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Item

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

Action taken or to be taken

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

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

Item

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

Action taken or to be taken

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

Item

Marfan Syndrome- The Committee commends NHLBI for its strong support of research on Marfan syndrome, particularly the Pediatric Heart Network clinical trial focused on the drug losartan. The Committee encourages the Institute to work with the Marfan syndrome community on strategies for establishing specialized treatment centers. (p. 94)

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

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

Item

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

Action taken or to be taken

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

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

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

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

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

Action taken or to be taken

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

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

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

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

National Institute of Dental and Craniofacial Research (NIDCR)

House Significant Items

Item

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

Action taken or to be taken

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

Senate Significant Items

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

House Significant Items

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

Item

Chronic Pediatric Kidney Disease - Translational and clinical research to understand the mechanisms involved in kidney injury and progression are important to develop and test new therapies in children. The Committee encourages NIDDK to initiate multi-center pediatric nephrology translational studies or treatment trials as the best opportunity to systematically gain new knowledge about children being treated for kidney disease, and to use this knowledge to improve care and reduce future costs. (p. 144)

Action taken or to be taken

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

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

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

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

Item

Digestive Diseases - Diseases of the digestive system continue to affect more than one-half of all Americans at some time in their lives. The Committee looks forward to the recommendations of the National Commission on Digestive Diseases and urges NIDDK to consider the Commission's recommendations (p. 144).

Action taken or to be taken

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

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

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

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

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

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

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

Action taken or to be taken

To resolve issues concerning optimal use of the many available therapies against hepatitis B, in October 2008, the NIDDK convened an NIH Consensus Development Conference on management of hepatitis B, together with the Office of Medical Applications of Research, and the Johns Hopkins University School of Medicine, with additional support from the National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAID), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA). The purpose of this 3-day conference was to examine important issues in hepatitis B therapy, including which groups of patients benefit from treatment and at what point during treatment is the benefit achieved, as well as which groups do not show a benefit from currently available treatments. The external experts serving on the conference panel addressed major questions regarding hepatitis B management related to current burden, disease development, benefits and risks of current treatment options, who should or should not be treated, appropriate measures to monitor treatment, and the greatest challenges and opportunities for future research on hepatitis B. Their recommendations were made available to the research community and the public following the conference. The panel's full statement and additional information about this conference are available at: *http://consensus.nih.gov/2008/2008HepatitisBCDC120main.htm*.

Item

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

Action taken or to be taken

The NIDDK, in collaboration with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the Office of Medical Applications of Research, sponsored a State-of-the-Science conference on Incontinence in Adults in December 2007. Following a series of scientific presentations by experts and open public discussions, an independent panel concluded that fewer than half of individuals experiencing incontinence report their symptoms to healthcare providers without being prompted. In response to the recommendation of the conference to raise public awareness of incontinence, the NIDDK, in consultation with advocacy organizations, is beginning to lay the groundwork for an awareness campaign for fecal incontinence. Regarding urinary incontinence, the NIDDK supports the Urinary Incontinence Treatment Network (UITN) to conduct a series of rigorous, long-term clinical trials of therapies for incontinence in women. The UITN has completed three trials and NIDDK anticipates that the results of the third trial will be available by late 2009. The UITN addresses a recommendation of the State-of-the-Science conference to determine the effects of interventions in women with urinary incontinence.

Item

Inflammatory Bowel Disease (IBD) - The Committee commends NIDDK for its leadership on IBD and encourages the institute to strengthen its support for

genetic and clinical IBD research and other opportunities outlined in the research agenda, “Challenges in Inflammatory Bowel Disease.” The Committee particularly encourages NIDDK to support pediatric IBD research. (p. 145)

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

development, TrialNet is considering and prioritizing the testing of other therapies that are in the pipeline for future study.

Item

Type 1 Diabetes Research Biosamples - The Committee commends NIDDK for establishing biorepositories to house data and biological specimens collected by studies such as the international Type 1 Diabetes Genetics Consortium, the Environmental Determinants of Diabetes in the Young Study, and the natural history study of TrialNet. The Committee urges NIDDK to advertise widely to the diabetes research community the availability of samples, take steps to ensure that the biorepositories implement efficient procedures to disseminate rapidly those samples to qualified researchers, and develop policies to expedite the availability of samples from other clinical trials in type 1 diabetes. (p. 146)

Action taken or to be taken

The NIDDK appreciates the Committee's commendation for establishing biorepositories and the desire to ensure that samples and data from type 1 diabetes clinical research studies are made available to qualified researchers. To facilitate sharing of samples and data collected in its clinical studies, the NIDDK established the Central NIDDK Repositories in 2003. The Central Repositories permit the broad research community to access biosamples and data from many studies, including type 1 diabetes clinical research studies. Data from several genome-wide association studies (GWAS) focused on type 1 diabetes and its complications, such as the Type 1 Diabetes Genetics Consortium (T1DGC), the Epidemiology of Diabetes Interventions and Complications study, and the Genetics of Kidneys in Diabetes study, are being made available through the Repository in collaboration with the National Library of Medicine's database of Genotype and Phenotype (dbGaP). Therefore, the data from these GWAS studies are available in one place, making them easy to find and access. Scientists can find information on available samples and data, as well as procedures to request materials, on the Central Repositories' public website: www.niddkrepository.org.

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

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

The NIDDK also uses the NIH Guide for Grants and Contracts to broadly advertise the availability of samples in its type 1 diabetes clinical research studies. For example, a May 2008 notice announced the availability of serum, RNA, and peripheral blood mononuclear cell samples from people enrolled in the Natural History Study of Type 1 Diabetes TrialNet, for the purpose of validating new molecular markers (biomarkers) of type 1 diabetes. The NIDDK will continue to use a variety of methods to ensure that the scientific research community is aware of samples and data available through its type 1 diabetes clinical research studies, in order to accelerate research progress and to maximize the usefulness of the studies.

Senate Significant Items

Item

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

Action taken or to be taken

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

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

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

Item

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

Action taken or to be taken

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

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

Item

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

Action taken or to be taken

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

Item

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

the NIDDK to widely advertise the availability of samples to the diabetes research community, ensure that the biorepositories implement efficient procedures to rapidly disseminate those samples to qualified researchers, and develop policies to expedite the availability of samples from other clinical trials in type 1 diabetes. (p. 97)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Action taken or to be taken
The NIDDK established the Hepatitis B Clinical Research Network in fall 2008 to promote translational research on hepatitis B by elucidating disease processes and natural history, as well as developing means of treatment and control. The Network consists of 12 clinical centers, a data coordinating center, and an immunology center. Research conducted by the Network will address hepatitis B research questions and goals identified through past NIH-sponsored meetings on hepatitis B management, as well as in the trans-NIH *Action Plan for Liver Disease Research*.

For example, research recommendations from the NIH Consensus Development Conference on management of hepatitis B, held in October 2008, are informing research conducted by the Network. The NIDDK convened this Conference together with the Office of Medical Applications of Research and the Johns Hopkins University School of Medicine, with additional support from the NCI, NIAID, CDC, and FDA. The purpose of this 3-day Conference was to examine important issues in hepatitis B therapy, including hepatitis B management related to current burden, disease development, benefits and risks of current treatment options, which groups of patients benefit from currently available treatments, appropriate measures to monitor treatment, and the greatest challenges and opportunities for future research on hepatitis B. The recommendations from this Conference were made available to the research community and the public

following the Conference. The panel's full statement and additional information about this conference are available at:
http://consensus.nih.gov/2008/2008HepatitisBCDC120main.htm

Item
Hepatitis C - The Committee continues to strongly support the HALT-C clinical study on hepatitis C. The Committee also understands that nearly one-half of all persons with hemophilia have contracted the hepatitis C virus, and many of these individuals are co-infected with HIV. The NIDDK is encouraged to pursue research initiatives on co-infection and the progression of liver disease in this population. (p. 97)

Action taken or to be taken
Consistent with the stated goals of the trans-NIH *Action Plan for Liver Disease Research*, the NIDDK and other NIH Institutes and Centers continue to support research on liver disease associated with hepatitis C virus (HCV) infection, with or without human immunodeficiency virus (HIV) co-infection, in highly affected patient populations. Such populations include individuals with hemophilia who were infected by contaminated blood transfusions prior to a screening program for these pathogens in donor blood.

In a recent review of progress made toward achieving the goals of the *Action Plan*, advances were noted in research on HCV/HIV co-infection. For example, the Adult AIDS Clinical Trials Group funded by the NIAID is sponsoring a clinical trial entitled "Suppressive Long-term Antiviral Management of Hepatitis C Virus (HCV) in HIV-1 Co-infected Subjects," to evaluate the safety and efficacy of long-term antiviral treatment in co-infected individuals. Several NIH-funded prospective studies that are actively assessing factors associated with progression of liver disease in patients with HIV/HCV co-infection include: the Natural History of HCV infection in HIV disease study, sponsored by the National Institute on Drug Abuse (NIDA); the HIV/HCV-Coinfection, Antiretroviral Therapy and Fibrosis study, sponsored by the NIDA; and the Women's Interagency HIV Study, sponsored by the NIAID, NIDA, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and NCI. Additionally, the NIDDK has helped support research on genetic factors contributing to liver disease progression in persons with hemophilia who are infected with HCV, many of whom are co-infected with HIV, using data collected through the ongoing Multicenter Hemophilia Cohort Study sponsored by the NCI.

The NIDDK also continues to support clinical research on hepatitis C, with co-sponsorship by the NIAID and the NCI, through a multi-center clinical study of long-term therapy of chronic hepatitis C known as the Hepatitis C Antiviral Long-term Treatment Against Cirrhosis trial ("HALT-C"). The randomized clinical trial phase of HALT-C was completed in 2007, providing clear evidence that long-term treatment with low-dose peg-interferon was ineffective in preventing liver disease progression due to hepatitis C. However, the HALT-C trial is being

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

Item

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

Action taken or to be taken

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

In exploring the relationship between urologic chronic pelvic pain syndromes and other chronic pain conditions, MAPP Network scientists are focusing on conditions most strongly associated with IC/PBS and CP/CPPS in scientific studies thus far—chronic fatigue syndrome, fibromyalgia, and irritable bowel syndrome. NIH is also conducting efforts to promote research and education on the poorly understood urogenital pain condition, vulvodynia. The lead Institute for vulvodynia research, the NICHD, has collaborated with the ORWH to promote studies and raise awareness of this condition. Currently, NICHD and ORWH are cosponsoring an initiative to address basic, clinical, translational, epidemiologic and/or behavioral research that concentrates on studies of relevance to vulvodynia and that may lead to prevention and therapeutic opportunities. In fall 2007, ORWH, in partnership with NICHD, NINDS, and the NIH Pain Consortium, as well as the National Vulvodynia Association, the American College of Obstetricians and Gynecologists, and other professional groups, launched the Vulvodynia Awareness Campaign to inform the public about this condition and NIH research efforts to combat it. The NIH will continue to foster and support research on vulvodynia, and to coordinate educational efforts for patients and physicians based on research and scientific evidence.

Item

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

Action taken or to be taken

The NIDDK continues to sponsor the multi-center Nonalcoholic Steatohepatitis (NASH) Clinical Research Network to study the causes, contributing factors, natural history, complications, diagnosis, prevention, and therapy of this form of non-alcoholic fatty liver disease in both adults and children. Funding for this Network will be renewed in FY 2009 to continue this research for an additional five years, through 2014.

This Network of eight clinical centers and a data coordinating center is investigating the nature and management of NASH, and is conducting two clinical trials of potential therapies. One of the clinical trials is in adults, evaluating the safety and efficacy of potential treatments for NASH, the drug pioglitazone or vitamin E, as compared to a placebo. Results of this trial are expected in 2009. The other clinical trial is in children and is comparing the drug metformin, vitamin E, and placebo in the treatment of non-alcoholic fatty liver disease, with results expected in 2010. Renewal of funding for the Network is enabling expansion of a database to collect samples from additional adult and pediatric participants. Non-Federal sponsorship by industry partners has been significant for this Network and the NIDDK is exploring the possibility of involvement by several potential industry sponsors who have expressed interest in supporting additional clinical trials within the Network.

Item

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

Action taken or to be taken

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

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

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

identifying gaps in the current knowledge base. These examples of new and ongoing program enhancements in urology research studies, strategic planning, and research training, demonstrate the NIDDK's continuing commitment to effectively bolstering support for research that can help reduce the burden of urologic diseases on men, women, and children in the United States now and for the future.

National Institute of Neurological Disorders and Stroke

House Significant Items

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

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

Senate Significant Items

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

NINDS continues its strong commitment to dystonia research in both its intramural and extramural programs. To follow up a 2006 scientific workshop on dystonia, the NINDS issued a program announcement in 2007, together with the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute of Environmental Health Sciences (NIEHS), in conjunction with the Dystonia Medical Research Foundation (DMRF) and the Bachmann-Strauss Dystonia and Parkinson Foundation, Inc. The announcement, which is scheduled to be active through July 2010, invites research grant applications aimed at understanding or treating generalized and focal dystonias and encourages basic, translational and clinical studies. In the past year, NINDS has funded four new grants related to dystonia through this and other programs, including the NINDS Cooperative Program in

Translational Research. The overall research program now includes a wide spectrum of projects that include study of dystonia at the level of genes, molecular pathways, and brain systems, as well as studies of epidemiology and the development of therapeutic strategies. In September 2008, the NINDS, together with the NIH Office of Rare Diseases and the Dystonia Medical Research Foundation, sponsored a scientific workshop focused on advancing translational research in dystonia. The NINDS Intramural Research Program also continues to conduct research to understand what goes wrong in the brain during dystonia and to translate those insights into therapies, including clinical trials to test drugs and other treatments.

Item

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

Action taken or to be taken

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

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

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

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

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

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

Item

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

National Institute of Allergy and Infectious Diseases

House Significant Items

Item

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

Action taken or to be taken

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

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

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

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

Item

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

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

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

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

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

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

Action taken or to be taken
NIAID remains committed to understanding the cause and improving the treatment of scleroderma, an autoimmune disease. For example, the Autoimmunity Centers of Excellence (ACEs) conduct collaborative basic and clinical research on autoimmune diseases, including scleroderma. The ACEs

support close interaction between clinicians and basic researchers to facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. The ACEs are cosponsored by NIAID, NIDDK and the NIH Office of Research on Women's Health.

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

Senate Significant Items

Item

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

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

Action taken or to be taken

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

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

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

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

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

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

Item

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

Action taken or to be taken

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

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

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

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

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

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

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

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

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

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