

NATIONAL INSTITUTES OF HEALTH

OFFICE OF THE DIRECTOR

**SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATIONS
COMMITTEE REPORTS**

FY 2002 House Appropriations Committee Report Language (H. Rpt. 107-229)

Item

Autoimmune Diseases -- NIH and the Autoimmune Diseases Coordination Committee are encouraged to enhance research aimed at improving awareness, diagnosis and treatment for the entire family of autoimmune diseases through all available mechanisms, as appropriate, including the study of overlapping genetics and environmental triggers of autoimmune diseases. (p. 64)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains deeply committed to research on autoimmune diseases and continues to intensify its efforts to enhance research aimed at improving awareness, diagnosis and treatment of autoimmune diseases.

NIAID will continue to work with its sister institutes and other members of the Autoimmune Diseases Coordinating Committee (ADCC) to increase collaboration on autoimmune diseases and to facilitate the development of a comprehensive strategic and collaborative research plan for these diseases. In FY 2001, the Committee, chaired by NIAID, issued a report highlighting NIH activities in several areas, including genetics, clinical trials, environmental and viral triggers, pathogenesis and immune mechanisms, and health services research. The NIH ADCC established several working groups (including Vaccines for Autoimmune Diseases, Gender and Autoimmunity, and Environment and Autoimmunity) to coordinate efforts in the study of autoimmune diseases.

The development of strategies to prevent autoimmune diseases is an area of NIAID's focus. In FY 2001, NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development, the NIH Office of Research on Women's Health (ORWH), and the Juvenile Diabetes Research Foundation International established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research on the development of new targets and approaches to prevent autoimmune diseases and to evaluate novel approaches in pilot and clinical studies.

Treatment of autoimmune diseases remains another area of NIAID's focus. Through the Autoimmunity Centers of Excellence (ACE), established in 1999, NIAID will evaluate the efficacy of potential therapies for multiple immune diseases including systemic lupus erythematosus (SLE), lupus nephritis, and multiple sclerosis through the conduct of basic and clinical research. The ACEs are co-sponsored by NIDDK, the National Institute of Arthritis and

Musculoskeletal and Skin Diseases, and the NIH ORWH. Final planning is in progress for clinical trials to study the efficacy of a stem cell therapy approach using adult stem cells for the treatment of multiple sclerosis, scleroderma, and SLE through the Clinical Trials Network for Stem Cell Transplantation in Autoimmune Diseases, which was established by NIAID in FY 2001. Under the Hyperaccelerated Award Mechanisms in Immune Disease Trials, NIAID supports mechanistic studies associated with clinical trials of immunotherapies for immune-mediated diseases, including autoimmune diseases. In FY 2003, NIAID will support new and ongoing clinical trials of immune therapies for multiple autoimmune diseases through the autoimmunity centers of excellence.

Tolerance, the selective blocking or prevention of harmful immune responses, is a therapeutic approach for the treatment of autoimmune diseases. In FY 1999, the NIAID established the Immune Tolerance Network (ITN). The ITN is developing clinical trials involving tolerance induction approaches for multiple autoimmune diseases, including the use of specific antibodies to treat multiple sclerosis and type 1 diabetes. Several clinical trials for autoimmune diseases have been approved for implementation. In addition to the ITN, in FY 2001, NIAID, NIDDK, and the National Heart, Lung, and Blood Institute co-sponsored an initiative, "Innovative Research on Immune Tolerance," to support pilot research projects on the molecular mechanisms and applications of immune tolerance to specific molecules recognized as foreign by the immune system in FY 2001. In FY 2002, NIAID plans to expand the ongoing Non-Human Primate Immune Tolerance Cooperative Study Group to encompass studies of promising approaches to tolerance induction in large animals.

In other studies, investigators supported by NIAID are focusing on the analysis of the influence of genetics on autoimmune disease, the role of gender in autoimmune diseases, and studies of animal models of autoimmune diseases. In an effort to promote research aimed at discovering the human genes associated with the immune system response that may be involved in susceptibility to autoimmune diseases, NIAID established the Multiple Autoimmune Diseases Genetics Consortium in FY 1999. The Consortium collects clinical data and genetic material from families in which two or more individuals are affected by two or more distinct autoimmune diseases.

In FY 2002, NIAID plans to fund a new research initiative to study gender differences in immune response. The goal of this new research initiative is to identify, characterize, and define differences in the immune response between males and females.

Animal models provide a tool for the study of diseases, including autoimmune diseases. In FY 2002, the NIAID together with the NIH Office of Rare Diseases, the NIH ORWH and the American Autoimmune Related Diseases Association will sponsor a meeting on "Animal Models in Autoimmunity." This meeting will bring together clinical researchers and animal model experts to discuss models for many autoimmune diseases including: lupus, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, alopecia, and inflammatory bowel disease and to determine the requirements for translating findings in animal models of disease to human disease.

Item

Office of Research on Women's Health- For the past decade, ORWH has advanced research on women's health, ensured that women participate in NIH studies, and supported women in biomedical careers. The Committee urges the Director to continue to provide fiscal and administrative support that will permit the Office to serve as the central focus for all NIH on women's health research and career development. The additional funding provided in fiscal year 2002 will permit the Office to continue to enhance, stimulate, and co-fund meritorious research on sex and gender factors in basic and clinical studies. These funds should also be used for new research activities in a variety of health issues and new and expanded career development programs for women scientists, such as BIRCWH. The Committee also urges ORWH to enhance research on multi-systemic diseases in women through all available mechanisms, as appropriate, including the establishment of interdisciplinary research centers. The Director should be prepared to provide a progress report at the fiscal year 2003 appropriations hearing. (p. 93)

Action taken or to be taken

For more than a decade, the Office of Research on Women's Health (ORWH) has worked in concert with the NIH institutes and centers (ICs), other Federal agencies, and the research, health care, policy and advocacy communities to foster and support a comprehensive approach to research on women's health. ORWH does not have direct funding authority; ORWH implements its research and other program objectives by funding and co-funding programs in collaboration with the NIH institutes and centers, sponsoring research planning conferences on women's health, and developing new research and career development initiatives.

The current priorities for research on women's health, based on *An Agenda for Research on Women's Health for the 21st Century* and the recommendations from the NIH ICs and the ACRWH, emphasize multi-disciplinary basic, translational, behavioral and clinical research in women's health, especially to determine sex/gender differences or other variables that pertain to women's health, especially for conditions which may be chronic and/or multi-systemic. This priority is an overarching theme for all research priorities. ORWH is also encouraging increased research that focuses on "Healthy Living" and the Prevention of Chronic Disorders, including the impact of diet, nutrition, hormones, exercise, tobacco and alcohol use, obesity and eating disorders. Expanding areas within the realm of reproductive health, ORWH is promoting increased research on the menopausal transition, on myomas (uterine fibroids), and endometriosis. Working across multiple ICs, ORWH is fostering increased research on the impact of diabetes on cardiovascular and peripheral vascular diseases, and diabetic retinopathy, as well as several other ophthalmic conditions such as "dry eye". Expanded areas within musculoskeletal system health priorities include promoting more research on girls and women who are actively pursuing athletics, and injuries in female athletes.

Building Interdisciplinary Research Careers in Women's Health (BIRCWH I and II): Interdisciplinary collaboration, for research initiatives and career development, has been central

to the mission of ORWH since its inception. The ORWH implemented an institutional career development award for “Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Career Development Programs” in FY 2000 as an innovative mechanism to facilitate the development of women's health researchers in a mentored interdisciplinary environment. This program was developed in response to the identified need for expanded support for interdisciplinary research, bridging the completion of training with an independent career in research addressing women's health, including sex and/or gender similarities or differences, as recommended in *An Agenda for Research on Women's Health for the 21st Century* (“Career Issues for Women Scientists” in vol 2, pp. 187-198; “Multidisciplinary Perspectives,” pp. 223-228 [NIH Pub. No. 99-4386, 1999]). Therefore, facilitating research initiatives that foster multidisciplinary collaborations is a research priority. These programs, utilizing the K-12 mechanism, support interdisciplinary research career development of junior faculty members, known as Interdisciplinary Women's Health Research (IWHR) Scholars, who have recently completed clinical training or postdoctoral fellowships, and who are commencing basic, translational, clinical, and/or health services research relevant to women's health. ORWH, along with nine NIH institutes and the Agency for Healthcare Research and Quality, supports programs in 12 institutions for developing faculty scholars in interdisciplinary women's health research under BIRCWH I (originally issued as OD-99-008).

This career development program, enthusiastically received by the research community, was expanded in FY 2002 through BIRCWH II, to continue the goals of BIRCWH I, in promoting the performance of interdisciplinary research and transfer of findings that will benefit the health of women. The BIRCWH programs accomplish these goals by bridging advanced training with research independence for future investigators in women's health research, as well as bridging scientific disciplines or areas of interest. These awards are designed to increase the number and skills of investigators at awardee institutions through a mentored research experience leading to an independent scientific career addressing research on women's health issues. The BIRCWH programs, while primarily funded by the ORWH with support from many ICs, are administered by the National Institute of Child Health and Human Development. The BIRCWH II Request for Applications (RFA) was published in the *NIH Guide* on December 7, 2001, as RFA OD-02-001 and is being supported by NIA, NIAAA, NIAMS, NICHD, NIDCR, NIDDK, and ODS. AHRQ continues to be a Federal partner on this RFA.

Specialized Centers of Research: In FY 2003, interdisciplinary research on sex and gender differences is receiving new impetus through “Specialized Centers of Research (SCOR) on Sex and Gender Factors Affecting Women's Health,” a ORWH-sponsored program that embodies many of the concepts set forth in the Institute of Medicine report, *Exploring the Biological Contributions to Human Health: Does Sex Matter?*. These centers, to be funded late in FY 2002, will be administered through the National Institute on Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and supported by NICHD, NIDCR, NIDDK, NIDA, NIEHS, NIAMS and NIMH. The Federal partner for this RFA is the FDA. These centers will be providing new opportunities for interdisciplinary approaches to advance studies on how sex and gender factors affect women's health. Each SCOR must develop its own research program bridging basic and clinical research on sex/gender factors underlying a priority health issue. Awards will provide

clinical, life sciences, or public health institutions an opportunity to build national capacity for investigators in women's health research. This includes research on sex and/or gender differences, as well as research on factors that contribute to disparities in health status or health outcomes for different populations of women.

Item

Alpha-1 Antitrypsin.-- Alpha-1 Antitrypsin is a devastating, potentially lethal hereditary disorder which can cause lung and liver disease. It is the leading genetic killer of adults in the United States and a leading cause of liver transplants in children. The Committee encourages NIH to enhance its research portfolio through all available mechanisms, as appropriate, including clinical trials. NIH is also encouraged to expand efforts to raise public awareness and to provide information about Alpha-1 to the public and health professionals. (P. 96)

Action taken or to be taken

In fiscal year 2001, the National Heart, Lung, and Blood Institute (NHLBI) supported a variety of research projects related to alpha-1 antitrypsin (AAT) deficiency. They include efforts to develop improved methods for diagnosis and characterization of patients, to characterize the role of AAT in other lung diseases, to identify subcellular defects involved in disease progression and possible modifier genes, and to develop potentially curative new treatments based on gene therapy techniques or chemical chaperones of protein folding. In addition, the NHLBI and the NIH Office of Rare Diseases cosponsored a workshop, *Protein Processing and Degradation*, in 2001 to review recent progress and research opportunities in pulmonary diseases, such as AAT deficiency, characterized by defects in protein processing and folding. The NHLBI and the NIH Office of Rare Diseases also cosponsored a conference for patients and investigators, organized by the Alpha One Foundation, entitled *AAT Deficiency: The Challenge of a Genetic Condition*. The NHLBI and the Alpha One Foundation are continuing to work on jointly sponsored conferences and research projects.

Item

Autism.--The Committee is pleased with the expansion that has occurred in autism research and with the activities of the NIH Autism Coordinating Committee. The Committee continues to be aware of concerns about reports of a possible association between the measles component of the MMR vaccine and a subset of autism termed autistic enterocolitis. The Committee continues its interest in this issue and urges the NIH Coordinating Committee to continue to give serious attention to these reports. The Committee also urges NIH to continue to pursue appropriate research that will permit scientific analysis and evaluation of the concerns that have been raised through all available mechanisms, as appropriate, including an attempt to replicate the molecular evidence of persistent measles virus infection in children with autistic enterocolitis. The research should be pursued in a way that does not cause undue harm to the Nation's efforts to protect children against vaccine-preventable diseases.

The Committee encourages NIH to pursue the recommended research initiatives outlined in the Institute of Medicine's (IOM) Immunization Review Committee report issued April 23, 2001. These activities should be coordinated with CDC where appropriate. The Committee also notes that the IOM Review Committee will be issuing a report on mercury exposures in childhood vaccines. The Committee urges NIH and CDC to pursue research recommendations the IOM panel may issue in regard to this research. (P. 96)

Action taken or to be taken

The member institutes of the NIH Autism Coordinating Committee continue to vigorously encourage and support research into a large number of genetic, neural, environmental, and other factors that influence the development of autism. In terms of the vaccine issue, there have been two postulated links between childhood vaccination and the development of autism, related to the administration of the combined measles-mumps-rubella (MMR) vaccine and the possibility that thimerosal, a mercury-containing preservative contained in a number of vaccines, contributes to autism (it should be noted that thimerosal-free vaccines are now available for all of the recommended childhood vaccines). There have been a number of scientific investigations published recently, as well as a report by the Institute of Medicine (IOM), that have examined the possible connection between the MMR vaccine and autism and, at this point in time, the available data do not support a causal link. The IOM committee specifically found that no evidence currently exists that proves a link between thimerosal-containing vaccines and autism. However, the committee also concluded that there is a need for more evidence on the risks and benefits associated with thimerosal-containing vaccines and other products, as well as other mercury exposures, both pre-and postnatally. To examine these issues further, the Collaborative Programs of Excellence in Autism network (funded by the National Institute of Child Health and Human Development (NICHD) and the National Institute on Deafness and Other Communication Disorders) is conducting a large-scale study of the individuals enrolled in their research programs to compare people who have shown autistic symptoms since birth, to those who appeared to have developed normally and then started to show signs of autism, and to people who do not have autism. In this study, vaccination records will be compared among the three groups to determine if the onset of autism was associated with the administration of the MMR or other vaccines. Exposures to other sources of mercury, such as the mother having been exposed to mercury in medications during pregnancy, will also be examined. The NICHD fact sheet, *Autism and the MMR Vaccine*, addresses concerns by members of the public of a possible association between this vaccine and autism in greater detail (this can also be found at <http://www.nichd.nih.gov/autism/>). As mentioned above, further research into the potential link between mercury exposure and the development of autism will be conducted. It should be noted that the National Vaccine Program Office has recently formed a Thimerosal Research Workgroup, which includes representatives from the NIH, Centers for Disease Control (CDC), Food and Drug Administration (FDA) and the Health Resources and Services Administration (HRSA).

In response to the Children's Health Act of 2000, the NIH, with the National Institute of Mental Health in the lead role, has formed an Interagency Autism Coordinating Committee, with representatives from parents' groups and several federal agencies, including NIH, CDC, and

FDA. A description of the committee can be found at <http://www.nimh.nih.gov/events/interagencyautism.cfm>). The committee will help coordinate research into numerous issues, including any potential relationship between vaccinations and autism.

Item

Bayh-Dole Act.--The Committee continues to support the principles of the Bayh-Dole Act with respect to the utilization, commercialization and public availability of government funded inventions. As such, the Committee believes that patent protection may be necessary for the development of a research tool as a potential product for sale and distribution to the research community. However, the Committee is also concerned that products that are a result of Federal funding, especially those discoveries that should be the subject of widespread research, should not be restricted in their use, but should be available to the research community and the public. Therefore, recipients of NIH grants should not be discouraged from seeking patent protection, where appropriate, to bring a product to practical application, but should also license the intellectual property in a manner that maximizes the potential for broad distribution of the research tool. Intellectual property restrictions can stifle the dissemination of new discoveries and limit future avenues of research and product development. At the same time, reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development. Accordingly, NIH should continue to offer guidance to both funding recipients and their commercial sponsors to find the appropriate balance between these potentially competing interests. (P. 96-97)

Action taken or to be taken

The NIH policy document entitled "Sharing of Biomedical Research Resources, Principles and Guidelines for Recipients of NIH Research Grants and Contracts" provides excellent guidance on this matter to NIH grantees and contractors. The document has been applied as a term and condition of NIH grants and contracts. Although the policy is applicable to recipients of NIH funds, NIH staff are meeting with companies to inform them about the policy and explain the intent with which NIH grantees and contractors must comply. The NIH appreciates the continued congressional support for this policy and our efforts to improve the biomedical research enterprise.

The NIH has staff available to provide technical assistance to grantees and contractors on the implementation of the policy. Contacts for technical assistance on this matter are: Mark L. Rohrbaugh, PhD, JD, Acting Director, and Theodore J. Roumel, Assistant Director, Office of Technology Transfer, Office of the Director, NIH. Both can be reached at 301-594-7700.

Item

Breast Implants.--The Committee is aware of a recent Food and Drug Administration (FDA) study revealing alarmingly high rupture rates in silicone breast implants and that researchers concluded that the relationship of free silicone to development or progression of disease is unknown. The Committee is also aware of the FDA's recent decision to approve saline breast

implants. The Committee encourages NIH to support research to expand the understanding of the health implications of both silicone and saline breast implants through all available mechanisms, as appropriate. Such research should, if determined to be scientifically appropriate, include a multidisciplinary, clinical, case-controlled study of women with breast implants for at least eight years whether it be one prosthesis or multiple, and differentiate between women receiving implants for mastectomy, reconstructive or cosmetic purposes. (P. 97)

Action taken or to be taken

NCI intramural scientists have conducted a retrospective cohort study, the Women's Health Study, to assess the long term health effects of silicone breast implants. Analyses of cancer risk in this study have been completed, showing no alteration in the risk for most cancers, including breast cancer, which has been of concern given evidence that implants interfere with the mammographic visualization of breast lesions. Patients in the study did experience an elevation in the risk of lung and brain cancers, although the reasons for the excesses were unclear. Results from published analyses of mortality showed that women with implants were not at increased risk for most causes of death compared to controls, except for the cancers mentioned above. Currently underway are analyses of the risk of connective tissue diseases related to breast implants. The characteristics of the 13,500 participants and 4,000 comparison patients in the study have been described in a prior publication.

A number of previous studies have evaluated the relationship between breast implants and subsequent breast cancer risk. Most have shown that the risk of developing breast cancer is somewhat reduced among women with implants compared to women without implants. However, these studies generally did not have detailed information on patient characteristics that could affect the development of breast cancer, and had follow-up times of less than 10 years. NCI researchers found a slight decrease in breast cancer risk during the initial 10-year period. However, this decrease was not seen with increasing follow-up time. The NCI researchers also found a shift toward somewhat later detection of breast cancers among implant patients compared to the controls. However, there was no significant difference in breast cancer mortality between implant and comparison patients. Further surveillance of breast cancer death rates among implant patients is recommended.

When the cancer rates among the implant patients were compared to other plastic surgery patients, the rates for nearly every cancer, including mouth, stomach, large intestine, breast, cervix, uterus, ovary, bladder, thyroid, connective tissue, and immune system were not increased among implant patients. Prior anecdotal reports suggested that implant patients may have increased risks for tumors that develop from connective tissue, such as soft tissue sarcomas, or for cancers of the immune system, such as lymphomas and leukemia. However, the NCI researchers did not find an increased risk of sarcomas among implant patients, nor did Hodgkin's or non-Hodgkin's lymphomas develop at higher rates. Further, no increased risks were seen for multiple myeloma, a cancer site that has been of concern given its development in laboratory animals exposed to silicone. The only cancers that were greater in the implant group compared to the plastic surgery control group were respiratory and brain cancers. However, it is possible that the higher risks observed for respiratory and brain cancers are not related to exposure to

silicone, but are due to either chance findings or to factors common to women who choose to have implants.

The NCI study is one of the few to look at all causes of mortality of breast implant patients. Previous reports have focused on mortality from breast cancer and found, as in the NCI report, no increased risk in breast cancer mortality for implant patients compared to the general population.

The NCI researchers found that nearly every cause of death – including all cancers, circulatory and digestive system disease, endocrine, nutritional, metabolic and immune disease, and cirrhosis of the liver- was decreased among implant patients. The lower mortality rates of the implant population support previous findings that people who undergo elective surgery are generally healthier than their peers in the general population.

The lower rates are due primarily to fewer deaths from cancers and diseases of the circulatory system, the most common causes of death in the general population. The exceptions to the lower rates were deaths from brain cancer, suicide, pneumonia and emphysema. Breast implant patients were two to three times more likely to die from brain cancer, and nearly twice as likely to die from suicide, pneumonia, and emphysema, compared to the general population. The researchers also found, after 15 or more years of follow-up, an increased risk of respiratory tract cancer among implant patients.

The NCI researchers previously showed that other plastic surgery patients may be a more appropriate comparison group than women in the general population for studies of the health effects of breast implants because of certain similarities between the two groups of patients. These include the number of pregnancies, previous gynecologic operations, and operations for benign breast disease, levels of alcohol consumption, and rates of cigarette smoking.

Although both plastic surgery groups have lower mortality rates than the general population, in the NCI study women with breast implants had slightly higher overall mortality rates than other plastic surgery patients. Specifically, the researchers found that implant patients were three times more likely to die from respiratory tract cancer, two to three times more likely to die from brain cancer, and four to five times more likely to die from suicide. The reasons for the increase in respiratory tract cancers and brain cancers are not clear. It is possible that the higher risks observed for both brain and respiratory cancers are not related to exposure to silicone, but are due to either chance findings or to factors common to women who choose to have implants. The higher suicide rates of the implant patients correlate with characteristics described among implant patients in previous reports – marital difficulties, depression, emotional disorders, and low self-esteem. NCI researchers plan to follow the cohort for updated mortality status, and to continue to evaluate the observed excess risks of lung and brain cancers, and of suicide.

Analyses regarding silicone breast implants and connective tissue disorders are under way.

Item

Digital Human Concept.-- Advances in information technology make it possible to build powerful software-based simulations that integrate the explosion of information emanating from medical and biological science in ways that greatly enhance research, education and training, and medical practice, which can be useful in understanding biological processes that operate at all physical levels. The Committee urges the Director to facilitate the development and use of these new tools by leading a national effort to ensure that software components for simulation developed by NIH contractors and by other Federal agencies can interoperate and can easily be improved and reused. The Committee understands that NLM and NIBIB have missions that relate to the digital human integration effort. The Committee also urges the Director to continue to communicate with other Federal agencies, including the National Science Foundation, the Department of Defense and DARPA, and NASA about NIH's activities. (P. 97-98)

Action taken or to be taken

Since 1991, the NLM has been the sponsor of the Visible Human Project (VHP). This anatomical image dataset was put into the public domain in 1994, as soon as it became available for distribution. The data is in an interoperable format with over 1700 registered users in 43 countries.

In 1998 the VHP entered a new phase, sponsored by the NLM, six other NIH institutes and the National Science Foundation. A web based Functional Atlas of the Head and Neck is being developed. This atlas will interactively display anatomy in a 3-dimensional mode. It will also simulate the mechanical physiology associated with many of the anatomical parts such as chewing, swallowing and hearing based on underlying mechano-physiological models. The atlas conforms to a modular design so that it is easily added to and expanded in an interoperable manner.

In addition a set of software tools for image segmentation and alignment is being developed. These tools follow an open source model and are designed around a common public domain interface. They are being tested to run on Windows, Unix, and Macintosh based computers. They can be interfaced to the existing image processing and image display programs, thus not only insuring interoperability with existing imaging software, but acting as a common, public domain software interface for all existing image formats.

Through its membership in the cross government ITRD Program as the lead agency representing healthcare, the NLM has kept the other member Federal agencies, including the Department of Defense (DARPA) and NASA, aware of these developments.

Item

Hyperbaric Oxygen.-- Based on anecdotal evidence collected by clinicians in the field of hyperbaric medicine, hyperbaric oxygen therapy is currently in widespread use for a wide range of acute and chronic medical conditions such as stroke and brain injuries. The Committee understands that NIH is funding basic research on hyperbaric oxygen therapy, including studies at NINDS on its use in reperfusion injury and traumatic brain injury. The Committee encourages

NIH to support meritorious studies in this area through all available mechanisms, as appropriate including controlled clinical trials to test the safety and efficacy of this treatment for a variety of conditions. The Director of NIH is encouraged to coordinate activities across all appropriate Institutes and Centers. (P.98)

Action taken or to be taken

For many years, investigators have been interested in hyperbaric oxygen therapy for a variety of neurological disorders and other conditions. A number of Institutes and Centers (ICs) at the National Institutes of Health (NIH) are already supporting this work, including National Institute of Neurological Disorders and Stroke (NINDS) and several others. While some research has supported the use of this treatment for certain disorders, definitive evidence in support of hyperbaric oxygen therapy is not available in all cases. Additional pre-clinical and clinical studies would be extremely useful in providing clear evidence of the safety, tolerability, and effectiveness of hyperbaric oxygen therapy, with the gold standard considered to be the randomized, controlled clinical trial. For this reason, NINDS, as well as other ICs at NIH, would welcome applications for both basic research and well-designed clinical trials of hyperbaric oxygen therapy. For example, National Institute of Allergy and Infectious Diseases (NIAID) remains interested in grant applications that are consistent with the Institute's research goals in basic and clinical immunology and NIAID staff have met with representatives of the Undersea and Hyperbaric Medicine Society to discuss research on the use of hyperbaric oxygen therapy for transplantation and immune-mediated diseases. In addition, steps have been taken by NINDS, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and other NIH ICs to aid clinical investigators in a broad range of research areas, including hyperbaric oxygen therapy, in developing competitive clinical trial applications.

Item

Lyme Disease.-- The Committee encourages NIH to improve its communication across Institutes to better coordinate Lyme disease research and outreach to public and private scientists about Lyme disease with the goal of stimulating research interest and encouraging investigators to bring their research interests to bear in this field. The Committee also encourages NIH to identify appropriate NIH advisory committees for Lyme disease representation and appoint qualified persons thereon and to include a broad range of scientific viewpoints in the research planning process, including those from community-based clinicians, voluntary agencies, and patient advocates. NIH is encouraged to enhance research in Lyme disease and other tick borne disorders through all available mechanisms, as appropriate, including establishment of a pathology lab. (P. 98)

Action taken or to be taken

The National Institutes of Health (NIH) continues its long-standing commitment to extra- and intramural research on Lyme disease and other tick-borne disorders and endeavors to ensure coordination of this research across its Institutes. In addition, the NIH strives to include a broad range of scientific and patient viewpoints in the research planning and implementation process.

The NIH Director encourages the representation of NIH advocacy and constituent group organizations on all Institute and Center advisory councils, as appropriate.

Established in 1992, the NIH Lyme Disease Coordinating Committee (LDCC) works to coordinate Lyme disease research among the NIH Institutes and Centers as well as across other agencies within the Department of Health and Human Services. The National Institute of Allergy and Infectious Diseases (NIAID), a component of the NIH, chairs the Committee, which includes representatives from several NIH Institutes and Centers as well as the Centers for Disease Control and Prevention and the Food and Drug Administration. Under NIAID's leadership, the LDCC facilitates cooperative research efforts, informs scientific researchers on the state of Lyme disease science, and provides information and outreach to Lyme disease patients, their advocates, and community-based physicians. The LDCC meetings are open to the public and patients, physicians, and representatives from Lyme disease patient advocacy organizations are encouraged to attend.

In September 2001, the National Institute of Neurological Disorders and Stroke (NINDS), in coordination with the NIH Office of Rare Diseases, held a conference entitled, "Workshop on Research Opportunities on Human Neuroborreliosis." The goals of the workshop were to evaluate the current state of the art in diagnosis, treatment, and follow-up of neuroborreliosis in the United States and to facilitate research by bringing together scientists in the field. Currently, the NINDS is preparing a Program Announcement calling for grant applications for research on the neurological consequences of Lyme disease.

The NIH continues to support intramural research collaborations on Lyme disease among its Institutes. For example, NIAID and NINDS scientists are working together to elucidate the role of the immune system in Lyme disease. In addition, NIAID researchers collaborate with the National Institute of Deafness and Communication Disorders scientists in the audiological evaluation of Lyme disease patients, and with the Warren Grant Magnuson Clinical Pathology

Laboratory in the evaluation and development of tests for Lyme disease. Also, a Neuroborreliosis Interest Study Group will be formed to bring together scientists interested the neurologic aspects of Lyme disease.

Lyme disease and other tick borne illness research will continue to be an important area of emphasis for NIH. For example, NIAID plans to support basic research to: (1) characterize and treat acute and chronic infection; (2) determine the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment, and severity of Lyme disease; and (3) develop rapid, sensitive and specific diagnostic tests and prevention strategies, including vaccines and vector control measures. In addition, to further facilitate collaborative partnerships between government, academia, and the private sector for development of novel approaches for controlling infectious diseases, NIAID is planning an FY 2003 research initiative entitled "Partnerships for Novel Approaches to Controlling Infectious Diseases." One of the proposed research areas to be included in this initiative may be focused on strategies for reducing tick-borne bacterial diseases.

Item

Micronutrient and Trace Mineral Deficiencies.-- In addition to the Chromium research initiative being conducted, NIH is encouraged to work with the Department of Agriculture to examine micronutrient and mineral deficiency diseases throughout life. Factors that influence the development and progression of these diseases should also be examined, such as bioavailability, altered physiology, and age-specific absorption rates. This initiative could include investigations of the basic science that underlies the various disease processes, evaluation of the available veterinary, farm, and other animal models for consideration of their relevance to the analogous human diseases, and assessment of potential utility of dietary regimens and/or dietary supplements for improving clinical outcomes. Extensive animal experimentation has been conducted on nutrient supplementation in birth defects, improving resistance to infectious disease and infertility. Each of these areas has potential for reducing health care costs and increasing the effectiveness of medical treatments for disease. NCCAM and ODS should coordinate these activities across all appropriate NIH disease-related Institutes and Centers. (P. 99)

Action taken or to be taken

NIH will coordinate information sharing on this activity through the trans-agency Nutrition Coordinating Committee, which is hosted by the NIH Division of Nutrition Research Coordination in the National Institute of Diabetes and Digestive and Kidney Diseases.

The NCC recently established a trans-agency Subcommittee on International Nutrition Research, which is co-chaired by representatives from the National Institute of Child Health and Human Development (NICHD) and the NIH Fogarty International Center (FIC). The subcommittee will focus its efforts on reviewing the current status of international nutrition research and identifying gaps in the research efforts, including micronutrient insufficiency. These research efforts will lead to a better understanding of the role nutrition and malnutrition may play in many disease that heavily affect U.S. population, including cardiovascular disease, diabetes, bone health, and child development. Samples of other NIH research follow.

The National Heart, Lung, and Blood Institute (NHLBI) currently funds research on the deficiencies of micronutrients and trace minerals related to cardiovascular, lung, and blood diseases. NHLBI also has a long history of working collaboratively with the Department of Agriculture.

The NIAID supports studies on the impact of micronutrient deficiencies on respiratory and enteric diseases, and on HIV-AIDS. Some of these studies are directed at understanding the effects of nutritional deficiencies on host immune response. In addition, in FY 2002 the NIAID will fund a multi-center pilot study to determine whether omega-3 fatty acid and arginine supplements will improve transplant survival in pediatric and adult transplant recipients.

The NIEHS supports several studies related to deficiencies in micronutrients and trace minerals, including selenium, vitamin E and cysteine. Most of these studies are concerned with the

mechanisms by which deficiencies in these substances contribute to oxidative stress. Associated conditions under study include arteriosclerosis and teratogenesis.

Item

Minority Health Research.--The Committee commends NIH's implementation of various programs focused on developing research infrastructure at minority health professions institutions, including Research Centers at Minority Institutions, Extramural Biomedical Research Facilities and the recently established National Center for Minority Health and Health Disparities. Due to the number of new competitive mechanisms at NIH for these research institutions, the Director is encouraged to work with the Director of NCMHD to establish a program of coordination among these various mechanisms to partner minority health professions schools to address their infrastructure needs. (P. 99)

Action taken or to be taken

Both provisions, "Minority Health Research" and "Research Endowments", address assurances that minority health professions schools benefit broadly from the sum total of NIH programs for research infrastructure development. Accordingly, the NIH coordination effort will specifically focus on four programs: the Endowment Program (NCMHD), Research Centers in Minority Institutions (NCR), Extramural Biomedical Research Facilities Program (NCR), and Project EXPORT, the NCMHD's center of excellence program.

The NCMHD endowment funds supports building research and training capacity in institutions that make investments in the education and training of underrepresented minority and socio-economically disadvantaged individuals. For maximum impact, the NCMHD selected to make "institutional grant awards" under the Endowment Program. The implication: any program within the grantee institution that participates in research training and/or conducts biomedical and biobehavioral research may benefit from the income that accrues from the endowment corpus income in accordance with the priority of that institution.

Two NIH programs support construction and renovation activities: Project EXPORT and Extramural Biomedical Research Facilities. Coordination will focus on: (1) clarifying the differences and similarities between the two programs so institutions may make the best possible decision in selecting the program of choice for supporting their research infrastructure development, and (2) advising the Directors NIH and NCR with respect to increasing the accessibility of NIH sponsored construction/renovation programs to minority health progressions schools and other minority-serving institutions. While the two programs do not complement each other – the same entity cannot receive a construction and improvement grant from both NCMHD and NCR, each has its distinct advantages. For example, the NCR program has broader eligibility criteria but places limits on the amounts that may be appropriated both in terms of the overall amount and the per project amount. The NCMHD program does not have such limits but the eligibility criterion is more narrow – must be an NCMHD sponsored center of excellence. Clearly, the NCR sponsored program may be a better source of support for certain research infrastructure development projects.

Item

Parasitic Diseases.-- The Committee encourages NIH to enhance research on parasitic diseases, including schistosomiasis, leishmaniasis, African Sleeping Sickness and Chagas disease through all available mechanisms, as appropriate. (P. 99)

Action taken or to be taken

The National Institutes of Health (NIH) has taken a leadership role in the prevention, control, and treatment of a variety of parasitic diseases. The National Institute of Allergy and Infectious Diseases (NIAID) serves as the lead NIH institute in research on parasitic diseases and continues to make progress in research on these diseases. NIAID researchers developed a novel vaccination strategy using components of sand fly saliva to immunize against Leishmania; determined that two substances produced by white blood cells in response to infection are important for adequate host defense against *Trypanosoma cruzi* (the agent of Chagas' disease); revealed a novel strategy to block or reduce the adverse reactions associated with schistosomiasis; developed a rapid diagnostic test for onchocerciasis (a parasitic disease caused by a worm and also known as river blindness); and are working to describe clinical definitions of filarial (worm) parasitic diseases. NIAID continues to enhance research on parasitic diseases through support of genome projects relevant to parasitic diseases. The microbial genome sequencing projects for parasites, including *Plasmodium falciparum*, *Leishmania*, *Giardia*, *Toxoplasma gondii*, *Brugia malayi*, *Schistosoma mansoni*, *Trypanosoma cruzi* and African trypanosomes are supplying the genetic blueprint for the organisms' adaptation to parasitism as well as providing leads for the development of new diagnostics, drugs and vaccines. The availability of complete genome sequence information is accelerating the pace of gene identification and characterization using new technologies.

Building upon these science advances and successes, NIAID continues to support research on parasitic diseases through its domestic and foreign programs. Within the International Centers for Tropical Disease Research (ICTDR) Network, NIAID-supported investigators are conducting basic, field, and clinical research that seeks to discover and develop vaccines, drugs, and vector-control methods to prevent and treat tropical diseases. NIAID supports approximately 20 international research sites in approximately 15 different countries. Awards are made through Tropical Disease Research Units (TDRU), International Collaborations in Infectious Diseases Research (ICIDR), and Tropical Medicine Research Centers (TMRC). On May 7-9, 2001, NIAID sponsored the 10th Annual ICTDR Network meeting to discuss diagnostics, pathogenesis, vector research, drug treatments, and vaccines for tropical diseases, including parasitic diseases. The NIAID global health plan for HIV-AIDS, tuberculosis, and malaria (a parasitic disease) was presented at the meeting. The next iteration of NIAID's Global Health Research Plan, which includes research on parasitic diseases, is in development.

NIAID has also encouraged research to develop environmentally sound insecticides to control vector-borne diseases. NIAID has developed a "Partnerships for Development of Novel Therapeutic and Vector Control Strategies in Infectious Diseases" Request for Proposals. This solicitation will be issued in early FY 2002, with awards planned in late FY 2002. NIAID is

planning a FY 2003 research initiative entitled "Partnerships for Novel Approaches to Controlling Infectious Diseases" to develop novel approaches for controlling infectious diseases and to facilitate collaborative partnerships between government, academia, and the private sector. One of the proposed research areas to be included in this initiative is the evaluation of the impact and effectiveness of vector control products.

In the future, NIAID will continue to support research on tropical diseases including parasitic diseases, primarily through investigator-initiated mechanisms, thus enabling scientists to follow-up on innovative areas of study. NIAID will continue to support domestic and foreign programs/centers of excellence through the TDRU, ICIDR, and TMRC. In addition, NIAID will continue to support meetings (e.g., Annual Meeting of the ICTDR) to highlight research advances and develop collaborative studies and joint ventures to address pressing research needs in tropical diseases, including parasitic diseases.

NIAID will continue to provide support for large-scale sequencing of parasite and invertebrate vector genomes and promote activities for decoding the genomic information. NIAID scientists will determine whether pre-exposure to uninfected sand fly bites will protect against a form of leishmaniasis and will evaluate the efficacy of vaccines for leishmaniasis through natural exposure to sand flies. In a schistosomiasis model of disease, NIAID investigators plan to test several novel inhibitors of a chemical factor associated with the pathogenesis of schistosomiasis. NIAID will continue studies focused on developing a vaccine for schistosomiasis. A major focus for future filarial clinical studies will be to prevent or ameliorate the serious adverse reactions that occur in filarial infections post-treatment. Future studies of Chagas' disease will focus on substances produced by white blood cells that are important in host defense.

Item

Parkinson's Disease.-- NIH has developed a five-year Parkinson's Disease Research Agenda. To carry out the plan, the professional judgment budget estimates call for increases over existing Parkinson's research of \$143,400,000 in year two (fiscal year 2002). The Committee strongly urges the Director to work toward the implementation of the research agenda through all available mechanisms, as appropriate, including hosting a consortium in collaboration with the Parkinson's research-related Institutes and the extramural research community to identify the full extent of available scientific opportunity and the research and funding needed to implement the Research Agenda. The Committee requests that the Director be prepared to provide a status report on the research agenda at the fiscal year 2003 appropriations hearing.

The Committee commends NIH for encouraging and supporting workshops and other collaborations between sectors of the Parkinson's research community, including the NIEHS-supported consortia and the NINDS-supported workshop on gene therapy and encourages similar collaborative models. (P. 99)

Action taken or to be taken

Parkinson's disease has been a major priority at NIH for many years, and since the development of the Parkinson's Disease Research Agenda, an unprecedented level of programmatic activity

and staff resources have been committed to this field. This has resulted in an aggressive implementation of the Agenda, which has provided Parkinson's disease researchers with new areas of research to explore and the funding necessary to explore them. NIH is planning to host a meeting in January 2002 that will include researchers, Institute representatives, and members of the advocacy community. At this meeting, attendees will evaluate the progress to date in the implementation of the Agenda, and will discuss how the success of these past efforts in moving research forward should shape the goals of the Agenda for the next several years. Specifically, the balance of ongoing and newly-initiated research in different areas of the Agenda will be examined, such that future NIH initiatives will complement our current research portfolio. As part of this process, a series of research priorities which are based on the original Agenda but take into account current scientific opportunities and funding, will be developed.

NIH Staff continue to facilitate the development of research consortia in fields that have reached an appropriate capacity, both logistically and scientifically. Currently, NINDS and NIA staff are organizing the first meeting of the Deep Brain Stimulation Consortium, planned for early 2002. This meeting will provide participants with an opportunity to share their results, plan collaborations, and contribute patient data to a central database, critical for the assessment of the efficacy of DBS. NINDS has also provided support for a meeting of investigators interested in gene therapy approaches for Parkinson's disease research. This group came together following an October 2000 gene therapy workshop sponsored in part by NINDS, and the Institute looks forward to a productive relationship with these researchers. In addition, a Consortium meeting for investigators supported by NINDS to screen FDA-approved drug compounds in neurodegeneration assays is also planned for early 2002. NIEHS is also aggressively developing a consortium of investigators who will address the relationship between Parkinson's disease and the environment, using a multidisciplinary approach that encompasses genetics and epidemiology, and involves both basic scientists as well as clinical researchers.

Item

Pediatric Research – The Committee has previously urged NIH to continue to strengthen and expand its portfolio of pediatric research across all Institutes and establish priorities based on the severity and impact of pediatric diseases and on the potential for scientific breakthroughs. The Committee understands that the Acting Director has asked the NICHD Director to co-chair a committee developing recommendations to operate the Pediatric Research Initiative authorized as part of the Children's Health Act of 2000. The flexibility afforded to NIH in the implementation of the Initiative will facilitate the development of the most effective means to achieve the program's objectives. Within the total provided to NIH, the Committee believes adequate funds are available to continue implementing this activity. The Committee requests that the Director be prepared to provide a status of this initiative at the fiscal year 2003 appropriations hearing. (P. 100)

Action taken or to be taken

The Children's Health Act of 2000 directed the Secretary of HHS to establish a Pediatric Research Initiative within the Office of the Director of NIH. This initiative is intended to

increase support for pediatric biomedical research within NIH, to enhance collaborative efforts among the Institutes, and to increase the development of adequate pediatric clinical trials and pediatric drug use information.

As authorized by the Act, the Acting Director of NIH has established the NIH Inter-Institute Committee on Pediatric Research. Reflecting National Institute of Child Health and Human Development's (NICHD's) longstanding goals of improving and promoting children's health, the Director of NIH asked the Director, NICHD, to chair the new Committee.

The purpose of the Committee is to encourage the development of initiatives for new pediatric research from all interested Institutes and Centers, and to nominate some of these for full or partial support. The Office of the Director of NIH will provide initial funding for some of the successful applicants. These initiatives, along with new pediatric research funded by the Institutes, and identified by them as such, will comprise the Pediatric Research Initiative. NICHD has also expanded its efforts to bring new investigators into the field of pediatric research, and to provide them the training necessary to ensure their retention. Earlier this fall, NIH officially published notice of its new pediatric loan repayment program, and requested comments. The Pediatric Research Loan Repayment Program is intended to provide funds to repay student loans to individual researchers who agree to conduct research at their institutions in these areas. The Program is expected to become an important tool to recruit young scientists into the field of pediatric research.

NICHD is also funding two training programs for pediatricians at different stages of their academic careers. A request for applications was recently issued that would establish programs of postdoctoral pediatric training in basic science or clinical research at pediatrics departments throughout the country. Applications are still being received, and NICHD expects to fund a number of them in the coming fiscal year, with more to be funded in future years. Another NICHD training program for pediatricians, the Child Health Career Development Award, supports research career development of pediatricians who have recently completed subspecialty training. Over the past decade, this vital program's goals of increasing the number and effectiveness of established pediatric investigators who have a grounding in basic science and research skills that can be applied to the health problems of children have largely been met.

Item

Research to Improve Efficiency and Reduce Costs of Health Care.-- The cost of health care delivery continues to rise with many health care experts predicting nine percent increases for the foreseeable future. While recent research demonstrates that development and application of new health care technology is generally worthwhile or cost-effective in terms of improved survival and productivity in the workplace and reduced disability over the life span, there is some concern that some research discoveries that provide new remedies for health problems and the over use and misuse of available technology may also contribute to higher health care costs. The Committee recognizes that the development of new health care innovations and the appropriate application of available technology are necessary to assure access to affordable health care for all

Americans. The Committee urges NIH to work with the Agency for Healthcare Research and Quality to find the methods of evaluation and treatment that will reduce health care costs without sacrificing quality. (P. 100)

Action taken or to be taken

NIH supports research that is relevant to lowering the cost of medical care as well as promoting health. For example, vaccine development for AIDS, Alzheimer's disease, various cancers, and Otitis Media promises lower costs and more effective therapy than current treatments. Personal behaviors such as physical activity, diet, smoking, alcohol use, and other substance abuse are major risk factors for disease and have all been identified as a result of NIH-funded research. NIH-funded scientists continue to develop and test cost-effective interventions to achieve sustained change in health behaviors, especially in diverse populations.

NIH and the Agency for Healthcare Research Quality (AHRQ) have collaborated on a number of projects over the years. Examples of jointly issued grant announcements to encourage research to identify, develop and promote cost-effective health care delivery include: Economic Studies in Cancer Prevention, Screening and Care; Patient-centered Care: Customizing Care to Meet Patients Needs; Research on Emergency Medical Services for Children; Economic Evaluation in HIV and Mental Disorders Prevention; Research on Care at the End of Life; and Effectiveness of Children's Mental Health and Substance Abuse Treatment in the General Health Sector. Current co-funded research includes: How Nursing Affects the Volume-outcomes Relationship; Primary Care Performance and Outcomes in Medicare; Evaluating the Efficacy of Acupuncture for Back Pain; Measuring Mental Health Outcomes Fairly; Evaluating Quality Improvement Strategies; Understanding Variability in Community Mammography; Care Management by Nurse Practitioner/hospitalist Team; Understanding & Reducing Native Elder Health Disparities; Promoting Effective Communication and Decision-making; Economic Analysis of Pulmonary Artery Catheter Use.

NIH also collaborates with other Federal agencies and private organizations to support path-breaking research to develop or identify the most cost-effective treatments from the alternatives available. NIH research to identify and motivate healthy behaviors is the foundation for several collaborative public education programs designed to prevent disease or to improve management of chronic conditions. For example, the National Emphysema Treatment Trial [sponsored by NIH, the Centers for Medicare and Medicaid Services (CMS), and AHRQ] has already determined that certain types of emphysema patients do not benefit from lung volume reduction surgery (LVRS). The ongoing study will guide us further in determining if and when LVRS should be used to treat emphysema. The National Diabetes Education Program (sponsored by NIH, the Centers for Disease Control and Prevention and CMS) is aimed at reminding older adults with diabetes, including 4.5 million Medicare beneficiaries, about the importance of routine blood sugar monitoring, and that Medicare benefits are available to help them do this. An NIH and Industry partnership, the Osteoarthritis Initiative, is designed to identify the most effective treatment for osteoarthritis and avoid costly, ineffective care. In another partnership with the private sector, NIH and a pharmaceutical company will begin follow-up clinical trials of

a breakthrough oral drug to treat chronic myelogenous leukemia (CML) using molecular targeting. If effective, it will provide a lower cost alternative to bone marrow transplantation, the only known cure for the 4,500 Americans diagnosed each year with CML.

Item

Sjogren's Syndrome.-- Sjogren's syndrome is one of the most prevalent autoimmune diseases. The Committee encourages the NIH Autoimmune Diseases Coordination Committee to include Sjogren's syndrome in its strategic plan. (P. 100)

Action taken or to be taken

The National Institutes of Health is committed to the prevention, diagnosis, and treatment of autoimmune diseases, including Sjögren's syndrome. To bolster this effort, autoimmune disease research at NIH is coordinated through the NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC draws representation from NIH Institutes, Offices, and Centers as well as other pertinent Federal agencies and private organizations. In the spring of 2002, the ADCC plans to present a comprehensive strategic and collaborative research plan for autoimmune diseases to Congress. It is anticipated that the plan will address the need for studies into the biology, diagnosis, treatment and prevention of autoimmune diseases, including Sjögren's syndrome.

Item

Usher Syndrome.-- Usher Syndrome (US) is the leading cause of deaf-blindness in the United States. It is an inherited disorder that is characterized by moderate to profound hearing impairment and progressive vision loss due to retinitis pigmentosa and affects an estimated 30,000 Americans. Researchers have mapped the chromosomal locations of nine different genes that account for the various forms of US, of which four have been isolated and cloned. The Committee encourages NIH to enhance research aimed at finding a treatment or cure for US through all available mechanisms, as appropriate, including a better understanding of the etiology of the disorder. (P. 100)

Action taken or to be taken

NIDCD scientists are identifying new genes whose mutations result in hearing loss. Researchers have now mapped the chromosomal locations eleven different genes that account for the various forms of Usher Syndrome (USH), of which five have been isolated and cloned. Two of these USH genes, USH1DS and USH1F, were identified this year by scientist at the NIDCD. The Institute has developed a research portfolio to study existing mouse mutants as well as creating new mouse models to facilitate the discovery and analysis of genes whose mutation causes hereditary hearing impairment in humans.

The National Center for Research Resources is supporting research on the mouse waltzer gene, which is a mutation characterized by congenital deafness, and other symptoms. The specific goal of this research is to use molecular genetic techniques to isolate and characterize the mouse waltzer gene, as a possible model for human hereditary deafness. One specific aim of the research is to determine if the human waltzer gene is responsible for one of the types of Usher syndrome. This research may provide important insight into understanding human hereditary deafness.

In a recent study utilizing the mouse mutant waltzer, NIDCD Intramural scientists showed that mutations in members of the human cadherin gene family cause Usher Syndrome type 1D. Individuals that inherit two copies of this mutated gene are born profoundly deaf, have severe balance problems and gradually lose their sight beginning in adolescence. Less profound mutations of USH1D gene cause severe deafness but do not cause the loss of sight. This mouse model is a critical tool for research to determine the identification of the mechanisms by which cadherin mutations cause this devastating deafness and blindness syndrome. The scientists discovered that USH1D gene encodes a protein called cadherin-23. Studies are underway to determine the function of cadherin-23 in the ear and eye. Knowledge of the function of cadherin-23 will provide new insight into cellular processes essential for normal auditory function, which may ultimately guide the development of improved diagnosis and treatment methods.

The NEI currently funds several research projects and conducts research in its own laboratories with the goal of better understanding the causes of Usher Syndrome. The Institute has identified the prevention and treatment of Usher Syndrome and other retinal degenerative diseases as an important research priority and will continue to advance this area of investigation.

Item

Veterans Administration Cooperation.-- The Veterans Administration (VA) has over 900 hospitals and clinics that provide medical care to 4.1 million veterans. The VA system is an ideal setting for large multi-center studies and clinical trials and is a resource to facilitate and accelerate research. The Committee urges NIH to explore ways to increase cooperative research efforts with the VA. The Committee requests that the Director be prepared to provide a progress report on this initiative at the fiscal year 2003 appropriations hearing. (P. 100-101)

Action taken or to be taken

The NIH has for many years recognized that the Veterans Administration (VA) was a valuable resource in which to conduct certain large multi-center trials. This is particularly true for clinical trials in which the VA has large potential populations with the indication to be studied. Such indications include, but are not limited to: neurological diseases, cardiovascular diseases, age-related diseases, mental health, and substance abuse and addiction (including smoking)

For example, the National Institute on Drug Abuse (NIDA) currently utilizes the VA Cooperative Studies Program (CSP) to conduct its large-scale Phase III clinical trials for medications to treat

opiate and cocaine addiction. Use of the CSP has substantially assisted in the development of three (3) medications for the treatment of opiate addiction (ORLAAM, approved by the FDA in 1993; and buprenorphine and buprenorphine combined with naloxone, deemed “approvable” by the FDA and currently awaiting final review by the FDA). NIDA is also currently conducting a large multi-center clinical trial of seligilene for the treatment of cocaine addiction in the CSP.

The use of the Cooperative Studies Program to enlist VA hospitals and clinics in multi-center trials has proven effective for NIDA because 1) substance abuse is the number one diagnosis seen

within the VA psychiatric service, and 2) the CSP serves as an effective recruiting and coordinating entity within the VA system, and centralizes the pharmacy control, reporting, and statistical analysis functions for these trials.

A number of other NIH Institutes also utilize or are planning to collaborate with VA hospitals and clinics to facilitate and accelerate research. For example, The National Institute on Aging (NIA) has issued a joint solicitation with the Department of Veterans Affairs (DVA) for research in areas of common interest in geriatric medicine. The announcement was issued in November 2000 identifying priority areas for the conduct of multi-site, randomized clinical trials including: diagnostic strategies for prostate malignancies; osteoporosis in men; androgen replacement therapy; perioperative interventions for non-cardiac surgery; approaches to cardiovascular surgery in older patients; treatment for diastolic dysfunction; long-term care; group clinic models for chronic disease management; alternative treatment approaches for terminal illness; management of behavioral disturbances among institutionalized Alzheimer’s patients; nutritional interventions; interventions to prevent fall-related fractures; and studies on adverse effects of medication prescribing in geriatric patients. The first efforts of this collaboration is a proposal for a large-scale trial of testosterone replacement in hypogonadal, osteopenic older men with the primary endpoint of “time to first clinical fracture” which has received favorable reviews from the DVA and NIA review panels. Collaborative funding from the Department of Veterans Affairs, the pharmaceutical industry, the NIA, and other NIH Institutes is being explored.

An additional study at the University of Pittsburgh is currently being supported by the NIA to explore mediators for outcomes of HIV infection in a population of older patients from the Veterans Affairs Medical Centers at Cleveland, Houston, and Manhattan. The goal of this research is to improve outcomes for middle-aged and older patients with HIV.

The National Heart, Lung, and Blood Institute also utilizes the VA system for a number of its research endeavors. With regard to activities of the NHLBI, the VA Cooperative Studies Program has had an important place in hypertension treatment research for three decades. Indeed, the VA Cooperative Study on Antihypertensive Drugs in the 1960's was seminal in initiating the NHLBI-coordinated National High Blood Pressure Education Program, and a VA representative sits on its Coordinating Committee. With regard to NHLBI-sponsored hypertension intervention trials, one—the Prevention and Treatment of Hypertension Study (PATHS)--was conducted entirely through the VA (including a CSP Coordinating Center), prior to the requirement that all trials include adequate representation of women. This trial tested

whether a program of counseling to reduce alcohol consumption in non-dependent moderate-to-heavy consumers would reduce blood pressure. Subsequent large trials studying hypertension treatment have been conducted with substantial VA involvement. The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is designated as a VA Cooperative Study, and includes approximately 7,000 veterans among the 42,419 patients randomized. This trial is comparing drug regimens based on agents from 4 different classes for their effects on coronary heart disease, and is evaluating cholesterol-lowering drug treatment for an effect on total mortality in older moderately hypercholesterolemic patients. The lead investigator for the VA has served on the trial-wide Executive Committee and chairs the Endpoints Subcommittee. Action for Control of Cardiovascular Risk in Diabetes (ACCORD) is another large trial, currently in its vanguard phase, which is evaluating a hypertension treatment strategy along with questions about optimal control of blood glucose and of blood lipids. ACCORD includes a VA clinical center network among the 7 participating networks, as well as the VA pharmacy coordinating center, although this trial is not designated a VA cooperative study.

Two important NHLBI-sponsored multicenter trials on treatment of congestive heart failure have been conducted as VA Cooperative Studies, including a VA Coordinating Center and a substantial proportion of VA clinical sites. These were 1) the Digitalis Investigative Group trial, the only randomized trial that evaluated the effect of digitalis on survival with heart failure, and 2) the Beta-Blocker Evaluation of Survival Trial (BEST), the largest U.S. trial of the effect of beta-blocker therapy on survival in patients with heart failure.

The NHLBI has found the resources of the VA medical care system, including the Cooperative Studies Program, extremely valuable contributors to research on the prevention and treatment of cardiovascular disease over the years, and will continue to seek opportunities for collaboration. Beyond the top quality scientific/clinical resources and large patient population, the cooperation has been advantageous, because VA physicians are usually fully salaried, allowing research resources to be spread further. However, it appears that in some instances there may be inadequate local institutional recognition of the research commitment, i.e. "protected time" to function as an investigator in a collaborative trial. Another way in which resources could be freed up for support of a clinical trial would be if the VA hospitals would recognize the savings accruing to their pharmacy budgets when drugs supplied by a collaborative study substitute for those that would otherwise need to be provided by the VA.

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is another NIH Institute that utilizes the VA system. Veterans have a higher-than-average rate of alcohol-use disorders, thus providing valuable study cohorts for the NIAAA. For example, FDA approval of one of the most promising medications for alcoholism treatment in decades was based, in part, on information from a clinical trial conducted in a VA population. Six of the collaborating institutions conducting Project COMBINE, a clinical trial examining the effectiveness of combined pharmaceutical and behavioral therapies for treatment of alcoholism, recruit subjects from VA facilities. Six VA medical centers were among the institutions that received grants for a jointly funded NIAAA and NHLBI study, beginning in 1989, that examined the effect of reducing drinking on blood pressure. Although the study is now complete, the NIAAA continues to

contribute to the study's Operations Committee, in a long-term publication project, to ensure that the scientific community makes full use of the data this research generated.

The National Institute of Mental Health (NIMH) also supports research at Veteran Administration (VA) institutions in multi-center studies of schizophrenia, bipolar disorder (manic-depressive illness), Alzheimer's disease, treatment refractory depression, HIV/AIDS, and post-traumatic stress disorder (PTSD). All of NIMH's adult clinical trials incorporate VA sites and a large number of our research center grants have substantial VA involvement. In addition, NIMH supports several investigator-initiated research projects that are exploring the consequences to veterans of exposure to traumatic and violent events. Outcomes being studied include post-traumatic stress disorder (PTSD), depression, suicide, and anxiety. Finally, the National Institute of Neurological Disorders and Stroke (NINDS) is currently planning to collaborate with the VA on the largest trial to date of deep brain stimulation (DBS) in individuals with Parkinson's disease. The trial will be conducted in two phases - the first to compare DBS and best medical management, and the second to evaluate the effects of DBS in two different brain locations. NINDS will provide over \$7 million in support for this trial over a 4-year period, which will permit the recruitment of 150 of 300 total participants in the trial. Because NINDS participation allows recruitment of patients through the Universities affiliated with the VA sites, involvement of women and minorities in this study is expected to be enhanced as a result of this collaborative effort.

Sensorineural hearing loss is among the most prevalent disabilities reported in the United States, affecting an estimated 20-26 million people and present in about 40% of individuals older than 65 years. It adversely affects cognitive and social function, as well as the general quality of life, and has been linked to depression and dementia. While hearing aids are the most widely used form of assistance, only about 20% of those who could benefit from hearing aids wear them. Moreover, surveys have suggested that about 50% of users are dissatisfied with their hearing aids, calling into question the benefit of hearing aids.

The NIDCD and the Department of Veterans Affairs (VA) recently completed a clinical trial to compare the efficacy of three different hearing aid circuits. Efficacy was measured in a variety of listening situations using tests of speech understanding, sound quality, and patient rank-order ratings. The three hearing aid circuits together account for 70% of the U.S. hearing aid market. Each circuit provided significant benefit in quiet and noisy listening environments. The NIDCD/VA Hearing Aid Clinical Trial, the first large-scale double-blind, multicenter clinical trial, showed efficacy of hearing aids in both quiet and in noise for a wide range of individuals with hearing loss. Because concerted efforts were made to recruit patients into the study from both sexes and all racial groups, the study sample was a good representation of American adults who are candidates for hearing aids. The NIDCD and the VA are interested in conducting a follow-up trial to examine why some people fitted with hearing aids continue to use them successfully while others do not. Understanding and predicting these outcomes will provide the basis for designing better diagnostic tools, fitting protocols and aural rehabilitation programs.

FY 2002 Senate Appropriations Committee Report Language (S. Rpt. 107-84)

Item

Aphasia.- It has come to the Committee's attention that the scientific knowledge of this common and devastating acquired speech and language disorder has gone virtually unchanged for decades. The Committee, therefore, urges the appropriate Institutes and Centers to expand and better coordinate their support of research into the cause, incidence, treatment and prevention of aphasia. Furthermore, the Committee urges the Director to initiate a trans-NIH aphasia research planning and coordinating function, charged initially with developing an aggressive Aphasia Research Agenda that involves a comprehensive state-of-the-science review and a delineation of those areas with the most potential for yielding significant advances in near-term treatments and rehabilitation methodology. (P. 179)

Action taken or to be taken

The central goal of aphasia therapy is to improve an individual's ability to communicate by helping the person to use remaining abilities, to restore language abilities as much as possible, to compensate for language problems, and to learn other methods of communicating. In-depth testing of the language ability of individuals with the various aphasic syndromes is helping to design effective treatment strategies. Areas of aphasia treatment that National Institute on Deafness and Other Communication Disorders (NIDCD) are encouraging include enhanced communications for people with aphasia and medical rehabilitation. The Institute is studying the use of a computer-assisted visual communication system to assist aphasics who are unable to produce or comprehend language. Research in medical rehabilitation is providing treatment options for individuals with aphasia. Promising new drugs that may improve the rate of language recovery administered shortly after some types of stroke are being investigated as ways to reduce the severity of aphasia.

Greater understanding of how the brain performs differently for people with aphasic syndromes is rapidly advancing due to NIDCD's lead in the use of the latest neuroimaging technology. Functional imaging techniques are being used to characterize brain activation patterns in normal subjects and individuals with neurological disorders affecting human communication in the Voice, Speech and Language Branch of NIDCD's Division of Intramural Research. A goal of the branch is the development of neuroimaging methods to study aphasia in individuals recovering from stroke. Images of the living brain as it re-acquires the ability to speak provide valuable information on the physiology of language recovery. In addition, the use of neuroimaging technology to show functional reorganization of the brain during spontaneous recovery will also be an effective tool to evaluate treatment of aphasia. To further explore this research area, the NIDCD is establishing collaborations with major regional stroke centers at The John Hopkins University, National Rehabilitation Hospital, The University of Maryland, George Washington University and Suburban Hospital, and has also begun a pilot study using MR/EEG paradigms in control subjects.

NIDCD emphasizes the importance of focusing the scientific community on aphasia research through nurturing the development of scientific careers, and orchestrating aphasia research across NIH. NIDCD-supported Institutional Training Grants provide research training to individuals interested in communication sciences and disorders. A pre- and postdoctoral training program is based at the Aphasia Research Center in Boston and has produced 36 post-doctoral trainees, with

a high proportion who have gone on to careers in research and research training in the area of adult communication disorders.

Biomedical research has become complex and involves multidisciplinary approaches. When research opportunities overlap the mission of several institutes, collaborative efforts will be fostered. As the primary institute conducting aphasia research, the NIDCD has cosponsored over the past year a symposium series, "New Perspectives in Language Research," with the National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH) and National Institute on Aging (NIA). The September 2000 symposium, "Neural and Computational Bases of Language," highlighted leading contemporary approaches to the study of human language. The speakers, which included several scientists involved in aphasia research, presented and discussed new research exploring techniques of brain imaging, computational modeling, and linguistic analysis. The development of language across the lifespan and the effects of brain injury on language performance were major themes of this symposium. The March 2001 symposium on "Developmental Disorders of Language" also included scientists studying aphasia, language development, spatial cognition and the underlying neural systems.

The NIDCD is in the planning stages of a workshop focused on treatment and rehabilitation of adult aphasia. The workshop will involve formulating research recommendations on aphasia, and a subsequent initiative soliciting grant applications is anticipated. The workshop will involve participation by other NIH institutes conducting aphasia research and will be held in Spring, 2002.

Research currently supported by the NIA in the area of aphasia covers both basic research that informs the condition of aphasia as well as research that directly targets some types of aphasia. NIA-funded investigators are examining age-related changes in language, particularly the ability to produce words, such as names, on demand. The aphasia research currently supported by NINDS is focused primarily on the relationship of brain damage to aphasia and other disturbances of language function. For example, NINDS-funded investigators are exploring how the tissue surrounding the site of stroke damage to the brain contributes to the recovery from aphasia.

NIMH supports basic research in both normal and disordered populations to understand the normative behavioral and neural mechanisms underlying language comprehension and production. Recent advances in NIMH-supported basic language research point to new directions for understanding aphasia including the use of event-related functional MRI techniques. NICHD supports a regional medical rehabilitation network established to conduct clinical trials on cognitive rehabilitation interventions. One of the three initial projects focuses on a functional limitation-based treatment for aphasia.

Item

Asian Indians.- The Committee recognizes that Asian Indians worldwide have one of the highest rates of coronary artery disease (CAD) and diabetes mellitus (DM) of any community around the world, ranging from 2 to 10 times higher in any given age range. The Committee understands

that while there are data in other countries regarding the prevalence of and risk factors for CAD and DM of Asian Indians, there is a lack of such data in the U.S. The Committee recommends that the Director gather and analyze data from Indian-American communities to study the prevalence of DM and CAD within this population, and to create a registry for a longitudinal study to gain insight into effective intervention strategies.(P. 179-180)

Action taken or to be taken

The increased risk of cardiovascular disease and diabetes among Indians of Asian origin (south Asians) has been well documented. While data in the U.S. south Asian populations are sparse, a recent Canadian study confirmed the substantial differences in rates of death from ischemic heart disease among Canadians of European, south Asian and Chinese origin, with the highest rates found among those of south Asian origin. This may be an example of how a new environment interacts with an underlying genetic susceptibility to produce a changes in the rates of clinical disease. The excess in south Asians, however, was not as great as has been reported in some European studies. Asian Indian physicians in the U.S. and Canada are interested in further exploration of the reasons underlying this increased risk. During the coming year, the NHLBI will convene a small group of scientists with an interest in the increased risk of CVD, diabetes, and other components of the multiple CVD risk factor syndrome among Indians of Asian origin to explore the most efficient ways to get more information on this problem. The wide geographic dispersion of Asian Indians in the U.S., with concentrations of this minority in several large urban areas, provides both challenges and opportunities which must be considered in designing studies to assess the magnitude of the excess risk of CVD in members of this minority living in the U.S. and in determining whether any special efforts are necessary to identify and improve control of CVD risk factors in this group.

Item

Asthma and Allergic Diseases.- Given the widespread incidence of asthma and allergies and their high economic toll on society, the Committee urges the NIH to consider a cooperative effort by the appropriate Institutes and Centers, including the NHLBI and NIAID, to encourage and promote increased research in these areas. (P. 180)

Action taken or to be taken

The National Institutes of Health (NIH) has facilitated collaborative partnerships between its Institutes and Centers, and between NIH and other Federal agencies to encourage and promote increased research in the areas of allergy and asthma. A goal of this cooperative effort is to develop more effective treatments and interventions to prevent disease onset.

The NIH has encouraged a cooperative research effort among its Institutes. The National Institute of Allergy and Infectious Diseases (NIAID) funded four research project grants in FY 1998 that were submitted in response to the National Heart, Lung, and Blood Institute- and NIAID-sponsored Request for Applications, the “Role of Respiratory Infection in Childhood Asthma.” NIAID, together with the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International support the Immune

Tolerance Network (ITN) to pursue clinical trials involving tolerance induction approaches for asthma and allergy. Currently, the ITN supports a trial of DNA coupled to ragweed allergen for the treatment of allergic rhinitis. NIAID together with the National Institute of Environmental Health Sciences (NIEHS) co-funded the Asthma and Allergic Diseases Research Centers program to support basic and clinical research on the mechanisms, treatment, and prevention of asthma and allergic diseases. NIAID also co-funds a grant with NIEHS to investigate the epidemiology of home allergens and asthma.

NIH has also fostered collaborations with several Federal agencies. NIH (NIAID), with co-funding from NIEHS, established the Inner City Asthma Study (ICAS) in 1996, to evaluate the effectiveness of physician education and a comprehensive environmental intervention on asthma symptoms in inner-city children. Results of this study are expected in early FY 2002. The Environmental Protection Agency also lended research support to the ICAS in an effort to determine the influence of outdoor and indoor particulate matter and co-pollutants on asthma severity. NIH (NIAID) partnered with another Federal agency, the Centers for Disease Control and Prevention, in FY 2001 to launch a new project to disseminate and put into practice the highly successful National Cooperative Inner City Asthma Study (NCICAS) asthma intervention. This 4-year program will be implemented through 23 community health organizations nationwide and will target children with moderate to severe asthma living in poverty-stricken areas of the inner city. This collaboration will translate a product of NIAID research into a program that will directly benefit more than 6,000 disadvantaged children with asthma.

In the future, NIAID will continue to support the ITN and plans to pursue clinical trials involving tolerance induction approaches for asthma. In FY 2002, NIAID will establish a new clinical research program, the Inner City Asthma Consortium, to conduct clinical trials of immune-based therapies for the treatment of asthma and studies of the immunopathogenesis of asthma in inner-city children. In FY 2003, the NIAID will re-compete its long-standing Asthma and Allergic Diseases Research Centers, emphasizing studies aimed at understanding the immune mechanisms underlying the early life origins of asthma and allergic diseases in humans.

Item

Autism.- The Committee urges the Director, in coordination with NIAID, NIDCD, NIEHS, NIMH, and NINDS, to continue to fund and aggressively encourage researchers to engage in research related to the potential causes, treatments, prevention, and cure of autism spectrum disorders. In particular, the Committee wishes to see the meaningful implementation of the new Centers of Excellence in Autism Research, mandated in the Children's Health Act of 2000. To that end, the Committee urges the Director to allocate sufficient resources to advance the scientific and research agenda related to autism spectrum disorders. (P. 180)

Action taken or to be taken

The member institutes of the NIH Autism Coordinating Committee (NIMH, NICHD, NINDS, NIDCD, and NIEHS) have continued their efforts to encourage and provide program assistance

for the submission of grant applications in all major areas of autism research, including those of diagnosis, etiology, pathology, and treatment of autism spectrum disorders. Also, NIH has issued a formal solicitation for proposals for the new Centers of Excellence in Autism Research, mandated in the Children's Health Act of 2000. This new program is called the STAART Centers Program (Studies to Advance Autism Research and Treatment). The initial STAART submissions have now been received and are pending review. NIH has made a commitment of \$12 million per year to fund the full complement of at least 5 centers, some of which will come on-line in 2002 and some in 2003. In addition, NICHD and NIDCD are holding a competition to extend their ongoing CPEA (Collaborative Program for Excellence in Autism Research) program and to expand its funding to a level approximately equivalent to that of the STAART program. Thus, the NIH/ACC institutes have vigorously expanded the overall autism research program of NIH, as directed in the Children's Health Act. In addition, NIMH recently organized and held the inaugural meeting of the Interagency Autism Coordinating Committee as mandated in the Children's Health Act.

Item

Autoimmune Diseases.- [Autoimmunity is at the root of a family of over 80 genetically and clinically interrelated major diseases affecting some 50 million Americans. . . .] The Committee encourages NIH and its Autoimmune Disease Coordinating Committee to expand research aimed at improving awareness, diagnosis and treatment for the entire family of autoimmune diseases. Interrelated disease research will accelerate the application of important findings among the many medical specialties dealing with autoimmune diseases. . . . The Committee encourages NIH to study the overlapping genetics of autoimmune diseases in order to improve diagnostic procedures and effective treatments.(P. 180)

Action taken or to be taken

The National Institutes of Health (NIH) remains committed to its long-standing support of research aimed at improving awareness, diagnosis and treatment for autoimmune diseases. The NIH Autoimmune Diseases Coordinating Committee (ADCC), established in FY 1998 at the request of Congress and chaired by the National Institute of Allergy and Infectious Diseases (NIAID), facilitates the development of coordinated research plans and works to increase collaboration among the many NIH Institutes, private groups, and other federal agencies interested in these diseases. The first report of the NIH ADCC was published in December 2000, highlighting NIH activities in several areas, including genetics, clinical trials, environmental and viral triggers, pathogenesis and immune mechanisms, and health services research. The NIH ADCC established several working groups (including Vaccines for Autoimmune Diseases, Gender and Autoimmunity, and Environment and Autoimmunity) to coordinate efforts in specific areas among NIH Institutes and Centers, other Federal agencies, and private organizations. The NIH ADCC plans to present a comprehensive strategic and collaborative research plan for autoimmune diseases to Congress in Spring 2002.

The harnessing of interrelated autoimmune diseases research will aid in the application of important medical findings among the many medical specialties dealing with autoimmune

diseases. Selectively blocking the immune response, also known as immune tolerance, might have applicability to many autoimmune diseases. In FY 1999, the NIAID established the Immune Tolerance Network, which is developing clinical trials involving tolerance induction approaches for multiple autoimmune diseases, including the use of specific antibodies to treat multiple sclerosis and type 1 diabetes. In FY 2001, NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Heart, Lung, and Blood Institute co-sponsored an initiative, "Innovative Research on Immune Tolerance," to support pilot research projects on the molecular mechanisms and applications of antigen-specific immune tolerance. In FY 2002, the Non-Human Primate Immune Tolerance Cooperative Study Group will be expanded to include large animal studies on the safety and efficacy of promising tolerance induction therapies in kidney transplantation and islet cell transplantation for type 1 diabetes. The new Request for Applications will expand the number of centers that will collaborate to develop novel approaches to tolerance induction.

Interrelated disease research on autoimmune diseases also includes research on other treatment strategies. The Clinical Trials Network for Stem Cell Transplantation in Autoimmune Diseases, established by NIAID in FY 2001, is in the final planning stage of phase III efficacy trials of a stem cell therapy approach to treat multiple sclerosis, scleroderma, and systemic lupus erythematosus (SLE). Under the Hyperaccelerated Award Mechanisms in Immune Disease Trials, NIAID supports mechanistic studies associated with clinical trials of immunotherapies for immune-mediated diseases, including autoimmune diseases. In FY 1999, the NIAID established the Autoimmunity Centers of Excellence (ACE) to conduct basic and clinical research on multiple autoimmune diseases; clinical trials are underway to test the efficacy of potential therapies for SLE, lupus nephritis, and multiple sclerosis. The ACEs are co-sponsored by NIDDK, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the NIH Office of Research on Women's Health (ORWH). In FY 2003, the NIAID plans to renew and expand the ACE to support basic research and new and ongoing clinical trials of immune therapies for multiple autoimmune diseases.

In addition to research on the treatment of autoimmune diseases, research on the prevention of autoimmune diseases remains another area of NIH focus. In FY 2001, NIAID, NIDDK, the National Institute of Child Health and Human Development (NICHD), the NIH ORWH, and the Juvenile Diabetes Research Foundation International established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research on the development of new targets and approaches to prevent autoimmune diseases and to evaluate novel approaches in pilot and clinical studies.

NIH continues its commitment to the study of genetics of autoimmune diseases in order to improve diagnostic procedures and effective treatments. NIAID established the Multiple Autoimmune Diseases Genetics Consortium in FY 1999 to collect clinical data and genetic material from families in which two or more individuals are affected by two or more distinct autoimmune diseases. The consortium is intended to promote research aimed at discovering the human immune response genes involved in autoimmunity. The December 2000 ADCC report highlights NIH activities in several areas, including genetics.

In other research, multiple NIH Institutes (NIAID, the National Institute of Neurological Disorders and Stroke, and NIAMS), the NIH ORWH, and the National Multiple Sclerosis Society support a multidisciplinary study on gender differences in immune response that may be important in autoimmune diseases through an FY 2001 initiative titled "Sex Based Differences in the Immune Response." The goal of the initiative is to identify, characterize, and define differences in the immune response between males and females. Awards are planned for FY 2002. Animal models in autoimmune diseases remain a critical tool for research in autoimmune diseases. In FY 2002, the NIAID together with the NIH Office of Rare Diseases, NIH ORWH, and the American Autoimmune Related Diseases Association will sponsor a meeting on "Animal Models in Autoimmunity." This meeting will bring together clinical researchers and animal model experts to discuss models for lupus, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, alopecia, and inflammatory bowel disease and to determine the requirements for translating findings in animal models of disease to human disease.

Item

Behavioral Science.- There is growing public awareness of the behavioral underpinnings of disease. Heart disease, lung cancer, liver disease, AIDS, suicide, developmental disabilities, and many neurological and cognitive disorders in some cases can be attributed directly or indirectly to unhealthy behavior. The Committee urges NIH to incorporate behavioral research as part of its core public health mission. The Committee also urges the NIH to provide a detailed description of its ongoing work in the behavioral sciences, including a breakdown by Institute, and funds within each Institute of research and training activities included in NIH's behavioral and social science portfolio. (P. 180)

Action taken or to be taken

To date, NIH has submitted two reports describing ongoing work in the behavioral and social sciences at Office of Behavioral and Social Sciences Research (OBSSR) and at the various Institutes and Centers. The most recent report (<http://obsr.od.nih.gov/Publications/NIHBSSR2001.pdf> Senate.pdf) was prepared in June 2001 in response to a request from Congressman Patrick Kennedy to Dr. Ruth Kirschstein, during the May 16, 2001 Appropriations hearing of the House Subcommittee on Labor, HHS, Education, and Related Agencies. That report included behavioral and social sciences research funding levels by Institute and Center for Fiscal Years 1996-2000, and estimates for Fiscal Years 2001-2002. OBSSR will submit updated funding levels by Institute and Center on an annual basis, and will develop an agreeable timetable for submitting periodic substantive reports describing ongoing research.

Item

Biotechnology - Over the last decade, there has been an enormous growth in development of products from biotechnology. With the nearing completion of the Human Genome Project and the development of many new biological techniques, there are still a large number of untapped areas of research that may produce cures for many debilitating diseases. The Committee encourages the Director to explore new projects that link government, academia and industry,

and involve public-private partnerships across traditionally separated disciplines including genetics, nano-technology, material sciences, physics, biology and chemistry. (P. 180)

Action taken or to be taken

The National Human Genome Research Institute (NHGRI), together with the Wellcome Trust, an independent research-funding charitable organization in the UK, has participated in funding two projects which were partnerships between the private and public sectors. The first partnership, the Single Nucleotide Polymorphism (SNP) Consortium, was a project initially funded by the Wellcome Trust and a number of pharmaceutical companies to produce single nucleotide polymorphism (SNP) markers for genetic analysis. NHGRI contributed to this effort through the sequencing done at its large sequencing centers. The sequence produced by the centers yielded a significant number of additional SNPs as well as more human DNA sequence for the draft human genome sequence.

The second partnership between NHGRI, the Wellcome Trust, and a number of pharmaceutical companies was the Mouse Sequencing Consortium, which contributed additional funds to the NHGRI sequencing centers to produce sequence coverage of the mouse genome more quickly than would have been otherwise possible. In this partnership, the Foundation for National Institutes of Health, Inc. played an important role by handling the funds from the private partners.

Two National Institute of General Medical Sciences (NIGMS) programs currently have substantial public-private partnerships. As part of an NIGMS large scale consortium grant program, the Alliance for Cell Signaling has the goal of understanding as completely as possible the relationships between sets of inputs and outputs in signaling cells that vary both temporally and spatially. It receives major funding from NIGMS through one of these grants. Additional support comes from multiple pharmaceutical companies as well as a private foundation (The Agouron Research Institute and Anonymous Foundation, Dallas TX).

The NIGMS Protein Structure Initiative for structural genomics research centers supports nine consortia, with industrial scientists participating in several. All involve a mix of participating institutions. One, the Joint Center for Structural Genomics, consists of a consortium of two research institutes (The Scripps Research Institute, The Salk Institute), two universities (Stanford University and the University of California at San Diego) and a private company (Syrrx, Inc.). Another research center anticipates a major reorganization next year that will incorporate a biotechnology corporation.

Additionally, the Pharmacogenetics Research Network and Knowledge Base, which is supported by NIGMS, interacts with for-profit organizations through the Industry Liaison Group. This group is comprised of a mix of representatives of large pharmaceutical and small biotechnology companies. No government funds are provided except to support the members' travel, as needed. The Industry Liaison Group also exchanges information with the Pharmacogenetics (PGx) Working Group, a trans-industry open group that is working to develop universal standards for recruitment into pharmacogenetics studies that will ultimately be submitted to the FDA.

The National Institute of Allergy and Infectious Diseases (NIAID) engages in a number of activities to promote scientific partnerships between the private and public sectors. For example, under the Challenge Grants program, NIAID has provided matching funds to companies that commit their own dollars and resources toward developing new drugs and vaccines against malaria, tuberculosis (TB), influenza, and dengue virus. The Institute also has announced a new initiative that seeks to establish government-industry partnerships. Entitled “Partnerships for Novel Therapeutics and Vector Control Strategies in Infectious Diseases,” the initiative is designed to encourage drug, pesticide and diagnostic development in areas that are currently not a high priority for industry but are likely to have a high impact on public health. All projects must demonstrate substantive involvement by a private sector partner. In addition, NIAID plans to support research activities within the small business community, including collaborative efforts with the public sector, to develop and apply innovative platform technologies, alternative expression systems, novel adjuvants, and other new approaches in vaccinology to the development of effective vaccines for malaria and TB. Furthermore, NIAID supports HIV Vaccine Design and Development Teams (HVDDT), which are public-private partnerships of scientists from industry and/or academia that have identified specific vaccine concepts amenable to accelerated product development. They are milestone-driven contracts to encourage rapid HIV vaccine advancement into clinical studies.

The NIAID, in partnership with Management Science Associates (a scientific support firm) and Prosanos (an innovator in biomedical informatics software), fund a project to create new data-mining tools and intelligent systems to link large repositories of clinical, genetic, and biochemical data for sophisticated, multi-leveled analyses of renal disease. The analyses permitted by these technologies may further our understanding of the course of renal disease, and ultimately lead to improvements in diagnosis and treatment. Also, NIAID participates in funding the Alliance for Cellular Signaling (AfCS), a large-scale collaborative program including academia, industry, and private institutions. The AfCS seeks to further our understanding of how cells interpret and respond to external signals by defining the proteins that comprise the various signaling systems in both normal and disease states. This knowledge will aid in the development of novel therapeutics for a variety of conditions, including: inflammation, autoimmunity, allergy, and transplant rejection. The AfCS was established in response to a program developed by the National Institute of General Medical Sciences and receives additional support from the National Cancer Institute, a consortium of pharmaceutical companies, and private sources. Furthermore, NIAID supports a biotechnology program led by Novasite Pharmaceuticals, in collaboration with Axon Instruments and the University of New Mexico. This project focuses on the identification of anti-inflammatory and immunosuppressive agents using a novel high throughput screening system, which has the ability to analyze up to 1,000 target variants simultaneously and uses bioinformatic analysis and computational models to aid in drug discovery.

In addition, the National Institute of Neurological Disorders and Stroke has extensive activities in several areas of biotechnology that are crucial for progress against neurological disorders. Among the many areas of focus are mechanical and electronic devices for diagnosis and treatment, tests to screen biological products for transmissible spongiform encephalopathies, high-throughput drug screening, and a variety of genetic technologies, such as microarray analysis of gene expression and vectors for gene therapy in the nervous system. These programs

call upon specialists from engineering, physical sciences, biological sciences, computer technologies, and medicine, as appropriate, and work closely with academia, private industry, and with non-profit organizations.

NIH will continue to have discussions and collaborations with partners in the private sector about funding additional projects. Several new public-private partnership efforts have been implemented or are being considered in the future by NIH. An example of this is the Osteoarthritis Initiative

where NIH and the Food and Drug Administration have partnered with a number of pharmaceutical companies to develop a resource of patient data on biological markers for the progression of osteoarthritis. This resource will stimulate additional research on the causes and treatment of this disease.

Item

Child Abuse and Neglect.- The Committee recognizes the significance of child abuse and neglect as a serious public health problem claiming an estimated 826,000 victims in 1999, according to the most recent data reported by the Department of Health and Human Services. In 1996, the Committee called upon NIH to develop a research agenda designed to address the problems and gaps that currently exist in the State of research in child abuse and neglect. The Committee encourages NIH to proceed at a high level of attention with addressing the research agenda with which it began in examining the National Research Council report entitled Understanding Child Abuse and Neglect, and requests that the working group be prepared to report on current NIH research efforts in this area, the accomplishments of that research, and on plans for future coordination efforts at NIH at the fiscal year 2003 hearings.(P. 181)

Action taken or to be taken

The NIH Child Abuse and Neglect Working Group (NIH CANWG) continues to draw upon its April, 1997 blueprint for action --"NIH Research on Child Abuse and Neglect: Current Status and Future Plans"-- submitted to Congress by the NIH Director. The NIH CANWG has regular monthly meetings with other federal partners within the Departments of Health and Human Services, Education, and Justice. Since 1997, the NIH CANWG has focused on three major initiatives: (1) refining definitions and classification of child maltreatment; (2) expanding the pool of investigators focused on child abuse and neglect; and (3) fostering research in the area of child neglect. First, the NIH CANWG initiated a major effort to increase the accuracy, reliability, and validity of definitions and classifications used in research on child abuse and neglect. In partnership with the Children's Bureau of DHHS, a computerized version of a child maltreatment instrument based on these refined definitions was developed and is being tested in the field. Second, NIH issued a cross-institute Program Announcement (PA) to announce funding opportunities for research career awards in child abuse and neglect. This ongoing research announcement has yielded several new career research awards in child abuse and neglect since its release and during this past fiscal year. Third, multiple federal agencies co-sponsored a major research initiative focused on child neglect that resulted in 15 funded research

projects. These projects form the core of the new “Federal Child Neglect Research Consortium,” which is expected to grow over the next several years. The area of child neglect had previously received little systematic research attention despite the fact that it is the most frequently reported type of maltreatment. An ongoing “Research on Child Neglect” Program Announcement will continue to highlight funding opportunities in this area.

Item

Childhood Birth Defects and Developmental Disorders.- The Committee recognizes the importance of helping children suffering from birth defects and developmental disorders. Thousands of children each year suffer from birth defects and developmental disorders including cleft lip, cleft palate, missing limbs and other facial deformities from hemangiomas, hemifacial microsomia, microtia, aural atresia, and craniosynostosis. The Committee, therefore, urges the appropriate Institutes and Centers to expand and better coordinate their support of research into the causes, incidence, treatment and prevention of these and other children's congenital or developmental conditions and to develop a comprehensive action plan targeting these conditions. (P. 181)

Action taken or to be taken

In the United States, birth defects are the leading cause of infant mortality. While great progress has been made in preventing infant deaths resulting from low-birth-weight, prematurity, respiratory distress syndrome and Sudden Infant Death Syndrome (SIDS), birth defects remain the leading cause of death in infants under one year in age, accounting for one in five infant deaths. It is estimated that more than 120,000 babies in the United States (about 4% of all live births) are born with major birth defects each year.¹ Birth defects are involved in about half of all pediatric hospital admissions and, next to accidents, are the leading cause of death in children. Moreover, the estimated lifetime cost to the U.S. economy of children born each year with any of seventeen major birth defects is in the billions of dollars. Considering the great impact of structural birth defects on public health, socioeconomics and family life, the NICHD, as the lead NIH Institute for this research area, is focusing its long-held interest in understanding the underlying basic mechanisms of normal development to develop a comprehensive program and strategy to support epidemiological, basic, translational, and clinical research on human congenital malformations.

The culmination of a series of NICHD-convened workshops, designed to make recommendations for prioritized areas of future research, was the development of a Birth Defects Initiative and a strategic plan on "Developmental Biology: Understanding Normal and Abnormal Development." The Birth Defects Initiative was inaugurated with an RFA entitled "Genetic Susceptibility and Variability of

¹ March of Dimes: [Birth Defects Information](http://www.modimes.org/HealthLibrary2/BirthDefects/Default.htm).
<<http://www.modimes.org/HealthLibrary2/BirthDefects/Default.htm>>.

Human Malformations." Ten projects from this RFA were funded in Spring 2000 by NICHD in collaboration with the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Environmental Health Sciences (NIEHS), and the Environmental Protection Agency (EPA). These studies on the genetic epidemiology of human malformations focus on the contributions of genetic and environmental factors to the etiology and distribution of disease within families and across populations. They examine such congenital defects as spina bifida and other neural tube defects, craniofacial anomalies [cleft lip and palate], congenital heart defects, craniosynostosis, hypospadias and limb defects. We believe these projects will lay the foundation for the development of future initiatives focusing on the molecular genetics and developmental biology of structural birth defects.

A second NICHD-sponsored RFA, "Developmental Mechanisms of Human Malformations," followed through on earlier recommendations to foster interactions between basic and clinical investigators with common interests in birth defects. This approach, also encouraged by the President's Task Force on Children's Environmental Health and Safety Risks, resulted in this RFA for program projects establishing interdisciplinary and integrated basic, clinical, and translational research projects to study the developmental biology and the molecular genetics of human malformations. The program project mechanism was selected because it is ideal for combining multiple basic and clinical component projects with a central theme and for fostering interactions and collaborations between basic and clinical scientists. Furthermore, the nucleus of multidisciplinary scientists in each program project will provide a fertile environment for cross-training basic and clinical investigators.

Item

Clinical Research Loan Repayment.- The Committee is concerned about the declining numbers of physician-scientists pursuing careers in clinical research. In 1994, the Institute of Medicine recommended the creation of an NIH extramural loan repayment program. Last year, the Congress authorized the program in the Clinical Research Enhancement Act. The Committee believes that this program is critically important and that tuition loan repayment should be made available to the largest possible number of health professionals who are pursuing structured training experience in clinical research; actively engaged in clinical research career development activities with the guidance of a mentor; or conducting clinical research with independent support from NIH.

Action taken or to be taken

Implementation of the Loan Repayment Program (LRP) Regarding Clinical Researchers [Section 487F (42 USC 288-5a) of the PHS Act] is proceeding. Program announcements were published on September 6, 2001 in the Federal Register, and on September 17, 2001 and January 11, 2002 in the NIH Guide to Grants and Contracts.

The Office of Management and Budget provided a three year approval of the information collection on December 28, 2001, and the program was implemented on January 7, 2002, with a due date for

applications of February 28, 2002, for Fiscal Year (FY) 2002. LRP awards will be announced by the third quarter of FY 2002.

Item

Collaboration with the CDC.- The Committee urges the Office of Behavioral and Social Sciences Research (OBSSR) to develop a working group or groups in collaboration with the Centers for Disease Control in order to speed translation of behavioral research to practice. The Committee

recognizes that without dedicated resources it is difficult for staff in different agencies to collaborate as closely as may be needed. NIH is urged to use its increased funding to intensify collaboration, as well as facilitate communication and the transfer of information.(P. 181-182)

Action taken or to be taken

After reviewing successful current collaborations with CDC by existing NIH working groups, OBSSR will either expand the work of one or more of these existing groups, or establish a new working group to ensure that additional progress is made over FY 2002 in translating behavioral research into clinical practice and/or public health practice. We will ensure that the findings discussed in two recent Institute of Medicine reports (Promoting Health: Intervention Strategies From Social and Behavioral Research (National Academy of Sciences, 2000) and Health and Behavior: The Interplay of Biological, Behavioral and Societal Influences (National Academy of Sciences, 2001)) are conveyed to the larger public health community to which CDC regularly provides leadership.

Item

Epilepsy.- The Committee recognizes that while the NINDS is the primary Institute for addressing epilepsy, several other Institutes are also involved in related research. As 75 percent of epilepsy cases begin in childhood, the NICHD has an important role to play in studying this disease. So, too, does the NHGRI, which is urged to assist the NINDS in the search for a genetic fingerprint diagnostic test aimed at improving drug therapy for epilepsy, and the NIMH, which is urged to explore the link between epilepsy and mood disorders, both of which are often treated with anticonvulsant medications. Finally, the NIA is encouraged to examine epilepsy in patients over age 65. The Committee urges the Director to coordinate research efforts among all these Institutes through an Interagency Epilepsy Coordinating Committee that includes agency scientists and industry and patient representatives. (P. 182)

Action taken or to be taken

NIH is committed to both understanding the causes of and developing effective therapies for all forms of epilepsy. While NINDS is the lead NIH Institute for epilepsy research, several other NIH Institutes also fund epilepsy related projects. NINDS will work with National Institute of Mental Health (NIMH), National Institute on Aging (NIA), National Institute of Child Health and Human Development (NICHD), and National Human Genome Research Institute (NHGRI) to coordinate

epilepsy research efforts, including their involvement, as appropriate, in the implementation of the 13 research benchmarks which were a major outcome of the March 2000 White House Conference on “Curing Epilepsy: Focus on the Future.” The benchmarks will help epilepsy investigators maximize their research efforts towards the translation of basic science research findings into improved clinical therapies. The Institutes will work toward coordinating their efforts through joint sponsorship of workshops and conferences, joint funding of initiatives, and periodic meetings to identify and discuss areas of common interest and opportunities for collaboration.

Item

Information Technology.- The Committee urges the Director to facilitate the development and use of these new tools by leading a national effort to ensure that software components for simulations developed by NIH contractors and by other Federal agencies can interoperate and easily be improved and reused. The Director should also encourage researchers to form an open-source community that would facilitate sharing of software components and ensure thorough peer review and testing of simulations against empirical data. The Committee also urges the Director to coordinate NIH's activities with other Federal agencies including the National Science Foundation, the Department of Defense and DARPA, and NASA. (P. 182)

Action taken or to be taken

A year ago, NIH formed the Biomedical Information Science and Technology Initiative Consortium (BISTIC), a committee that represents all of the NIH Institutes that have significant research activities in the area of biological computing. A major focus of this committee is establishing principles to ensure interoperability of the software developed by its contractors and grantees. The issue of the development of open source software consistent with the legislated need to protect intellectual property rights is also being discussed and principles developed. Another major focus of BISTIC is the coordination of NIH funded activities in the area of computer science with those of other funded agencies. To this end, the NIH will invite representatives of those agencies to be members of BISTIC. In addition, BISTIC will work closely with the National Coordinating Office to ensure close cooperation with the other federal funding agencies.

Item

Juvenile Arthritis.- The Committee urges the Director, in collaboration with the NIAMS, NICHD, and NIAID, to strengthen its investment in and commit additional resources to basic, clinical, and translational research efforts and related activities specific to juvenile arthritis as authorized by the Children's Health Act. (P. 182)

Action taken or to be taken

The NIAMS recognizes that juvenile forms of arthritis can pose different challenges than adult disease. In an effort to address some of these unique issues, the Institute's intramural research

program opened an NIH Pediatric Rheumatology Clinic in the summer of 2000, which is staffed by physicians from the NIAMS and the National Institute of Allergy and Infectious Diseases (NIAID). In addition to providing diagnosis, evaluation, and treatment of juvenile arthritis and other rheumatic diseases, the clinic facilitates the translation of research advances to improve patient care. A new study underway at the clinic is designed to determine the best medication combinations for treating children with juvenile rheumatoid arthritis. Because the chronic inflammation associated with this disease affects children's growth and development, researchers hope this study will point to anti-inflammatory drug treatments which minimize the adverse effects of drugs on growth and development.

In related efforts, the NIAMS is actively engaged with the Pediatric Rheumatology Research Network (PRRN) designed to foster cooperation among researchers in Pediatric Rheumatology and currently in the early stages of organization. Members of the network, with support from the NIAMS, are already in the planning stages of two clinical trials in pediatric diseases. Potential roles of the NIAMS intramural program include scientific collaborations involving patient evaluation, imaging studies, genetic analysis, specialized treatment interventions, training of extramural clinicians and investigators, and the development of resources such as gene chips or SNP maps. The NIAID is aware and following closely the efforts of the PRRN. Opportunities may arise as the PRRN begins trials to collaborate with several research programs supported by the NIAID, including the Immune Tolerance Network, the Autoimmunity Centers of Excellence, and the Stem Cell Transplantation Consortium.

The NIAMS is also working to provide research training for pediatric rheumatologists, to help develop a cadre of individuals trained in research methods, as well as clinical practice in this field. The NIAMS, NIAID, and NICHD support the recently established NIH Extramural Loan Repayment Program for Clinical Research and the Extramural Loan Repayment Program for Pediatric Research. These programs provide for the repayment of the educational debt of qualified health professionals who agree to conduct clinical and pediatric research.

In a major treatment advance, clinical trial results from a NIAMS-funded research center have shown that Enbrel[®] (etanercept) is a safe and effective drug for children and teenagers with juvenile rheumatoid arthritis (JRA). Scientists are continuing to make improvements in treating juvenile arthritis and to find new and better medicines with fewer side effects. For example, researchers are studying the long-term effects of using methotrexate in children. The Institute is also supporting a multidisciplinary clinical research center where scientists focus on pediatric rheumatic diseases such as JRA, childhood-onset dermatomyositis, and juvenile fibromyalgia.

The NIAMS also recently funded a new core center to strengthen our understanding of the causes of, and to find novel approaches for treating, pediatric rheumatic diseases. The center consists of five components, including a repository to make tissues available to all researchers; magnetic resonance imaging (MRI) to monitor disease progression; identification of cells involved in rheumatic diseases; data processing and bioinformatics; and administrative support to coordinate project activities.

Furthermore, the Institute funds a research registry for the genetics of juvenile rheumatoid arthritis, which serves as a national resource for scientists studying pediatric rheumatic diseases, including juvenile forms of arthritis. Finally, the NIAMS is committed to disseminating science-based health

information for patients and families affected by juvenile arthritis. To this end, the Institute has recently updated its “Questions and Answers” fact sheet on juvenile rheumatoid arthritis.

At the request of Congress, the Autoimmune Diseases Coordinating Committee was established in 1998, under the direction of the NIAID, to increase collaboration among the many NIH Institutes, private groups, and other Federal agencies supporting research on these diseases. The ADCC plans to present a comprehensive strategic and collaborative research plan for autoimmune diseases. The first report of the Autoimmune Diseases Coordinating Committee published in December 2000, provides further details on the individual initiatives, sponsors, and current and planned research on autoimmune diseases, including juvenile rheumatoid arthritis. The report is located at the following web address: http://www.niaid.nih.gov/dait/pdf/adcc_rev.pdf

Item

Lyme Disease.- The Committee recommends that the NIH improve its communication across Institutes in order to better coordinate Lyme disease research and outreach to public and private scientists with the goal of stimulating research interest in this field. The Committee encourages the Office of the Director to involve NIAID, NHLBI, NINDS, NEI, NIMH, and NCCAM in promising areas of research. The Committee urges NIH officials to identify appropriate NIH advisory committees for Lyme disease representation and ensure the appointment of qualified persons. The NIH is encouraged to include a broad range of scientific viewpoints in the process of planning and executing these efforts, including community-based clinicians with extensive experience in treating these patients, voluntary agencies who have advocacy in their mission, and patient advocates. (P. 183)

Action taken or to be taken

Please refer to page 46 of this document for the OD response to this item regarding Lyme Disease.

Item

Neurofibromatosis.- The Committee recognizes that neurofibromatosis (NF) research involves many Institutes and Centers, including NCI, NINDS, NHLBI, NEI, NIDCD, and NIAMS. The Committee urges the Director to develop a plan to identify new research opportunities regarding NF that cuts across Institutes and Centers. The Committee encourages the Director to intensify and expand its NF research portfolio, and to work with NF advocacy groups when identifying and pursuing new scientific opportunities that will ultimately allow for the development of effective treatments of NF. (P. 183)

Action taken or to be taken

In May 2000, the NIH held a two-day, multi-institute, interagency workshop to assess the status of NF research and to identify future research opportunities that could be developed in FY2001 and beyond. This scientific workshop was initiated and sponsored by National Institute of Neurological Disorders and Stroke (NINDS), the lead institute for NF research at the NIH, and involved National Institute of Child Health and Human Development (NICHD), National Eye Institute (NEI), National

Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), and National Institute on Deafness and Other Communication Disorders (NIDCD), as well as the Department of Defense (DoD) and the Veterans Affairs (VA). Several representatives of NF advocacy groups were also in attendance. Since then, the NIH, through the leadership of NINDS, has been aggressively developing a broad spectrum of activities to respond to the needs and pursue the opportunities that were identified at the workshop.

In March 2001, a multi-institute Request for Applications (RFA-NS-02-002) was issued to promote research on the identification of genes that cause or contribute to human neurological and neurobehavioral diseases. This RFA was developed by NINDS as a direct result of the May 2000 workshop, as well as the comments provided by leading NF researchers on the type of directed research solicitations that likely would prove most useful in advancing NF research. This solicitation was designed to encourage applications for genetics research projects to identify the gene or genes that produce disease susceptibility; to identify “modifier” genes that affect disease susceptibility or outcome; and to investigate the relationship between genotype and disease phenotype. These goals are particularly important with respect to NF research; indeed, the identification of such modifier genes was considered a research priority by the workshop participants. The RFA specifically cites NF as a disease within the scope of its objectives.

A wide variety of extraaxial tumors arise in the spinal and cranial nerves and sometimes affect the brain by compression. Extraaxial tumors that affect the brain include the schwannomas that characterize NF2. Because they are common and can be difficult to manage, schwannomas are one of the two tumor types identified as a future research priority in the recent report by the joint NCI-NINDS Brain Tumor Progress Group (BT-PRG). Several leading NF researchers were members of this particular working group which recommended long term scientific research priorities as well as resource needs to address these uniquely interesting brain tumors.

A critical bottleneck for NF research has been translating advances in basic research into diagnostic tools and clinical therapies. To accelerate this process, NINDS has developed a broad, overarching concept and series of mechanisms to facilitate translational research. The needs of the NF research and patient communities, as expressed in the May 2000 workshop and subsequent related discussions, served as both the impetus and a coalescing model for its development. NINDS expects to finalize and issue this translational research package by early 2002, and its major provisions were recently discussed with a group of NF patient advocates.

The NIH continues its longstanding outreach and support to the NF research and advocacy communities. Several institutes - NINDS, NHLBI, NCI, and NIDCD - provided major support for the National Neurofibromatosis Foundation (NNFF)-sponsored meeting of the International Consortium for the Molecular Biology of NF1 and NF2 held in May 2001 in Aspen, Colorado. At this gathering of the world's leading scientists working on NF, new and exciting results were reported by a number of different investigators in studies ranging from animal models to tumors to learning disabilities. The meeting was also structured to attract exceptional new investigators to the field of NF research. NINDS also funded and moderated an NF “satellite” conference as part of a Child Neurology Society meeting in early November 2001 in Vancouver, British Columbia, which was extremely well-attended and well-received. Finally, NINDS is actively engaged in an advisory

capacity with the NF research community, in conjunction with NF patient advocates, in exploring the development of a strategic plan for NF research, particularly in the area of clinical trials; NCI has been providing advice on establishing the infrastructure requirements that would be needed for conducting clinical trials based on its experiences with the NCI's Pediatric Oncology Group.

Item

NIH/DOE Medical Technology Partnership.- The Committee urges the NIH to continue to collaborate with the Department of Energy (DOE) to evaluate the technologies developed within the nuclear weapons program and other DOE programs in terms of their potential to enhance health sciences, with the goal of achieving clinical applications and improved national health care. (P. 183)

Action taken or to be taken

The NIH recognizes the potential benefits associated with applying technologies developed within the DOE's programs at their nuclear weapons and multi-purpose laboratories to biomedical and clinical research. To facilitate the communication and possible application of DOE laboratory technological resources and capabilities to NIH health-related programs, several cooperative efforts have been initiated. In February 2001, representatives of the DOE's Office of Biological and Environmental Research met with the NIH Scientific Advisory Council to discuss possible interaction with NIH intramural research programs and appropriate mechanisms to facilitate collaboration. As a result of this meeting and subsequent discussions, several joint DOE/NIH technically-focused workshops aimed at identifying specific projects for possible research collaborations and transfer of DOE technologies were planned for late 2001 and 2002. The first joint DOE/NIH workshop was conducted on December 3-4, 2001, and was aimed at thermographic applications of imaging technologies to disease diagnosis and therapy. About 35 investigators from academia, DOE national laboratories, and NIH intramural and extramural programs attended this focused meeting and identified research needs and possible collaborative opportunities in image-guided therapy and thermographic diagnosis. A second joint workshop on molecular imaging technologies is scheduled for late Spring 2002. Workshop attendees will include DOE laboratory investigators, NIH intramural researchers, and NIH extramural program staff. Topics for the initial workshops include diagnostic and therapeutic thermography, biosensors, and molecular imaging technologies. In addition to the intramural interaction, the DOE is an active member of the NIH's Bioengineering Consortium (BECON) which coordinates multi-disciplinary biomedical research and training activities for all NIH institutes and centers and other Federal agencies. Besides participating in BECON coordination activities, DOE laboratory investigators will participate in the planning and conduct of a major symposium on biosensors scheduled for June 2002 on the NIH main campus. The overall goals of the DOE/NIH collaborations are to achieve clinical applications, better health care, and improved quality of life consistent with national needs and agency missions.

Item

Office of Dietary Supplements.- The use of dietary supplements has increased significantly among Americans who want to improve their health and prevent disease, and there is a great need for additional research to better inform consumers of the benefits of these supplements. The Committee expects the Office to allocate sufficient funds to expand the number of botanical research centers, and it urges that hypericum and echinacea be studied at one of these new centers.

The Committee has included sufficient funds to speed up ongoing collaborative efforts to develop, validate, and disseminate analytical methods, and reference materials for the most commonly used botanicals and other dietary supplements.

The Committee is pleased that the ODS has followed through on its recommendation to begin a major research initiative on the safety and efficacy of products containing ephedra, and it urges the Office to continue and expand this important effort. The results of this expanded research should be evaluated by the FDA to ensure that any final action on the proposed rule on products containing ephedrine alkaloids is based on sound science. The Committee believes the Department should immediately take necessary interim action that addresses scientifically supportable safety activities (such as adopting appropriate warning labels that include contraindications and warn against sales to minors) while this research is being completed. (P. 183-184)

Action taken or to be taken

The Office of Dietary Supplements has initiated a program to develop, validate, and disseminate analytical methods and standard reference materials, in response to this Senate language. We have recruited a highly-trained pharmacognosist/analytical chemist to administer the program. We will use all relevant NIH mechanisms in order to encourage and speed up the collaborative efforts that are currently underway. Partners for these activities will include other NIH ICs, other Federal agencies (including FDA and NIST), non-governmental organizations, academia, and industry.

The Office is encouraged that the Committee is pleased with our progress in developing a research initiative on the safety and efficacy of ephedra. The Office has commissioned an evidence report on this subject, in collaboration with NCCAM, using the Evidence-Based Practice Center network of AHRQ. This report is expected to be released in the summer of 2002 and will assist us and NCCAM in shaping the appropriate research agenda. We have recently nominated ephedra for study by the National Toxicology Program of NIEHS. We have joined forces with CFSAN in FDA to fund a contract with AOAC International for the development and validation of analytical methods for ephedra. We have also joined forces with NIST and FDA for the development and dissemination of standard reference materials for ephedra.

Item

Office of Research on Women's Health – The Office of Research on Women's Health (ORWH) works in collaboration with the Institutes and Centers (ICs) of the NIH to promote and foster efforts to address gaps in knowledge related to women's health through the enhancement and expansion of funded research and the initiation of new investigative studies. The ORWH is responsible for ensuring the inclusion of women in clinical research funded by the NIH, including the development and implementation of a computerized tracking system and the implementation of guidelines on such

inclusion. The Office is also involved in promoting programs to increase the number of women in biomedical science careers, and in developing women's health and sex and gender factors in biology as a focus of medical/scientific research. The Committee urges the Director to use the increased funds provided to ORWH for new research activities in a variety of health issues and new and expanded career development programs for women scientists, such as Building Interdisciplinary Research Careers in Women's Health. In addition, the Committee strongly supports the creation of new interdisciplinary research centers to focus on multi-systemic diseases in women, and urges ORWH, in conjunction with the NIH ICs, to move forward with this proposal without delay. The Director is asked to present a progress report to the Committee by April 1, 2002. (P. 184)

Action taken or to be taken

Please refer to pages 38-40 of this document for the OD response to this significant item on the Office of Research on Women's Health (ORWH).

Item

Omega-3 fatty acids.- The Committee is aware of promising research showing significant positive heart health effects related to the consumption of omega-3 fatty acids through foods or supplements. Given the significant human and financial costs associated with coronary heart disease, the Committee urges the Office to begin preliminary work on a major assessment of the health benefits of omega-3 fatty acid consumption. (P. 184)

Action taken or to be taken

The NHLBI is supporting two clinical trials to determine whether consuming omega-3 fatty acids assists in preventing arrhythmias, as well as a small clinical study to investigate whether omega-3 fatty acids can prevent graft failure, vascular inflammation, and formation of blood clots in hemodialysis patients with arteriovenous grafts. It also is funding basic research studies of omega-3 fatty acid metabolism. In 2001 the NHLBI co-sponsored an international workshop, *Omega-3 Fatty Acids, Diabetes and Cardiovascular Risk*, to explore the question of whether omega-3 fatty acids may reduce risk for cardiovascular disease in patients with type 2 diabetes. Within the next few years, researchers hope to establish whether consuming omega-3 fatty acids assists in preventing or treating coronary heart disease.

The Office of Dietary Supplements (ODS) has in place a program for the systematic review of dietary supplement efficacy and safety, a program developed in part as a result of Congressional language in the FY 2001 appropriation. This program is overseen by a Federal working group consisting of several NIH Institute and Center representatives and staff from other Federal agencies with an interest in this area (e.g., NCCAM, AHRQ, FDA, CDC, Department of Defense, among others), who assist the ODS in setting priorities for these reviews. One of the major goals of such reviews is to guide the further development of a research agenda for particular supplements or ingredients.

In the case of omega-3 fatty acids, the promising research to which the Senate Report refers involves

animal research, observational studies conducted in humans, and a few clinical trials conducted in patients with heart disease. However, several questions remain, including mechanism of action, types of omega-3 fatty acids, their effective doses, effects on individuals without heart disease, and public health applicability. A thorough, objective examination of the scientific evidence available needs to be conducted to help identify research needs before the NIH can consider the most appropriate research directions to take. ODS and NHLBI, along with other appropriate agencies, will commission a systematic review of the literature on the relationship between omega-3 fatty acid consumption and its potential benefit for atherosclerotic cardiovascular disease (ASCVD). The review will be conducted in collaboration with AHRQ, using their network of Evidence-Based Practice Centers. It is expected to yield an evidence report, with meta-analysis as appropriate, and with recommendations about gaps in scientific knowledge that may exist that will help us determine future research needs.

Item

Parkinson's disease - The Committee commends the NIH for encouraging and supporting workshops and other collaboration between sectors of the Parkinson's research community, including the NIEHS-supported consortia and the NINDS-supported workshop on gene therapy, and encourages similar collaborative models. The Committee also urges the NIH to continue support of the Udall Centers program and to continue expansion thereof. (P. 184-185)

Action taken or to be taken

Parkinson's disease has been a major priority at NIH for many years, and since the development of the Parkinson's Disease Research Agenda, an unprecedented level of programmatic activity and staff resources have been committed to this field. This has resulted in an aggressive implementation of the Agenda, which has provided Parkinson's disease researchers with new areas of research to explore and the funding necessary to explore them. NIH hosted a meeting in January 2002 which included researchers, Institute representatives, and members of the advocacy community. At this meeting, attendees evaluated the progress to date in the implementation of the Agenda, and discussed how the success of these past efforts in moving research forward should shape the goals of the Agenda for the next several years. Specifically, the balance of ongoing and newly-initiated research in different areas of the Agenda was examined, so that future NIH initiatives will complement our current research portfolio. As part of this process, a series of research priorities which are based on the original Agenda but take into account current scientific opportunities and funding, was developed.

NIH Staff continue to facilitate the development of research consortia in fields that have reached an appropriate capacity, both logistically and scientifically. Currently, NINDS and NIA staff are organizing the first meeting of the Deep Brain Stimulation Consortium, planned for early 2002. This meeting will provide participants with an opportunity to share their results, plan collaborations, and contribute patient data to a central database, critical for the assessment of the efficacy of DBS. NINDS has also provided support for a meeting of investigators interested in gene therapy approaches for Parkinson's disease research. This group came together following an October 2000 gene therapy workshop sponsored in part by NINDS, and the Institute looks forward to a productive relationship with these researchers. In addition, a Consortium meeting for investigators supported by NINDS to screen FDA-approved drug compounds in neurodegeneration assays is also planned for

April 7-8, 2002. NIEHS is also aggressively developing a consortium of investigators who will address the relationship between Parkinson's disease and the environment, using a multidisciplinary approach that encompasses genetics and epidemiology, and involves both basic scientists as well as clinical researchers.

The eleven Morris K. Udall Centers of Excellence for Parkinson's Disease Research that are supported by NINDS are the centerpiece of the Institute's ongoing efforts in Parkinson's disease, and their work impacts every major area of research highlighted in the PD Agenda. The Centers have been very successful, and serve as a model for research groups to establish productive scientific collaborations, while carrying out independent research programs. NINDS is committed to the continuation of this program, and is currently evaluating options for renewal of these awards within a framework of peer review and evolving priorities in the area of Parkinson's disease research.

Item

Pediatric Research Initiative – The Committee is aware that the Children's Health Act of 2000 authorized the establishment of the Pediatric Research Initiative within the Office of the NIH Director, for the purpose of encouraging an increased emphasis on research addressing children's illnesses and conditions across the various Institutes and Centers. The Committee urges the Office of the NIH Director to carry out the Initiative, including supporting training for pediatric researchers, as authorized by Title X of the Children's Health Act. The Committee requests NIH to provide a report to the Committee by April 1, 2002, on the pediatric research activities supported with these Initiative funds. (P. 185)

Action taken or to be taken

The Children's Health Act of 2000 directed the Secretary of HHS to establish a Pediatric Research Initiative within the Office of the Director of NIH. This initiative is intended to increase support for pediatric biomedical research within NIH, to enhance collaborative efforts among the Institutes, and to increase the development of adequate pediatric clinical trials and pediatric drug use information.

As authorized by the Act, the Director of NIH has established the NIH Inter-Institute Committee on Pediatric Research. Reflecting NICHD's longstanding goals of improving and promoting children's health, the Director of NIH asked the Director, NICHD, to chair the new Committee.

The purpose of the Committee is to encourage the development of initiatives for new pediatric research from all interested Institutes and Centers, and to nominate some of these for full or partial support. The Office of the Director of NIH will provide initial funding for some of the successful applicants. These initiatives, along with new pediatric research funded by the Institutes, and identified by them as such, will comprise the Pediatric Research Initiative.

NICHD has also expanded its efforts to bring new investigators into the field of pediatric research, and to provide them the training necessary to ensure their retention. Earlier this fall, NIH officially published notice of its new pediatric loan repayment program, and requested comments. The

Pediatric Research Loan Repayment Program is intended to provide funds to repay student loans to individual researchers who agree to conduct research at their institutions in these areas. The Program is expected to become an important tool to recruit young scientists into the field of pediatric research.

NICHHD is also funding two training programs for pediatricians at different stages of their academic careers. A request for applications was recently issued that would establish programs of postdoctoral pediatric training in basic science or clinical research at pediatrics departments throughout the country. Applications are still being received, and NICHHD expects to fund a number of them in the coming fiscal year, with more to be funded in future years. Another NICHHD training program for pediatricians, the Child Health Career Development Award, supports research career development of pediatricians who have recently completed subspecialty training. Over the past decade, this vital program's goals of increasing the number and effectiveness of established pediatric investigators who have a grounding in basic science and research skills that can be applied to the health problems of children have largely been met.

Item

Promoting adherence to medical and behavioral therapies – The Committee notes that failure to follow medical recommendations causes tens of thousands of deaths a year, increased hospitalizations and delayed recovery. The Committee encourages the Institute to expand research on innovative theories about behavioral, cultural, social, psychological and environmental methods to increase adherence to lifestyle and medical regimen. The Committee further encourages the Institute to take steps to inform medical personnel of effective indicators to measure the standard of delivery of care of health systems and to change physician behavior and practices. (P. 143)

Action taken or to be taken

The Office of Behavioral and Social Sciences Research (OBSSR) continues to facilitate the support of research on adherence to medical and behavioral therapies. With the participation of 12 NIH Institutes and Centers, OBSSR initiated, coordinated, and released a call for research on *Testing Interventions to Improve Adherence to Pharmacological Treatment Regimens* (<http://obssr.od.nih.gov/RFA_PAs/Adherence/AdherenceAwards.htm>). The participating NIH Institutes made seven awards in September 2000, using \$3,000,000 provided by OBSSR and, in some cases, supplemented by their own funds. Also in 2000 and continuing to today, OBSSR initiated a Trans-NIH Coordinating Network for Adherence Research, which meets periodically to consider means for promoting research on adherence. Currently, the network is organizing a one-day workshop in conjunction with the 2002 annual meeting of the Society of Behavioral Medicine. NIH program officers as well as external scientists will participate in this special workshop. Presentations and discussions will focus on: (a) *Translational research* (how to implement known effective techniques that are underutilized), and (b) *New techniques* to improve adherence. Discussion in both of these areas will include the appropriateness of interventions and translational efforts to various ethnic and socioeconomic groups. In June 2002 OBSSR is sponsoring a special, scientific symposium for NIH program managers on *Using Qualitative Methods to Promote Self-Care in Diverse Populations*. In addition to these efforts to expand research and to inform medical personnel about the best evidence practices, OBSSR is examining ways to further the partnership between the Agency for Healthcare Research and Quality (AHRQ) and the Robert Wood Johnson Foundation.

This partnership seeks to fund research and dissemination activities to improve primary care practices that promote a wide range of healthy behaviors. In addition, OBSSR is examining ways to ensure that medical school curricula address clinically-relevant behavioral and social science research that describes successful behavioral and medical therapies for risky personal habits and chronic diseases.

Item

Resuscitation Research.- Some 600 Americans die each day from cardiac arrest. The Committee understands that cardiopulmonary and trauma resuscitation techniques have only about a 10 to 15 percent success rate, and the average survival rate has not improved significantly over the last four decades. The Committee is pleased that the NHLBI, the NINDS, the NICHD, the NIGMS, the Department of Defense, and the Food and Drug Administration supported a forum to set a broad research agenda on novel life-saving therapies and to identify promising new directions in CPR and trauma resuscitation research. The Committee encourages these agencies to pursue these new areas of investigation.(P. 186)

Action taken or to be taken

As a result of the “Post-Resuscitation and Initial Utility in Life Saving Efforts (PULSE)” Workshop, a collaborative forum cosponsored by several NIH Institutes (the NHLBI, the NINDS, the NICHD, and the NIGMS) and other federal agencies (the Food and Drug Administration and the Department of Defense) in June 2000, the NHLBI is soliciting applications to develop effective new strategies to restore heart function and preserve neurological function after cardiopulmonary arrest. It is encouraging small businesses to cooperate with scientific researchers to develop new approaches, tools, methods, devices, and biomaterials that provide bioengineering-based methods for monitoring and performing resuscitation. The NHLBI also is collaborating with the NINDS on a Request for Applications, titled *Basic Research to Improve Cardiopulmonary and Neurological Outcomes Following Resuscitation from Cardiopulmonary Arrest*, to encourage identification and characterization of effects of whole-body ischemia and subsequent blood flow restoration on cardiovascular and neurological function. In addition, the NHLBI will continue to foster research to improve resuscitation outcomes by sponsoring meetings with expert researchers and has formed an agreement with the U.S. Army Medical Research and Materiel Command (USAMRMC) to encourage research to improve both resuscitation outcomes in civilian and military patients.

Item

Sjogren’s Syndrome.- Sjogren’s syndrome is an autoimmune disease with significant impact, and the Committee recommends that the NIH Autoimmune Diseases Coordinating Committee include Sjogren’s syndrome as a priority in its strategic plan. Sjogren’s crosses many specialties and falls under the auspices of many NIH institutes, including the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Allergy and Infectious Diseases, the National Institute of Dental and Craniofacial Research, and the National Eye Institute. The Committee recognizes the need for NIH to develop an integrated plan to cover Sjogren's syndrome that cuts across the Institutes and meets the diverse needs of Sjogren’s patients.(P. 186)

Action taken or to be taken

Please refer to page 55 of this document for the OD response to this item regarding Sjogren's Syndrome.

Item

Systems and Integrated Biology.- The Committee recommends increased support for research and training in whole-systems pharmacology, physiology, toxicology, and other integrative biological disciplines that help to define the effects of therapy on disease and the overall function of the human body. Over the past two decades, there has been an emphasis on supporting research and training at the cellular and molecular levels, but diminished support for training and research in systems and integrated biology. The erosion of support in the area of integrated systems threatens to slow the rate at which fundamental discoveries made at the cellular and subcellular levels are translated into useful therapies. The Committee understands that the Center for Scientific Review (CSR) is currently reorganizing its peer review panels. It hopes that the CSR will ensure that scientists with whole-systems expertise will be represented on those panels. (P. 186-187)

Action taken or to be taken

The National Institute of General Medical Sciences has long had an institutional predoctoral training program in the area of Systems and Integrated Biology. NIGMS continues to welcome and encourage applications that emphasize training in the integrated disciplines requested in the Senate language. In addition to this training program, one of the foci of the newly formed NIGMS Center for Bioinformatics and Computational Biology will be systems approaches for the delineation of principles that can be applied to integrative biology. The Center for Scientific Review is currently undergoing a complete revamping of its review panel organization. Based on initial meetings involving members of the scientific community and NIH extramural personnel, it is anticipated that the new study sections will be formed that will readily accommodate the review of proposals in the area of integrative biology.

Item

Tobacco Products.- The Committee urges that the NIH, including NCI, NIDA, NHLBI, and NIMH, increase its commitment to tobacco-related research, especially regarding cigarette design, including ingredients and constituents. There is a growing consensus in the scientific community that cigarettes could be made less toxic and that changes in tobacco products could reduce the risk of the disease and death in people who continue to use them. However, there are major gaps in the science base necessary for guiding such efforts. For example, research is needed to understand the impact of tobacco product variations on the development of cancer, heart disease, brain diseases, fetal growth and nicotine addiction itself. A specific request for research applications, along with support for intramural researchers to conduct such research, would accelerate the process of discovery and cultivation of expertise on this critical subject. (P. 187)

Action taken or to be taken

Over the past four decades there has been an ongoing debate among public health advocates, the scientific, policymaking, and regulatory communities, and the tobacco industry, about health risks of

tobacco use and addiction. Currently, the tobacco industry promotes three categories of products on the U.S. market: (1) cigarettes made with modified tobacco containing reduced levels of cancer-causing agents (e.g., Advance, Omni, Omni Free); (2) cigarette-like products designed to deliver significantly lower smoke using advanced technologies (e.g., Eclipse, Accord); and (3) smokeless tobacco products made with modified tobacco from which cancer causing agents were either completely eliminated or significantly reduced (e.g., Stonewall, Ariva, Revel, Exalt, Firebreak). New potential reduced-exposure products (PREPs) are heavily advertised and promoted to smokers who: can not or do not want to quit smoking; want products that contains lower amounts of cancer-causing agents, and; want an alternative to cigarettes when they are in smoke free environments such as the workplace and during travel. The public health concern is that alluring messages about harmless, “safer” properties of new PREPs may cause a wide range of undesirable effects such as attracting new tobacco users, especially adolescents; diverting smokers from quitting; or facilitating the relapse of those who were able to quit smoking. The subsequent tobacco-related morbidity and mortality may be greater with PREPs on the population level because there are likely to be more smokers and tobacco

users than if people did not use tobacco at all. “Harm reduction” is an old concept that allows smokers to believe they are reducing their risk of illness when there are no scientific data to support this concept.

Rapid and thorough evaluation of the differential toxicity of PREPs is required; along with research that will examine if “harm reduction” is a viable public health strategy. In 2001, the Institute of Medicine (IOM) issued an FDA commissioned report entitled, Clearing the Smoke: The Science Base for Tobacco Harm Reduction. The primary recommendation calls for research to inform policies and programs on the methods and products purported to reduce exposure to tobacco-derived toxins. The IOM was followed by the 2001 conference “Reducing Tobacco Harm” (sponsored by NCI, NIDA, CDC, Robert Wood Johnson Foundation, American Legacy Foundation). Leading scientists identified the highest scientific priorities as evaluation of products and methods for reduced tobacco toxin exposure and harm reduction, assessment of exposure and toxicity for reducing tobacco harm, and assurance for the public health, communication, surveillance and regulation. These priorities will be discussed in greater detail in a special issue of the journal Nicotine and Tobacco Research.

There is considerable research on the addictive nature of nicotine and the role of various tobacco and cigarette smoke constituents in the development and course of diseases. Currently, there are only eight active NIH-funded grants investigating aspects of tobacco harm reduction. However, none of them were specifically designed in response to a targeted initiative aimed at advancing the knowledge on health risk or safety of PREPs or on reducing harm from tobacco.

In 1999, seven academic institutions were awarded grants by NCI and NIDA to create Transdisciplinary Tobacco Use Research Centers (TTURCs) for studying tobacco use and new ways to combat it and its consequences. The Robert Wood Johnson Foundation is complementing this effort with funds to improve policy understanding and communications practices of the tobacco research teams. Two of the TTURCs are conducting research related to PREPs or reducing harm from tobacco:

- The University of Minnesota TTURC, “Methods for Tobacco Exposure Reduction” is examining tobacco use (exposure) reduction, aided by nicotine medication and behavioral modification as a method for harm reduction. Measurements of nicotine metabolites and biomarkers of carcinogen uptake are being used to assess the relationship of tobacco exposure at various levels of uptake of nicotine and carcinogens.
- The University of Pennsylvania/Georgetown University TTURC, “Biobehavioral Determinants of Tobacco Exposure and Harm” is exploring the association between genetic predisposition for nicotine addiction, smoking behavior, and exposure (i.e., smoking topography, carbon monoxide and nicotine boost) and resultant harm from tobacco.

The NCI Program Announcement (PA), “Review and Analysis of Tobacco Industry Documents,” seeks to stimulate research on a wide variety of scientific, technical, marketing and tactical undertakings by tobacco industries, which were documented in papers, memos, and other records. The evaluation of these documents will enhance understanding of the tobacco industry’s knowledge, strategies and tactics, provide a greater understanding of the determinants of tobacco use and addiction and help researchers and public health practitioners identify effective strategies to prevent and reduce tobacco use. Two grants funded under this PA address PREPs:

- American Health Foundation, “Analysis for Nitrosamines, Changing Cigarette, Additives”. The goal of this project is to provide an insight on the development of PREPs, tobacco and smoke composition by searching internal tobacco industry documents.
- Massachusetts Department of Public Health, “Design and Characterization of Cigarettes”. This study investigates how changes in cigarette design contribute to youth smoking and nicotine dependence. The investigators will also analyze the scientific knowledge about the toxic and addictive properties of cigarettes by reviewing tobacco industry research on smokers’ behavior, changes in toxic constituents in smoke, and changes in nicotine delivery over time.

In addition, the following four investigator-initiated research projects are currently being conducted at NIH in this area:

- University of California San Francisco, “Safety of Nicotine Reduction Strategy”. The goal of this grant is to investigate the safety of gradual reduction of the nicotine content of cigarettes to a level that does not sustain nicotine addiction. This study will also assess changes in biological markers that are associated with smoking-related disease.
- Oregon Health & Science University, “Behavior of Nicotine and N-Nitrosamines in Tobacco Smoke”. This research is focused on improving the understanding of tobacco addiction and cancer-causing agents by studying the partitioning of nicotine and N-nitrosamines between tobacco smoke particles and gas phase. The addition of ammonia and other pH-boosting bases to cigarette tobacco during manufacturing can affect gas/particle partitioning of nicotine and carcinogens in favor of gas phase thus increasing the bio-availability of these compounds and their subsequent physiological consequences.

- University of Vermont, Department of Psychiatry, “Reduced Smoking to Prompt Smoking Cessation”. The goal of this study is to: a) survey populations using cigarette substitutes (such as Eclipse) including whether the use of these products undermines motivation to stop smoking and whether the exposure to nicotine and other toxins is reduced among users of new products; and b) test whether a behavioral instruction program plus nicotine gum will induce a large and durable reduction in smoking.
- American Health Foundation, ”Dosimetry of Risk for Lung and Bladder Cancer among Cigarette Smokers “. The goal of this study is to assess whether low-nicotine cigarettes are less “harmful” than medium- and high-nicotine brands by establishing the relationship among product types, smoking behaviors, delivered dosages of smoke nicotine and carcinogens, as well as the internal dose as measured by biomarkers.

NCI designated “Research on Tobacco and Tobacco-Related Cancers” as a scientific priority area beginning in fiscal year 2001. One of the objectives outlined for fiscal year 2003 in The Nation’s Investment in Cancer Research, is to support the development of biomarkers of tobacco exposure and risk through collaborative work with NIH and the CDC’s National Center for Environmental Health.

On November 27, 2001, NCI issued the new monograph, “Risks Associated with Smoking Cigarettes with Low-Machine-Measured Yields of Tar and Nicotine.” Millions of Americans smoke “low-tar,” “mild,” or “light” cigarettes, believing those cigarettes are less harmful than other cigarettes. In this monograph, national scientific experts conclude that evidence does not indicate a benefit to public health from changes in cigarette design and manufacturing over the past 50 years. The Federal Trade Commission (FTC) uses a test method for measuring tar, nicotine, and carbon monoxide, however, this test method does not appropriately mimic human smoking behaviors. Consequently, the FTC has asked DHHS for guidance to improve its testing method for tar and nicotine. NCI and other DHHS agencies will convene a working group to review and synthesize the science and determine what changes should be made to the testing method to correct the limitations identified in the monograph.

In October 2000, the National Cancer Institute convened the Lung Cancer Progress Review Group (PRG) to identify high-priority areas of research that have the potential to reduce the great toll of this disease through advances in prevention, diagnosis, and treatment. One of the top priorities of the PRG's 30 expert clinicians, scientists, industry representatives, and consumer advocates is to develop and expand new approaches to the biology and treatment of nicotine addiction and mount studies to explore the differential toxicity of various tobacco products, including so-called "safer" or low-tar cigarettes.