NATIONAL INSTITUTES OF HEALTH

National Institute for Allergy and Infectious Disease

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Asthma – The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee encourages NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. Additionally, recent studies suggest that a variety of viral and bacterial agents may play a role in the development of asthma. The Committee suggests the Institute expand research into the role that infections and vaccines may play in the development of asthma. (p. 82)

Action to be taken

Recognizing the impact treatment for asthma attacks has on healthcare delivery systems, specifically emergency department visits, and asthma morbidity, the National Institute of Allergy and Infectious Diseases (NIAID) continues to pursue research toward the prevention, treatment, and management of asthma. An example of NIAID's research efforts is the Inter-City Asthma Study (ICAS) and the Inner-City Asthma Consortium (ICAC) cosponsored by the National Institute for Environmental Health Sciences (NIEHS).

The ICAS demonstrated that a physician feedback intervention reduced unscheduled asthma visits for children with moderate to severe asthma and that an environmental intervention reduced unscheduled asthma visits and missed school days and led to approximately three weeks of additional symptom-free days per year. NIAID sponsored a workshop at the May 2004 annual meeting of the American Thoracic Society to present new results of the ICAS.

In 2004, the ICAC, comprised of community health organizations and health care providers nationwide, launched a cockroach allergen standardization protocol, a study to evaluate the usefulness of measurements of exhaled nitric oxide in the clinical management of asthma in children, and a birth cohort to investigate the allergic and environmental factors that contribute to the development of asthma in inner-city children. The ICAC continues to evaluate the safety and efficacy of promising immune-based therapies; investigate the mechanisms of action of immune-based therapies; develop and validate biomarkers of disease stage, progression, and therapeutic effect; and investigate the immunopathogenesis of asthma in inner-city children.

Advancing the understanding of the immune mechanisms underlying the development of asthma and the causes of asthma exacerbations, including the role of viral and bacterial infections,

remains a high priority for NIAID. For example, in FY2004, NIAID co-sponsored with the National Heart, Lung and Blood Institute (NHLBI) the initiative, "Immune System Development and the Genesis of Asthma," to support research on the early life changes in immune function that lead to the development of asthma and the cellular and molecular processes involved in the onset of asthma, including the effects of bacteria and viruses on the function of the developing immune system.

Additionally, NIAID has participated with other NIH Institutes and Centers, Federal agencies, and non-federal investigators in the Asthma Workgroup of the National Children's Study. Led by the National Institute of Child Health and Human Development, the National Children's Study plans to follow a cohort of 100,000 children from before birth to at least age 25 to evaluate the effects of environmental exposures on the natural history of diseases, including asthma.

NIAID will continue to support research to understand the mechanisms of asthma; in FY 2005, the Institute will co-sponsor with NHLBI the initiative, "Asthma Exacerbations: Biology and Disease Progression," to increase the understanding of the mechanisms involved in acute exacerbations of asthma, including the cellular and molecular processes that cause some viral infections to trigger asthma attacks.

Item

Atopic dermatitis – Atopic dermatitis (AD) is one of the most common skin disorders experienced in infants and children. Over 90% of cases are diagnosed before the age of five. Patients with AD suffer with chronic skin inflammation and itching that disrupt sleep and reduce quality of life. An estimated 17 percent of children in the United States have atopic dermatitis, a dramatic increase above the pre-1960s level of approximately 3 percent. The reason for this increase is unknown, but mirrors the increased rates of asthma and requires greater study. Of additional concern, individuals who have active or dormant AD are at high risk for serious adverse reaction to the smallpox vaccine. The Committee encourages NIAID to work with NIAMS to spearhead a multidisciplinary, multi-institute initiative to encourage investigator-initiated research on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. (p. 83)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) and other components of the National Institutes of Health are committed to supporting research efforts aimed at reducing the incidence and severity of atopic dermatitis and its complications. For example, through the Immune Tolerance Network, NIAID-supported scientists are currently developing a clinical trial of children with atopic dermatitis and food allergy. This trial will help determine whether oral administration of allergens will prevent the development of asthma and other allergic diseases in children with atopic dermatitis.

In addition, NIAID remains committed to reducing adverse reactions to the smallpox vaccine. Because vaccinia, the virus used to vaccinate against smallpox, can be transmitted by close contact, individuals with atopic dermatitis are at risk not only if they are immunized with

vaccinia, but also if their families or other close contacts have been immunized. Protection against this complication is a critical element in biodefense programs. The Institute supports contracts to two pharmaceutical manufacturers for the advanced development of modified vaccinia Ankara (MVA), a live, non-replicating form of vaccinia virus, vaccine to prevent smallpox. These contracts require studies of the safety and efficacy of the MVA vaccine in immunocompromised individuals and those with atopic disorders. The goal of MVA-based vaccine research is to develop a vaccine that can be used safely in all populations who are at risk for complications from the current vaccine made from a live form of vaccine virus.

In FY 2004, NIAID, with expert advice and support from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, established the Atopic Dermatitis and Vaccinia Immunization Network (ADVN). The ADVN will develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum and protect individuals with atopic dermatitis from the adverse consequences of vaccinia exposure; several human and animal protocols are currently in development. Components of the ADVN include the Clinical Studies Consortium for investigating the immune system of atopic dermatitis patients, as well as their immune responses to cutaneous viruses; the Animal Studies Consortium for developing animal models of atopic dermatitis; and the Statistical and Data Coordinating Center for data analysis, clinical coordination, regulatory activities and patient registry development.

Item

Condom Effectiveness – The Committee recognizes the interest in the June 2000 NIH–STD Condom Report and the attention that this report calls to the epidemic of sexually transmitted diseases (STDs) that the nation is experiencing. The Committee encourages NIH to continue its practice of making advances in STD research available to the public and to health practitioners through web sites and other publications. (p. 83-84)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a diverse portfolio of research toward more effective prevention and treatment approaches to control sexually transmitted infections (STIs). This research includes basic research on pathogenesis, immunity, molecular and structural biology of sexually transmitted pathogens, and the impact of STIs in various populations; research for safe and effective vaccines, topical microbicides, therapeutics, and strategies for prevention and treatment of STIs and their sequelae; and the development of rapid and more effective diagnostic tools for STIs.

In December 2002, NIAID participated in an NICHD-sponsored conference entitled “Critical Issues in Study Design of Research on Condoms and Prevention of Sexually Transmitted Infections,” which followed up on those scientific gaps identified during the NIAID 2000 condom effectiveness workshop. The goal of this second workshop was to focus on the development of study design guidance for less experienced researchers to use when designing new research projects on condoms and STIs.

While the U.S. Centers for Disease Control and Prevention is the lead Federal agency for the publication and dissemination of educational material on public health, NIAID maintains, and will continue to maintain, a comprehensive web site on STI information for the general public and health care practitioners.

Item

Genomics – The Committee is pleased that NIAID has focused on research efforts associated with multiple categories of pathogens. The Committee understands that microarray technology has enhanced the progress of pathogen-related research. The Committee encourages NIAID to continue to use this technology to further support an aggressive agenda of pathogen research activities. (p. 83)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a robust extramural research portfolio in the area of microbial genomics and continues to encourage scientists to take full advantage of emerging genomic technologies, such as microarrays, to study key questions in microbiology and infectious diseases. For example, NIAID continues to support the Pathogen Functional Genomics Resource Center (PFGRC) at The Institute for Genomic Research, which was established in FY 2001. The PFGRC provides and distributes to the broader research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens, including those that cause emerging and re-emerging infectious diseases and those that are considered to be potential agents of bioterrorism.

The number of organism-specific microarrays produced and distributed through the PFGRC to the scientific community increased to twenty in FY 2004 and includes microarrays for the causative agents for infectious diseases such as SARS, anthrax, tuberculosis, and plague. NIAID will continue to support the PFGRC in FY 2005 when the PFGRC will make available to the scientific community additional genomic resources, including protein expression clone sets and DNA microarrays. In addition, the PFGRC will undertake the genomic analysis of additional human pathogens as well as a comparative genetic analysis to identify genetic variations and relatedness within and between species for forensic strain identification and for the development of therapeutics, vaccines, and diagnostics. The expansion will also include the development and validation of protein arrays for future distribution to the scientific community.

In addition to the PFGRC, NIAID supports two Microbial Genome Sequencing Centers, which allow for the rapid, high quality, and cost-efficient sequencing of microbial genomes. These Centers have the capacity to respond to national needs and Federal agencies' priorities for genome sequencing and providing genomic sequencing data for multiple usages, including basic research on the biology of microbes, forensic identification of strains, and the identification of targets for therapeutics, vaccines, and diagnostics to combat infectious diseases. Two additional initiatives launched in FY 2004, the Bioinformatic Resource Centers and the Biodefense Proteomics Research Programs, will provide comprehensive genomic, bioinformatics, functional genomics, and proteomic research resources to the basic and applied infectious diseases research community.

In addition to the extramural program in microbial genomics, NIAID also supports a Microarray Research Facility (MRF) to provide its intramural investigators with the expertise and resources for all phases of microarray-based research projects. NIAID scientists have used microarrays produced by the MRF to elucidate the genes involved in the host immune responses to viral hepatitis, to understand the molecular mechanisms underlying resistance to malarial drugs, and to examine the human immune response to *Borrelia burgdorferi*, the causative agent of Lyme disease.

Recognizing the significance of microbial genomics to infectious disease research, NIAID will continue to expand its genomics-related activities in this area.

Item

Hemophilia – The Committee appreciates NIAID's efforts to improve HIV and hepatitis C virus (HCV) treatment for persons with hemophilia or other bleeding disorders and encourages NIAID to work with private non-profit groups to strengthen support for research on liver disease progression. (p. 82)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to supporting research targeted to the hemophiliac population. Transmission of HIV to people with hemophilia has been virtually eliminated by the use of treated blood products. As the population of HIV-infected hemophiliacs declines, the focus of hemophilia research has shifted to the impact of hepatitis C virus. To meet the research needs in this area, the Institute is supporting a University of Cincinnati study of liver disease progression and HCV genomic variability in HIV-infected hemophiliacs. NIAID will continue to support this study in FY 2005.

NIAID and the National Hemophilia Foundation continue to encourage the participation of people with hemophilia in its extra- and intramural research studies, including clinical trials for HIV infection and its sequelae.

Item

Hepatitis C vaccine – The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been awarded and urges the consideration of other creative approaches and new paradigms, including the development of DNA vaccines. (p. 82)

Action taken or to be taken

Research to develop vaccines against hepatitis C virus (HCV) remains a high priority for the National Institute of Allergy and Infectious Diseases (NIAID). NIAID supports an HCV research agenda that includes basic research as well as the development of vaccine candidates, including preclinical evaluation and clinical trials of these candidate vaccines.

The Institute also supports the establishment of research resources to facilitate research towards HCV vaccines. For example, NIAID continues to foster the development of an *in vitro* culture system for HCV as well as new animal models for basic research and for adequately testing vaccine candidates and antiviral drugs. To this end, in FY 2005, NIAID plans to renew the Hepatitis Animal Model Network, which will focus on the development of animal models to screen therapies and vaccines for HCV as well as hepatitis B.

NIAID scientists continue their efforts to develop a DNA vaccine against hepatitis C using various forms of the hepatitis C envelope proteins E1 and E2. In 2004, the Institute launched a Phase I trial using Chiron Corporation's prototype E1/E2 hepatitis C vaccine. This study will evaluate the safety, tolerability and immunogenicity of the vaccine in healthy, uninfected human subjects. In addition, NIAID-supported investigators at the New York Blood Center found that recombinant vaccinia viruses carrying hepatitis C virus DNA provided strong cell-mediated immune responses. Primate studies to assess the immune responses to this recombinant virus are currently in progress.

NIAID is planning to hold a workshop on HCV vaccines in early 2005 to discuss and evaluate the current status of efforts towards development of HCV vaccines with the goal of spurring their development and testing.

Item

Inflammatory Bowel Disease – The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) entitled "Challenges to Inflammatory Bowel Disease (IBD)." This report identifies strong linkages between the functions of the immune system and IBD. The Committee encourages the Institute to enhance its support of research focused on the immunology of IBD, as well as the interaction of genetics and environmental factors in the development of the disease. (p. 82)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID), through its extra- and intramural programs, maintains a strong commitment to basic and clinical research to improve the diagnosis, treatment, and prevention of inflammatory bowel disease (IBD). For example, NIAID scientists have completed a Phase II trial of a novel immune-based therapy for Crohn's disease, monoclonal anti-interleukin-12 antibody, and have demonstrated that it is an effective treatment for active Crohn's disease. This finding is paving the way for a Phase III trial in a large patient cohort.

The Institute, in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), supports the Autoimmunity Centers of Excellence (ACEs), which conduct collaborative basic and clinical research on multiple autoimmune diseases, including clinical trials and mechanistic studies of immunomodulatory therapies. A Phase II clinical trial of anti-

CD3 (Visilizumab) therapy for ulcerative colitis is currently under development to be conducted through the ACEs.

NIAID intramural researchers have expanded their investigations of IBD, including basic studies of the immunology of IBD. NIAID scientists recently published an important finding which explains the mechanism by which certain mutations (CARD15/NOD2) cause Crohn's diseases. The study reveals a new mechanism by which immune responses to bacterial products are regulated; abnormalities in this regulation lead to inflammation and Crohn's disease. Intramural researchers are also conducting other studies to evaluate the safety and efficacy of therapies such as G-CSF in Crohn's diseases and interferon-beta in ulcerative colitis. Lastly, NIAID scientists are conducting a longitudinal study of IBD that combines immune monitoring and conventional therapy; data from this study will allow investigators to dissect the interaction of genetics and environmental factors in the development of disease.

The support of research to understand how genetics and environmental factors play a role in the development of IBD remains a priority for the Institute. For example, NIAID supports the Multiple Autoimmune Diseases Genetics Consortium, which collects clinical information and DNA and cell samples from families who have members with more than one autoimmune disease, including IBD. The information and samples collected from the more than 260 families who have enrolled to date will be used for genetic studies to understand the genetic factors that play a role in the development of autoimmune diseases.

NIAID also supports research to study the role of infectious agents in the development of IBD. For example, the Institute continues to fund several research projects focused on IBD through the initiative, "Microbial Etiology of Chronic Diseases," including research that is studying the possible role of *Mycobacterium paratuberculosis* in Crohn's disease. In addition, NIAID is planning to hold a workshop in the summer of 2005 to discuss the most recent research on IBD and to identify scientific opportunities in this area.

Item

Meningococcal disease – Although meningococcal disease is vaccine-preventable in most cases, approximately 30 percent of the deaths and disabilities from this bacterial infection are attributed to serogroup B, which is not vaccine-preventable. The Committee encourages NIAID to increase research efforts to develop an effective, low-cost vaccine against serogroup B that will help protect infants and adolescents. (p. 83)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to supporting and conducting research to prevent meningococcal disease. In October 2004, NIAID and the National Vaccine Program Office co-sponsored a workshop titled "Carbohydrate Moieties as Vaccine Candidates." This workshop brought together research scientists, clinicians, and representatives from industry to identify research needs and scientific gap areas in an effort to promote vaccine development for meningococcal disease. The workshop examined the mechanisms involved in generating an appropriate immune response to selected antigens,

highlighted recent advances and discussed how this information could be used in the development of effective vaccines. Additional focus was given to discussing the obstacles involved with developing a vaccine against serogroup B meningococcus. The fruits of this discussion are still under evaluation for potential use in generating a serogroup B vaccine.

The Institute continues to support pre-clinical and clinical studies to control selected human respiratory pathogens through its Respiratory Pathogen Research Units (RPRUs). Respiratory pathogens studied at the RPRUs include meningococci, pneumococci, group A streptococcus, pseudomonas, *Chlamydia pneumoniae* and non-typable *Haemophilus influenzae*.

NIAID will continue to pursue research in support of development and licensing of vaccines and therapeutic agents for respiratory pathogens. Among the Institute's goals are to further understand the etiology and long-term health impact of acute respiratory infections, and to stimulate basic research to provide additional information on the pathogenesis, immunity, and functional components of respiratory pathogens.

Item

Nasal aerosol and spray vaccine delivery systems – Recent developments exploring new routes of immunization such as delivery of measles vaccine via aerosol and nasal spray may generate significant savings and result in fewer side effects than immunization by injection. The Committee encourages NIAID to support research in developing and testing these new approaches, building upon the testing already completed in older children, to investigate this delivery method in younger children. (p. 83)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) intra- and extramural research programs have a long history of research and development of vaccines against childhood diseases and of research on the nasal delivery of vaccines. For example, NIAID both conducted and supported the research and development of intranasally administered live, attenuated influenza vaccines. This work was critical to the development of FluMist, the licensed nasal spray influenza vaccine.

NIAID researchers are developing several candidate vaccines that are specifically designed for nasal delivery. For example, an experimental intranasal combination vaccine against respiratory syncytial virus (RSV), the most important pediatric respiratory pathogen worldwide, and parainfluenza virus type 3 (PIV3) has been tested for safety and immunogenicity in children 6-18 months of age; further studies in larger numbers of young children are planned. NIAID researchers are also developing nasally administered vaccine candidates against human metapneumovirus (HMPV), a virus first identified in 2001 that is a significant cause of respiratory tract disease around the world.

Scientists at NIAID have also developed a live, attenuated vaccine for severe acute respiratory syndrome (SARS) that is administered directly to the respiratory tract. In preclinical studies, a

single immunization with this vaccine induced a high level of protective immunity. This experimental vaccine would be appropriate for further evaluation in infants and young children, for whom the vaccine might be more effective than for adults.

In addition to intramural research, the Institute also supports extramural research on alternative vaccine delivery systems, including nasal vaccine delivery. In December 2003, NIAID co-sponsored, with the Department of Health and Human Services, the Centers for Disease Control and Prevention, and the Food and Drug Administration, a conference on innovative administration systems for vaccines, including jet injectors, transdermal administration (i.e., a patch), and transmucosal administration (i.e., oral or nasal administration). The conference was a forum for academic, clinical, and industry communities as well as Federal agencies to discuss the state of the science and current status of the development of the various vaccine delivery techniques.

NIAID will continue to conduct and support the research and development of novel approaches and technologies for vaccine candidates that are suitable for nasal delivery in young children and to test promising candidates in clinical trials.

Item

Scleroderma – The Committee encourages NIAID to conduct research to study the cause and treatment of scleroderma, a chronic progressive disease that predominantly strikes women. Scleroderma is disfiguring and can be life-threatening, affecting multiple systems. More research is needed in order to develop safe, effective treatments and to identify the causes of scleroderma and its complications. NIAID is encouraged to consider including scleroderma as one of the diseases in the Autoimmune Centers of Excellence (ACE) program in order to address these important questions. (p. 83)

Action to be taken

Although we have gained considerable understanding of the mechanisms that mediate tissue injury in autoimmune diseases, significant gaps remain. The National Institute for Allergy and Infectious Diseases (NIAID) remains committed to understanding the cause and improving the treatment of scleroderma, an autoimmune disease. For example, the Autoimmunity Centers of Excellence (ACEs) conduct collaborative basic and clinical research on autoimmune diseases, including scleroderma.

The ACEs support close interaction between clinicians and basic researchers to facilitate the identification of effective tolerance induction and immune modulation strategies to treat or prevent disease, and accelerate the translation of scientific advances to the clinic. NIAID expanded the number of ACEs from four to nine in FY 2004. This expansion will enable a wider range of autoimmune diseases to be studied as it facilitates collaboration and draws on the expertise of a larger network of scientists and physicians. The ACEs are cosponsored by NIAID, the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) and National Institutes of Health (NIH) Office of Research on Women's Health (ORWH).

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

Finally, in December 2004, the NIH Autoimmune Diseases Coordinating Committee plans to submit its second report to Congress. This report will summarize NIH funding for autoimmune diseases research, and accomplishments and activities, including ongoing research projects and future initiatives.

Item

Transplantation research – The Committee urges NIAID to convene an expert conference during fiscal year 2005 to develop a Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The Committee requests a report on the results of this conference including a breakdown of resources committed to this category of research. (p. 83)

Action to be taken

Although one-year organ transplantation survival has improved markedly over the last fifteen years, there has been little success in reversing the decline in long-term graft and patient survival. The National Institute of Allergy and Infectious Diseases (NIAID), through its extra- and intramural programs, supports an extensive portfolio of research aimed at understanding the mechanisms of immune-mediated graft rejection in solid organ, tissue and cell transplantation. Understanding these mechanisms will lead to the development of immunosuppressive therapies with fewer side effects, reductions in the numbers of re-transplants, and improvement in long-term graft survival without the need for life-long, global immunosuppressive therapy.

An example of NIAID support for clinical research on solid organ, tissue, and cell transplantation is the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) program, established in 1994, to conduct multicenter clinical trials of novel approaches to prevent acute and chronic graft rejection in pediatric kidney transplant recipients. Also, in FY 2004, NIAID launched the Clinical Trials in Organ Transplantation consortium, a multicenter initiative to evaluate novel therapies for preventing graft rejection and prolonging transplant graft survival in kidney, liver, and heart transplantation. This consortium, cosponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute, has been charged with defining a five-year scientific agenda for clinical research in organ transplantation and with implementing collaborative multicenter clinical trials in organ transplantation with associated mechanistic studies.

In FY 2005, the Institute will continue to support research to understand the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues or cells. For example, NIAID will support the initiative, “HLA Region Genetics in Immune-

Mediated Diseases," which will support research to identify the variations in immune response genes that may account for the increased susceptibility of certain individuals to immune-mediated diseases, such as graft rejection.

NIAID will lead NIH-wide efforts to convene an expert panel on transplantation research in FY 2005. This panel will assess basic and clinical research programs and make recommendations for future efforts. These recommendations will form the basis of the Transplantation Research Action Plan, which will be provided to Congress.

Item

Tuberculosis – The World Health Organization estimates that nearly one billion people will become infected with tuberculosis (TB), 200 million will become sick, and 70 million will die worldwide between now and 2020 of this disease. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine. The Committee encourages the Institute to continue its TB vaccine development work and to expand efforts to develop new drugs to treat TB. (p. 82)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) Tuberculosis (TB) Program supports research to gain in-depth knowledge about *Mycobacterium tuberculosis* (Mtb) and how the body responds to this invasive pathogen, and to translate this knowledge into improved health care interventions. The focus of the program is to develop drugs that will shorten TB therapy and make it easier for patients to complete therapy, as well as to develop vaccines that will lead to long-lasting protection against TB.

This year, as a result of NIAID's longstanding support for TB vaccine development, the first new TB vaccine in 60 years underwent human clinical testing in the United States. The trial is being conducted by Corixa and GlaxoSmithKline Biologicals. NIAID funding was instrumental in the discovery, development and animal testing of this vaccine candidate. A second TB vaccine developed with NIAID grant support also entered human clinical trials recently; this candidate vaccine is a derivative of the currently available TB vaccine, BCG.

A key component of NIAID's successful contribution to TB vaccine development is the recently renewed TB Research Materials and Vaccine Testing contract. This contract provides exploratory and preclinical evaluation of promising new TB vaccine candidates in animal models. In addition, TB researchers around the world can request a variety of Mtb-derived research reagents from the TB Research Materials and Vaccine Testing program, which enables them to study the disease without handling contagious and technically demanding mycobacterial pathogens.

Many promising new anti-TB drug candidates, developed by NIAID-supported scientists, are now nearing initial evaluations in humans. The most promising candidate, SQ109, which is being developed as a part of NIAID's Challenge Grant program, is nearing completion of preclinical development and may enter human trials in 2005. Another drug, PA-824, is currently

in preclinical development by the Global Alliance for TB Drug Development, a public-private partnership involving NIAID.

NIAID also maintains a robust intramural research program on TB. For example, NIAID scientists are collaborating with colleagues at GlaxoSmithKline and St. Jude Children's Research Hospital to develop an improved drug to treat TB based on the drug thiolactomycin. In addition, researchers at the Institute are synthesizing analogs of PA-824 to elucidate the drug's mechanism of action and to improve the characteristics of this class of compounds as drug candidates. This work has been enhanced by NIAID scientists' development of a novel DNA microarray tool for determining the molecular mechanisms of anti-TB drug action. This tool will allow scientists studying new drugs against TB to immediately understand their mechanism of action, and will greatly facilitate the drug discovery process.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Arthritis – The Committee encourages the NIAID to coordinate its research efforts with other NIH institutes to find a cure for arthritis and related diseases. (p. 125)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) collaborates with other National Institutes of Health (NIH) Institutes and Centers (ICs) as well as with private research groups to conduct research toward a cure for rheumatoid arthritis, which afflicts more than 2 million Americans. For example, NIAID, along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the NIH Office for Research on Women's Health (ORWH), supports nine Autoimmunity Centers of Excellence (ACEs), which conduct collaborative basic and clinical research on autoimmune diseases, including rheumatoid arthritis. Phase II studies of Anti-CD20 and Lovastatin for the treatment of rheumatoid arthritis are currently in development to be conducted through the ACEs.

The Institute also sponsors with NICHD, NIDDK, ORWH, and JDRF, the Cooperative Study Group on Autoimmune Disease Prevention. This group currently supports three core projects and three pilot projects to investigate the prevention of rheumatoid arthritis.

Another NIAID-supported program, the International Histocompatibility Working Group (IHWG), which is cosponsored by the National Cancer Institute, NIDDK, the National Human Genome Research Institute, the National Center for Biotechnology Information at the National Library of Medicine, the Centers for Disease Control and Prevention, and the Juvenile Diabetes Research Foundation, aims to identify the variations in immune response genes that may account for the increased susceptibility of certain individuals to immune-mediated diseases including rheumatoid arthritis. This program will be renewed in FY 2005 as the initiative, "HLA Region Genetics in Immune-Mediated Diseases."

NIAID further collaborates with other NIH ICs in supporting the "Hyperaccelerated Award/Mechanisms in Immunomodulation Trials". The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIDDK, and the National Institute of Neurological Disorders and Stroke also support this initiative which conducts mechanistic studies to investigate at the molecular level how immunomodulatory interventions can impact immune-mediated diseases, such as rheumatoid arthritis. NIAID also cosponsors with NIAMS and the Arthritis Foundation the North American Rheumatoid Arthritis Consortium, a registry and repository of information on families with rheumatoid arthritis.

Lastly, the NIH Autoimmune Diseases Coordinating Committee (ADCC), chaired by NIAID, was established in FY 1998 at the request of Congress to increase collaboration and facilitate coordination of research among NIH ICs, other federal agencies, and private organizations and patient advocacy groups with an interest in autoimmune diseases, including rheumatoid arthritis. The ADCC will submit its second report to Congress in the spring of 2005. This report will summarize NIH funding for autoimmune diseases research, and accomplishments and activities, including ongoing research projects and future initiatives that address components of the ADCC Autoimmune Diseases Plan.

Item

Asthma – The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee urges NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also urges the NIAID to collaborate more aggressively with voluntary health organizations to support asthma prevention, treatment, and research activities. Additionally, recent studies suggest that a variety of viral and bacterial agents, including agents used for immunization may play a role in the development of asthma. The Committee urges the Institute to expand research into the role that infections and vaccines play in the development of asthma. (p. 125)

Action to be taken

Please refer to page 39 of this document for NIAID's response to this significant item regarding asthma.

Item

Atopic dermatitis – Atopic dermatitis (AD) is one of the most common skin disorders experienced by infants and children. Patients with AD suffer with chronic skin inflammation and itching that disrupt sleep and reduce quality of life. Of additional concern, individuals who have active or dormant AD are at high risk for serious adverse reaction to the smallpox vaccine. The Committee encourages NIAID to work with NIAMS to spearhead a multidisciplinary, multi-institute initiative to encourage investigator-initiated research on AD as it relates to smallpox vaccination as well as the progression to asthma and other allergic diseases. (p. 125)

Action taken or to be taken

Please refer to page 38 of this document for NIAID's response to this significant item regarding atopic dermatitis.

Item

Genomics – The Committee is pleased that the NIAID has focused its attentions on research efforts associated with multiple categories of pathogens. The Committee understands that commercially available research tools, such as microarray technology, can enhance the progress of pathogen-related research. The Committee urges the NIAID to utilize this technology to further support an aggressive agenda of pathogen research activities. (p. 125)

Action to be taken

Please refer to page 42 of this document for NIAID's response to this significant item on genomics.

Item

Hemophilia – The Committee appreciates NIAID's efforts to improve HIV and hepatitis C virus (HCV) treatment for persons with hemophilia or other bleeding disorders. The Committee encourages NIAID to work with the National Hemophilia Foundation in strengthening its support for research on liver disease progression to improve HIV and HCV treatment among persons with bleeding disorders. (p. 125)

Action to be taken

Please refer to page 43 for NIAID's response to this significant item of hemophilia.

Item

Hepatitis C vaccine – The Committee is encouraged to learn that a small hepatitis C vaccine human trial has been awarded and urges the consideration of other creative approaches and new paradigms, including the development of DNA vaccines. (p. 125)

Action taken or to be taken

Please refer to page 43 of this document for NIAID's response to this significant item regarding hepatitis C vaccine.

Item

Hepatitis – The Committee continues to be concerned about the prevalence of hepatitis and urges NIAID to work with public health organizations to promote liver wellness, education, and prevention of hepatitis. (p. 125)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports biomedical research, spanning basic through clinical research, toward the prevention and treatment of viral hepatitis. Although the U. S. Centers for Disease Control and Prevention is the lead agency for outreach and education activities related to public health, NIAID does support some activities to promote liver wellness and education on hepatitis. For example, the NIAID web site includes several publications that focus on hepatitis disease management. In addition, the NIAID fact sheet on hepatitis C includes links to web sites for public health organizations that promote liver wellness and hepatitis prevention.

NIAID also educates clinicians and researchers about advances in hepatitis research and about resources available through the Institute. In December 2003, NIAID staff presented a talk at the "Frontiers in Drug Development for Viral Hepatitis" to promote NIAID resources and reagents available to the hepatitis research community, such as repository contents and available therapeutic screening options. In November 2004, NIAID participated in the Princeton Hepatitis B Virus Workshop, an annual workshop sponsored by the Hepatitis B Foundation to discuss critical issues in basic hepatitis research and disease management. This workshop is attended by investigators from academia, industry, and the government. The Hepatitis B Foundation supports hepatitis research, promotes disease awareness, supports immunization and treatment initiatives and serves as a source of information for patients and their families, the medical and scientific communities, and the general public.

NIAID will continue to support a robust research agenda in viral hepatitis and to maintain a comprehensive web site on hepatitis information for the general public and health care practitioners.

Item

Inflammatory Bowel Disease – Recent research identifies strong linkages between Crohn's disease and ulcerative colitis (collectively known as inflammatory bowel disease) and the functions of the immune system. The Committee encourages the Institute to expand its research partnerships with the IBD community, and to increase funding for research focused on the immunology of IBD and the interaction of genetics and environmental factors in the development of the disease. (p. 125-126)

Action to be taken

Please refer to page 44 of this document for NIAID's response to this significant item regarding inflammatory bowel disease.

Item

Juvenile Diabetes – The Committee is encouraged by the Institute's efforts regarding the Autoimmune Prevention Centers, and it encourages the Institute to develop pilot projects,

initiated with the support of the Prevention Centers of Autoimmunity, into full research proposals with special emphasis on pre-clinical studies related to juvenile diabetes (p. 126)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains deeply committed to supporting research to improve the diagnosis, treatment, and prevention of many immune-mediated diseases, including type 1 diabetes. For example, in FY 2001, NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development (NICHD), the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), and the Juvenile Diabetes Research Foundation International (JDRF) established the Centers for the Prevention of Autoimmune Diseases (Autoimmunity Prevention Centers) to conduct basic research on the development of new targets and approaches to prevent autoimmune diseases, with a special emphasis on type 1 diabetes, and to evaluate these novel approaches in pilot and clinical trials.

Since their inception, the Autoimmunity Prevention Centers have supported 25 pilot projects, eight of which are directly related to type 1 diabetes. For example, the Autoimmunity Prevention Centers recently funded a collaborative pilot project which seeks to describe the spectrum of immune responses and gene and protein expression in a mouse model of type 1 diabetes. This project will generate a publicly available dataset that may serve as a starting point for numerous hypothesis-driven projects related to the prevention of type 1 diabetes. Of the eight pilot projects on type 1 diabetes that are supported by the Autoimmunity Prevention Centers, two have been developed into full investigator-initiated research grants.

The objective of the Centers for the Prevention of Autoimmune Diseases is to continue to identify promising interventions, including vaccines, which may prevent the onset of type 1 diabetes. These candidate interventions will then be evaluated through NIAID clinical research programs such as the Autoimmunity Centers of Excellence, which is cosponsored by NIDDK, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and NIH ORWH; the Immune Tolerance Network, which is cosponsored by NIDDK and JDRF; and the Type 1 Diabetes TrialNet, which is cosponsored by NIDDK and NICHD. NIAID plans to renew the Centers for the Prevention of Autoimmune Diseases in FY 2006.

Item

Nontuberculous Mycobacteria (NTM) – Mycobacteria are environmental organisms found in both water and soil that can cause significant respiratory damage. The Committee is aware of the increasing incidence of nontuberculous mycobacteria (NTM) pulmonary infections in women, particularly involving rapidly growing mycobacteria, an inherently resistant subspecies. The Committee encourages NIAID to advance diagnostic and treatment protocols for patients suffering from NTM diseases. (p. 126)

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad range of research on respiratory pathogens, including non-tuberculosis mycobacteria (NTM). For example, NIAID scientists are conducting a clinical study to examine the symptoms, course of disease, and treatment of NTM infections, as well as the genetics involved in these infections. The goals of this study are to identify the critical mechanisms involved in mycobacterial resistance, identify and develop therapies based on these mechanisms of resistance, and develop novel therapies for the treatment of severe mycobacterial infections. These researchers have identified immune system abnormalities that may aid in diagnosis of NTM infection and screening of those at higher risk of NTM infection.

Many of NIAID's NTM research activities focus on NTM as a cause of opportunistic infections in HIV-infected individuals. For example, prior to the introduction of highly active antiretroviral therapy (HAART) for the treatment of HIV/AIDS, disseminated infection with *Mycobacterium avium* complex was a common, life threatening infection in HIV-positive patients. The standard of care was lifelong treatment with antibiotics. NIAID-supported scientists determined that this maintenance therapy can be safely discontinued in patients on HAART regimens. This change contributes significantly to an improved standard of care for HIV-infected persons.

The Institute awarded a seven year contract to California Pacific Medical Center Research Institute, San Francisco, in FY 2002 to test new drug candidates against *Mycobacterium avium* complex in cell culture and animal models. Additionally, NTM are used as model organisms in NIAID-supported research on tuberculosis. It is likely that such research may lead to further understanding of these mycobacteria.

NIAID will continue to support both investigator-initiated research and its intramural research program on NTM, including both basic research to understand the biology of NTM and research towards therapeutics to treat NTM infections.

Item

Primary Immunodeficiency Diseases – The Committee notes that more than 150 primary immune deficiency diseases have been identified to date. These diseases, which impair the body's immune system, strike more severely in children, many of whom do not survive beyond their teens or early twenties. Primary immune deficiencies afflict more than 50,000 Americans, regardless of age, race, or gender. The Committee believes that NIAID should play a significant role in addressing this seriously under-diagnosed class of diseases. Research is being funded at many institutions, including several of the twelve Jeffrey Modell Diagnostic and Research Centers, as part of a consortium created to expand and enhance the research in this group of diseases. However, that research only helps people if physicians know to look for the disease; the public is aware of it; and, patients are diagnosed early and accurately. For this reason, the Committee encourages NIAID to increase its support for the public outreach campaign principally funded by the CDC, while maintaining its research portfolio. The Committee commends NIAID for the establishment of its primary immunodeficiency disease research

consortium (USIDNet) in partnership with the Immune Deficiency Foundation and encourages continued support for this program. (p. 126)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is deeply committed to supporting research efforts aimed at understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases and to working with other agencies within the Department of Health and Human Services to increase public awareness of primary immunodeficiency diseases.

The recently initiated U.S. Immunodeficiency Network (USIDNet) is sponsoring training sessions for new and young investigators as well as providing support for exploratory research. USIDNet provides leadership and mentoring; facilitates research collaborations; enhances the coordination of primary immunodeficiency diseases research efforts; and solicits, reviews, and makes awards for pilot and small research projects. In addition, USIDNet maintains a primary immunodeficiency diseases registry to provide data to the research community about the clinical characteristics and prevalence of these diseases and a repository of specimens from subjects with primary immunodeficiency diseases. The Consortium has funded nine research proposals and continues to review new research proposals three times a year, with the goal of funding 6-9 new research proposals each of the next several years.

NIAID continues to work with the Centers for Disease Control and Prevention and other organizations such as the Immune Deficiency Foundation and Jeffrey Modell Foundation in public outreach on primary immunodeficiency diseases. NIAID scientists are active members of the Medical Advisory Board of the Immune Deficiency Foundation. NIAID scientists also participate as expert speakers at patient advocate group meetings where they update patients and families about current and future therapies. In addition, NIAID researchers actively seek patients for enrollment in clinical studies of primary immunodeficiency disease and have developed information booklets about these diseases for distribution to patients and their families as well as to physicians in the community who may care for these patients. NIAID clinicians also provide lectures to the clinical community about inherited primary immunodeficiency diseases and participate in scientific meetings and conferences which disseminate important information about research and treatments these diseases.

In addition to public outreach activities, the Institute also supports research to improve the diagnosis of primary immunodeficiencies, such as the development of a computer algorithm to identify potentially immunodeficient hospital patients, including underdiagnosed minority patients, and the development of a testing system to allow the identification of some primary immunodeficiency diseases as part of newborn screening.

Item

Scleroderma – The Committee encourages NIAID to undertake research to study the cause and treatment of scleroderma, a chronic progressive disease that predominantly strikes women. Scleroderma is disfiguring and can be life-threatening, affecting multiple systems. More research

is critically needed in order to develop safe, effective treatments and to identify the cause or causes of scleroderma and its complications. Therefore, the Committee urges NIAID to include scleroderma research in the portfolio of the Autoimmune Centers of Excellence. (p. 126)

Action taken or to be taken

Please refer to page 47 of this document for NIAID's response to this significant item regarding scleroderma.

Item

Transplantation research – The Committee urges NIAID to convene an expert conference during fiscal year 2005 to develop a Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The Committee requests a report on the results of this conference including a breakdown of resources committed to this category of research. (p. 127)

Action to be taken

Please refer to page 48 of this document for NIAID's response to this significant item on transplantation research.

Item

Tuberculosis – The World Health Organization estimates that nearly 1 billion people will become infected with tuberculosis [TB], 200 million will become sick, and 70 million will die worldwide between now and 2020. The Committee is pleased with NIAID's efforts to develop an effective TB vaccine and encourages the Institute to continue its TB vaccine development work and to expand efforts to develop new drugs to treat TB. (p. 127)

Action taken or to be taken

Please refer to page 49 of this document for NIAID's response to this significant item regarding tuberculosis.

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$4,340,883,000	Indefinite	$4,398,027,000
Infectious Diseases	Section 446	42§285f	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	61,958,000		61,368,000
Total, Budget Authority				4,402,841,000		4,459,395,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.