is also funding a program focused on training new investigators with interdisciplinary skills necessary to better understand and reduce the health disparities experienced by women and girls of underserved minorities. Finally, another NINR-funded program is focusing on using information technology and informatics to advance research in health disparities.

In addition to research, NINR is committed to supporting training opportunities for new minority investigators. The Nursing Partnership Centers for Health Disparities Research, co-sponsored with the National Center for Minority Health and Health Disparities (NCMHD), seek to establish partnerships between research-intensive schools of nursing and growing, minority-serving institutions. This program has established 8 partnerships, involving 17 schools of nursing, and has successfully built emerging research programs at minority-serving institutions using the expertise and resources of experienced schools of nursing research. These Centers represent a major investment aimed at expanding and diversifying the cadre of nurse researchers involved in health disparities research.

Item

End-Of-Life-Research – The Committee recognizes that improving the care of terminally ill patients and their loved ones at the end of life is an urgent public health need, especially in view of the increasing numbers of older Americans; and that additional research is needed in improving palliative care, improving patient/clinician communication, and reducing caregiver burden. The Committee appreciates NINR's

leadership in promoting end-of-life research and encourages the institute's continued focus in this area. (p. 141)

Action taken or to be taken

Consistent with its role as the lead NIH Institute for end-of-life research, NINR remains committed to improving the care of patients and family members at the end of life. In response to the 1997 Institute of Medicine report “Approaching Death: Improving Care at the End of Life,” NINR issued a number of research solicitations, with the goal of establishing a robust portfolio in end-of-life research. Since that time, NINR has funded many projects examining end-of-life health care, and NINR-funded researchers have published numerous findings that have greatly improved the health care community’s understanding of end-of-life situations. In FY 2005, NINR sponsored the NIH State-of-the-Science Conference on Improving End-of-Life Care, along with NIH’s Office of Medical Applications of Research. Findings from the conference guided the development of research goals in NINR’s new strategic plan, where end-of-life research is highlighted as a major Institute research priority.

NINR-supported scientists explore multiple aspects of end-of-life research, including: improving the symptom management of dying patients to make the end-of-life experience as comfortable as possible; understanding the decision-making process of patients and caregivers to better educate everyone involved about end-of-life treatment options and why people choose these options; and reducing the burdens on families of dying patients. NINR will continue to fund research to improve what we know about end-of-life health care and to translate these findings into better clinical practice. Consistent with the Institute’s commitment to end-of-life research, NINR proposes in FY 2008 to increase efforts in this area of research, in part through the support of larger multidisciplinary clinical studies.

Senate Significant items

Item

Behavioral Research – The Committee realizes the importance of behavioral research in preventing and treating disease. While understanding the biological basis of disease is essential, it is understood that behavioral factors have a critical influence on the onset, course, and duration of disease and in the successful management of many disease conditions. The Committee encourages NINR to devote significant efforts to behavioral research, including research that examines the interactions of biological and behavioral factors and their effect on treatment and prevention. (p. 141)

Action taken or to be taken

Please refer to page 229 of this document for NINR’s response to this item on behavioral research.

Item

Eliminating Health Disparities – Health disparities, whether in race, ethnicity, or socioeconomic status, continue to be of concern to our Nation’s healthcare system and to

this Committee. Reducing, and ultimately eliminating, health disparities is a critical priority for all areas of healthcare research. The Committee urges NINR to fund research into the causes of health disparities and into new ways to overcome such disparities. Developing new nurse scientists from underserved populations will prove valuable for encouraging new health disparities research. (p. 141)

Action taken or to be taken

Please refer to page 230 of this document for NINR's response to this item on eliminating health disparities.

Item

End-of-Life Research – Improving the care of terminally ill patients and their loved ones at the end-of-life is an urgent public health need, especially in view of the increasing numbers of older Americans. Additional research is needed in improving palliative care, improving patient/clinician communication, and reducing caregiver burden. The Committee recognizes NINR's leadership in promoting end-of-life research and encourages the Institute's continued focus in this area. (p. 141)

Action taken or to be taken

Please refer to page 230 of this document for NINR's response to this item on end-of-life research.

Item

Nurse-Managed Health Centers – The Committee urges the NINR to increase support for research and demonstration projects involving nurse-managed health centers and advanced practice nurses. (p. 141)

Action taken or to be taken

NINR recognizes the value of nurse-managed health centers and advanced practice nurses in the field of nursing research. NINR supports research on the effectiveness of advanced practice nurses and their impact upon patient health outcomes. Once recent study found that case management by advanced practice nurses of adults with high cholesterol and coronary heart disease was a cost-effective approach to improving patient care.

NINR remains committed to funding research that translates effective nurse-managed interventions into practice settings. As an active participant in the NIH Roadmap, NINR seeks to increase collaborations between its nurse scientists and other biomedical researchers. These collaborations will allow new nurse-managed interventions to integrate more quickly into the everyday practice of health care, maintaining the quality and decreasing the cost of our health care system.

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. 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 NINR to facilitate research projects located in rural areas that serve minority nursing students through community colleges. (p. 141)

Action taken or to be taken

Through its training programs, NINR seeks to improve the pipeline of nursing faculty using strategies to encourage and change the career trajectories of nurse scientists. The Institute emphasizes early entry into research careers, including fast-track baccalaureate-to-doctoral programs, to increase the number of nurse investigators, and supports pre-doctoral and post-doctoral nurses who are the future researchers and nursing faculty. An on-line NINR program, Developing Nurse Scientists, is offered to help nursing faculty and doctoral students develop research skills, including applying for research grants. NINR remains committed to supporting the development of the next generation of nurse scientists.

Item

Research Training – Increasing the number of new nurse scientists is critical for advancing nursing research, especially in light of the ongoing nursing shortage. Innovative strategies for recruiting and training new researchers are needed. 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. 142)

Action taken or to be taken

Consistent with NINR's commitment to research training, developing the next generation of scientists is a major initiative in the Institute's new strategic plan. The Institute has developed and supported several innovative programs for training new nurse scientists. For example, NINR's *Summer Genetics Institute* teaches highly qualified nurse scientists fundamental techniques in genetics research, taking advantage of state-of-the-art facilities at NIH's Bethesda, Maryland campus. Graduates of the program incorporate genetic knowledge into extramural research settings across the country. Many graduates have published in the scientific literature, submitted research applications, and integrated content on genetics into university curricula. NINR has also developed an online research training module, designed to help new researchers develop skills in developing research programs and applying for NIH funding. Finally, NINR continues to collaborate with universities throughout the U.S. on training students in fast-track baccalaureate-to-doctoral programs to speed the process of developing new nurse scientists and faculty.

The interdisciplinary focus of nursing science has led to multiple efforts to develop new nurse scientists with multidisciplinary research skills. For example, NINR is funding one training program that incorporates rigorous training in new technology into standard

nursing curricula. Prevention and treatment interventions increasingly use technology to better improve behavioral outcomes, and nurse scientists of the future must be increasingly adept at incorporating new technologies into their research. NINR is also funding a project focused on training new investigators with interdisciplinary skills necessary to better understand and reduce the health disparities experienced by women and girls of underserved minorities. Finally, an NINR-funded program is focusing on using information technology and informatics to advance research in health disparities. These are only a few examples of NINR-supported innovative training programs that are currently developing the next generation of interdisciplinary scientists.

National Human Genome Research Institute

House Significant Items

Item

Genes and Environment – The Committee commends NIH and the Foundation for the NIH (FNIH) for initiating the Genetic Association Information Network (GAIN), a public-private partnership using genetic analysis of existing case-control studies to identify the genetic roots of common illnesses. The Committee also commends NIH for building on the momentum of GAIN to advance the trans-NIH and DHHS Genes, Environment and Health Initiative (GEI), beginning in fiscal year 2007. This new research effort combines genetic analysis and environmental technology development to understand the causes of common diseases such as Alzheimer’s, diabetes, stroke, cancer, asthma, and heart disease. The Committee encourages NHGRI to work with the NIEHS on this important project. The Committee also encourages NHGRI to follow up on the working group recommendations on a “Population-Based Cohort Study to Determine the Relationships among Genes, Environment, and Health.” This kind of prospective cohort study of a large sample of Americans could provide a valuable complement to the work of GAIN and GEI. (p. 115/116)

Action taken or to be taken

The NHGRI is prepared to play a major role in the Genes, Environment and Health Initiative through administrative leadership of one of its two main components, the Genetics Program, which is projected to receive roughly two-thirds of GEI funding. The Genetics Program is planned to include three elements: genotyping facilities to perform high-throughput genotyping for genome wide association (GWA) over 4 years; a Coordinating Center to carry out analytic support, data assessment quality control, and logistical management; and the implementation of analytic approaches to GWA data. GEI plans to go beyond the collection of genotype data by including support for data analysis, replication and fine-mapping studies, sequencing, functional studies, database development, and clinical translation. However, the primary focus of GEI in the initial stages is projected to be on acquisition and analysis of the high-throughput GWA genotyping data. Similar to the Genetic Association Information Network project, a controlled access system is being designed to make all of the information and data collected widely available to the scientific community. As GAIN promises to uncover new information regarding the association of genetic variation and disease, GEI plans to build on GAIN’s mission by incorporating environmental data collected via current and novel methods. Roughly one-third of funding for GEI is projected to be devoted to development of new technologies for acquiring environmental exposure data; NIEHS will administer this component, the Exposure Biology Program. These novel technologies will aid in measuring environmental cues such as dietary intake and physical activity. A combined effort to understand the interaction between genes and environment is essential for properly understanding the impact of both genetic and non-genetic factors on human health and disease.

Item

Primary Immunodeficiency Diseases (PI) – The Committee commends NHGRI for its outstanding work in creating a collaboration to develop a newborn screening test for X-linked SCID, the most severe form of primary immunodeficiency. The Committee looks forward to learning of the results of this effort and encourages further use of this model of public-private partnerships. (Page 116)

Action taken or to be taken

Although the NHGRI's leading intramural primary immunodeficiency investigator left the NIH this year, the NHGRI continues to work in this important area of applied research. NHGRI researchers have an ongoing Clinical Research Protocol that allows them to receive immunodeficient patients' samples and study them with an X-linked SCID screening assay. Since this protocol is not limited to recruiting only X-linked SCID patients, once the system is fully tested for X-linked SCID, samples from patients affected with other forms of SCID (e.g. ADA-SCID, JAK3-SCID) and other T-cell immunodeficiencies (e.g., Wiskott-Aldrich syndrome) will extend the study to these other diseases, potentially in partnership with the public sector.

Senate Significant Items

Item

Genes and Environment – The Committee commends NIH and the Foundation for the NIH (FNIH) for initiating the Genetic Association Information Network (GAIN), a public-private partnership using genetic analysis of existing case-control studies to identify the genetic roots of common illnesses. The Committee also commends NIH for building on the momentum of GAIN to advance the trans-NIH and DHHS Genes, Environment and Health Initiative (GEI), beginning in fiscal year 2007. This new research effort combines genetic analysis and environmental technology development to understand the causes of common diseases such as Alzheimer's, diabetes, stroke, cancer, asthma, and heart disease. The Committee encourages NHGRI to work with the NIEHS on this important project. The Committee also encourages NHGRI to follow up on the working group recommendations on a "Population-Based Cohort Study to Determine the Relationships among Genes, Environment, and Health." This kind of prospective cohort study of a large sample of Americans could provide a valuable complement to the work of GAIN and GEI. (p. 150)

Action taken or to be taken

Please refer to page 235 of this document for NHGRI's response to this significant item regarding genes and the environment.

Item

Liver Disease – The Committee urges NHGRI to focus on the genetic component of biliary atresia and other liver diseases with an identified genetic component. (p. 150)

Action taken or to be taken

NHGRI researchers continue to make important progress towards understanding the genetic factors that can lead to a variety of liver diseases. Researchers at the NHGRI have implemented a number of strategies to uncover the underlying cause(s) of liver disorders such as autosomal recessive polycystic kidney disease (ARPKD), nodular regenerating hyperplasia (NRH), and Alagille syndrome (AGS). The outcome for patients suffering from these disorders is severe; ARPKD, NRH and AGS each can potentially lead to end-stage renal or liver disease. Thirty to fifty percent of ARPKD patients die during the first months of life; other presentations range from primarily kidney involvement in the newborn period to complications of congenital hepatic fibrosis (CFH). As part of an ongoing clinical study, NHGRI researchers will perform mutation analysis of the causative gene in ARPKD to investigate genotype-phenotype correlations. Functional studies are also being carried out in AGS. Specifically, researchers have identified the *JAG1* gene as the cause of AGS, a congenital disorder characterized by a paucity of bile ducts. Currently, NHGRI investigators are using antibodies developed against *JAG* proteins to monitor liver development at the protein level. This provides hope for a model that will yield insights into the development and treatment of AGS. Rare liver diseases, such as NRH, are also a component of liver disease research within the NHGRI. NHGRI investigators have described two post-transplant cystinosis patients who died of liver disease, which was characterized as NRH. Cystinosis is a rare autosomal recessive lysosomal storage disease characterized by the intracellular accumulation of the amino acid cystine, which is responsible for widespread tissue destruction. NRH may represent a rare, late complication of cystinosis, for which the mechanism is, as yet, undefined.

Item

Mapping Human Genes – The Committee commends NHGRI for its leadership in developing technologies that will help accelerate the delivery of molecular medicine. The completion of the HapMap is a helpful tool in the identification of genes that determine susceptibility to diseases such as diabetes and heart disease. The Committee encourages NHGRI to continue its efforts to make these resources available to the research community. (p, 150)

Action taken or to be taken

NHGRI's mission to understand more fully the function of the human genome in health and disease is being accomplished through projects like the HapMap. The HapMap has allowed a closer look at the human genome and is identifying markers that will reduce the work and expense of future genomic research. On the genetic level, any two people are approximately 99.9% identical across the three billion base pairs that make up our genome. However, while 0.1% is a very small percentage, it accounts for three million letters of our genetic alphabet. Understanding this genetic variation will help explain why, for example, some people are more susceptible to certain disease than others. The HapMap was constructed to highlight the areas where variation occurs, and followed the tradition of the Human Genome project in releasing all data immediately into the public domain. Identifying genetic variation can pinpoint variants that contribute to a variety of health-related issues, such as protection against infectious diseases, longevity, and a

person's response to therapeutic drugs, toxic substances, and environmental factors. Understanding genetic variation can also change the way diseases are diagnosed and treated, and lead to disease prevention. Since the completion of the initial data collection phase of the HapMap, its use has uncovered genetic links to a number of diseases, including macular degeneration, type II diabetes, and prostate cancer. The HapMap will continue to catalyze future studies regarding mutations and disease. Specifically, analysis of samples from across the world will be genotyped in the coming year, which will enable researchers to assess the utility of the HapMap in different populations.

Item

Parkinson's Disease – The Committee encourages the National Human Genome Research Institute to work with NINDS and other Institutes conducting Parkinson's research to derive biological and therapeutic insights from recently discovered Parkinson's susceptibility genes and the completed Human Genome Project. The Committee encourages continued collaborations including additional intramural activities between NINDS, NIMH, NIA and NHGRI to enhance understanding of neurodegenerative diseases and develop therapeutic applications for gene discoveries, particularly for Parkinson's. (p. 150)

Action taken or to be taken

The NHGRI continues to work towards identifying the genetic contributions to common diseases such as Parkinson's disease, through projects such as the Genetic Association Information Network (GAIN) and the NIH-wide Genes and Environment Initiative (GEI).

The NHGRI also has ongoing intramural research on a link between Parkinson's disease and the *GBA* gene, which codes for the enzyme glucocerebrosidase. This lysosomal enzyme is responsible for breaking down a specific kind of fat called glucocerebroside, and is involved in Gaucher's disease. The NHGRI researchers previously discovered that several families carrying *GBA* mutations had an unusually high incidence of Parkinson disease. Evidence exists that alterations in *GBA* may contribute to the development of a relatively common neurodegenerative disease known as dementia with Lewy bodies, or DLB. Lewy bodies are abnormal aggregates of protein that develop inside nerve cells in both DLB and Parkinson's disease. This ongoing research program is a collaboration between NHGRI, NIA and NIMH.

Item

Spinal Muscular Atrophy [SMA] – The Committee is aware that SMA carrier testing is available to help persons of childbearing age make more informed reproductive decisions with regard to the risk of SMA in their offspring. The Committee strongly encourages NHGRI to develop a pilot program to assess the optimal practices for delivery of population-based screening for SMA carriers. (p. 150/151)

Action taken or to be taken

The NHGRI has been actively engaged with the Claire Altman Heine Foundation to discuss concerns about SMA carrier testing and to explore how specific institutes of the

NIH might be most appropriately engaged in bringing SMA carrier testing to the clinic. Through that dialogue, the parties have agreed upon a plan to move this effort forward. Specifically, the NHGRI agrees that increased awareness and/or utilization of carrier screening programs for genetic disorders such as SMA is desirable and achievable, and to that end has begun collaborations to identify challenges to, and solutions for, developing and implementing carrier screening programs. The overall goal of this cooperative effort is to formulate a plan to address research-related needs relevant to fostering improvements in carrier screening technology, enhancing education of professional and patient communities, and understanding the economic issues pertinent to implementing carrier screening for disorders such as SMA.

Recently, the NHGRI and NICHD Directors met, along with senior staff of their Institutes, to discuss the scientific needs and opportunities relevant to carrier screening programs. It was decided to hold a workshop in FY2007 to define with the community how NIH can most effectively stimulate both necessary technology development and policy-related conversations pertaining to the ethical and social issues of launching and implementing new carrier screening programs. Staff from each institute have been assigned to lead development of the workshop and begin outreach to stakeholders in this conversation, including other Institutes and Centers, sister agencies within HHS, the research community, and the public.

Item

Tuberous Sclerosis Complex – Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body. The Committee urges NHGRI to provide assistance and advice to the TSC research community on TSC gene and genome-wide sequencing projects. (p. 151)

Action taken or to be taken

Tuberous sclerosis results from genetic defects affecting the tumor suppressor proteins TSC 1 and TSC 2. TSC causes tumor growth in multiple organ systems and is associated with a wide variety of symptoms, including epilepsy, autism, developmental delays, and lung and skin abnormalities. In FY 2004, the NIH established a trans-NIH Tuberous Sclerosis Working Group to identify research portfolio gaps and develop new initiatives. The Working Group includes program staff representatives from NINDS, NCI, NIDDK, NHLBI, NIAMS, NIMH, NICHD, NIGMS, NHGRI and the Office of Rare Diseases, as well as representatives from the Tuberous Sclerosis Alliance. The Working Group met in April 2004, August 2005, and June 2006 to review the NIH TSC portfolio and discuss potential collaborations, and will continue to meet on a regular basis.

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National Institute of Biomedical Imaging and Bioengineering

House Significant Items

Item

Liver Tissue Engineering – The Committee encourages NIBIB to focus efforts on expanding the Tissue Engineering Program to examine how the development and function of engineered tissues and organs can improve treatment techniques for patients afflicted with liver disease. (p. 116)

Action taken or to be taken

Tissue engineering is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. Engineered tissues can also be used to study disease pathogenesis and drug development. The ability to repair or replace tissues or organs opens the door to the treatment of debilitating diseases and disorders of the liver.

NIBIB supports a broad portfolio of tissue engineering research to determine how cells interact with their environment to define tissue structure and function, as well as how the environment regulates and controls cells. The Institute also supports the development of novel biomaterials for scaffolds.

As part of NIBIB's planning process, staff met with leaders in the tissue engineering community to garner input into future research opportunities. As a result of this meeting, NIBIB is co-sponsoring, along with five other NIH Institutes, the National Institute of Standards and Technology, and the National Science Foundation, an initiative released in August 2006 to stimulate design or hypothesis-driven research to promote the development of new technologies, tool, methods, and devices that will further advances in tissue engineering.

NIBIB will continue to support ongoing research in applications for engineered tissues, including three-dimensional human tissue model systems to study questions related to developmental biology, normal physiology, and disease pathogenesis.

Item

Liver Imaging Techniques – Consistent with NIBIB's mission to improve all diagnostic imaging technologies, the Committee encourages NIBIB to continue to make liver imaging techniques a primary focus, speeding the development of new modalities that better capture the early stages of various liver diseases, including cancer, as well as offering the potential for less invasive combinations of diagnosis and treatment and the evaluation of livers from cadaver donors. The Committee encourages NIBIB to participate actively in trans-NIH initiatives that address these priorities. (p. 116)

Action taken or to be taken

For many years, radiologists have relied on structural information obtained with imaging techniques for assessing liver disease and monitoring treatments. Computerized

tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US), in combination with new diagnostic contrast agents, have greatly improved our ability to examine the liver. However, no reliable non-invasive methods exist for monitoring the progression of liver disease that is characterized by fibrosis. Current imaging methods cannot reliably distinguish hepatitis from benign processes, nor reliably detect cirrhosis development. NIBIB-supported investigators are developing and validating non-invasive MRI techniques to detect and monitor the progression of liver disease from early to end-stage (cirrhosis) in animal models, and to demonstrate the feasibility of using these methods in humans. These non-invasive approaches may provide safe alternatives to serial needle biopsies, which can pose significant risk of bleeding, infection or death.

Imaging technology advances have spurred a variety of new *minimally-invasive* procedures to localize disease and injury, obtain diagnostic tissue, administer treatment, and monitor responses to therapeutic interventions. In this respect, image-guided interventions are not only more efficient in terms of time and cost, but their less invasive nature may result in fewer complications and less damage to normal tissue. For example, shunt placements bypass liver blockages and relieve a serious symptom of cirrhosis and other liver diseases. Using X-rays, surgeons can generate images of the hollow needle used to penetrate the vessels, but cannot visualize the vessels themselves. To overcome this challenge, in 2006 NIBIB researchers reported the development of an integrated X-ray/MRI hybrid system, in which the X-ray and MRI systems are integrated. This modified system combines images with complimentary information, and allows surgeons to reliably enter target vessels.

NIBIB co-sponsored a federal interagency retreat in January 2006 to identify grand challenges in image-guided interventions (IGI) that could serve as goals to advance the field. In response to the expressed need for development of a broad range of IGI technologies, NIBIB and the National Cancer Institute are co-sponsoring an initiative aimed at developing new technologies that can replace current invasive treatment with minimally-invasive image-guided interventions. NIBIB was also active in developing an Interagency “Action Plan for Liver Disease Research,” which emphasized the need for developing novel molecular imaging approaches to detect and characterize liver disease in early stages, when it can be treated more successfully.

Senate Significant Items

Item

Artificial Pancreas – Maintaining blood glucose levels as close to normal values as possible is proven to reduce the risk of long-term complications in diabetes. However, tight glucose control is difficult to achieve, especially in young children. The NIBIB is encouraged to expedite research on “closing the loop” between glucose monitoring technologies and insulin delivery devices as a means to automate glucose control and improve disease management. (p. 151)

Action taken or to be taken

Effective management of diabetes requires regular measurement of blood glucose levels. Improvements in glucose sensing technology will enable improved care and regulation of blood glucose levels in diabetic individuals. NIBIB supports research on the development of novel glucose sensors. For example, researchers are developing minimally-invasive nanoparticle-based optical sensors to monitor glucose levels in tissues just underneath the skin. A long-term goal is to further develop this technology for continuous monitoring of glucose and to develop a closed-loop controlled insulin delivery system for improved blood glucose control in diabetics.

Further understanding of beta cell function and successful islet transplantation are important to the ultimate goal of a cure for type 1 diabetes. NIBIB-supported researchers are using nuclear magnetic resonance spectroscopy and microimaging to non-invasively assess function and viability of transplanted pancreatic islets. This technique will lead to greater understanding of beta cell function, factors influencing successful islet transplantation, and the further development of encapsulated pancreatic beta cells necessary for a bioartificial pancreas.

NIBIB, along with the Juvenile Diabetes Research Foundation International, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases, co-sponsored a workshop entitled “Imaging the Pancreatic Beta Cell in Health and Disease” held in April 2006. The purpose of the workshop was to explore progress in the field of imaging or otherwise visualizing the pancreatic islet cell mass to assess its functionality in health and disease. Information from this workshop will be used to develop future initiatives. NIBIB will continue to support technology-driven research to advance all areas of diabetes-related research and to translate these discoveries to improve the health of individuals with diabetes.

Item

Liver Imaging Techniques – Consistent with the NIBIB’s mission to improve all diagnostic imaging technologies, the Committee urges NIBIB to continue to make liver techniques a primary focus, speeding the development of new modalities that better capture the early stages of various liver diseases, including cancer, as well as offering the potential for less invasive combinations of diagnosis and treatment and the evaluation of livers from cadaver donors. The Committee urges NIBIB to participate actively in trans-NIH initiatives that address these priorities. (p. 151)

Action taken or to be taken

Please refer to pages 241 of this document for NIBIB’s response to this significant item regarding liver imaging techniques.

Item

Liver Tissue Engineering – The Committee urges NIBIB to focus efforts on expanding the Tissue Engineering Program to examine how the development and function of

engineered tissues and organs can improve treatment techniques for patients afflicted with liver disease. (p. 151)

Action taken or to be taken

Please refer to pages 241 of this document for NIBIB's response to this significant item regarding liver tissue engineering.

Item

PET and MicroPET – The Committee continues to encourage the Institute to provide increased support for molecular imaging technologies such as positron emission tomography [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 Institute to develop its research agenda in close collaboration with other disease-specific Institutes at NIH, so that new imaging technologies are closely tied to the research projects being undertaken by the various other Institutes of NIH. (p. 151/152)

Action taken or to be taken

It is understood by NIBIB that one of the most promising, and rapidly evolving areas of imaging used for diagnosis and evaluation of the efficacy of interventions is that of molecular imaging, which includes positron emission tomography (PET), functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and a range of optically-based technologies. Along with these are corresponding approaches devised for the study of small laboratory animals, such as microPET, microSPECT, microCT, and microMRI. NIBIB continues to give these efforts high priority by supporting grants and major symposia and conferences. For example, in FY 2006, NIBIB co-sponsored the fifth Inter-Institute Workshop on Optical Imaging from Bench to Bedside. In addition, components of the NIBIB intramural radiochemistry laboratory focus on the development of new molecular probes, and tools developed in this laboratory serve also to support research in other NIH Institutes. Likewise, NIBIB and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration have established a joint Laboratory for the Assessment of Medical Imaging Systems (LAMIS); an important aspect of this joint effort is to assess and optimize molecular and other medical imaging systems.

National Center for Research Resources

House Significant Items

Item

Institutional Development Awards (IDeA) —The Committee recommends \$215,938,000 for the IDeA program, which is the same as the budget request and \$4,048,000 below the fiscal year 2006 appropriation. The Committee recognizes the importance of the Centers of Biomedical Research Excellence (COBRE) and the IDeA Networks of Biomedical Research Excellence (INBRE) programs, and expects funding for COBRE to be at a level of at least \$130,000,000 and INBRE funding to be at least \$85,000,000. (p. 117/118)

Action taken or to be taken

The FY 2007 budget for the IDeA program is \$215,938,000. The INBRE program supports a comprehensive state-wide network of institutions, one INBRE award per IDeA state. In FY 2007, funding for the INBRE program is estimated to be \$73,000,000 to support existing commitments only. No new INBRE grants will be funded in FY 2007 because all current INBRE awards are on a 5-year cycle and will not re-compete for new funding until FY 2009 at the earliest. FY 2007 funding for the COBRE program will support existing COBRE commitments of \$108,000,000. The remaining funds will be used to support new and competing COBRE awards and/or supplements to existing IDeA awards.

Item

Research Centers at Minority Institutions (RCMI) —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. These programs help facilitate the preparation of a new generation of scientists at these institutions. The RCMI program continues to impact significantly on these problems. The Committee encourages NIH to strengthen participation from minority institutions and increase resources available in this area. The Committee also encourages NIH to work with minority institutions with a track record of producing minority scholars in science and technology. (p. 118)

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 research by developing the appropriate infrastructure at minority institutions with affiliated medical schools through the RCMI Clinical Research Infrastructure Initiative. The 18 institutions currently funded via this program have an outstanding track record of producing minority scholars in science, medicine, and technology. These institutions produced 36 percent of the minority Ph.D.'s in the biomedical and behavioral sciences,

and the seven medical schools included in this group produced 31 percent of the minority M.D.'s in the U.S. in FY 2003.

NCRR staff will continue to work with the RCMI institutions on the development of the RCMI Translational Research Network, a cooperative research network to facilitate clinical research in health disparity areas. This Network will consist 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.

Senate Significant Items

Item

Human Islet Cell Resource Centers —The Committee is encouraged that the Islet Cell Resource Centers [ICR] program has been renewed. The Committee supports the Centers' goals of providing islets for transplantation into diabetes patients and making human islets readily available for research. Further, the Committee is supportive of the Centers serving as regional islet isolation facilities with the ability to transport high-quality human islets to many transplant centers, thus expanding the availability of islet transplantation to a larger pool of diabetes patients across the Nation. (p. 153)

Action taken or to be taken

With co-funding from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and support from the Juvenile Diabetes Research Foundation (JDRF), NCRR administers a cooperative agreement that supports seven Islet Cell Resource Centers (ICRs) that optimize the isolation, characterization, preservation, and shipping of clinical grade human pancreatic islets for transplantation into patients with unmanageable hypoglycemic episodes caused by unstable Type 1 diabetes. The centers also provide pancreatic islets for basic research, which they ship throughout the country at no charge to the investigators. To ensure quality, outside auditors inspect and certify that each ICR is able to produce islets according to Good Manufacturing Practice specifications. A Steering Committee composed of ICR directors, outside experts, NIH staff, and JDRF staff provides oversight of this cooperative agreement.

The Administrative and Bioinformatics Coordinating Center (ABCC), located at the Beckman Research Center at City of Hope, Duarte, CA, maintains a data repository, supports information exchange, facilitates the execution of protocols, coordinates shipping, analyzes ICR performance, and assists in the management of funds for the acquisition of cadaver pancreata by the ICRs. To support its functions, the ABCC has developed and maintained an informatics system that enables it to interface with the NIDDK-sponsored Collaborative Islet Transplant Registry and the United Network for

Organ Sharing-sponsored clinical and donor registries. Thus, a single data entry procedure results in inclusion into all three databases. The ABCC biostatisticians correlate information from the three data sources to develop formulae that predict the likelihood that transplantation of specific batches of islets yield clinical success. The ABCC has also integrated the data from the Clinical Islet Transplantation Consortium (CIT), a program jointly sponsored by Medicare, NIDDK and NIAID. The ABCC has coordinated efforts with the CIT-sponsored demonstration project to enable research partners to share data with the ICR network in order to achieve greater synergy with this NIH-sponsored program.

Item

Research Centers at Minority Institutions (RCMI)—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. These programs help facilitate the preparation of a new generation of scientists at these institutions. The Research Centers in Minority Institutions [RCMI] Program continues to impact significantly on these problems. The Committee encourages NIH to strengthen participation from minority institutions and increase resources available in this area. The Committee also encourages NIH to work with minority institutions with a track record of producing minority scholars in science and technology. (p. 153)

Action taken or to be taken

Please refer to page 245 of this document for NCRRC's response to this significant item on research centers at minority institutions (RCMI).

Item

Research Resource Center—The Committee continues to urge NCRRC to support research resource centers for the development and refinement of positron emission tomography [PET] as a unique imaging technology to diagnose end stage diseases of the brain, including Alzheimer's disease. (p. 153)

Action taken or to be taken

In FY 2006, NCRRC provided funds to acquire PET scanners at the Massachusetts General Hospital and at the Beth Israel Deaconess Medical Center in Boston. These PET scanners are being used in research environments which pursue new applications of PET technology in preclinical studies. The PET scanners will be used for high resolution brain imaging in humans and primates and for assessing the efficacy of experimental drugs in animal models of human cancer.

Item

Human Tissue Supply—The Committee remains interested in matching the increased needs of NIH grantees, intramural, and university-based researchers who rely upon human tissues and organs to study human diseases and search for cures, including for those researchers dedicated to the study and cure of rare diseases. The Committee is aware that one of the leaders in this competitive field, the National Disease Research

Interchange [NDRI], is positioned to obtain this valuable and effective alternative research resource. More than 500 peer-reviewed research advances made by NDRI-dependent researchers have been published in recent years, contributing to the research community's fund of knowledge. The Committee encourages the Director to increase support NDRI receives from NCCR, and to broaden the scope of the multi-Institute initiative by strongly urging the Institute Directors of NCI, NHGRI, NHLBI, NICHD, NIMH, and NINDS to identify and expand support for NDRI. (p. 163)

Action taken or to be taken

Please refer to page 281 of this document for NIH/OD response to this item on human tissue supply.

Item

National Primate Research Centers—The Committee recognizes the need to raise awareness of the availability of the National Primate Research Centers' [NPRCs] nonhuman primate resources amongst Institute and Center Directors and within the NIH-funded research community. The NPRCs provide access to resources such as: nonhuman primates for NIH-funded experiments; nonhuman cells, fluids, tissues, organs, proteins, cell lines, and nucleic acid samples; immunological reagents for nonhuman primate research; comprehensive genetic and genomic information for nonhuman primates; and venues for the assessment of nonhuman primate behavior and cognition. These unique resources and expertise contribute to the overall effectiveness of the Federal investment in biomedical research. (p. 165)

Action taken or to be taken:

The NCCR continues to conduct outreach activities to inform the NIH Institute/Center Directors and staff and the NIH-funded research community about the resources available through the National Primate Research Centers (NPRCs). NCCR's Web site contains extensive information and materials that describe the activities of the NPRCs, including specific information for NIH grantees on how to access NPRC resources. NCCR staff also present this information at scientific meetings, including at the 24th Annual Symposium on Non Human Primate Models of AIDS, the International Neuroscience meeting, and the Sixth Comparative Medicine Resource Directors' meeting. These meetings were held in October and November of 2006.

In April 2006, the NCCR organized and convened a workshop entitled, "Genetic Tools for Optimizing the Use of Rhesus Macaques for Translational Research." Workshop participants included representatives of the all eight NPRCs, many other NIH-funded scientists who utilize the rhesus for translational studies, and Program representatives from all of the NIH Institutes and Centers that fund significant activities utilizing the rhesus as an animal model of human disease. The workshop provided specific recommendations that are being implemented by the NCCR and a follow-up workshop is planned for the spring of 2007.

The NPRCs support research on infectious diseases, such as AIDS and malaria, and emerging threats, such as avian flu. NCCR staff collaborate closely with staff from other

NIH Institutes and Centers to inform them of NPRC resources that could enhance the infectious disease research activities that their IC supports. For example, NCRR staff have met with NIAID staff and discussed the potential role of the NPRCs in research involving radiation exposures and antidotes.

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National Center for Complementary and Alternative Medicine

House Significant Items

Item

Ameliorating Liver Disease -The Committee is pleased with NCCAM's efforts to conduct clinical trials in collaboration with NIDDK regarding the use of milk thistle as a possible treatment in slowing the progression of nonalcoholic steatohepatitis and to reduce the side effects of hepatitis C interferon treatments. The Committee looks forward to the development and dissemination of the research results associated with the use of milk thistle as a treatment to ameliorate liver disease. (p. 118).

Action taken or to be taken

Milk thistle (silymarin) is a botanical frequently used to treat liver diseases. However, its safety and efficacy for this purpose remain unproven. The National Center for Complementary and Alternative Medicine (NCCAM) has a research initiative to evaluate milk thistle for liver disease.

In FY 2006, NCCAM, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, issued awards to five research institutions -- the University of North Carolina, Temple University, the University of Pennsylvania, the University of Pittsburgh, and Harvard University's Beth Israel Deaconess Medical Center -- to investigate silymarin (milk thistle) for nonalcoholic steatohepatitis (NASH), which is frequently caused by obesity and chronic hepatitis C. The aims of this large, multi-site study are to determine the pharmacokinetics (absorption and metabolism) and appropriate dose of milk thistle in humans, including those who are diabetic or obese, and the safety and efficacy of milk thistle in patients with NASH and chronic hepatitis C. The outcomes of this investigation will determine whether larger Phase III studies of milk thistle are warranted in people with chronic liver disease. In addition, in FY 2006, NCCAM funded a study at the Medical University of South Carolina to investigate how silymarin may interact with drugs used by patients with chronic liver disease.

Item

Parkinson's Disease (PD)-The Committee encourages NCCAM to continue exploration of exercise in its many forms including aerobic, anaerobic and exercises such as Tai Chi Chuan in the treatment of PD. Recent studies show exercise may increase neuroprotective chemicals in the brain and decrease falls in the elderly. The Committee also encourages continued research into significant non-motor co-morbidities in Parkinson's including magnetic stimulation for depression, and the phytomedicine Valerian for sleep dysfunction. Finally, NCCAM is encouraged to work with (*sic*) the Office of Dietary Supplements in investigating supplements which may be neuroprotective, such as berries, alpha lipoic acid, N-acetyl-L-cysteine, acetyl-L-carnitine, vitamin E, ginkgo biloba, vitamin D, vitamin B12, phosphatidylcholine, and glyconutrients. In light of the many ways cell death can occur, NCCAM is encouraged to study the concurrent implementation of multiple exercise and nutrition-based strategies. (p. 118).

Action taken or to be taken

NCCAM continues to support research on the safety and efficacy of complementary and alternative medicine (CAM) therapies for Parkinson's disease (PD). Through FY 2007, as part of its Centers of Excellence for Research on CAM program, NCCAM will continue to support the Center for CAM in Neurodegenerative Diseases at the Emory University School of Medicine. The Emory Center is investigating CAM treatments for PD, including repetitive transcranial magnetic stimulation to relieve depression and the mind-body practices of tai chi and qi gong to improve motor disturbances. In addition, in FY 2006, NCCAM funded a study to evaluate whether near infrared light can improve mitochondrial function (energy metabolism) and stimulate antioxidant production in cell and animal models of PD. NCCAM will use the results of these studies to build on its future PD research agenda. In FY 2006, NCCAM supported several other projects on PD, including an animal model study at the Medical University of South Carolina to determine whether blueberry supplementation can improve the survival of transplanted neural tissue. NCCAM also funded an award to the Pennsylvania State University, Hershey Medical Center, to evaluate the potential of *Mucuna pruriens*, a compound used in Indian Ayurvedic medicine, to prevent or ameliorate the effects of the movement-related side effects associated with long-term drug treatment of PD.

In FY 2006, under the NIH Botanical Research Center Program, NCCAM and the NIH Office of Dietary Supplements (ODS) funded a center to investigate plant polyphenols for age related diseases. NCCAM and ODS also provided funds to the Agency for Healthcare Research and Quality (AHRQ) to conduct an evidence-based review⁵ of the role of B vitamins and berries in age-related neurodegenerative disorders. This analysis indicated that only limited evidence supports an association between either B vitamins or berries and age-related neurocognitive function. In FY 2007, NCCAM and ODS are reviewing the AHRQ report and the implications for each of their research agendas.

⁵ Agency for Healthcare Research and Quality, Department of Health and Human Services. "B Vitamins and Berries and Age-Related Neurodegenerative Disorders." *Evidence Report/Technology Assessment*. Number 134. Accessed at <http://www.ahrq.gov/downloads/pub/evidence/pdf/berry/berry.pdf> [April 2006]

Senate Significant Items

Item

Ameliorating Liver Disease -The Committee is pleased with NCCAM's efforts to conduct clinical trials in collaboration with NIDDK regarding the use of milk thistle as a possible treatment in slowing the progression of nonalcoholic steatohepatitis and to reduce the side effects of hepatitis C interferon treatments. The Committee looks forward to the development and dissemination of the research results associated with the use of milk thistle as a treatment to ameliorate liver disease (p. 154).

Action taken or to be taken

Please refer to page 251 of this document for NCCAM's response to this item on ameliorating liver disease.

Item

Parkinson's Disease - The Committee encourages NCCAM to continue exploration of exercise in its many forms including aerobic, anaerobic and Chinese exercises such as Tai Chi Chuan in the treatment of Parkinson's. Recent studies show exercise may increase neuroprotective chemicals in the brain and decrease falls in the elderly. The Committee also encourages continued research into significant non-motor co-morbidities in Parkinson's including magnetic stimulation for depression, and the phytochemistry Valerian for sleep dysfunction. Finally, NCCAM is encouraged to work with (*sic*) the Office of Dietary Supplements in investigating supplements which may be neuroprotective, such as berries, alpha lipoic acid, N-acetyl-L-cysteine, acetyl-L-carnitine, vitamin E, ginkgo biloba, vitamin D, vitamin B12, phosphatidylcholine, and glyconutrients. In light of the many ways cell death can occur, NCCAM is encouraged to study the concurrent implementation of multiple exercise and nutrition-based strategies (p. 154).

Action taken or to be taken

Please refer to page 251 of this document for NCCAM's response to this item on Parkinson's disease.

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National Center on Minority Health and Health Disparities

House Significant Items

Item

Cancer in Minority Communities – The Committee commends NCMHD for its leadership in addressing the disproportionate impact of cancer in minority communities. The Committee encourages NCMHD to consider collaborating with NCRR and NCI to support the establishment of a cancer center at a historically minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 119)

Action taken or to be taken

The NCMHD will continue to support the Centers of Excellence program (Project EXPORT) for health disparities research. The first set of institutions that were funded during the first five years of the program, have demonstrated the potential of the program to advance the contributions of the NCMHD towards eliminating health disparities through their partnerships, research, training and community outreach activities. In fiscal year 2007, the NCMHD funded a new set of institutions to conduct research on a number of diseases and health conditions that disproportionately impact racial and ethnic minorities and other underserved populations. It is anticipated that these institutions will continue to study the complex nature of health disparities and further the understanding of the causes and solutions for health disparities. Being able to engage in cutting-edge research depends on having the infrastructure. In the past, the NCMHD/NCRR partnership led to the creation of the Tuskegee University National Center for Bioethics in Research and Health Care aimed at addressing ethical and human values issues in science, technology and health as they impact racial and ethnic minorities.

Item

Extramural Facility Construction – The Committee commends NCMHD for its successful “Project EXPORT” initiative and encourages continued support for this important program. Finally, the Committee encourages the director of NCMHD to coordinate with the NIH Director and the National Center for Research Resources to support extramural facility construction and the development of other research and research library infrastructure at minority health professions schools. (p. 119)

Action taken or to be taken

The NCMHD will continue to support the Centers of Excellence program (Project EXPORT) for health disparities research. The first set of institutions that were funded during the first five-years of the program have demonstrated the potential of the program to advance the contributions of the NCMHD towards eliminating health disparities through their partnerships, research, training, and community outreach activities. In fiscal year 2007, the NCMHD funded a new set of institutions to conduct research on a

number of diseases and health conditions that disproportionately impact racial and ethnic minorities and medically underserved populations. It is anticipated that these institutions will continue to study the complex nature of health disparities and further the understanding of the causes and solutions for health disparities. Being able to engage in cutting-edge research depends on having the infrastructure. The NCMHD, working with the NIH Director and the NCRP, will continue to support other research infrastructure development at minority health professions schools, no funds are available for extramural construction. The NCMHD/NCRP partnership led to the creation of the Tuskegee University National Center for Bioethics in Research and Health Care aimed at addressing ethical and human values issues in science, technology, and health as they impact racial and ethnic minorities.

Item

Health Disparities Among Hispanic-Americans – The Committee is aware of promising research about health disparities among Hispanic-Americans that is being conducted, and is particularly impressed that this is the first study of its scope that has been implemented in a Hispanic population in the United States. The Committee therefore encourages NCMHD to continue to conduct similar research, in close coordination with Hispanic researchers and faculty at institutes of higher education that have experience in regional factors affecting such health disparities, with the goal of identifying the best proposals and the most promising avenues for national, regional and disease-specific research in order to continue to make progress in addressing health disparities among Hispanic-Americans. (p. 119/120)

Action taken or to be taken

The NCMHD will continue its collaborations with Hispanic-American researchers, Hispanic-Serving Institutions, Hispanic Health Professions Schools, and Hispanic community-based organizations and professional associations to continue making progress in addressing health disparities among Hispanic-Americans. NCMHD funding opportunities will continue to be made available to the Hispanic-American population. The NCMHD has been able to address health disparities in the Hispanic community through its own programs --Loan Repayment Program, Centers of Excellence, Community-Based Participatory Research, Research Infrastructure in Minority Institutions, and Minority Health and Health Disparities International Research Training programs. Each of these programs involves the participation of Hispanic researchers, students, Hispanic-serving institutions, or research on Hispanic American health. In addition, NCMHD partners with other NIH Institutes and Centers, and other federal agencies such as the Department of Health and Human Services' Office of Minority Health (OMH) to expand its capacity to address health disparities in Hispanic Americans. Partnerships with others including the Hispanic Association of Colleges and Universities, the National Hispanic Medical Association, the National Council of La Raza, and the National Alliance for Hispanic Health have all aided the reach of the NCMHD to the Hispanic American community.

The NCMHD also funds a longitudinal study on Hispanics with the National Heart Lung and Blood Institute (NHLBI) that is expected to contribute to increased understanding of

health disparities in this population. The overall objectives of this research are to identify the prevalence of and risk factors (protective or harmful) for diseases, disorders, and conditions in Hispanic populations, and to determine the role of acculturation and disparities in their prevalence and development. This study is intended to be broad-based and will address a wide variety of conditions, including heart disease, stroke, asthma, chronic obstructive lung disease, sleep disorders, dental carries and disease, hearing impairment and tinnitus, diabetes, kidney and liver disease, and cognitive impairment.

Item

Lung Disease – The Committee is concerned with the disproportionate impact of lung diseases on minority populations. The Committee encourages the NCMHD to partner with other NIH institutes, including NHLBI, to develop an epidemiological approach to determine the disproportionate impact of airway disease on minority populations. (p. 120)

Action taken or to be taken

The NCMHD will continue its partnerships with the other NIH Institutes and Centers, including the NHLBI, to study lung diseases in minority populations. It has already engaged in an epidemiological study with NHLBI to identify the prevalence of and risk factors for diseases, disorders, and conditions including lung diseases in Hispanic populations. The NCMHD' Centers of Excellence program will also continue to place research emphasis on lung diseases in minority populations as it did with the most recent release of Requests for Applications to support its efforts to reduce and eliminate health disparities.

Item

Research Endowment – The Committee commends NCMHD for its leadership in addressing the longstanding problem of health disparities in minority and medically underserved populations. For fiscal year 2007, the Committee continues to encourage NCMHD to implement its successful Research Endowment program as an ongoing initiative. Moreover, the Committee encourages NCMHD to implement the program in a manner that is consistent with the authorizing legislation. (p. 120)

Action taken or to be taken

NCMHD' Research Endowment program plays a unique role in building our nation's research and training capacity to address health disparities. As intended by the authorizing legislation, the research endowment grants provide multi-year awards to support activities such as research, training, infrastructure and endowed faculty chairs. The seventeen grants awarded since the program's inception have enabled these institutions to leverage resources to secure additional funding for health disparities activities. The NCMHD will continue to take measures to ensure that the program is implemented consistent with the authorizing legislation including linkage to the NCMHD Centers of Excellence program.

Item

Health Disparities – The Committee expects the OMH and the National Center for Minority Health and Health Disparities at NIH to play a joint role in coordinating and monitoring the implementation of the Department’s elimination of health disparities initiatives and strategic plans. The Committee expects the Secretary to report to Congress on the progress and implementation of the strategic plans in general and as related to the IOM’s assessment and recommendations regarding the strategic plan during next year's appropriations hearings, and to include a progress update in the Department’s Budget Justification. (p. 217)

Action taken or to be taken

The Office of Minority Health (OMH), within the Office of the Secretary, and the National Center on Minority Health (NCMHD) work together in partnership with the other agencies of the Department of Health and Human Services (DHHS) through the DHHS Council on Health Disparities, which is chaired by the Assistant Secretary for Health and co-chaired by the Director, OMH. The DHHS Council, an integral part of the Department’s Closing the Health Gap Initiative, coordinates and monitors the implementation of the Department’s strategic plans and initiatives to eliminate health disparities. The 2006 DHHS National Leadership Summit on Eliminating Racial and Ethnic Disparities in Health was a major outcome of DHHS Council collaborations. The Summit brought together leaders from all levels of government, academia, public health, mental health, minority-serving institutions, and minority communities to advance key issues and to develop opportunities for improving minority health and closing the health gap. Under the leadership and coordination of the DHHS Council and based upon direct input from stakeholders across the country, the Department’s strategic plans and initiatives continue to evolve, translating knowledge gained at the Summit and from the Institute of Medicine into actions designed to improve our approach to eliminating health disparities. The Department would be pleased to provide a progress update at the next appropriations hearing.

Senate Significant Items

Item

Cancer in Minority Communities – The Committee commends NCMHD for its leadership in addressing the disproportionate impact of cancer in minority communities. The Committee encourages NCMHD to consider collaborating with the National Center for Research Resources and the National Cancer Institute in supporting the establishment of a cancer center at a historically minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 154)

Action taken or to be taken

Please refer to page 255 (Cancer in Minority Communities) of this document for the NCMHD response to this significant item regarding cancer in minorities.

Item

Genomic Analysis of Disease – The Committee is encouraged by the opportunities that exist for NCMHD. The Center is encouraged to strengthen its focus on efforts to unravel the genomic analysis of diseases that disproportionately affect minorities; applying advances stemming from unraveling the physiology and genetics of diabetes; furthering implementation of recommendations stemming from the IOM report Examining the Health Disparities Research Plan of the National Institutes of Health: Unfinished Business; developing innovative strategies for improving the health status and health outcomes of minorities; furthering the understanding of the dietary link in disease prevention and control; strengthening and expanding the involvement and participation of minority organizations including minority community-based organizations in research, outreach, awareness and prevention activities. (p. 154)

Action taken or to be taken

The NCMHD will continue to enhance its existing partnerships and identify opportunities to develop innovative initiatives and foster new partnerships to examine the genomics of diseases that affect the populations it serves. Collaborations with other NIH Institutes and Centers, such as NHGRI, and other external partners in the public and private sector will be crucial to the Center's effort in this area.

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 NCMHD to explore collaboration with NIDDK to support research activities related to glomerular injury and requests a status report on progress made in this area during the fiscal year 2008 appropriations hearings. (p. 155)

Action taken or to be taken

Glomerular disease will remain an area of research emphasis for the NCMHD. In addition to the research that its Centers of Excellence will undertake in this area, the NCMHD will explore collaborations with NIDDK to advance its research activities on glomerular injury.

Item

Health Professions – To help close the gaps in research training and clinical applications with respect to racial and ethnic health disparities, the Committee encourages the NCMHD to work with the HRSA via pre and post doctoral training of health professions in these areas. Also, important in this area is capacity and infrastructure building for strengthening support in the areas of faculty and student research and training in an effort to build transitional bridges between high schools, junior colleges and 4-year institutions. Steps also need to be taken to intensify participatory community research that addresses priority areas in which wide gaps in health status exist as delineated in Healthy People 2010, and other national epidemiological and surveillance data sets. (p. 155)

Action taken or to be taken

The NCMHD supports a number of programs and partnerships that address training in the health professions, research capacity, as well as community-based participatory research. Efforts will be made to continue support of these programs and explore opportunities to enhance these areas through partnerships with the Health Resources and Services Administration (HRSA), NIH Institutes and Centers, and other federal agencies. Some of the programs supported include:

Community-Based Participatory Research Program: The goal of this program is to promote research collaboration between academic researchers and their community partners, and to support community intervention research studies using community-based participatory research (CBPR) principles and methods to reduce and eliminate health disparities in major diseases affecting racial & ethnic minority populations in the U.S.

Research Infrastructure in Minority Institutions (RIMI) Program: The purpose of the RIMI Program is to establish, strengthen and/or improve the scientific infrastructure and environment of predominantly minority-serving academic institutions through grant support to develop and/or expand existing capacities and programs for institutional and individual faculty initiated basic, biomedical, clinical and/or behavioral research and research training programs that contribute to building a cadre of research scientists in the elimination of health disparities.

Loan Repayment Program: The goal 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.

Research Endowment: The mission of the Research Endowment is to build research and training capacity at institutions that have been designated Programs of Excellence in Health Professions Education for Underrepresented Minority Individuals by HRSA in order to facilitate minority health disparities research and other health disparities research.

Bridges To The Future Programs: These programs (Bridges to the Baccalaureate Degree and Bridges to the Doctoral Degree) supports institutions to assist students who are transitioning at a critical stage in the development of their careers as scientists. The NCMHD co-funds the programs with NIGMS.

DHHS-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 with the OMH, NCMHD, and the Hispanic Association of Colleges and Universities.

Item

Liver Disease – The Committee notes that many liver diseases, such as hepatitis C, hepatitis B and nonalcoholic steatohepatitis, are more common in the African-American, Hispanic, Asian Pacific Islander, and Native American populations than in European-Americans. In addition, access to and acceptance of care is particularly problematic in these populations. The Committee therefore continues to urge the Center of Excellence program to initiate and participate with NIDDK, NIDA, and NCI in research focused on addressing and reducing these disparities. (p. 155)

Action taken or to be taken

The NCMHD will continue to fund research related to liver disease through its Centers of Excellence program and collaborations with other NIH Institutes and Centers such as NIDDK, NIAAA, NIDA, and NCI. Most recently, in partnership with NCI, the NCMHD has supported a liver cancer control intervention for Asian-Americans. Research on liver diseases in racial and ethnic minority and other underserved populations will continue to be supported.

Item

Minority Health Disparities – The Committee commends the National Center on Minority Health and Health Disparities for its leadership in addressing the longstanding problem of health status disparities in minority and medically underserved populations. For fiscal year 2007, the Committee continues to encourage NCMHD to implement its successful Research Endowment program as an ongoing initiative. Moreover, the Committee encourages NCMHD to implement the program in a manner that is consistent with the authorizing legislation. The Committee believes that implementation of recommendations stemming from the IOM Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care study offer significant opportunities for improving health across communities of color. NCMHD is encouraged to work with minority organizations and minority community-based efforts to disseminate research-based health information to further engage minority national organizations and minority community-based organizations in implementing recommendations of the Institute of Medicine study. (p. 155)

Action taken or to be taken

NCMHD's Research Endowment program plays a unique role in building our nation's research and training capacity to address health disparities. As intended by the authorizing legislation, the research endowment grants provide multi-year awards to support activities such as research, training, infrastructure and endowed faculty chairs. The NCMHD will continue to support this program. It will also continue support for its Community-Based Participatory Research program, which has a planning, research, and information dissemination component to it. The NCMHD will continue to partner with community-based organizations and national organizations. It will also develop a public health communication initiative and a faith-based health initiative to advance its efforts in translating and disseminating scientific information to health disparity populations.

Item

Project EXPORT – The Committee commends NCMHD for its successful 'Project EXPORT' initiative and urges continued support for this important program. The Committee encourages the director of NCMHD to coordinate with the NIH Director and the National Center for Research Resources in support of extramural facility construction and the development of other research and research library infrastructure at minority health professions schools. (p. 155)

Action taken or to be taken

The NCMHD will continue to support the Centers of Excellence program (Project EXPORT) for health disparities research. The first set of institutions that were funded during the first five years of the program, have demonstrated the potential of the program to advance the contributions of the NCMHD towards eliminating health disparities through their partnerships, research, training and community outreach activities. In fiscal year 2007, the NCMHD funded a new set of institutions to conduct research on a number of diseases and health conditions that disproportionately impact racial and ethnic minorities and other underserved populations. It is anticipated that these institutions will continue to study the complex nature of health disparities and further the understanding of the causes and solutions for health disparities. Being able to engage in cutting-edge research depends on having the infrastructure. In the past, the NCMHD/NCRR partnership led to the creation of the Tuskegee University National Center for Bioethics in Research and Health Care aimed at addressing ethical and human values issues in science, technology and health as they impact racial and ethnic minorities. The Center aims to address the ethical and human values issues in science, technology, and health as they impact racial and ethnic minorities.

Item

Health Disparities – The Committee expects the OMH and the National Center for Minority Health and Health Disparities at NIH to play a joint role in coordinating and monitoring the implementation of the Department's elimination of health disparities initiatives and strategic plans. The Committee expects the Secretary to report to Congress on the progress and implementation of the strategic plans in general and as related to the IOM's assessment and recommendations regarding the strategic plan during next year's appropriations hearings, and to include a progress update in the Department's Budget Justification. (p. 217)

Action taken or to be taken

Please refer page 258 for NCMHD response to this item on Health Disparities.

John E. Fogarty International Center

House Significant Items

Item

American Russian Cancer Alliance (ARCA) -The Committee again recognizes the members of ARCA in their continued pursuit of novel cancer research activities that capitalize on the particular strengths of the respective participating institutions, and notes the achievements in the ARCA-sponsored projects in molecular imaging and radioisotope-targeted cancer therapy and diagnosis. As the principal NIH institute charged with overseeing and supporting international biomedical scientific activities and initiatives, FIC is well positioned to provide grant support for bi-national pilot studies, and the Committee looks to Fogarty to assist the Alliance in identifying and, when appropriate, in applying for support of pilot studies in cancer prevention, treatment, or diagnosis research. (p. 120)

Action taken or to be taken

FIC supports a number of programs relevant to the interests of the American Russian Cancer Alliance (ARCA). It welcomes ARCA scientists to apply for support through the Global Health Research Initiative Program for New Foreign Investigators (GRIP), the Fogarty International Research Collaboration Award (FIRCA), the International Tobacco and Health Research and Capacity Building Program, and others.

GRIP promotes productive re-entry of NIH-trained foreign investigators into their home countries as part of a broader program to enhance the scientific research infrastructure in developing countries, to stimulate research on a wide variety of high priority health-related issues in these countries, and to advance NIH efforts to address health issues of global import. The specific goal of this initiative is to provide funding opportunities upon return home for the increasing pool of foreign biomedical & behavioral scientists, clinical investigators, nurses, and other health professionals with state-of-the-art knowledge of research methods to advance critical issues in global health when they return home. Russian scientists who have trained in the U.S. through FIC programs or in the NIH intramural community are eligible.

FIRCAs foster international research partnerships between NIH-supported U.S. scientists and their collaborators in low- and middle-income countries, including Russia. It aims to benefit the research interests of both the U.S. and foreign collaborators while increasing research capacity at the foreign site.

Of particular interest to ARCA may be FIC's Tobacco Program. This new program supports trans-disciplinary research and capacity building projects that address the burden of tobacco consumption in low- and/or middle-income nations by pursuing observational, intervention and policy research of local importance, and, by building capacity in these regions in epidemiological and behavioral research, prevention, treatment, communications, health services and policy research. The program is designed to promote international cooperation between investigators in the U.S. and other high-

income nation(s) pursuing research programs on tobacco control, and scientists and institutions in low- and/or middle-income nation(s), where tobacco consumption is a current or anticipated public health urgency. The Tobacco Program addresses the largest preventable cause of cancer in the world.

Item

Chronic Obstructive Pulmonary Disease (COPD)-The Committee encourages FIC to expand its COPD research and training activities. (p. 121)

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. The FIC and eight partners, including the National Cancer Institute and the National Institute on Drug Abuse, made 14 awards to institutions working in 20 developing countries to support research and training on the impact of smoking-associated adverse health consequences. These awards will enhance 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. Among the studies supported are those that focus on the use of the Internet for education related to smoking in rural Dominican Republic, economic analysis and smoking policies in China, smoking cessation in Syria, the use of water pipes in Egypt, and adolescent smoking prevention and cessation in South Africa. It should be noted that waterpipes are becoming more popular in the U.S. as well. The knowledge gained and interventions developed abroad through this program will benefit the United States since risk factors are similar in communities at home and abroad, and since effective interventions developed overseas may have particular effectiveness in U.S. groups. The FIC is pleased with progress under this program and publications are beginning to appear in the scientific literature based on support from this program. For example, in an article in the journal *Lancet*, authored by Jha and Peto, two FIC Principal Investigators, they were able to show a strong link between smoking and tuberculosis, indicating that TB was not only more common than expected in smokers, but also much more lethal. A recent publication in the *American Journal of Public Health* (June 2005, vol. 95, no. 6) indicates that this program is the most significant international tobacco research program in the world. FIC is planning to re-compete this program in FY 2007 with an announcement for this re-competition having been issued in FY 2006.

In addition to the tobacco program, 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 also the National Institute for Occupational Health and Safety (NIOSH) within the Centers for Disease Control and Prevention. Examples include efforts to reduce environmental and occupational health risks associated with mining and mineral processing in sub-Saharan Africa, in countries such as Zambia, Zimbabwe, and South Africa, as well as prevention of silicosis (a serious

lung disease caused by occupational exposure to silica) in Vietnam, and reduction of smoking and exposure to environmental tobacco smoke in China. For the first time, global programs are making in-roads with more coordinated efforts with the goal of educating people on the dangers of tobacco, thus reducing initial uptake as well as overall exposure, and thereby ultimately reducing illness and disease associated with tobacco use.

Item

Tuberculosis Training – The Committee is pleased with FIC's efforts to supplement grants in the AIDS International Training and Research Program (AITRP) and International Training and Research Program in Emerging Infectious Diseases (ERID), which train tuberculosis experts in the developing world. Given the magnitude of global TB, the Committee encourages FIC to develop a specific free-standing TB training program. (p. 121).

Action taken or to be taken

Given the impact of tuberculosis (TB) on the global health agenda, FIC has integrated TB research and training efforts across the spectrum of extramural programs, allowing leveraging of resources and multi-disciplinary approaches to tackle this urgent problem. This approach to leverage and utilize existing programs is considered a more effective way to address this problem than by establishing a separate free standing tuberculosis program. TB continues to be an important focus of several FIC extramural programs, including: the Global Infectious Disease (GID) Research Training program; the International Clinical, Operational, and Health Services Research and Training Award for AIDS and TB program (ICOHRTA AIDS/TB); the AIDS International Training and Research Program (AITRP); and the International Biodiversity Cooperative Groups. By building on infrastructure in place for a range of infectious diseases, the GID program allows TB researchers in low- and middle-income nations to leverage resources of a range of partners, including the National Institute of Allergy and Infectious Diseases (NIAID), the Centers for Disease Control and Prevention (CDC), and the Aeras Global TB Vaccine Foundation, supported by the Bill and Melinda Gates Foundation involving TB vaccine research in South Africa. By linking clinical, operational and health services research training on AIDS with that of TB, the ICOHRTA AIDS/TB program allows FIC and its partner agencies, including the National Institute on Drug Abuse (NIDA), and also CDC and USAID, to bolster efforts in these linked epidemics in the developing world. Training and research on TB has been an important part of AITRP since its inception eighteen years ago.

In FY 2006, FIC convened a TB Network Meeting across all of its major TB-related programs in conjunction with a meeting of the National Tuberculosis Curriculum Consortium, supported by the National Heart Lung and Blood Institute. The meeting was in response to TB XDR (extreme drug resistance) which now has a global perspective and attention, and served to enhance and emphasize TB research and training at FIC.

Senate Significant Items

Item

Chronic Obstructive Pulmonary Disease – The Committee notes that Chronic Obstructive Pulmonary Disease [COPD] is the fourth leading cause of death worldwide, and encourages the Fogarty International Center to expand its COPD research and training activities. (p. 156)

Action taken or to be taken

Please refer to pages 264 of this document for FIC’s response to this significant item regarding Chronic Obstructive Pulmonary Disease.

Item

Fragile X.--International collaboration among scientists is an essential element in Fragile X research. The Committee encourages the Fogarty International Center to consider Fragile X syndrome through all appropriate programs, such as the Fogarty International Research Collaboration Award and the FIC Brain Disorders in the Developing World Program. The Committee also encourages the Fogarty International Center to establish public/private partnerships that will increase the number of international fragile X research projects and collaborations. (p. 156)

Action taken or to be taken

The Fogarty International Center was invited by Ms. Karen Fay, the Director of the Conquer Fragile X Foundation (CFXF: <http://www.sfxf.org/index.html>) to speak to their scientific advisory board and grantees during the annual Fragile X meeting. This presentation entitled “Funding Opportunities for International Research in Fragile X Syndrome” highlighted a variety of FIC Programs in which Fragile X Syndrome could be addressed including Brain Disorders, Fogarty International Research Collaboration Award (FIRCA), Stigma, International Clinical, Operational, and Health Services Research and Training Award (ICOHRTA-I), Genetics, and International Research Scientist Development Award (IRSDA) programs. Participants were introduced to the FIC mission and website. Discussions were held on how the CFXF’s international funding activities might synergize with NIH opportunities in this field. FIC staff had further follow-up discussions with a number of the Foundation’s grantees regarding FIC funding opportunities

Item

Tuberculosis Training – The Committee is pleased with the Fogarty International Center's efforts to supplement grants in AIDS International Training and Research Program [AITRP] or International Training and Research Program in Emerging Infectious Diseases [ERID], which trains tuberculosis experts in the developing world. Given the magnitude of global tuberculosis, the Committee encourages FIC to develop a specific free-standing TB training program. (p. 156)

Action taken or to be taken

Please refer to pages 265 of this document for FIC's response to this significant item regarding Tuberculosis Training.

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National Library Of Medicine

House Significant Items

Item

PubMed Central — The Committee commends NLM for its leadership in developing PubMed Central, an electronic online repository for life science articles. Because of the high level of expertise health information specialists have in the organization, collection, and dissemination of medical information, the Committee believes that health sciences librarians have a key role to play in the further development of PubMed Central. The Committee encourages NLM to work with the medical library community regarding issues related to copyright, fair use, peer-review and classification of information on PubMed Central. (p.121)

Action taken or to be taken

NLM has been fortunate to work closely with the medical library community from the creation of PubMed Central and throughout its development. 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 850,000 articles are now freely available in PubMed Central, many dating back to the 19th century. In November 2006, more than 3 million unique users retrieved more than 12.4 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 actively promoted and supported the deposition of author manuscripts. The Scholarly Communication Committees of the Medical Library Association and the Association of Academic Health Sciences Libraries have provided valuable insights to NIH on barriers to participation by scientists in their institutions and on the probable impact of the policy on library subscriptions. 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 Medical Library Association and the Association of Academic Health Sciences Libraries on matters related to copyright, fair use, and peer review and the potential impact of these matters on PubMed Central, other NLM activities, and services provided through the National Network of Libraries of Medicine.

Senate Significant Items

Item

Disease Management Technology —The Committee urges 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. (p.156)

Action taken or to be taken

NLM regularly demonstrates its products and services at health professional meetings, such as the American Medical Informatics Association, that are aimed at public and private sector organizations with demonstrated capabilities in health information technology. The Library continues to offer training courses in the use of its Unified Medical Language System (UMLS) resources, which are designed for health information system developers, including those working on disease management technology. Many of NLM's services and databases assist developers of disease management technology in building and improving their products. NLM staff members have met with the scientific director of the Disease Management Association of America (DMAA) to exchange ideas for their improved utilization of NLM products and services. In addition, NLM has supported the programmatic interests of the Arthritis, Osteoporosis, and Chronic Back Association, the Chronic Kidney Disease Association, and others interested in disease management technology as it relates to improving care for chronically ill and reducing health costs.

Item

Native Hawaiian Healing —The Committee encourages the preservation and documentation of Native Hawaiian traditional cultural healing practices. (p.157)

Action taken to be taken

NLM is implementing changes and refinements in its collection development and preservation policies and practices in response to recommendations from an NLM Working Group on documenting traditional Native American healing practices - including those of Native Hawaiians. These changes include collecting materials in additional formats and subject areas such as ethnobotany and additional aspects of anthropology and religion. The Library's manuscript collection policy, which already included language that is inclusive of Native American traditional health and healing, has been made more specific in this area. In addition to developing its own collections, the Library is working with other interested agencies and organizations to plan national programs and develop standards and to support the development of the capacity of Native archives and libraries to develop and maintain their own archives and collections, with the understanding that the material should also be made widely available. As an example, NLM supported the development of "Native American Protocols for American Libraries, Museums, and Information Services." Whenever possible, NLM will promote the digitization of information and materials and will link to such materials through its American Indian Health web site. 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.

In July 2006 NLM held consultations in Hawaii with representatives of local archives, libraries, Native Hawaiian health organizations and Native Hawaiian community organizations to discuss these issues. One of the results of the consultation was the prioritization of activities that must be undertaken in order to ensure preservation of and access to materials that document Native Hawaiian traditional cultural healing practices. Cataloguing existing collections was determined to be the highest initial priority, since it is a prerequisite for improving access and identifying appropriate materials for digitization, which are also high priorities. At present, none of the existing repositories of Hawaiian healing materials has an oral history program. This is an important concern as the collecting and preserving of oral histories from elders may be the only way to capture stories and memories that are an important component of an oral culture. NLM has plans to initiate a test oral history project to record a small number of these histories. A longer-term goal is to identify any written materials held by individuals (outside of organizational collections) and try to ensure their preservation either as artifacts within institutions that could care for them, or as digital representations so that at least the content would be accessible. In all cases, intellectual property rights will be respected with negotiation to ensure access to all materials collected.

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. (p.157)

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). In Fiscal Year 2008, these contracts will award 50-60 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, HIV/AIDS, and public health and will cover an equal number of states. Special emphasis will be on projects that target minority and underserved populations.

Item

PubMed Central — The Committee commends NLM for its leadership in developing PubMed Central, an electronic online repository for life science articles. Because of the high level of expertise health information specialists have in the organization, collection, and dissemination of medical information, the Committee believes that health sciences librarians have a key role to play in the further development of PubMed Central. The Committee encourages NLM to work with the medical library community regarding issues related to copyright, fair use, peer-review and classification of information on PubMed Central. (p.157)

Action taken or to be taken

Please refer to page 269 of this document for NLM's response to this item on PubMed Central.

Office of the Director

House Significant Items

Item

Alpha-1 antitrypsin deficiency. – The Committee is aware that Alpha-1 antitrypsin deficiency (Alpha-1) is a major genetic risk factor for Chronic Obstructive Pulmonary Disease (COPD). The Committee commends NIH, particularly NHLBI, for its plans to focus additional research in the area of COPD. The Committee encourages **NHLBI**, NIDDK, NHGRI and other appropriate institutes to enhance the NIH research portfolio, encourage targeted detection, raise public awareness about Alpha-1 and provide appropriate information to health professionals. (p. 125)

Action taken or to be taken

The NHLBI sponsors many activities to enhance understanding and treatment of Alpha-1. A COPD awareness program was initiated in 2006 with the Alpha-1 Foundation and others that is disseminating information about Alpha-1, including the importance of genetic factors in COPD development and the occurrence of COPD in some middle-aged adults and lifelong nonsmokers. NHLBI research includes studies of better ways to produce and deliver exogenous Alpha-1 antitrypsin for therapy, use of stem cells as an endogenous source of Alpha-1 antitrypsin, and a trial of aerosolized hyaluronic acid for treatment of emphysema. In 2006, the NHLBI convened a working group on COPD in nonsmokers and another group to identify research needs in bronchiectasis, an airway abnormality associated with Alpha-1.

The NIDDK supports research and awareness efforts on liver disease associated with Alpha-1, including studies of mutations that cause misfolded Alpha-1 antitrypsin and the resulting liver damage and cancer. With the NCRR and the NIH Office of Rare Diseases (ORD), the NIDDK supports studies of Alpha-1 through the Cholestatic Liver Disease Consortium. The NIDDK also supports research on pediatric liver transplantation, which is required in some cases of Alpha-1. In 2006, the NIDDK, the ORD, and the Alpha-1 Foundation sponsored a meeting led by the American Association for the Study of Liver Diseases to raise awareness of Alpha-1 among scientists, clinicians, and the lay community and encourage further research.

The Rare Lung Diseases Consortium, a network of cooperating clinical centers and patient support organizations that work with the NIH to accelerate clinical research and improve the delivery of medical care to individuals affected by rare lung diseases, is studying Alpha-1.

The NHGRI Ethical Legal and Social Issues (ELSI) program funds a study to explore the privacy and confidentiality issues of patients with Alpha-1.

Item

Autism and vaccines- The Committee continues to be aware of concerns about reports of a possible association between the measles component of the measles-mumps-rubella

(MMR) vaccine and a subset of autism termed autistic enterocolitis. The Committee continues its interest in this issue and encourages the Interagency Coordinating Committee to continue to give serious attention to these reports. The Committee is aware that NIH-supported research is underway, and encourages NIH to avoid further delays in this research.

The Committee is also concerned that there is some evidence that infant exposures to thimerosal in the 1990s may be related to the epidemic of neurodevelopmental disorders in children. CDC's most extensive review of Vaccine Safety Datalink data concluded that more research needs to be conducted in this arena to answer these questions with certainty. The Committee concurs with the need for this continued research, particularly given the recent expansion of flu vaccine for children and the fact that most childhood vaccines administered in developing countries still contain thimerosal.

The Committee encourages NIH to dedicate significant resources to pursue the recommended research initiatives outlined in the Institute of Medicine's (IOM) Immunization Review. These reports have identified the research needed to understand better why a number of children suffer severe adverse reactions to childhood vaccines. Continuation of this research to develop a better understanding of biological mechanism is critical to understanding with certainty whether or not thimerosal and other vaccines exposures might cause increased risks for some children. (p. 125-126)

Action taken or to be taken

NIH continues to support research to elucidate potential genetic and environmental causes of autism and other neurodevelopmental disorders. Many of these are joint initiatives and activities sponsored by the NIH Autism Coordinating Committee; others are spearheaded by individual institutes.

The National Institute of Environmental Health Sciences (NIEHS) and other relevant NIH Institutes, in collaboration with the Centers for Disease Control and Prevention (CDC), convened an expert panel in May, 2006 to review the use of the CDC-supported Vaccine Safety Datalink (VSD) to address questions about changes in autism rates and their potential association with thimerosal exposure through childhood vaccination. The panel reached consensus that comparing the rates of Autism Disorder/Autism Spectrum Disorder in the VSD over the time period before, during and after the removal of thimerosal from most childhood vaccines would be uninformative and potentially misleading and recommended that these gaps be addressed prior to consideration of further studies of autism and thimerosal using the VSD.

NINDS is providing support for a five-year prospective epidemiological study of a large Norwegian birth cohort of 75,000 women and their babies. The study will examine the contribution of genetic and environmental factors to the development of autism and other neurodevelopmental disorders; these factors include infection history, low birth weight, dietary and environmental exposure to methyl-mercury, and vaccination history.

In partnership with the Environmental Protection Agency (EPA), NIEHS supports a five-year study on environmental etiologies of autism at the University of California at Davis (UC-Davis) through the Centers for Children's Environmental Health and Disease Prevention program. This Childhood Autism Risk from Genetics and the Environment (CHARGE) study is the first large, population-based epidemiologic case-control study of children with autism. UC-Davis is examining exposures, including vaccination histories, to determine their possible association with risk of autism. UC-Davis is also studying how exposure to environmental chemicals, including thimerosal, may increase the risk and severity of autism. UC-Davis is investigating mechanisms by which these environmental chemicals may contribute to abnormal development of the nervous system, thereby influencing brain structure and social behavior. NIEHS plans to fund an independent five-year grant to UC-Davis to continue the CHARGE study and enroll 900 additional subjects to enable examination of rarer exposures and exposures in subgroups of children with autism.

In July 2006, NIEHS awarded a grant to Johns Hopkins University to develop sensitive methods to measure individual differences in the effects of mercury on immune cells to test the hypothesis that individuals with autism are more susceptible to mercury-induced immunotoxicity.

Item

Autism spectrum disorders - The Committee is encouraged by NIH's autism research matrix and encourages NIH to devote sufficient resources to this research agenda. The Committee encourages NIH when implementing the autism research matrix to coordinate with autism organizations already funding research initiatives to ensure the most efficient use of its resources. The Committee also notes the promise of particular areas cited in the matrix, including genetic, gene-environment interactions, behavioral characterizations of the disorder, screening and early diagnosis, and the development of evidence-based interventions. (p.126)

Action taken or to be taken

Since its creation in 2003, the Interagency Autism Coordinating Committee (IACC) Autism Research Matrix has been a resource for directing the expansion and intensification of autism research. The IACC, which is comprised of several NIH Institutes, government agencies, and autism advocacy organizations, is working in partnership with representatives from the scientific community and advocacy community to conduct an evaluation of progress on the IACC Autism Research Matrix. In September 2006, a panel of scientific experts and representatives from the autism advocacy community was convened in a full-day meeting to review the state of autism research and to evaluate research progress using the matrix as a guide. The panel evaluated whether the research goals and activities outlined in the matrix were achieved, were in progress, or had yet to begin. In addition, the panel discussed gap areas not covered in the original matrix. The matrix outlines a ten year effort, and the panel agreed that significant progress in capacity building has been made during these first three years. Researchers have opportunities and resources that did not previously exist, and the field is poised to make important advances in autism research. A draft report from this

meeting was presented at the November 2006 IACC meeting and then released for public comment. Once finalized, the report will form the basis for updating the matrix. The autism research matrix is a living document. Through careful evaluation of research progress and the recognition of new and exciting avenues of science to pursue, it will continue to serve as a useful guide to the autism research effort.

NIH supports a number of efforts that address the research areas outlined in the matrix. For example, in 2007, NIMH, NICHD, NINDS, NIDCD, and NIEHS will implement the new Autism Centers of Excellence (ACE) Research Program. The ACEs are being created to maximize coordination and cohesion of NIH-sponsored efforts, avoid duplication, allow the most efficient use of resources, and involve a large number of investigators. The ACE Centers will be required to focus on priority areas identified in the Autism Research Matrix, specifically in the areas of etiology and treatment. The ACE awards encourage public-private partnerships, particularly in the areas of genetics, gene-environment interactions, and intervention. Also, to facilitate data sharing among autism researchers, NIH has created the National Database for Autism Research (NDAR). NDAR will allow scientists to share data, as well as reach consensus on common measures and methodologies to enhance the comparison of data among various centers. NDAR will also coordinate 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

Item

Basic behavioral research – The Committee encourages OBSSR to continue working to build alliances among institutes that support and nurture basic behavioral and social sciences research. In particular, the Committee encourages OBSSR to partner with NIGMS and other funders of basic research to enhance support for work on methods, animal models, and the interplay of biological factors, behavioral and social influences underlying phenomena such as stress that influence multiple health conditions. (p. 124)

Action taken or to be taken

In FY 2005 NIH supported over \$1 billion in basic behavioral and social sciences research (BSSR). OBSSR works with numerous Institutes and Centers (ICs) to support basic BSSR. In FYs 2004 and 2005 OBSSR led the development of several trans-NIH Roadmap initiatives targeting methodological development in the behavioral and social sciences and stronger integration of these disciplines into interdisciplinary research with the biological, computational and physical sciences and engineering. The funded projects include basic BSSR on dietary intake, physical activity, stress, child development, stress-immune interactions, environmental exposures, treatment decision-making, patient quality of life, gene-environment interactions, socioeconomic status, pain, treatment adherence, emotion, memory, cognition, and aging. RFA RM 07-004, *Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences (R21)*, another Roadmap initiative developed under OBSSR and NIDA leadership, budgets \$3 million/year in FY 2007-2010 to support the development of new/innovative measures, methods, and technologies that support the

interdisciplinary integration of human social and/or behavioral science with other disciplines across varying levels of analysis.

OBSSR continues to coordinate research initiatives on Mind-Body Interactions and Health. The initial Centers (FY 1999-2003) were exemplars of interdisciplinary collaborative efforts doing basic and applied research on stress-immune interactions, the neural basis of emotion, resilience and vulnerability, interactions of psychosocial states (beliefs, attitudes, affective states, values, and social relationships), their determinants, stress and other factors in child development, health disparities, and aging. Additional initiatives developed by OBSSR in collaboration with numerous ICs are currently supporting infrastructure, developmental/exploratory efforts, and new research projects on mind-body interactions and health.

OBSSR, NHGRI and NIGMS co-sponsored the Institute of Medicine to convene a committee to explore research gaps and opportunities on the topic of interactions between the social environment and genetics that affect human health. OBSSR will work with ICs to consider the recommendations in the committee's report, *Genes, Behavior, and the Social Environment. Moving Beyond the Nature/Nurture Debate*, released in June, 2006.

Item

Chromosome abnormalities - The Committee commends NIH for its efforts over the past year to encourage new research into molecular, genetic, clinical and therapeutic aspects of chromosome abnormalities. Because of the multisystemic consequences of a chromosome abnormality, multidisciplinary and multi-institute support by NIH will be required in order to make progress that will be meaningful to those affected. The Committee continues to encourage NIH to seek ways to expand and intensify such research, especially studies involving the syndromes of chromosome 18. (p.126)

Action taken or to be taken

The National Institute of Child Health and Human Development (NICHD) supports a number of independent investigators who study chromosome abnormalities, in which there are extra or missing chromosomes, extra or missing pieces of chromosomes, or more complicated abnormalities with broken chromosomes that have been incorrectly re-connected leading to extra and/or missing material or other abnormal results. These can range from abnormalities of single genes to missing or extra chromosome segments containing many genes. While the multi-system effects of chromosome abnormalities are gaining in recognition and thus necessitating cooperation among institutes at NIH and at other agencies, the most focused effort in this regard to date has been the organization of several Trans NIH Taskforces, including ones on amyloidosis, tuberous sclerosis, neurofibromatosis, and Down syndrome. Research in chromosomal abnormalities supported by NICHD include independent investigator and program project grants that focus on biomedical, behavioral, and biobehavioral aspects of Down syndrome, Smith-Magenis syndrome, Prader-Willi and Angelman syndromes, Williams syndrome, Velocardiofacial/Di George syndrome, Turner syndrome, Klinefelter syndrome, and 18q-syndrome. In addition to these efforts, NICHD has partnered with other institutes and the Office of Rare Diseases (ORD) to sponsor a number of meetings involving many of these conditions. NICHD also participates in the Rare Disease Cooperative Research Center

Network along with ORD and National Center for Research Resources (NCRR), providing scientific support for a Center that studies chromosomal, genetic and epigenetic aspects of Rett syndrome, Prader-Willi syndrome and Angelman syndrome. The goal of this center is to identify improved therapies for these conditions based upon a better understanding of the actual adverse effects of the underlying chromosomal abnormalities.

Item

Cystic fibrosis.—The Committee commends the Director and NIH for facilitating progress in finding new ways to treat individuals with cystic fibrosis (CF). Progress from the 1960s when children with CF did not live long enough to attend elementary school to today's median life expectancy of 35 years has resulted from significant contributions of both NIH and the private sector. The Committee encourages NIH to support more research in CF to cure this disease, a goal that is achievable, and can result in lessons to benefit research on other rare, genetic diseases.

The Committee commends the Director for recent initiatives in the NIH Roadmap to re-engineer the clinical research system by issuing grants to establish integrative academic homes for clinical and translational science. The Committee encourages the Director to consider as a model the CF clinical trials network, and to continue to support this model network, which is making great advances in developing new treatments for cystic fibrosis. (p. 126)

Action taken or to be taken

The NIH is pursuing multiple avenues to enhance research on cystic fibrosis (CF). For example, with respect to research involving the Cystic Fibrosis Foundation's Therapeutics Development Network (CFF TDN), the National Heart, Lung, and Blood Institute (NHLBI), with co-support from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and National Center for Research Resources (NCRR), is continuing sponsorship of the Early Pseudomonas Infection Control (EPIC) trial. This trial's objective is to determine the best treatment for initial infection with *Pseudomonas* (a type of bacteria) to delay or prevent the development of chronic infections that lead to progressive lung destruction and premature death in CF patients. The trial is currently ahead of schedule for recruiting patients. For the EPIC trial, the NHLBI and NIDDK are providing support for the CFF Network's data coordinating center. The NCRR is also providing support to the Network for another study that will examine an intervention in CF patients who are not infected with *Pseudomonas aeruginosa* bacteria. The NCRR also continues to provide support for the Network's bioinformatics component, called CFnet. NCRR took its experiences with CFnet into account during the development of the NIH Roadmap initiative on institutional clinical and translational science awards and also approached the President of the CFF and the Network's Director for input.

In other research areas, the NHLBI provides support to the NIH Rare Diseases Clinical Research Network to test therapies or drugs in a variety of rare diseases, including CF. Additionally, in 2006, the NHLBI initiated a Specialized Center of Clinical Research (SCCOR) focused on understanding the key structural and regulatory processes mediating mucus clearance — the principal form of innate defense in the human airways

— and their dysfunction in CF and chronic obstructive pulmonary disease. The concepts emerging from this SCCOR will spur the development of novel therapies to transform the treatment of these major human diseases early in their course. Also in 2006, the NIDDK released a new solicitation for CF Research and Translation Core Centers to support research on potential therapies and enhance communication and collaboration between basic and clinical scientists. As a result of an earlier solicitation to encourage research on small molecular reagents that ameliorate protein misfolding or misprocessing defects that cause diseases such as CF, the NIDDK in 2006 funded a new project on CF, and is also expanding upon these efforts with new solicitations.

Item

Down Syndrome -- NICHD is encouraged to partner with 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 also encourages NICHD to work with the Office of the Director, OPASI and the other Institutes to develop a strategic plan for Down syndrome research and to coordinate its research within NIH. (p. 127)

Action taken or to be taken

Mouse models developed with NICHD funding have made possible work on the region of the human chromosome 21, known as Down Syndrome Critical Region, including potential therapeutic interventions and a better understanding of the molecular commonalities between Down syndrome and Alzheimer disease. NICHD currently supports a contract with the Jackson Laboratories to provide investigators around the world with mouse models for research related to Down syndrome. In addition, a number of individual investigators have successfully applied for NICHD funding to conduct studies on and continue the creation of mouse models. Continued support for the production of the mouse stock, along with verification that the stock provided meets consistently high genetic and behavioral criteria, has ensured that the demands of researchers can be met.

To facilitate this and other issues related to research on Down syndrome across the NIH, the NIH Down Syndrome Working Group established in early 2006, comprises those institutes and centers with an interest in some aspect of Down syndrome research. NICHD leads the effort, along with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA). The group is currently developing a draft research plan, based on recent scientific meetings on Down syndrome, its genetics, its developmental consequences, and its impact on cognition and synaptic function. Input on this plan will be sought from national constituency organizations and scientific experts to define further and address clearly strategies for basic and clinical research in this area.

Item

Gene Therapy Research – The Committee is encouraged by promising research being undertaken in gene therapy, especially in regard to thalassemia, or Cooley's anemia. The Committee is concerned, however, that the current mechanism for funding gene therapy

research, while promoting advancement of individual components of gene therapy, lacks an overarching strategy that will coalesce these advances and encourage the ultimate goal of curing genetic disorders expeditiously. The Committee is equally concerned that the most innovative research in curative gene therapy is being conducted in Europe rather than in the U.S. Last year, the Committee urged the Director to assess the prospects for the most promising areas for breakthroughs in this field and to develop an aggressive program to focus resources on it. A meeting was convened on the topic, but the Committee believes that more focused and aggressive action is needed. NIH should assess the prospects for success in a broad range of diseases, with the goal of curing a single gene disorder in the shortest possible time utilizing gene therapy. The Committee requests a plan for implementing an aggressive research agenda by January 1, 2007.

(p. 127)

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 red blood cells. The first human trial of gene therapy for hemoglobinopathies (funded by industry in France) will include both Cooley's anemia and sickle cell disease patients. The initial patient was 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 in June 2005 a working group of leading U.S. investigators, representatives of the Cooley's Anemia Foundation, the Sickle Cell Disease Association of America, and the FDA, physicians who treat hemoglobinopathies, and a bioethicist. Barriers to starting a U.S. human trial were identified as funding, lentiviral vector production, and preparation of applications to regulatory agencies (e.g., FDA) and advisory committees (e.g., the NIH Recombinant DNA Advisory Committee). A second NHLBI Working Group was held in June 2005 to identify critical resources for gene therapy research in all the NHLBI mission areas, and similar themes were brought to light and conclusions reached.

To address these challenges, the NHLBI is initiating a Gene Therapy Resource Program. It will include a preclinical vector-production core, two clinical grade vector-production cores (one for lentivirus vectors and one for adeno-associated vectors), a toxicology/pharmacokinetics core, and a clinical coordinating center to assist with regulatory requirements and support Phase I/II clinical trials. The program will serve all the NHLBI mission areas, including hemoglobinopathies, hemophilia, Fanconi anemia, several cardiovascular disorders, and pulmonary diseases such as cystic fibrosis and alpha-1 antitrypsin deficiency. Ongoing NHLBI programs that could also facilitate trials in this area include the Production Assistance for Cellular Therapies Program, the Comprehensive Sickle Cell Center Program, the Thalassemia Clinical Research Network, and the Center for Fetal Gene Transfer in nonhuman primates.

Through these programs, the NHLBI is actively encouraging movement toward conducting U.S. human gene therapy trials for hemoglobinopathies, and has in place experienced staff, a safety monitoring committee, and standard operating procedures to

monitor patient safety, which is paramount. 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

Human Tissue Supply —The Committee remains interested in matching the increased needs of NIH grantees and intramural researchers who rely upon human tissues and organs to study disease and search for cures, including for those researchers dedicated to the study and cure of rare diseases. The Committee is aware that NIH has established a multi-institute initiative on human tissue supply. While this is promising, there is still an unmet demand for the use of human tissue in research. The Committee encourages the Director to strengthen the core for this initiative and to broaden its scope to other institutes such as NCI, NHLBI, and NINDS that have not previously participated in the initiative's core support. (p. 127)

Action taken or to be taken

The National Disease Research Interchange (NDRI) is one of many organizations in the United States that provide human tissue for basic research. The National Center for Research Resources (NCRR) is the lead Institute/Center for the cooperative agreement that funds one of the three divisions of NDRI. This division, named HTOR (Human Tissues and Organs for Research), provides tissues primarily to academic scientists. In the past year, a total of 5,588 tissues were shipped by HTOR to investigators. Of the other two divisions, one provides tissues to for-profit organizations and the other serves as a genetics database and cell/DNA repository.

NCRR maintains the core funding for the HTOR cooperative agreement, now in its fifteenth 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 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 needs of their researchers, provide funds for mission-specific repositories.

Item

Lymphatic Research and Lymphatic Diseases-- In light of the transformational impact of lymphatic biology and disease research, which requires the participation of multiple institutes and centers, the Committee encourages the Director to give careful consideration to the development of an initiative for lymphatic biology and disease under the auspices of OPASI. In addition, the Committee encourages the Director and the Trans-NIH Coordinating Committee on the Lymphatic System to pursue the goals of fostering lymphatic research initiatives and awareness across all NIH institutes and centers. (p.128)

Action taken or to be taken

Lymphatic research is a prime example of an area that will benefit from collaboration across multiple NIH components. To that end, the Trans-NIH Coordinating Committee on the Lymphatic System, led by the NHLBI, is building and expanding its activities to foster research. First, NIH institutes and centers are being reminded and encouraged to review their program initiatives for applicability to lymphatic research and, where relevant, add appropriate language to include lymphatic research topics. Next, the Coordinating Committee is developing a new trans-NIH program announcement for which a special emphasis panel with appropriate expertise will be convened to review the resulting applications. The Coordinating Committee is also planning a trans-NIH working group on lymphatic biology and disease that will focus special attention on basic, clinical, and translational issues and develop a Web site to promote and facilitate lymphatic disease research in the intramural and extramural programs across the NIH. In addition to these Coordinating Committee activities, OPASI will give careful consideration to all lymphatic-focused initiative ideas that are submitted during the Roadmap idea-solicitation process. Future OPASI actions in this area will be coordinated with the Coordinating Committee.

Item

Microbicides - There is an urgent need to expand the development pipeline with more microbicide candidate products, particularly those that target HIV in new ways. In addition to candidates that may arise from basic research efforts, the best possibilities may be found within pharmaceutical companies where there are, today, dozens of potential compounds already developed as therapeutics that could move into clinical development as microbicides if made available. As outlined in the “NIH Roadmap,” NIH has mechanisms in place to encourage partnerships among researchers in academia, government and the private sector. The Committee encourages the leadership at NIH to support the microbicide field by encouraging the pharmaceutical industry to allow its drug candidates to be developed as microbicides. In recent years, the International Partnership for Microbicides has entered into innovative agreements with leading pharmaceutical companies to test and develop leading AIDS drugs as microbicides. More partnerships like these between the pharmaceutical industry and the non-profit community will be critical. (p. 128)

Action taken or to be taken

Topical microbicides represent an important potential strategy for preventing the sexual transmission of HIV, and the National Institutes of Health (NIH) continues to support research and development through public-private partnerships.

In fiscal year (FY) 2006, the National Institute of Allergy and Infectious Diseases (NIAID) restructured its HIV/AIDS clinical trials networks and formed the Microbicide Trials Network (MTN). The MTN will develop a highly focused microbicide research and development strategy to advance candidates toward licensure. Other awards in FY 2006 included fifteen awards under the Microbicide Innovation Program to stimulate discovery and development of new microbicides and science and technology associated with their evaluation. Three awards were also made in the Integrated Preclinical/Clinical

Program for HIV Topical Microbicides (IPCP-HTM), which is designed to stimulate iterative preclinical and clinical research for novel microbicide strategies with involvement of the private sector.

The NIAID continues to support partnerships with industry initiated in FY 2005. This support includes an award to Starpharma through the Microbicide Design and Development Teams (MDDT) program, which is designed to streamline development of microbicide candidates, emphasizing combination products with multiple active agents or targets; an ongoing Phase II/IIb safety and effectiveness trial of two candidate microbicides at sites in Africa and the United States; and five awards made under the Partnerships for Topical Microbicides program, which seeks to develop topical microbicides targeted against more than one sexually transmitted infection.

To enhance global collaboration and coordination, the NIH also actively participates in the Microbicides Coordinating Board convened by the Bill and Melinda Gates Foundation and the Alliance for Microbicide Development to facilitate and execute a range of international activities aimed at moving the microbicide field forward through collaborative efforts such as formulating a global Microbicide Development Strategy.

Item

Microbicides to Prevent HIV/AIDS - The Committee notes with alarm that being female, married and poor are often the most significant risk factors for acquiring HIV. Once developed, microbicides will be a critical element of a comprehensive response to HIV/AIDS that takes into account the unequal impact of the epidemic on women. The Committee encourages greater emphasis on microbicide research and development at NIH. The Committee has long advocated that NIH establish a dedicated microbicide unit with clearly identified leadership, funding and staffing to accelerate and coordinate NIH-supported microbicide research. Greater leadership and coordination on this issue is especially critical given that a microbicide-specific clinical trial network is under active review for approval. (p. 128)

Action taken or to be taken

The vulnerability of women to acquiring HIV infection requires the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. The Office of AIDS Research coordinates microbicide research across the NIH and with other federal agencies, providing administrative accountability and funding coordination for this priority research area. The science of microbicides is moving rapidly, and OAR has announced a number of important changes to improve NIH management and support for this crucial high priority area of science. The annual *Trans-NIH Plan for HIV-Related Research*, developed by OAR in collaboration with the NIH ICs and non-government experts, includes priorities, objectives, and strategies for microbicide research. A separate staff division of OAR now will be dedicated to microbicide research and other issues relevant to women. OAR is convening a trans-NIH Microbicide Research Coordinating Committee with members from the ICs with significant microbicide portfolios to assist in the development of the microbicides component of the Trans-NIH Plan, foster

information-sharing and trans-NIH coordination, and help identify scientific opportunities and gaps for increased attention. OAR will support a number of conferences, workshops, and symposia to enhance scientific interest in this area. The National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) is developing a new Prevention Sciences Program that will include a Microbicide Research Branch to coordinate all DAIDS-supported microbicide research and provide oversight for the recently awarded Microbicide Trials Network. A Microbicide Research Working Group of non-government experts will be established to advise OAR, NIAID, NIH, and others in this priority area.

Microbicide research priorities include: the establishment of clinical trial sites, especially in developing countries; the development of criteria for selecting potential products to be evaluated and advanced through the different phases of clinical studies; and research on ethical and behavioral issues impacting clinical trials; the evaluation of lead candidates in non-human primate models; a new initiative for development of innovative microbicide concepts; and an integrated pre-clinical/clinical program for development of microbicide candidates. OAR will also support a U.S.-India research project on HIV/AIDS, with high priority given to collaborative microbicide research projects.

Item

Minority Institution Research Infrastructure – The Committee continues to be pleased with the NIH Director’s implementation of various programs focused on developing research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions, extramural biomedical research facilities, and the National Center on Minority Health and Health Disparities. The Committee encourages the NIH Director to work closely with the Director of NCMHD to establish a program of coordination among these various mechanisms to partner with minority health professions schools to address their infrastructure needs. (p. 128/129)

Action taken or to be taken

The NIH will continue to support and foster the development of research infrastructure at minority health professions institutions through a number of mechanisms among its Institutes and Centers. The NCMHD, as the NIH body responsible for coordinating minority health and health disparities research activities at NIH, will continue to work in close collaboration with the NIH Office of the Director and the NIH Institutes and Centers to enhance the coordination of new and existing mechanisms to support the research infrastructure needs at minority health professions schools. Programs such as the NCMHD Research Infrastructure in Minority Institutions Program, NCMHD Research Endowment Program, NCRH Research Centers in Minority Institutions Program, NCRH Comprehensive Centers on Health Disparities, NIGMS Bridges to the Future Program, and NIGMS Minority Biomedical Research Support Program are some of the key NIH programs that demonstrate the agency’s commitment to research infrastructure development at minority health professions schools. The NIH through the NCMHD will examine opportunities to link and strengthen these and other research infrastructure building programs to bolster the research capacity at minority health professions schools.

Item

Mucopolipidosis IV (ML4) - The Committee commends NINDS, NIMH and NICHD for efforts to create a strain of mice that replicates the genetic mutation that causes ML4 in humans. The Committee encourages continued research in the effort to cure ML4 and similar genetic disorders. (p. 129)

Action taken or to be taken

Mucopolipidosis IV (ML4) is a disease characterized by abnormal accumulation of material in the lysosome, a cellular compartment that breaks down and recycles macromolecules. ML4 is part of a class of diseases known as lysosomal storage disorders (LSDs). Mutations in the gene which codes for the mucopolipin-1 protein have been shown to be responsible for ML4. Several NIH Institutes support research projects that aim to increase our understanding of ML4 and provide therapies for those afflicted.

The National Institute of Neurological Disorders and Stroke (NINDS) supports a variety of projects including a study of the gastrointestinal defects of ML4, studies characterizing the function of mucopolipin-1 and associated proteins, and two intramural studies of ML4, one of which is tracking clinical expression of the disease to improve diagnosis, another which is following retinal degeneration. The National Institute of Child Health and Human Development (NICHD) funds an investigation that aims to develop therapeutic strategies based on gene replacement and/or a combination of diet and drugs. The National Center for Complementary and Alternative Medicine (NCCAM) supports an exploratory grant investigating the effects of dietary agents on LSDs. The National Heart, Lung, and Blood Institute (NHLBI) has an intramural project investigating the proteins that interact with mucopolipin-1 and the ways this protein is targeted to its appropriate place in the cell. Finally, the National Institute of General Medical Sciences (NIGMS) supports a project that uses the roundworm *C. elegans*, an organism amenable to genetic studies, to dissect the cellular pathway where mucopolipin-1 is involved.

Several Institutes have also been involved in efforts to create an animal model of ML4. In FY 2006, intramural researchers from the National Institute of Dental and Craniofacial Research (NIDCR) collaborated with NINDS to produce a mouse line with the genetic defect found in ML4. The mouse line was successfully created although, because the animals were not found to exhibit the major symptoms of the disease, it seems the gene function was not completely abolished. The NINDS currently continues to support a separate project to create a useful mouse model of ML4. This project has received technical support from the National Institute of Mental Health (NIMH) intramural Transgenic Core Facility.

In conjunction with the NIH Office of Rare Diseases, and the Lysosomal Storage Disease Research Consortium, the NINDS has also issued two program announcements with set-aside funds to promote the translation of basic science findings to new or improved therapies for the neurological defects associated with LSDs. The announcements will be active until the end of 2007. Several projects investigating therapies relevant to LSDs, including ML4, are currently being funded as a result of this effort. These projects include gene therapy approaches for LSDs, the use of stem cells to replace dying nerve

cells or produce lysosomal proteins, therapies to prevent accumulation of material in the lysosome, caloric restriction to reduce inflammation, and investigations into strategies to improve the transport into the brain of proteins that can aid lysosomal breakdown.

Item

Musculoskeletal Trauma and Skeletal Pain. - The Committee encourages NIAMS, NIA, NIDCR, and NCCAM to study ways to understand better the epidemiology of back pain, and improve on or develop new diagnostic techniques for back pain. The Committee also encourages expansion of research to improve diagnostic and therapeutic approaches to lower the impact of musculoskeletal trauma. (p. 129)

Action taken or to be taken

Low back pain is one of the most common musculoskeletal conditions in the United States resulting in increased disability and reduced productivity. Additionally, accidental injury and chronic disease cause musculoskeletal pain that can be difficult to diagnose and treat. Several NIH components are exploring new treatment and diagnostic methods for reducing the burden of these conditions and improving the quality of life for patients and their families. For example, several NIH components, including the National Institute of Nursing Research, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Institute of Dental and Craniofacial Research (NIDCR), the National Center for Complementary and Alternative Medicine (NCCAM), and others, recently released a Program Announcement entitled, “Mechanisms, Models, Measurement, and Management in Pain Research.” Researchers are invited to submit proposals that seek to improve the understanding of the causes, costs, and societal effects of both acute and chronic pain and the relationships between the two. Additionally, proposals that link such understandings to the development of better approaches to therapeutic interventions, including complementary and alternative medicine interventions, and management of acute and chronic pain are encouraged.

The transmission of unpleasant sensory signals, or nociception, has long been an area of interest for researchers. Recent advances have shown that nociception is a dynamic process that often involves multiple routes to the spinal cord and brain. A major challenge has been defining these routes. Recently, researchers supported by the NIDCR reported a completely new pathway involved in the pain process. The pathway’s relevance to pain processing was suggested by the finding in rats that its activity increased dramatically with three different kinds of painful nerve injury. This finding was reinforced by the group’s discovery that people born with a certain variant of the GCH1 gene, which participates in this pathway, are less sensitive to acute experimental pain. Patients with the variant GCH1 gene who underwent a surgical procedure for low back pain reported less pain following surgery. The GCH1 gene encodes an enzyme called GTP cyclohydrolase, which is involved in folate and biopterin biosynthesis. These data suggest that inhibiting this enzyme might help to prevent or control chronic pain associated with various conditions of the musculoskeletal system, including low back pain.

Additionally, investigators supported by the NIAMS have published results from the Spine Patient Outcomes Research Trial (SPORT), the largest trial to date comparing surgical and non-surgical interventions for the treatment of low back and associated leg pain caused by lumbar intervertebral disk herniation. Patients receiving surgery underwent a lumbar discectomy, a procedure involving the removal, in part or whole, of an intervertebral disk. The non-surgical intervention consisted of physical therapy, education/counseling, home exercise instruction, and nonsteroidal anti-inflammatory drugs. After 2 years, improvements in levels of reported pain were seen in all patients regardless of their treatment protocol; however, patients receiving surgery reported having the highest level of improvement across both groups. The results of this study have broadened our understanding of the effectiveness of surgical versus non-surgical interventions for treating these common and often debilitating musculoskeletal conditions. Patients and their health care providers will be able to use the results of this study to help them select a treatment intervention based on their preferences.

Lastly, NCCAM-supported researchers have demonstrated that yoga may be an effective therapy for chronic low back pain. Other NCCAM-funded research is examining whether traditional Chinese medicine is effective as an adjuvant therapy for the treatment of osteoarthritis of the knee, and whether electro-acupuncture can treat chronic lower back pain in older adults. The results of this research may give patients and their health care providers additional options to consider as part of their treatment plans. Additionally, NCCAM is working in collaboration with NIA to recruit patients for participation in a clinical trial to test the effects of electrical acupuncture and exercise in older adults with chronic low back pain.

Item

Psoriasis - The Committee encourages the Director to expand and coordinate research and related activities with respect to psoriasis and psoriatic arthritis across all relevant ICs, particularly at NIAMS and NIAID, to help foster new, safe and effective treatments for these diseases and move toward a cure. (p. 129)

Action taken or to be taken

NIH funds a variety of research aimed at uncovering the cellular and molecular processes that contribute to the development of psoriasis and psoriatic arthritis, expanding our knowledge of genes that play a role in the development of these diseases, and developing more effective treatments in order to help increase the quality of life for patients. Researchers are also working to develop new diagnostic tools for these diseases.

Knowledge gained from NIH-funded research on psoriasis and other autoimmune diseases, as well as on basic immunology, has led to the development of multiple new biological therapies for psoriasis. To support these efforts, the NIH is funding several Small Business Innovation Research grants allowing small companies to translate our basic knowledge of psoriasis, immunology, and skin biology into promising new therapies for psoriasis, as well as the generation of cell culture models for psoriasis that can be used for drug screening. This research will help maintain the pipeline of new drugs for psoriasis. Additionally, NIH continues to support the Immune Tolerance

Network, which is conducting a clinical trial for the treatment of psoriatic arthritis. This collaborative research effort solicits, develops, implements, and assesses clinical strategies and biological assays for the purposes of inducing, maintaining, and monitoring treatment tolerance in humans.

Genome-wide association studies of psoriasis are being addressed through a new funding mechanism at the NIH, the Genetic Association Information Network (GAIN). One project within the network will comprehensively evaluate the subtle differences between the genomes of healthy volunteers and the genomes of patients with psoriasis. In addition to other advances such as the recent identification of PSORS-1, a gene that appears to play a role in determining who gets psoriasis, information obtained from GAIN will help scientists to develop targeted therapies which could result in the prevention or improved treatment of the disease. Current treatments for psoriasis often suppress the entire immune system, leaving the person vulnerable to various infections. Ideally, treatments aimed at a particular gene would shut down only the process which causes the disease, providing relief from the psoriasis, while still leaving a functioning immune system.

Item

Rett Syndrome - The Committee applauds NIH's continued commitment to Rett syndrome research, a genetically-based neurological disorder seen almost exclusive in females, which is estimated to occur in approximately one in ten thousand female births. Recent discoveries suggest that mutations in the gene responsible for Rett syndrome are associated with other disorders including learning disability, autism, schizophrenia, mental retardation, and in infant males, a progressive, fatal encephalopathy. New basic biomedical discoveries are also providing insights on general mechanisms of postnatal brain development, providing a roadmap of new avenues of interventions with the potential to treat Rett syndrome and other neurological disorders. (p. 129)

The Committee is pleased that NINDS, NIMH, and NICHD have partnered with existing advocacy groups in the development of co funded projects, and encourages additional support for development of new animal models and for continuation of the ongoing genotype/phenotype investigations to hasten progress in eliminating this and other neurologically based disorders.

The Committee encourages expansion of research in applied areas that will improve the quality of life for individuals with Rett syndrome and others with communicative disorders, and encourages NIH to redouble its effort to integrate the work of appropriate institutes in this area, including NICHD, NINDS, NIA, NIMH, NIDCD, NHGRI, NHLBI, NIAMS, NIDDK, NIGMS, and NCRR. The Committee also admires the progress made by the Office of Rare Diseases in the development of the Rare Disease Clinical Research Network, and is pleased by the implementation of clinical research protocols to create better understanding of the scope of Rett syndrome and other rare disorders. (pp. 129-130)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Mental Health (NIMH), and the National Institute on Child Health and Human Development (NICHD) have partnered with the International Rett Syndrome Association (IRSA) and the Rett Syndrome Research Foundation (RSRF) to support a Program Announcement with set-aside funds on Rett syndrome and MECP2. This initiative encourages applications on the pathogenesis of Rett syndrome, the function and regulation of MECP2, as well as therapy development and clinical studies. The studies funded under this initiative are using various genetically-altered mice for genotype-phenotype studies, examining how the abnormal activity of certain genes regulated by MECP2 might correlate with the various neurological and behavioral abnormalities associated with Rett syndrome. These projects will provide information about the molecular mechanisms of action of MeCP2 and may identify potential therapeutic targets.

Many of the 27 NIH Institutes and Centers (ICs) support research related to the different aspects of Rett syndrome. For instance, NINDS is supporting a number of studies using various approaches to identify the mechanisms of action of the MECP2 protein in nerve cells. The National Institute of General Medical Sciences (NIGMS) supports several grants examining the structure and function of domains of the MECP2 protein, which should clarify how MECP2 influences the expression of other genes. In addition, the National Heart Lung and Blood Institute (NHLBI) supports research on the cellular regulation of respiratory rhythms, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports a broad portfolio of research related to the understanding, treatment and prevention of Rett syndrome related disorders, such as scoliosis and loss of muscle mass. The National Human Genome Research Institute (NHGRI) is funding the Encyclopedia of DNA Elements project, or ENCODE, which seeks to identify all functional elements in the human genome, and could lead to a better understanding of the function of the MECP2 protein. Finally, the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) supports molecular therapy centers that may yield new therapeutic modalities relevant to multiple genetic disorders including Rett syndrome.

The Office of Rare Diseases (ORD) serves to coordinate and integrate research by the ICs on disorders such as Rett syndrome. ORD recently organized a conference on *Clinical Trials in Rett Syndrome: Potential for Early Intervention*. The conference provided a forum for scientists to exchange scientific information regarding Rett syndrome diagnosis and treatment and stimulated the interest and involvement of additional researchers, including trainees and junior faculty from different disciplines, in the field of Rett syndrome diagnosis and treatment.

Finally, Rett is one of the syndromes investigated in the Angelman, Rett, and Prader-Willi Syndromes Consortium that is part of the larger Rare Diseases Clinical Research Network, an effort coordinated by ORD and the National Center for Research Resources (NCRR). The Consortium is affiliated with IRSA and aims to provide clinical expertise and up-to-date information to patients, to facilitate research and clinical trials and to train

clinicians. A new study within the Consortium, the Rett Syndrome Natural History Clinical Protocol, has started enrolling research participants.

Item

Shaken Baby Syndrome – The Committee encourages NIH to expand its programs to raise public awareness of shaken baby syndrome (SBS) and to expand its programs of research on the prevention and treatment of the syndrome. (p. 130)

Action Taken or to be Taken

In 2002, NICHD and ORD, NIH, convened a cross-disciplinary conference, “Inflicted Childhood Neurotrauma.” The purpose of the conference was to review and discuss the evidence-based medical literature available at the time. The proceedings, co-edited by an NICHD scientist and published by the American Academy of Pediatrics the following year, are still considered a standard reference in the field. Nonetheless, in the intervening years, there have been significant advances in neuroimaging and neurocritical care, in the development of diagnostic screening tools and of appropriate animal models, a number of which have been funded by NICHD. These advances may help to answer critical underlying questions such as the mechanism of injury; it is not known absolutely whether shaking can precipitate critical head injury characterized by hemorrhage. Careful, thorough research is essential to clarify forensic findings that are often clouded with the understandable emotions surrounding these cases. NICHD has begun to explore the feasibility of updating its earlier multidisciplinary effort.

Item

Spinal Muscular Atrophy - The Committee encourages the Director to ensure the success of the SMA project by providing active and ongoing support from the OD as well as from other related institutes. The Committee is aware that the current SMA project is scheduled to conclude in 2007 and encourages the Director to begin planning for the necessary follow-on effort to maximize the results of this innovative project for SMA and to ensure it serves as a model for other diseases. (p. 130)

Action taken or to be taken

The SMA Project is making encouraging progress toward its goal of having a drug ready for clinical testing for SMA. At the beginning of the SMA Project, the NINDS engaged a Steering Committee with extensive experience in drug development from industry, academia, the FDA, and the NIH. The Committee recommended that the project establish, through sub-contracts, a “virtual pharma” organization, rather than contracting with an existing entity to carry out drug development. Following this suggestion, and guided by detailed drug development planning by the Committee, the SMA Project has now established the facilities, resources, and expertise necessary for drug development. Because establishing this customized organization took longer than contracting with an existing organization, the NINDS was able to extend the funding for the SMA Project beyond 2007.

The SMA Project is now rapidly developing potential drugs. The project has tested more than 600 chemically modified versions of one of the “lead compounds,” indoprofen with

improvements of more than 100 fold in efficiency of delivery to the brain and spinal cord, more than 200 fold in potency, and 2.5 fold in maximum effectiveness, as well as elimination of the major unwanted effect of the indoprofen molecule. Not all of these desirable attributes are yet combined in one drug, but progress toward that goal is moving forward. The NINDS has applied for provisional patents to cover the newly discovered compounds. This will allow the NINDS to grant a license that would enable a company to invest in the extensive clinical testing that will be necessary to bring a drug to market. In 2007 and 2008, the project will continue drug development, extending to additional lead compounds, and moving the most promising candidate drugs through efficacy testing in a mouse model of SMA and additional safety studies.

The NINDS is also applying lessons learned from the SMA Project in a 2007 initiative to provide medicinal chemistry resources for the development of drugs for other neurological disorders. The SMA Project highlighted the lack of access to medicinal chemistry as a major roadblock to drug development and demonstrated that these resources can be provided efficiently and effectively via a contract approach.

Item

Sturge-Weber Syndrome - The Committee encourages the Director to develop collaborative, multidisciplinary research, translational and clinical studies on SWS with appropriate institutes and centers, as well as with other, appropriate government agencies. The Committee encourages NIH to utilize all appropriate mechanisms and resources in carrying out these studies. (p. 130)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad program of research to better understand congenital seizure disorders, including Sturge-Weber syndrome. For example, an NINDS-funded project is collecting images of the brains of children with Sturge-Weber syndrome to look for correlations between changes in brain structure and activity and the clinical outcome for these individuals. Results from this study may provide neuroimaging markers which could be used to predict the clinical progression in Sturge-Weber syndrome and to guide treatment choices.

NINDS also supports research on the basic biological mechanisms underlying epilepsy and normal brain development, both of which may contribute to a better understanding of the progressive nature of Sturge-Weber syndrome. Several studies are looking at the role of neurotrophins, small proteins that regulate the growth and survival of nerve cells. One newly funded study is examining whether blocking one of the neurotrophin receptors may be limit the initiation of epileptic activity in a mouse model. Other studies are characterizing the role of neurotrophins and other molecules in typical brain development. Further research is characterizing when and how seizures induce long-term changes in the brain development, changes which could lead to cognitive or other impairments. A better understanding of the detailed mechanisms of normal brain development, and of the consequences of epilepsy may aid in determining the most appropriate strategies to treat many of the symptoms of Sturge-Weber syndrome.

The NINDS has collaborated and will continue to partner with other Institutes and Centers at NIH on initiatives and other activities of relevance to seizure disorders such as Sturge-Weber syndrome, including in the areas of epilepsy, nervous system development, and the interaction between the brain vasculature and neuronal function. For example, the Office of the Director, the NINDS, and 14 other NIH Institutes which support neuroscience research have created a framework called the NIH Blueprint for Neuroscience Research to enhance cooperative activities. The NIH Blueprint goal for fiscal year 2008 is to generate novel research tools and resources to rapidly advance the field of neural development. While the NIH Blueprint does not focus on diseases, the tools and resources developed by the Blueprint will be relevant to research on all neurodevelopmental disorders, including Sturge-Weber syndrome.

Item

Tuberous Sclerosis Complex (TSC) - 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. Because of the effects of TSC on multiple organ systems, the Committee encourages the Office of the Director to work with all institutes involved in TSC research to revise the 10-year TSC Research Plan into a comprehensive TSC Research Strategy for a Cure. The Committee encourages NIH to organize a conference with all institutes supporting TSC research. Also, the Committee encourages the Director to support translational research and to fund new investigators in the TSC research field. The Committee is encouraged by the collaborative efforts that have been brought forth to produce the Program Announcement on Understanding and Treating Tuberous Sclerosis Complex. The Committee encourages NIH to continue this program announcement in future years and expand the number of participating institutes. (p.130/131)

Action taken or to be taken

The NIH established a trans-NIH Tuberous Sclerosis Working Group, with representatives from the NINDS, NCI, NIDDK, NHLBI, NIAMS, NIMH, NICHD, NIGMS, NHGRI, the Office of Rare Diseases, and from the Tuberous Sclerosis Alliance, to identify research portfolio gaps and develop new initiatives. One of the major activities of the group is to review the status of the trans-NIH Research Plan for Tuberous Sclerosis, developed in July 2003 as a ten-year strategic research plan to improve TSC detection and treatment. The plan includes both long-range (greater than ten-year) goals as well as specific objectives expected to be achieved within a five-year timeframe. The Working Group will develop a mid-course implementation update of the current Research Plan, focusing on scientific advances over the last three years, current opportunities in the field, and potential implementation strategies. The NIH also coordinates its activities with the Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP) on TSC. For example, the Program Director for TSC at NINDS serves on the CDMRP Integration Panel for TSC research which prioritizes and recommends the funding of grant applications.

The NIH Institutes and Centers support many investigator-initiated grants related to TSC. In addition, the NINDS, NIDDK, NIMH, NCI, NIAMS, and the TS Alliance released a

program announcement with set-aside funds (PAS) to further stimulate research on understanding and treating TSC. The PAS, which is active until March 2008, is intended to stimulate research on the molecular, genetic, developmental, and pathophysiological aspects of the disease, and on preclinical therapy development and clinical research. The grants awarded under this initiative so far address a number of critical questions, including TSC protein signaling pathways and the development of skin tumors and seizures. All of these studies have the potential to identify and develop new treatment strategies for some of the major clinical complications found in TSC, and each is directly relevant to the goals of the NIH Research Plan for Tuberous Sclerosis to determine the molecular and cellular basis of TSC, and to understand and treat the symptoms of TSC.

Item

Vulvodynia – Since fiscal year 1998, Congress has highlighted the need for research on the prevalence, causes and treatment of vulvodynia, a painful and often debilitating disorder of the female reproductive system. The Committee is pleased that some progress has been made since that time. For example, NICHD has supported a major study of the prevalence of this disorder. The Committee calls upon the Director to build upon these initial successes by coordinating through the Office of Research on Women’s Health an expanded and collaborative extramural and intramural research effort into the causes of and treatments for vulvodynia. This expanded effort should involve ORWH, NICHD, NINDS and other relevant ICs as well as the NIH Pain Consortium and should emphasize etiology and multi-center therapeutic trials. In addition, the Committee is concerned that many women with vulvodynia remain undiagnosed. To address this shortcoming, the Committee encourages NIH to include information about vulvodynia on its website and that it work with relevant groups to implement a national education program for primary care health professionals, patients and the general public on vulvodynia its symptoms, diagnosis and treatment options. The Committee encourages the Director to include experts on vulvodynia and related chronic pain and female reproductive system conditions on peer review panels. Finally, the Committee encourages NICHD to reissue its request for applications in this area and to fund high quality applications. (p. 131)

Action taken or to be taken

Multiple activities have advanced NIH’s efforts to develop a research portfolio and outreach program in vulvodynia. ORWH has collaborated with NICHD, NINDS, and the NIH Pain Consortium to expand NIH funding for vulvodynia including two currently active program announcements. The Center for Scientific Review's role in this instance is to include appropriate experts in vulvodynia and related chronic pain and female reproductive system conditions on peer review panels by consulting with leaders in the scientific community as well as NIH program officials to ensure that the needed expertise is identified and recruited. In addition to funding scientific research for this disorder, NIH has supported three scientific workshops in 1997, 2003 and 2004. The Director of the Office of Research on Women’s Health served as the co-chair for the 2004 state of the art conference, convened by the University of Medicine and Dentistry of New Jersey, titled “Vulvodynia – Toward Understanding a Pain Syndrome” with the founding president of the North American Menopause Society, and with key participation from

The National Vulvodynia Association and NICHD. The outcome of this meeting was recently published in the Journal of Reproductive Medicine. This article details the important issues for researchers and patients such as the need to standardize the definition of vulvodynia, to precisely characterize the pain, and to establish the natural progression of vulvodynia. With input from NICHD, NINDS, and other ICs, the ORWH and NIDDK are currently leading the development of a Women's Urologic Health Outreach Program that intends to focus on urinary incontinence, urinary tract infections, and chronic pelvic pain conditions in women, including vulvodynia. Finally, ORWH has posted general information and facts about vulvodynia and conference proceedings on the ORWH website.

To further outreach efforts, ORWH is actively working with the National Vulvodynia Association to explore development of a national educational program for primary health care professionals, patients and the general public on vulvodynia's symptoms, diagnosis and treatment options. NICHD, NINDS, The Pain Consortium and other relevant DHHS agencies such as the CDC, HRSA, FDA, and HHS will collaborate with ORWH on the efforts aimed at advancing research and education on vulvodynia.

Senate Significant Items

Item

Autism Spectrum Disorders - The Committee is encouraged by NIH's autism research matrix and encourages NIH to devote sufficient resources to this research agenda. The Committee encourages NIH when implementing the autism research matrix to coordinate with autism organizations already funding research initiatives to ensure the most efficient use of its resources. The Committee also notes the promise of particular areas cited in the matrix, including genetic, gene-environment interactions, behavioral characterizations of the disorder, screening and early diagnosis, and the development of evidence-based interventions. (p.160)

Action taken or to be taken

Please refer to pages 275 of this document for the NIH response to this item on Autism spectrum disorders.

Item

Autoimmune Diseases -- Congress commends the NIH Autoimmune Diseases Coordinating Committee [ADCC] for fostering collaborative, integrated multi-Institute research on issues affecting the genetically related family of autoimmune diseases. The ADCC should focus on the role of environmental and infectious agents in the initiation and/or exacerbation of autoimmune diseases. Additionally, the Committee encourages the ADCC to be proactive in identifying promising areas of autoimmune research where collaboration among the NIH institutes enhances the potential for major advances. (p. 160/161)

Action taken or to be taken

The Environment/Infection/Gene Interactions in Autoimmune Diseases program, cosponsored by more than a dozen Institutes and Centers of the National Institutes of Health (NIH), supports basic and population-based research on the role that environmental, infectious, and genetic factors play in initiating or exacerbating autoimmune diseases. Infectious agents have received particular attention. For example, the product of a human gene that confers susceptibility to Crohn's disease recognizes components of certain bacteria. Viral infections have long been suspected as triggers of type 1 diabetes. Other recent research suggests that the numbers of immune system cells that normally hold potentially destructive immune responses in check are reduced by viral infection. New data have also emerged that link dietary exposure to certain foods, particularly the timing of introduction of cereals in infant diets, as a possible etiologic factor in type 1 diabetes. Another NIH program, the Fetal Basis of Adult Disease: Role of the Environment initiative, investigates whether *in utero* exposures to environmental agents or chemicals cause increased susceptibility to autoimmune or other diseases later in life.

The Gene and Environmental Initiative (GEI), a trans-NIH initiative led by the National Human Genome Research Institute (NHGRI) and the National Institute of Environment Health Sciences (NIEHS), provides support for research to identify major genetic and environmental susceptibility factors for diseases of substantial public health impact. The GEI is aimed at developing programs for cutting-edge approaches to whole genome analysis with an emphasis on how environmental exposures affect gene expression patterns and confer epigenetic changes. Eight solicitations for grant applications have been issued to date.

The NIH will continue to work through the ADCC to provide a forum for discussion of possible areas of collaboration between NIH Institutes and Centers that will advance research on autoimmune diseases.

Item

Basic Behavioral Research – OBSSR is congratulated on its tenth anniversary at NIH. The Committee encourages OBSSR to continue working to build alliances among institutes that support and nurture basic behavioral and social sciences research. In particular, the Committee encourages OBSSR to partner with NIGMS and other funders of basic research to enhance support for work on methods, animal models, and the interplay of biological factors, behavioral and social influences underlying phenomena such as stress that influence multiple health conditions. (p. 158)

Action taken or to be taken

Please refer to page 276 of this document for the NIH response to this item on Basic Behavioral Research.

Item

Center for Scientific Review [CSR] – The Committee has received reports from scientists and professional organizations that many grant applications are referred to study sections that do not include reviewers with the appropriate expertise. The Committee is concerned that this may be adversely impacting research in important areas of science and medicine, such as cardiothoracic surgery. The Committee requests that CSR examine the pattern of grant application referral to study sections, especially as it relates to cardiothoracic surgery grants, and be prepared to report at the fiscal year 2008 hearings on the results of the examination and what recommended steps may be needed to assure that applications are reviewed by study sections that have the expertise to provide a thorough, impartial review. (p. 161)

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).

CSR has a close working relationship with the cardiothoracic surgery research community. The Director of CSR and the Scientific Review Administrators (SRAs) that manage these three 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.

SRAs 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. Routinely, the CICS study section has one to two temporary members attending the study section to review applications in this area. 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

Clinical Research – The Committee is aware that NIH is establishing large, validated databases to measure patient-reported outcomes from clinical trials that cover a wide range of chronic diseases and demographic characteristics. NIH is urged to create databases to measure and track outcomes for surgical procedures, in order to establish common data standards and facilitate comparisons among surgical clinical research studies. A report on the development of these surgical databases is expected in the fiscal year 2008 Congressional budget justifications. (p. 161/162)

Action taken or to be taken

The NIH Patient-Reported Outcomes Measurement Information System (PROMIS), a project of the NIH Roadmap for Medical Research, is a 5-year effort to develop and validate measurements of self-reported symptoms and other health-related quality-of-life outcomes (e.g., pain, fatigue, anxiety, social functioning) that are associated with many chronic diseases. It began in FY 2004 with the funding of six primary research sites and a statistical coordinating center. Since then, investigators decided what information will be collected, agreed on data collection methods, developed data collection software, and began gathering details about the physical, mental, and social health of about 8,000 members of the general population and about 4,000 people known to have a chronic disease. PROMIS focuses solely on measures that can accurately describe the day-to-day functioning of patients with chronic pain conditions or chronic diseases such as arthritis, multiple sclerosis, or asthma. While developing common measures and tracking outcomes from surgical procedures is beyond the mission of the NIH, the scope of the PROMIS initiative, an ability to quantify changes in patients' physical, mental, and social well-being has important applications for surgical intervention evaluations. To this end, the PROMIS could serve as a potential model for researchers who are interested in developing a similar resource for tracking surgical outcomes.

Item

Down Syndrome – The Committee urges the Director of NIH to establish an NIH Down syndrome research task force on cognition to develop a strategic plan for genetic and neurobiological research relating to the cognitive dysfunction and the progressive late-life dementia associated with Down syndrome. The purpose of the strategic plan is to

provide a guide for coordinating Down syndrome research on cognition across NIH and for enhancing the development of new research efforts based on identification of areas of greatest scientific opportunity, especially as they relate to the development of future treatments. The plan should include short-, intermediate- and long-term goals for basic and clinical research with strategies for achieving goals and with specified time frames for implementation. (p. 162)

Action taken or to be taken

Please refer to pages 279 of this document for the NIH/OD response to this item on Down Syndrome.

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 encourages continued work in this important area of study and treatment. (p.162)

Action taken or to be taken:

Intramural researchers at the National Institutes of Health (NIH) continue to explore the use of botulinum toxin (sold under the trade names of Botox®, Myobloc™, and Dysport®) for treating focal dystonias, that is, those dystonias that are limited to a single area of the body such as the neck, eyelid, hand, or voicebox (larynx). Currently, NIH investigators and their collaborators are trying to improve upon the current success of this therapy; for example, they are combining botulinum toxin injection with a medication taken orally and are planning to explore the combination of botulinum toxin with physical therapy.

The National Institute of Neurological Disorders and Stroke (NINDS) has also funded extramural researchers to study many areas of dystonia research, some of which may impact the use of botulinum therapy. For example, a research team recently explored the relative contributions of the sensory and motor systems to dystonic movements. In this study, they used multiple imaging techniques to examine the activation of motor and sensory brain areas during motor tasks in individuals with focal hand dystonia. This information will help to further characterize the abnormal neural circuitry that underlies the disorder, so that subsequent studies can more carefully explore how current therapies - including botulinum toxin - interact with this system and how the effectiveness of these therapies can be enhanced. Another research team funded in part by the NINDS, the National Institute for Research Resources, the National Institute of Biomedical Imaging and Bioengineering, and the NIH Roadmap for Medical Research has also demonstrated that botulinum toxin treatment can reverse abnormalities in neuronal connectivity and fiber pathways observed in regions of the brain implicated in dystonia. In addition to these advances, the NINDS will also be supporting exploratory extramural research on how the immune response to botulinum toxin can be reduced. This reaction can reduce the prolonged effectiveness of the toxin; thus strategies for limiting or eliminating the immune reaction may improve the benefits of botulinum toxin to patients.

Item

Education and the Workplace - The Committee encourages OBSSR to intensify its efforts to increase scientific understanding of the elements of education and the workplace that most affect health. The Committee strongly encourages OBSSR to increase its investment in projects and studies that focus on maintaining behavior change in the areas of disease prevention, control, and health outcomes especially in cancer, diabetes, obesity, asthma, heart disease, HIV/AIDS, chronic obstructive pulmonary disease, and stroke. (p. 158)

Action taken or to be taken

In FY 2004 the National Institute of Child Health and Human Development (NICHD), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the Office of Behavioral and Social Sciences Research (OBSSR) and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention invited applications for cooperative agreements (U01) to participate in a research network to design model protocols for intervention studies that examine the health consequences of workplace policies and practices. The purpose of the RFA was to support the development of research plans focused on the interrelations among work, family, health, and well-being that are state of the art in conceptualization and measurement techniques.

In regard to maintaining behavior change, OBSSR continues to coordinate a five-year research grant program that is co-sponsored by several NIH components, including the Office of Disease Prevention, the National Cancer Institute, the National Institute on Aging, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Child Health and Human Development, the National Institute on Drug Abuse, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Mental Health, the National Institute of Nursing Research, and the National Heart Blood and Lung Institute. Applications funded under this program were required to focus on important health-related behaviors already demonstrated amenable to short-term change, such as tobacco use, exercise, eating habits, alcohol and drug use, inoculation obtainment, disease screening, stress reduction, adherence to health care regimens, human immunodeficiency virus (HIV) or sexually transmitted infection (STI) risk practices. OBSSR is providing annual support to a coordinating center: The Health Maintenance Consortium (HMC) is comprised of NIH program staff, research investigators at the individual sites, and representatives from co-sponsoring private foundations and it is encouraging and facilitating collaboration across the research projects.

Item

Fragile X - The Committee notes the impressive progress made by Fragile X researchers in understanding the basic neural defects that cause this developmental disorder. The success of these translational research efforts has made treatment of Fragile X a near-term possibility. However, collaborative efforts between industry, academia and NIH Institutes are likely to be necessary to develop promising therapies. The Committee

further notes that while Fragile X is a relatively common genetic disease, the treatments being developed for Fragile X may also be effective for a much larger number of people with related autism spectrum disorders. Research has shown many possible treatment strategies which merit human Fragile X clinical trials, including, but not limited to, mGluR5 antagonists, Ampakines, aripiprazole, and lithium. The Committee strongly urges the Director to facilitate and fund public/private partnerships that will enable these vital studies to proceed. The Committee also urges the Director to take an active role in coordinating Fragile X research at NIH, by organizing regular intramural meetings of program directors from all institutes sponsoring Fragile X research projects. (p. 162)

Action taken or to be taken

The NICHD is the lead NIH institute in funding Fragile X (FX) research. It funded the initial discovery of the genetic basis for FX and the most likely first target of drug therapy. In FY 2005, NICHD funded about 30 research grants and other awards that support FX research. This portfolio is continually updated with new applications and investigators, ensuring the quality of the FX research effort. The NICHD works with other NIH I/Cs that fund FX research, such as NIMH and NINDS, and FX advocacy groups. A common initiative was the jointly solicited Program Announcement “Shared Neurobiology of Fragile X Syndrome and Autism” that attracted 17 new applications. The NICHD organizes regular trans-NIH meetings of FX research program directors, which jointly issued an RFA to re-compete the FX Research Centers in FY 2008, encourages the submission of applications on high priority topics, and fosters cooperation among institutions, funding agencies, and advocacy constituencies in creating a coherent national translational research infrastructure for FX studies.

The NICHD leads NIH’s implementation of the Best Pharmaceuticals for Children Act. In July 2006 it sponsored a workshop on approaches to new pharmacological approaches in treatment of FX. Attendees including scientific experts and representatives of FX advocacy groups, who assessed the state of interventions research in FX, particularly interventions for children, and identified key areas for future emphasis. The workshop pointed to the need for physicians experienced in clinical trials to enter the field of FX research. NICHD, NIMH, and NINDS are exploring ways to jointly support the public/private testing of new pharmaceuticals for the treatment of FX.

The NICHD-funded Pediatric Pharmacology Research Network is poised to facilitate testing of therapeutic agents after pre-clinical tests evaluate their safety and potential to ameliorate FX. Already NICHD has received a high quality application to screen potential drugs for FX. NICHD is also collaborating with investigators to develop and test new methods for screening newborn infants for FX, an important part of NICHD’s broader initiative on newborn screening for genetic disorders.

Item

Gene Therapy Research – The Committee is encouraged by promising research being undertaken in gene therapy, especially in regard to thalassemia, or Cooley’s anemia. It is concerned, however, that the current mechanism for funding gene therapy research, while promoting advancement of individual components of gene therapy, lacks an overarching

strategy that will coalesce these advances and encourage the ultimate goal of curing genetic disorders expeditiously. Last year, the Committee urged the Director to assess the prospects for the most promising areas for breakthroughs in this field and to develop an aggressive program to focus resources on it. A meeting was convened on the topic, but the Committee believes that more focused and aggressive action is needed. NIH is strongly urged to develop a plan for assessing the prospects for success in Cooley's anemia and a broad range of diseases, with the goal of curing a single gene disorder in the shortest possible time utilizing gene therapy. (p. 162/163)

Action taken or to be taken

Please refer to page OD-6 and 7 of this document for the NIH response to this item on Gene Therapy Research.

Item

Hereditary Hemorrhagic Telangiectasia (HHT) – The Committee is aware that HHT is a rare, multi-system genetic disorder of the blood vessels that can result in stroke, hemorrhage, and death. The Committee encourages the NIH to explore opportunities for additional clinical and basic research on HHT. (p. 163)

Action taken or to be taken

The NHLBI has been funding research on HHT for many years, and this work has resulted in important contributions to understanding the underlying disease process. Gene mutations in two endothelial cell proteins were identified in samples from HHT patients and studies are being conducted to understand the biological effects of these mutations. In June 2006, NHLBI participated in the NIH Workshop “Hereditary Hemorrhagic Telangiectasia: Vascular biology and pathophysiology.” About 100 scientists and physicians attended this meeting, which featured presentations on the state of the art and expert subgroup discussions on promising research opportunities in HHT, major obstacles to progress, approaches to advance HHT research. A grant-writing and training workshop was also offered, primarily to assist young investigators in obtaining independent NIH support for HHT research. In addition, NHLBI staff met with the leaders of the HHT community and the executive secretary of the HHT Foundation. They will continue discussions about research opportunities in HHT. Also, NHLBI has received a new grant application to study the molecular basis for vascular defects such as those seen in HHT. Understanding the molecular defects could provide new therapeutic targets for treating HHT patients.

Item

Human Embryonic Stem Cell Research --The Committee also strongly urges that the NIH explore all avenues of stem cell research including adult stem cells and alternative methods of establishing human embryonic stem cell lines that do not involve the destruction of an embryo. The Committee is also deeply concerned with the slow pace of implementation of the current stem cell policy. The Committee was informed that, under the budget request, NIH plans to spend \$39,000,000, the same as fiscal year 2006, on human embryonic stem cell research. The Committee strongly urges the NIH to commit a substantial amount of resources to all methods of human embryonic stem cell research. Finally, the Committee expects the NIH to provide detailed reporting on funding for all forms of stem cell research in future congressional budget justifications. (p. 103)

Action taken or to be taken

The National Institutes of Health (NIH) continues to lead the federal effort in supporting stem cell research. For example, in FY 2006, NIH spent approximately \$38 million in research studying human embryonic 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 in FY 2006.

NIH continues its support of research in human non-embryonic stem cells. In a recent study, NIH-supported scientists have now been able to isolate and study single cells from human bone marrow that have characteristics of multipotent stem cells. The human cells seem to have the ability to repair rat heart muscle damaged by a heart attack. If this work can be repeated in humans, it offers the hope of treatment for those who suffer a heart attack.

NIH is supporting research on alternative methods to establish pluripotent stem cell lines that do not involve the destruction of an embryo. For example, a technique called “Altered Nuclear Transfer” (ANT) proposes to create patient-specific stem cells without destroying an embryo. The proponents of ANT attempt to address concerns about embryo destruction by suggesting that because the entity created is unable to implant in the uterus (due to turning off the *Cdx2* gene), it is not a true embryo. NIH-supported scientists recently reported proof of principle tests that ANT works in mice. This technique must still be tested with monkey embryos, and the manipulation needed to control *Cdx2* expression needs further study.

In addition, NIH continues to support and conduct numerous research projects studying hESCs. Examples of these projects include: Exploratory Centers for Human Embryonic Stem Cell Research, the National Stem Cell Bank, and Centers of Excellence in Translational Human Stem Cell Research. NIH’s continued support of hESC infrastructure grants have 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 recently awarded training grants to support seven hESC short-term training courses, enabling scientists to learn hESC culturing techniques.

NIH continues to stimulate the field of stem cell research by issuing numerous initiatives and announcements for research funding. The amount of research supported by NIH is based on research grant applications submitted by the research community that are deemed meritorious by peer review and there is no limit to the amount of funding that could be spent for this research.

Item

Human Tissue Supply —The Committee remains interested in matching the increased needs of NIH grantees, intramural, and university-based researchers who rely upon human tissues and organs to study human diseases and search for cures, including for those researchers dedicated to the study and cure of rare diseases. The Committee is

aware that one of the leaders in this competitive field, the National Disease Research Interchange [NDRI], is positioned to obtain this valuable and effective alternative research resource. More than 500 peer-reviewed research advances made by NDRI-dependent researchers have been published in recent years, contributing to the research community's fund of knowledge. The Committee encourages the Director to increase support NDRI receives from NCCR, and to broaden the scope of the multi-Institute initiative by strongly urging the Institute Directors of NCI, NHGRI, NHLBI, NICHD, NIMH, and NINDS to identify and expand support for NDRI. (p. 163)

Action taken or to be taken

Please refer to page 281 of this document for the NIH response to this item on Human Tissue Supply.

Item

Information, Dissemination and Outreach.—The Nation invests greatly in the NIH providing tremendous opportunities for accelerated improvements in health and quality of life. Research advances must be applied more expeditiously to ensure greater improvements in health outcomes across all communities of color and the general public. To maximize the benefits of this national Federal enterprise and resource, the Committee strongly urges the NIH to improve, strengthen, and expand its systems of information dissemination and outreach to healthcare providers, minority organizations, and the public. The NIH system must accelerate the dissemination and application of research findings and advances in prevention, diagnosis, treatment, behavioral response, awareness, and other health improvement opportunities. (p. 163/164)

Action Taken or To Be Taken

NIH research has resulted in groundbreaking treatment strategies and increased knowledge about prevention and the role of lifestyle modifications in maintaining health. The NIH websites make available a tremendous variety of health information, both scientific and consumer oriented, and they are accessed more than one billion times each year by health professionals, scientists, and the public. In addition, the NIH annually sends out nearly 30 million science-based publications to requestors who rely on the NIH and its news stories, press releases, and publications for authoritative information about the latest research developments. Surveys show that the majority of Americans who request NIH information not only use it, but share the materials they receive with someone else, often a family member, spouse, friend, coworker, and more than 40% take the material to discuss with their physician.

The NIH Office of Communications and Public Liaison and its 27 component public affairs offices continue to strengthen, expand, and accelerate information dissemination and outreach efforts. NIH has intensified its support for the evaluation of the websites of its component organizations. A redesigned NIH website will debut in 2007 and reflects new technologies that offer the agency additional means for disseminating health information. These include customized streaming news feeds such as RSS (Really Simple Syndication – can also be referred to as RSS Feed, web feed, RSS stream, or RSS channel) and Podcasting – a digital recording of a radio broadcast made available on the

Internet for downloading to a personal audio player or a computer. The Podcasting service begun this year had 55,000 downloads in October alone, and brings NIH research to the generation of health consumers who rely on portable devices for news. NIH continues to provide direct information to more than 700 radio stations each week. In addition, the NIH Radio News Service is now available to more than 4 million listeners on XM Satellite Radio through a radio feature called “NIH Health Matters.” Importantly, NIH is making major efforts in Spanish language radio, understanding this is a primary resource for health information for these communities. For public health workers and for community-based health centers, NIH publishes online and in print and accessible monthly, “News in Health.” A new magazine, “NIH MedlinePlus,” brings the latest and most authoritative information from NIH directly to patients in physicians’ offices.

The NIH recognizes the need to apply research advances in such a way as to ensure improved health for all Americans. This year, NIH released the third cycle of trans-NIH PARs supporting research on health literacy. The results from this research will inform the development of materials for the public. NIH also participated in the development and distribution of tool kits on health literacy as a part of an overall DHHS effort designed to address one of our greatest national challenges. The agency also seeks to take advantage of all available opportunities to bring health news and information to the public on a regional, local, and community level. The NIH MedlinePlus website has extensive health information from all the NIH components; a new feature provides more than one-third of Americans with a “Go Local” capability that puts them in touch with health resources in their communities. NIH also exhibits at or participates in the programs of leading national organizations such as the NAACP, AARP, and the APHA, as well as programs such as the “We Can!” Event held on the National Mall and at the Jackson Medical Mall in Jackson, Mississippi.

Collaborating with specialized populations provides an important and unique opportunity for NIH investigators. Special, targeted materials come directly from ongoing research. For example, NIH researchers are collaborating with Pima Indian volunteers who provide investigators with a unique opportunity to study insulin resistance, obesity, and diabetes. Also, there are NIH communication projects aimed at improving the lives of a number of specialized populations. There are extensive NIH websites aimed at the special health needs of American Indians, Asian Americans, those living in Arctic regions, and the elderly. In addition, the NIH continues to intensify its efforts to make health information available in Spanish. In addition to many printed publications, there is extensive online information in Spanish at <http://salud.nih.gov> and <http://MedlinePlus.gov/spanish>.

Item

Irritable Bowel Syndrome – The Committee is pleased with the increased focus on irritable bowel syndrome [IBS] at the NIH’s Office of Women's Health, and urges the office to continue expanding research on this prevalent functional gastrointestinal disorder. (p.158)

Action taken or to be taken

The Office of Research on Women's Health (ORWH), ensures that research conducted and supported by NIH adequately addresses issues regarding women's health, and that women are appropriately represented in biomedical and biobehavioral research studies supported by NIH. Within the NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has lead responsibility for digestive diseases research and supports a significant portfolio on irritable bowel syndrome (IBS) and related gastrointestinal and motility disorders. Because IBS is a disorder that affects far more women than men, ORWH is continuing to effectively partner with NIDDK to support and stimulate research on IBS. For example, NIDDK co-funds an ORWH Specialized Center of Research at UCLA that is focused on IBS and another poorly understood visceral pain syndrome, interstitial cystitis. This center is conducting both basic and clinical studies that are helping to advance understanding of IBS and its symptoms and to develop improved therapeutic approaches for this condition. With co-sponsorship from NIDDK and other ICs, ORWH recently reissued the Request for Applications (RFA), "Specialized Centers of Interdisciplinary Research (SCOR) on Sex and Gender Factors Affecting Women's Health," thus creating new opportunities for research on IBS. Some IBS patients experience fecal incontinence, and ORWH has contributed to planning efforts by the NIDDK and the NIH Office of Medical Applications of Research (OMAR) for a state-of-the-science conference on fecal and urinary incontinence to be held in 2007. The ORWH will continue to seek opportunities to partner with NIDDK in support of IBS research.

Moreover, in order to identify promising future research directions for digestive diseases, such as IBS and related motility disorders, the NIH has established a National Commission on Digestive Diseases, which is charged with developing a Long-Range Research Plan for the field. The ultimate goal of the Plan is to improve the Nation's health through advancing digestive diseases research. The Commission will conduct an overview of the state-of-the-science in digestive diseases research and make specific recommendations to improve approaches to diagnosis, treatment, and prevention. Convened for their first meeting in June 2006, the Commission identified 13 compelling research topic areas for chapters of the Research Plan including "Functional Gastrointestinal Disorders and Motility Disorders." The Commission reconvened on November 6, 2006, to hear progress reports from members chairing the 13 Working Groups assigned to the research topic areas. A third Commission meeting is planned for June 2007. The ORWH has joined the Commission as an *ex officio* member, and will help coordinate NIH efforts to implement the research recommendations in the Plan for IBS and other digestive diseases that disproportionately affect women.

Item

Lymphangioleiomyomatosis [LAM] – The Committee remains very interested in efforts to find a cure and treatments for LAM, a progressive and fatal lung disease that strikes women, usually in their childbearing years. Currently, there are no effective treatments. 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 urges the NHLBI, as well as the NCI, the Office of Rare Diseases, and the NINDS to find clinical treatment trials through both intramural and

extramural means and 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 also commends the NCCR and ORD for their roles in supporting the Rare Lung Disease Consortium. (p. 164)

Action taken or to be taken

NHLBI-supported basic research into the origins and growth of LAM cells is providing insights that may someday help control the disease. Investigators have identified proteins that promote the growth and movement of LAM cells and that also suggest an explanation for how LAM cells can metastasize among different organs, including the lung, kidney, and lymphatics. More is being learned about the role of estrogen and why LAM affects women almost exclusively.

NHLBI-funded scientists exploring the cellular pathways affected by genetic abnormalities in tuberous sclerosis complex (TSC) and LAM cells found that an essential protein for controlling cell size and growth was missing or misshaped. This finding led quickly to a potential target for treatment of LAM when it was discovered that sirolimus (rapamycin) mimics the function of the missing protein. A promising pilot study of sirolimus as a possible treatment for TSC and LAM, sponsored by the NCI through the Quick Trial Initiative, provided a basis for development of a larger and more definitive multicenter trial under the auspices of the Rare Lung Diseases Consortium supported by the ORD and NCCR. The protocol is currently in the final stages of approval. Additional therapeutic approaches will most likely be needed, however, because LAM cell lines derived from different individuals appear to vary in their sensitivity to sirolimus. This observation, and the evolving concept that LAM behaves like a neoplasm, suggests that multiple drug therapy will be the key to controlling the disease.

NHLBI intramural investigators have been able to isolate LAM cells from blood and other body fluids, thereby facilitating genetic diagnosis of the disease. LAM cells in the lungs and in culture have markers on their surface similar to those found in breast cancer and melanoma. These markers may target LAM cells to different organs in the body.

Researchers studying lung tissue from LAM patients have found increased production of proteins that cause the destruction of the lung. These and associated proteins are similar to those found in breast and other cancers. A collaborative extramural–intramural clinical trial is being planned to test whether these proteins can be safely inhibited and whether such inhibition improves lung function in patients with LAM.

The NHLBI intramural program continues to support the collection, processing, and distribution of LAM tissue. The Institute also continues to co-fund the annual scientific conference organized by the LAM Foundation. Information on LAM research is exchanged and discussed at trans-NIH TSC coordinating committee meetings, organized by the NINDS.

Item

Lymphatic Research – The lymphatic system plays a vital role in the immune system, the digestive system, and a wide range of diseases, including lymphedema, asthma, and cancer. There is growing evidence, for example, that intervening in the lymphatic system could help reduce the spread of tumors. Other research suggests that it contributes to unwanted inflammation. Until recently, however, the scientific and medical professions have not sufficiently recognized its importance. While substantial resources have been spent to study the blood circulatory system, far fewer have been devoted to the lymphatic circulatory system. Therefore, the Committee urges the NIH to consider research on the lymphatic system as an initiative within the newly created Office of Portfolio Analysis and Strategic Initiatives. In keeping with OPASI's purpose, such research would address an area of emerging scientific opportunity, and it would not focus on a specific group of diseases, but a broad range. Furthermore, while a better understanding of the lymphatic system would benefit numerous Institutes and Centers, basic research in this area currently falls both within and between existing IC missions – a situation that contributes to the scientific neglect of the lymphatic system. The Committee also urges the NHLBI, NCI, NIAID and other ICs to improve coordination for lymphatic system research through the Trans-NIH Coordinating Committee and to specifically cite lymphatic system research in NIH funding mechanisms such as program announcements and RFAs.
(p. 164)

Action taken or to be taken

The NIH OPASI is giving careful consideration to all lymphatic-focused initiatives proposed by NIH components. Last year the Trans-NIH Coordinating Committee for Lymphatic Research asked its member institutes and centers to review their initiatives for relevance to lymphatic research and to add appropriate language wherever possible; we continue to urge our members to include lymphatic research topics in their relevant initiatives. The NHLBI and the Coordinating Committee are developing a new trans-NIH program announcement in which a special emphasis panel with appropriate expertise to review the resulting applications will be convened. Further, the Coordinating Committee, under the leadership of the NHLBI, is planning a trans-NIH working group on lymphatic biology and disease that will address basic, clinical, and translational issues to develop further initiatives in these areas. The Coordinating Committee is also developing a Web site to promote lymphatic disease research in the intramural and extramural programs across the NIH.

Item

Medical Challenges - In light of new medical challenges such as SARS and the threat of bioweapons, the Director is encouraged to increase collaborative efforts to address these and other medical challenges. In addition the Committee encourages the Director to conduct multi-institute projects to address these challenges. (p. 164)

Action taken or to be taken

The NIH continues its long-standing commitment to encouraging research through a multi-institute and collaborative approach. This approach to research can lead to

important advances in emerging and re-emerging medical challenges which may not be possible through individual efforts.

NIH has encouraged industry participation in research for a number of years. Recently, NIH developed the Cooperative Research Partnerships for Biodefense initiative, which supports the discovery, design and development of vaccines, therapeutics, adjuvants and diagnostics for NIAID Category A-C priority pathogens and toxins. In addition, the NIH-supported Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases (RCEs), conduct research focused on countering threats from bioterror agents and emerging and re-emerging infectious diseases. Each Center is comprised of a consortium of universities and research institutions serving a region of the United States.

One trans-NIH research effort is the Influenza Genome Sequencing Project which is providing the scientific community with complete genome sequence data for thousands of human and animal influenza viruses. This Project is a collaborative effort which involves the NIAID and the National Library of Medicine. The Project also reaches beyond the NIH campus to collaborate with non-profit and academic research institutes, public health departments, the World Organization for Animal Health/ Food and Agriculture Organization of the United Nations International Reference Laboratory; and other agencies such as the Los Alamos National Laboratories.

Finally, the NIH has addressed obstacles to effective vaccine design, production, and delivery through a Roadmap-initiated Exploratory Center for Vaccinology Research. This center involves an interdisciplinary team approach to solving significant and complex problems in vaccine development, safety and adverse events, production and supply, acceptance and use. It also includes components that aim to explore the design and limitations of quantitative methodologies to define molecular signatures of adaptive and innate immune responses to influenza vaccines, and design novel approaches to influenza vaccine policy.

These multi-institute and collaborative research partnerships in infectious diseases, genomics and immunology and are examples of the NIH commitment to realizing scientific opportunities and addressing important public health challenges through research enabled by collaboration and multi-institute projects.

Item

Nanosystems Biology – The Committee encourages the Director, along with 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. 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 that 10 percent may represent a specific type of the disease, for which the drug in question may be 100 percent effective. 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.165)

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 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, NCI has established eight centers of excellence, 12 technology platform developmental partnerships, and multidisciplinary career training / teams. The aim is to develop nanotechnology and integrate it into cancer research to accelerate molecular-level assessment / intervention based on the new technology and systems approaches.

Furthermore, NCI's Nanotechnology Characterization Laboratory (NCL) formed a partnership with the National Institute of Standards and Technology and the Food and Drug Administration in 2005 to perform rigorous physical, in vitro, and in vivo characterization of nanomaterials. Characterization data is now being disseminated to the community on the NCL website (<http://NCL.cancer.gov>). NCI's Integrative Cancer Biology (ICB) program researchers 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 ICB 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 ICB program has continued partnership with the NIH Nanomedicine Roadmap initiative to expand micro and nanotechnology tool development and systems modeling approaches to further enable cancer signature detection, targeting, and treatment. NCI's Cancer Imaging Program (CIP) is leading clinical testing for the imaging agents ferumoxytol and Combidex. These iron oxide nanoparticles can be used to image lymph nodes, brain tumor margins and vasculature. An exploratory trial has been completed to assess the ability of ferumoxytol to better delineate brain tumor margins and new blood vessel growth. The results of this trial were presented at the Annual meeting of the American Society of Neuroradiology in May 2006 and a manuscript has been submitted to Neurosurgery. A follow-up trial to evaluate the response of high-grade brain tumors to therapy is in the final planning stages and is expected to open in the second quarter FY07. Additionally, a multicenter trial with Combidex to assess its utility in evaluation of lymph node metastases in cervical cancer will open in the first quarter FY07. NCI's CIP and NCL collaborate to combine complementary expertise and resources to more effectively develop and translate nanomaterials for both imaging and therapy applications. They are currently working together to assist a small company in bringing a multifunctional nanostructure with both imaging and drug delivery capabilities to the clinic. Realizing the vital role of imaging in the development of nanomedicines, NCI has established a

comprehensive pre-clinical imaging facility at Frederick that will expand the combined capabilities of CIP and NCL in the understanding of nanosystems biology.

Item

National Children's Study – The Committee was very disappointed that the President's budget proposed to eliminate funding for the National Children's Study. The Committee supports full and timely implementation of the Study [NCS] and has included funds within the Office of the Director to continue the study. This study aims to quantify the impacts of a broad range of environmental influences, including physical, chemical, biological and social influences, on child health and development. Now that the pilot phase of the project has gotten underway, the Committee believes it is timely to reconsider the scientific strategy to measure environmental exposures and genetic factors. Major scientific advances have occurred in several fields since the National Children's Study was first authorized, and the leadership of the NCS is urged to bring in additional objective scientific expertise to assess the scientific merit of the study components. The Committee further urges the NIH to coordinate the involvement of the Departments, the lead Federal partners and other interested institutes, agencies and non-Federal partners conducting research on children's environmental health and development, such that this study is ready for the field by no later than 2007. (p. 165)

Action taken or to be taken

The NIH acknowledges the Committee's support for the National Children's Study. The President's budget does not request funds to support the Study in FY 2007. As is described in the NICHD Congressional Justification, the FY 2008 President's budget request continues that policy.

Item

National Commission on Digestive Diseases.—The Committee directs the Director of the National Institutes of Health is planning to extend the charter for the National Commission on Digestive Diseases from 2 years to 4 years from the date of its establishment in order to provide for adequate consideration of all study, evaluation, and planning matters as directed by the Committee in Senate Report 108-345 for fiscal year 2005 (as carried out by the Director in the notice appearing in the Federal Register of August 26, 2005, volume 70, number 165, pages 50377-50378). (p.165)

Action taken or to be taken

The NIH has taken steps to extend the charter so that the Commission will have adequate time to complete its deliberations and develop a long-range research plan for the field. At its first public meeting on June 12, 2006, the Commission members planned their approach to this task. Since then, the Commission has: (1) determined the 13 topic areas within digestive diseases research that will make up the research plan; (2) assigned Commission members to chair 13 topical Working Groups; and (3) concluded an open call for nominations of additional experts to serve as Working Group members.

The Commission reconvened on November 6, 2006 to hear progress reports from Working Group chairs. A third Commission meeting is planned for June 2007.

Item

National Primate Research Centers.—The Committee recognizes the need to raise awareness of the availability of the National Primate Research Centers' [NPRCs] nonhuman primate resources amongst Institute and Center Directors and within the NIH-funded research community. The NPRCs provide access to resources such as: nonhuman primates for NIH-funded experiments; nonhuman cells, fluids, tissues, organs, proteins, cell lines, and nucleic acid samples; immunological reagents for nonhuman primate research; comprehensive genetic and genomic information for nonhuman primates; and venues for the assessment of nonhuman primate behavior and cognition. These unique resources and expertise contribute to the overall effectiveness of the Federal investment in biomedical research. (p. 165)

Action taken or to be taken

The NCRP continues to conduct outreach activities to inform the NIH Institute/Center Directors and staff and the NIH-funded research community about the resources available through the National Primate Research Centers (NPRCs). NCRP's Web site contains extensive information and materials that describe the activities of the NPRCs, including specific information for NIH grantees on how to access NPRC resources. NCRP staff also present this information at scientific meetings, including at the 24th Annual Symposium on Non Human Primate Models of AIDS, the International Neuroscience meeting, and the Sixth Comparative Medicine Resource Directors' meeting. These meetings were held in October and November of 2006.

In April 2006, the NCRP organized and convened a workshop entitled, "Genetic tools for optimizing the use of rhesus macaques for translational research." Workshop participants included representatives of the all eight NPRCs, many other NIH-funded scientists who utilize the rhesus for translational studies, and Program representatives from all of the NIH Institutes and Centers that fund significant activities utilizing the rhesus as an animal model of human disease. The workshop provided specific recommendations that are being implemented by the NCRP and a follow-up workshop is planned for the spring of 2007.

The NPRCs support research on infectious diseases, such as AIDS and malaria, and emerging threats, such as avian flu. NCRP staff collaborate closely with staff from other NIH Institutes and Centers to inform them of NPRC resources that could enhance the infectious disease research activities that their IC supports. For example, NCRP staff have met with NIAID staff and discussed regarding the potential role of the NPRCs in research involving radiation exposures and antidotes.

Neurobiology, including studies on Alzheimer's and Parkinson's' disease, is another field of research supported extensively by the NPRCs. To this end, the NPRCs have joined the Biomedical Informatics Research Network (BIRN) to expand interactions of neuroimaging studies to include non-human primates. Further, to better coordinate NIH activities, the NCRP participated in a meeting in November 2006, where the NPRC Directors met with representatives of the NIH Institutes that sponsor neurobiology-related

research. The meeting helped inform the staff about NPRC capabilities to enable neurobiology research.

Item

Obesity Research Task Force —The Committee commends the NIH for creation of an Obesity Research Task Force and for NIH’s recognition of the need to prevent and treat obesity beginning in childhood. However, the Committee strongly urges the Task Force to explicitly include, across the six proposed trans-NIH obesity initiatives, investigations into the genetic causes of obesity beginning with study of Prader-Willi syndrome. Furthermore, the Committee urges the Director of NIH to conduct outreach to the Prader-Willi Syndrome community to participate in research at the proposed “Obesity Clinical Research Center.” The NIH should be prepared to report on the progress made by the Obesity Research Task Force, and the trans-NIH research efforts to appropriately incorporate both children and genetics into the overall obesity research agenda during the fiscal year 2007 appropriations hearings. (p. 166)

Action taken or to be taken

An important component of the multifaceted, trans-NIH obesity research effort is studies of genetics in children and families. This research includes studies of Prader-Willi Syndrome (PWS). For example, as part of the NIH’s Rare Diseases Clinical Research Network., the NIH Office of Rare Diseases, NCRR, and NICHD support a consortium focused on PWS and two other syndromes, which includes a longitudinal study of PWS and early-onset morbid obesity. NICHD-supported genetic studies of children and families with PWS include correlating characteristic PWS symptoms with genetic subtypes and improving understanding of a genetic defect involved in PWS. In addition to these genetic studies, the NICHD also supports research on controlling the drive to overeat in children with PWS, family-based interventions to improve adherence to diet, and relevant brain imaging research.

Examples of other genetic research on obesity include NICHD intramural and extramural studies of genetic contributions to obesity in children of different racial/ethnic groups. The NIDDK and other NIH institutes also support studies of families, including those affected by extreme obesity, to identify additional genetic variations that contribute to obesity. The NHLBI recently launched the Framingham Genetic Research Study, and plans to apply similar approaches to other large cohort studies of cardiovascular disease. Genetic factors underlying obesity are expected to be an important component of the research, with implications for obesity in both children and adults. The NIDDK is also developing an initiative to encourage further genetic research with data from existing large clinical obesity studies. Animal models research, supported by multiple ICs, will also yield insight into human obesity genetics. The NIH is continuing the development of an intramural Obesity Clinical Research Center, called the Metabolic Clinical Research Unit (MCRU), as a unique resource for a broad range of pediatric and adult research, including genetic and other research. The NIH continues to seek guidance from external experts on research areas for the MCRU and strategies for fostering collaboration among extramural and intramural scientists. NICHD intramural scientists are planning studies of children with PWS to be conducted at the MCRU, and will work

with the PWS community to encourage participation. All of these efforts are integral to the vigorous trans-NIH basic and clinical obesity research efforts, and complement other NIH-supported pediatric obesity research, such as studies of prevention and treatment approaches in school, primary care, home, and other settings.

Item

Ombudsman Activities – The Committee understands that, with the exception of a limited number of topics such as the treatment of human subjects, neither the NIH nor the Department has a structure in place to process and address complaints by investigators and others about the ways in which NIH-funded research activities are conducted. In an agency with an annual appropriation of more than \$28,000,000,000, this is not acceptable. The Committee strongly urges the NIH to put in place a structure in which complaints about NIH-funded grants and other activities can be evaluated objectively. (p. 157)

Action taken or to be taken

The NIH has clearly established methods for addressing concerns and complaints raised by investigators and others about the conduct of NIH-funded research activities. Where appropriate, concerns about specific awards are normally addressed by the NIH Institute or Center that supports the grant in question. Issues that cannot be resolved by the Institute are generally referred to some component of the Office of Extramural Research. The Office handles a number of such concerns each year.

The disposition of any concern depends on the content. For example, if the complaint involves allegations of misconduct in research, well established procedures are followed to protect the identities of the involved individuals and the information is forwarded to the DHHS Office of Research Integrity (ORI), which has statutory authority to investigate these matters. Information on ORI can be found at <http://ori.dhhs.gov>. If there is a complaint regarding the management of grants (appropriate use of funds, etc.) the OER Office of Policy on Extramural Research Awards (OPERA) is responsible and has compliance processes in place to address them. Information on issues handled by OPERA is available at <http://grants1.nih.gov/grants/compliance/compliance.htm>. Issues involving human subjects are sent to the Office of Human Research Protections (OHRP). See the OHRP website at <http://www.hhs.gov/ohrp/>. If the complaint concerns laboratory animals, the NIH Office of Laboratory Animal Welfare (OLAW) is responsible and has procedures to handle such allegations. See information on OLAW at <http://grants1.nih.gov/grants/olaw/olaw.htm>. If there are general issues related to program integrity the NIH Office of Management Assessment (OMA) will investigate allegations. See information on OMA at <http://oma.od.nih.gov/index.html>.

The Office of Extramural Research (OER) already serves in an Ombudsman role, identifying the nature of concerns and addressing the issues either internally or by referring to the responsible offices or agencies. Although the availability of such services is widely known in the extramural research community, the NIH will examine ways to increase the visibility of these functions.

Item

Prader-Willi Syndrome – The Committee recognizes the commitment to establish a Rare Diseases Clinical Research Center as part of the Rare Diseases Clinical Research Network for the study of Prader-Willi syndrome and other rare disorders. The Committee strongly encourages that the RDCRC program be expanded to increase the level of research being conducted (p. 167)

Action taken or to be taken

Prader-Willi Syndrome (PWS) is a complex neurobehavioral syndrome with main clinical features of morbid obesity, long-term compulsive overeating (hyperphagia), food foraging and obsession with food, hypotonia, cognitive impairment, a distinct, difficult behavioral phenotype, hypogonadism, and poor weight gain in infancy, and excessive and rapid weight gain between ages one and six. Psychiatric and behavioral manifestations are also common in PWS. Prader-Willi Syndrome is one of three syndromes under study at the Angelman, Rett, and Prader-Willi Syndromes Consortium that is part of the larger Rare Diseases Clinical Research Network. The consortia have received five-year funding totaling \$6.25 million and are coordinated by the Office of Rare Diseases (ORD), the National Center for Research Resources (NCRR), and the National Institute of Child Health and Human Development (NICHD). Ultimately, the consortium will provide Prader-Willi patients and their physicians with the most up-to-date information possible about the syndrome; link patients with doctors who specialize in the syndrome; help patients learn about and become involved with clinical trials that may help in the treatment of their illness; research new treatments for the syndrome; ensure that clinical trials are held in multiple locations across the United States; better understand, diagnose and treat the syndrome; and provide better training for doctors and medical students. The consortium maintains an active affiliation with the Prader-Willi Syndrome Association (USA).

In 2006, the “Prader Willi Syndrome and Early-Onset Morbid Obesity Natural History Clinical Protocol” was approved and patient accrual has been initiated. The specific aims of the study are to establish a phenotype-genotype correlation among the molecular classes of PWS; evaluate the effects of growth hormone treatment in PWS started at different ages; and compare patients with PWS with other patients with early-onset morbid obesity.

Item

Psoriasis - The Committee urges the Director to expand and coordinate research and related activities with respect to psoriasis and psoriatic arthritis across all relevant institutes, centers and offices, particularly at NIAMS and NIAID, to help foster new, safe, and effective treatments for these diseases and move toward a cure. (p. 167)

Action taken or to be taken

Please refer to pages 287 of this document for the NIH response to this item on Psoriasis.

Item

[Research on health benefits of dietary supplement] – The Committee continues to strongly support the important work of this Office. Use of dietary supplements has increased significantly among Americans who want to improve their health and prevent disease. There is a great need for additional research to better inform consumers of the health benefits of supplements. (p. 158)

Action taken or to be taken

The NIH Office of Dietary Supplements (ODS) coordinates its programs to make the best use of available resources. This can be illustrated with the Congressionally-mandated Analytical Methods and Reference Materials (AMRM) Program, which develops and disseminates validated analytical methods and reference materials for commonly used dietary supplement ingredients such as vitamin D, ginkgo, and a multivitamin-mineral product.

Without good knowledge of the product being tested, it is difficult to compare the results of one study with another or to generalize results from studied ingredients to marketed products containing those ingredients. Funding studies with inadequately characterized products is not research money well spent. Just as important, the AMRM Program also provides tools to help manufacturers implement their quality-control procedures so that marketed products will contain the labeled ingredients at specified levels.

The AMRM Program is well underway for a wide range of dietary supplements. Examples of how it integrates with other ODS programs are as follows:

Evidence-Based Review Program: By systematically reviewing the scientific evidence on the effectiveness and safety of supplements, this program identifies research needs, which in turn helps the AMRM Program prioritize which ingredients to study.

Grants and Extramural Activities Program: The AMRM Program supports this activity by providing expert input to NIH on how best to select and characterize test ingredients for studies of dietary supplements.

Training and Career Development Program: The AMRM Program sponsors classes to ensure that research and industry laboratories use valid analytical methods and reference materials to characterize ingredients in supplements. This will expand the pool of scientists with the necessary skills.

Botanical Research Centers Program: Plans are underway to establish collaborations between the AMRM Program and the Congressionally mandated Botanical Research Centers that are jointly funded by ODS and the National Center for Complementary and Alternative Medicine to increase the number of supplement ingredients for which analytical methods and standard reference materials are developed. These collaborations facilitate the sharing of expertise common to these two different program areas.

To convey the results of its activities to the public, ODS is developing fact sheets on dietary supplements at various reading levels that reflect the latest research on these products to help consumers make informed choices and to help health professionals in answering consumer questions.

Item

Research Training - The Committee commends the NIH Director for his efforts to improve training for young investigators through the new Pathway to Independence program. The Committee encourages the NIH to maintain its commitment to training future biomedical and behavioral scientists, including women and minority researchers, who are instrumental in understanding health disparities. Given the importance of reducing health disparities in diseases such as cancer, diabetes, heart disease, as well as mental disorders, it is crucial that NIH increase the coordination of data collection and the development of objectives and long-term outcome measures across institutes and centers and review whether current reductions in training are having disproportionate impacts on minority investigators. (p. 167)

Action taken or to be taken

The NIH remains committed to training future generations of biomedical, behavioral, and clinical scientists, and is acutely aware of the need to support the recruitment of new investigators from diverse backgrounds. NIH routinely monitors needs for researchers in specific areas and the participation of various groups in its research training and career development programs both internally, across its Institutes and Centers, and externally, with the help of outside experts and evaluators. For example, NIH is currently planning the next in an ongoing series of studies by the National Academy of Sciences (NAS) that provide guidance on the number and type of new investigators that should be trained in various biomedical fields. At NIH's request, past NAS committees have considered the composition of the research workforce and made recommendations to the NIH for enhancing its diversity.

Over the past year, NIH has begun revising its research training funding announcements to include new wording designed to encourage increased participation of individuals underrepresented in science. NIH also has launched several new initiatives to modify its data analysis systems to provide more complete and accessible data on the participants in – and outcomes of – its research training programs. Moreover, in response to a 2005 NAS report that identified areas for improvement in NIH's efforts to train and retain minority investigators, the NIH Director has convened a committee to improve trans-NIH coordination, monitoring, and evaluation of its research training programs and policies aimed at improving the diversity of the scientific workforce. The committee, which includes Dr. Jeremy Berg, Director of the National Institute of General Medical Sciences, Dr. John Ruffin, Director of the National Center on Minority Health and Health Disparities, and is expected to issue its recommendations in 2007.

Item

Review of Grant Applications - The Committee is concerned that review time for proposals submitted to the Institute at NIH continues to average about 18 months from the submission of the grant proposal to the awarding of the grant. The Committee strongly urges the Director to speed up the grant process and award grants on an expedited basis. (Page 167)

Action taken or to be taken

The current NIH timeline from receipt of an application to grant award averages 10.3 months. NIH peer review of grant applications for scientific merit is legislatively mandated under section 492 of the Public Health Service Act as described in regulation at 42 CFR 52h. The Federal Advisory Committee Act (FACA) governs the establishment and operation of the NIH peer review committees. All applications submitted to NIH are evaluated using a two level review process that ensures an impartial and credible process employing the highest level of ethical standards. Conflict of interest by any participant in the process, in the form of financial, personal, or professional interests as defined by regulation and policy is avoided in order to reduce the appearance of bias.

NIH is working to reduce the time from receipt to award by moving to electronic grant applications and by using various technologies to process those applications. Technologies being tested include the use of knowledge management systems to assist in the referral to an SRG as well as to a funding Institute or Center. Such systems may ultimately help with the identification of peer reviewers and the identification of conflicts of interest. In some cases, electronic applications are sent to reviewers in advance of the meeting and special programs and interfaces allow reviewers to enter critiques in a secure fashion and to partially review applications in advance of the actual review meeting. In some cases, meetings can take place in secure webspace in order to reduce or avoid travel time. Some of the NIH Institutes and Centers use expedited second level review to accelerate the processing and approval of specific applications. The Center for Scientific Review is also piloting a process that provides summary reports to applicants on an expedited basis so that they can revise and resubmit for the next receipt date. The NIH will continue to look for other approaches to protect the integrity of the review process while reducing the time from receipt of an application until an award is made.

Item

Small Business Research.—Innovative ideas from small businesses have the potential to be rapidly translated into patient monitoring devices or treatments. The Committee urges all Institutes and Centers to take advantage of the Small Business Innovation Research [SBIR] and Small Business Technology Transfer [STTR] programs to speed research on new technologies that can lead to improvements in the prevention, diagnosis, and cure of diabetes and its complications. (p. 167-168)

Action taken or to be taken

The NIH has and will continue to encourage research on a range of program priorities, such as efforts to combat diabetes, through the SBIR/STTR program. Among the diabetes-related topics of interest listed in the 2006 SBIR and STTR NIH Omnibus Solicitation are: methods for predicting, preventing or delaying progression of diabetes and its complications; high throughput assays based on biologic pathways likely involved in the pathogenesis of diabetes and its complications; animal models or surrogate markers to monitor disease progression or therapeutic approaches for diabetic complications; behavioral approaches for prevention or treatment of type 2 diabetes; means to identify islet cell progenitors, to predict islet transplant success, and for non-invasive imaging of pancreatic beta cell mass; means to protect islet cell grafts after transplantation; means to

generate or expand the number of functional islets *in vitro*; strategies to modulate the immune system so as to prevent or slow progression of type 1 diabetes; and new therapies to prevent, delay or treat diabetes or its complications including behavioral approaches. In addition, recent SBIR and STTR diabetes-specific requests for applications include those for development of new therapeutics and monitoring technologies for type 1 diabetes, and for applying cutting edge technology for development of new approaches to prevent, treat, and cure type 1 diabetes and its complications. Current solicitations are encouraging research on the application of bioengineering approaches to obesity. A host of opportunities exists for SBIR projects to advance research on the prevention, treatment, and control of diseases such as diabetes.

Item

Spinal Muscular Atrophy - The Committee encourages the Director to ensure the success of the SMA project by providing active and ongoing support from the OD as well as from other related institutes. The Committee is aware that the current SMA project is scheduled to conclude in 2007 and encourages the Director to begin planning for the necessary follow-on effort to maximize the results of this innovative project for SMA and to ensure it serves as a model for other diseases. (p. 168)

Action taken or to be taken

Please refer to page 290 of this document for the NIH response to this item regarding Spinal muscular atrophy.

Item

Temporomandibular Joint [TMJ] Disorders – While much work remains, the Committee is encouraged by actions taken over the last year by NIH to expand research on TMJ disorders. The Committee commends the Directors of NIDCR, NINDS and ORWH for their efforts to increase research on genetic and environmental factors that may increase risk for the onset and progression of these disorders and attract new investigators to the field. The need for safe and effective prostheses for TMJ patients who have lost jaw tissue due to disease or disease treatments remains a critical issue, and the Committee applauds NIDCR for giving high priority to advancing tissue replacement technology. In cooperation with NIBIB, recommendations from the third scientific meeting of The TMJ Association provide bioengineering approaches that can be implemented which will improve diagnostics as well as treatments for TMJ 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 invigorate such collaborative efforts in these areas over the coming fiscal year and to coordinate the work of all relevant ICs and give priority to collaborative, cross-cutting research. The Committee also strongly urges the NIH to take concrete steps to develop informational materials directed to medical, dental and allied health professionals (e.g., nurses, dental hygienists) to improve understanding of TMJ diseases and disorders and their frequent co-morbidities. Such an effort should be directed and coordinated by OWRH in collaboration with other ICs, including NIDCR, NIAMS, NINDS, NIBIB and NHLBI. (p. 168/169)

Action taken or to be taken

Many of the issues mentioned in this item are and will continue to be addressed through the collaborative activities of the Temporomandibular Muscle and Joint Disease Interagency Working Group (TMJDIWG). This group is comprised of representatives from 11 ICs at NIH including ORWH, NIDCR, NIAMS, NINDS, NIBIB, and NHLBI, five non-NIH agencies, and non-federal observers including representatives from the TMJ Association and the Jaw Joints and Allied Musculoskeletal Diseases group. Approximately two years ago, the TMJDIWG spearheaded an interest in the relationship between Temporomandibular Joint Disorders (TMJDs) and co-morbid health conditions. This resulted in the issuance of an announcement sponsored jointly by several ICs for research aimed at uncovering the biological underpinnings of the connection between TMJDs and these co-morbidities. Further, the TMJDIWG will coordinate inter-institute activity aimed not only at addressing the recommendations of the 3rd scientific meeting of the TMJ Association about imaging the TMJ but also in reviewing progress on recommendations from a variety of other sources.

Recent NIBIB activities already are beginning to address the recommendations resulting from the Third Scientific Meeting of the TMJ Association. The NIBIB has funded a number of research grants supporting the development of imaging technologies that can address physiological and anatomical problems in bone and cartilage as well as the development of new bioengineering approaches that can improve biomaterials used for bone implants and scaffolds. Some of these grants involve collaborations with other ICs. Further, in the last year, NIBIB has joined with the NIDCR in co-funding the TMJ Bioengineering Conference and the TMJ Implant Registry and Repository.

The NIH is committed to providing resources for health care professionals on all diseases and conditions affecting the American people. We do so based only on the most current and complete scientific evidence. The NIDCR publication “TMJ Disorders” is available to the public and health care providers and provides information about the disorder and treatment approaches. While there is ample anecdotal evidence that a group of co-morbid conditions (e.g., CFS, irritable bowel syndrome, sleep disorders, cardiovascular problems) appear to occur along with TMJD, there are no data collected in a systematic way that confirm these reports. Thus, it would be premature to publish advisories for health care professionals until scientific evidence on this topic is available. Once such information is available, the ORWH in collaboration with NIDCR and other NIH ICs, will coordinate the development of informational materials for health care professionals.

Item

Translational Research – The Committee is very supportive of translational research and strongly encourages the NIH to integrate such research as a permanent component of the research portfolio of each institute and center. The Committee urges NIH to begin discussions to determine how best to facilitate progress in translating existing research findings and to disseminate and integrate these findings at the practice level. Translational research should also include the discovery and application of knowledge within the practice setting using such laboratories as practice-based research networks.

This research spans biological systems, patients, and communities, and arises from questions of importance to patients and their physicians, particularly those practicing primary care. The Committee strongly encourages all of the NIH Institutes and Centers to support translational research in the behavioral and social sciences to address how basic behavioral processes inform the diagnosis, prevention, treatment, and delivery of services. The Committee requests the Director of NIH to include a progress update in next year's budget Justification. (p. 169)

Action taken or to be taken

NIH has issued numerous funding opportunity announcements (FOAs) on translational research. There is great variety with respect to: 1) the Institutes and Centers (ICs) that are supporting translational research in the behavioral and social sciences; 2) the range of topics covered by the FOAs (e.g., obesity; diabetes; alcohol and drug abuse; sleep disorders; mental health issues; cognitive deficits; heart, lung, and blood diseases; stroke; pain; HIV/AIDS;); and 3) the funding mechanisms used. Examples include the following:

Mind-Body Interactions and Health (R24) <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-005.html> Total awarded: \$3.0 M by OBSSR, NCCAM, NIA, NIMH, NINDS. Studies of the effects of stress on health, are supported, including the translation of successful interventions into programs deliverable in clinical settings.

Focal Cognitive Deficits in CNS Disorders (R03, R21) <http://grants.nih.gov/grants/guide/pa-files/PA-07-034.html> NINR, NIA, OBSSR. This FOA invites applications to expand basic and translational research, including intervention research, on the types, nature, and functional consequences of focal or specific cognitive deficits experienced by persons with central nervous system disorder, especially translational studies on generalizing interventions to real-world settings.

Clinical and Translational Science Award (U54) <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-002.html> This NIH Roadmap initiative funds a national consortium that will transform how clinical and translational research is conducted, ultimately enabling researchers to provide new treatments more efficiently and quickly to patients. Twelve CTSA's have been awarded so far, with 60 expected by 2012. Total first year funding is \$100 million with \$500 million expected in 2012. A second solicitation for CTSA's has been issued, calling for the next round of submissions in January 2007, with awards expected in fall 2007. For more information about this program, see <http://www.nih.gov/news/pr/oct2006/ncrr-03.htm>.

More translational research FOAs: Drug Addiction (R03)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-07-011.html>; Community-Based Participatory Research (R21) <http://grants.nih.gov/grants/guide/pa-files/PA-07-004.html>; Pain Research (R21, R03, R01) <http://grants.nih.gov/grants/guide/pa-files/PA-06-542.html>; Diabetes and Obesity (R18/R34) <http://grants.nih.gov/grants/guide/pa-files/PA-06-532.html>; Cross-Disciplinary Translational Research (R21) <http://grants.nih.gov/grants/guide/pa-files/PA-06-321.html>; Health Services Research in NIDA's Practice Based Network (R01) <http://grants.nih.gov/grants/guide/pa-files/PA-06-495.html>; Dissemination and Implementation

Research (R01) <http://grants.nih.gov/grants/guide/pa-files/PA-07-086.html>; Research Demonstration and Dissemination(D&D) Grants (R18) <http://grants.nih.gov/grants/guide/pa-files/PA-07-017.html>

To further stimulate translational research in the behavioral and social sciences, OBSSR (with NCI, NIMH and other ICs) will hold the first of a series of annual workshops on dissemination and implementation in FY07. In the first year, the focus will be on attracting potential grant applicants and potential grant reviewers to listen to the research presented by investigators funded under the existing set of FOAs and presented by other investigators working in this area. An additional purpose will be to engage additional ICs on this topic and inspire them to sign on to sponsoring the existing announcement (PAR - 07-086) and future FOAs.

Item

Tuberous Sclerosis Complex (TSC) - 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. Because of the effects of TSC on multiple organ systems, the Committee encourages the Office of the Director to work with all institutes involved in TSC research to revise the 10-year TSC Research Plan into a comprehensive TSC Research Strategy for a Cure. The Committee encourages NIH to organize a conference with all institutes supporting TSC research. Also, the Committee encourages the Director to support translational research and to fund new investigators in the TSC research field. The Committee is encouraged by the collaborative efforts that have been brought forth to produce the Program Announcement on Understanding and Treating Tuberous Sclerosis Complex. The Committee encourages NIH to continue this program announcement in future years and expand the number of participating institutes. (p. 169 Senate)

Action taken or to be taken

Please refer to page 292 of this document for the NIH/OD response to this item on Tuberous sclerosis complex (TSC).

Item

Women and AIDS Treatments - While much progress has been made with regard to AIDS treatments, considerable work remains especially with regard to HIV/AIDS across communities of color and in women. The Committee encourages the NIH to further examine how these medications work in smaller frame women; how best to ensure women follow treatment regimens; mental health impact of HIV/AIDS in women including depression; and impact on memory, AIDS related cognitive dementia. (p. 160)

Action taken or to be taken

Issues of women and AIDS are an important part of the NIH AIDS research agenda, and the annual Trans-NIH Plan for HIV-Related Research, developed by the Office of AIDS Research, includes a specific chapter on women and girls. NIH research has demonstrated that women progress to AIDS at lower viral load levels and higher CD4 counts than men. Women also experience different clinical manifestations and complications of HIV disease. These findings may have implications for care and

treatment of HIV-infected women, particularly with antiretroviral therapy. The restructured AIDS clinical trials networks, including the International Maternal Pediatric Adolescent AIDS Clinical Trials Network, the AIDS Clinical Trials Group Network, and a number of studies in women are investigating questions about specific characteristics of women and girls that might play a role in transmission, acquisition, or resistance to HIV infection during different stages of the life course. These studies require large numbers of women, as there are many potential confounding issues that must be addressed, such as the impact of nutritional status, race/ethnicity, and hormonal status. NIH places high priority on the recruitment and retention of women in clinical trials. A new NIAID RFA will be funded in FY 2008 examining the pathogenesis of HIV infection in women, including the impact of treatment and the ramifications of treatment.

Adherence to antiretroviral therapy is essential for the adequate control of HIV infection, its symptoms, the impact upon quality of life, and ultimately upon life expectancy. NIH continues to examine factors that enhance or impede adherence behavior in the context of complex confounding issues, such as depression and substance abuse. The NIH-funded Women's Interagency HIV Study (WIHS) has published several papers in this area. NIH has funded seminal work on issues related to mental health in HIV-infected women. Studies conducted through both the NIH-funded networks (WIHS, Women-Infant Transmission Study, IMPAACT) and investigator-initiated research have documented the risk of depression and antiretroviral adherence, the impact of depression upon survival in HIV-infected women, and the role of Post Traumatic Stress Disorder in HIV risk, including a history of sexual abuse.

NIH-sponsored studies on the neurocognitive effects of HIV infection have provided insight into memory-deficits associated with HIV disease that persist during antiretroviral treatment. NIH continues to support studies delineating the immune-based mechanisms that lead to HIV-related neurocognitive disorders, the contributing role of opportunistic infections, and the impact of therapies that can successfully cross the blood-brain barrier and enter tissues that serve as viral sanctuaries.

Item

Vulvodynia – In recent years, NIH has supported two 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 expanded effort should involve ORWH, NICHD, NINDS and other relevant ICs, as well as the NIH Pain Consortium. The Committee commends ORWH for initiating a dialogue with the National Vulvodynia Association to determine the best approach for launching an educational outreach campaign on vulvodynia, as the Committee requested last year. ORWH is encouraged to implement this effort with the help of other relevant ICs and women's health offices in governmental agencies including HHS, FDA, HRSA and CDC. 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. 159)

Action taken or to be taken

Please refer to pages 293 of this document for the NIH response to this item on Vulvodynia.