

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

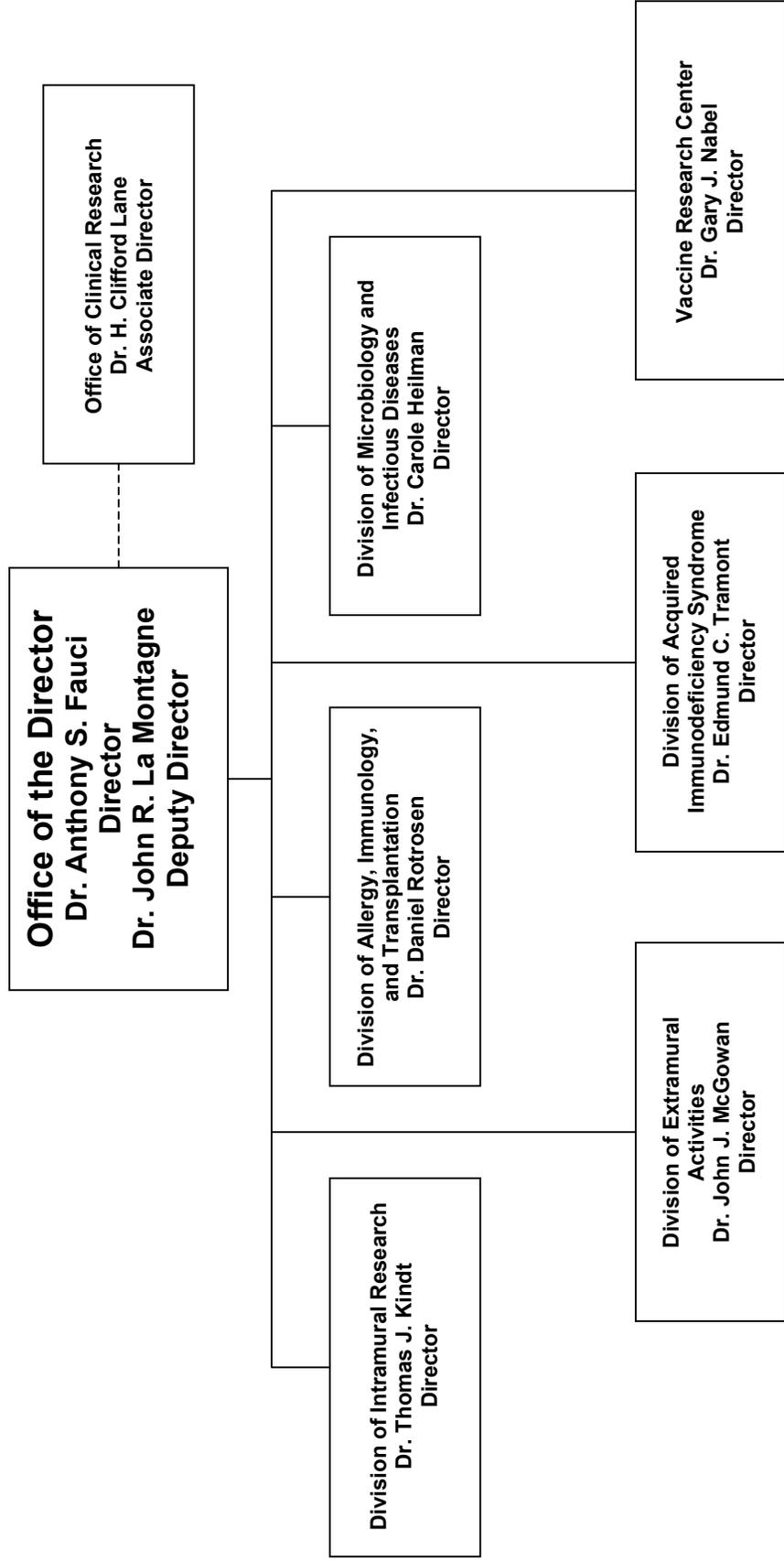
**NATIONAL INSTITUTES OF HEALTH**

**National Institute of Allergy and Infectious Diseases**

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# National Institutes of Health National Institute of Allergy and Infectious Diseases Organizational Structure

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**NATIONAL INSTITUTES OF HEALTH**

National Institute of Allergy and Infectious Diseases

*For carrying out section 301 and title IV of the Public Health Service Act with respect to allergy and infectious diseases, \$4,335,255,000: Provided, That \$100,000,000 may be made available to International Assistance Programs, “Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis”, to remain available until expended, to further the Institute’s efforts to prevent and alleviate these diseases.*

**National Institutes of Health  
National Institute of Allergy and Infectious Diseases**

**Amounts Available for Obligation <sup>1/</sup>**

Source of Funding	FY 2003 Amended		
	FY 2002 Actual	President's Budget	FY 2004 Estimate
Appropriation	\$2,372,278,000	\$3,983,693,000	\$4,335,255,000
Enacted Rescissions	(4,965,000)	---	---
Subtotal, Adjusted Appropriation	2,367,313,000	3,983,693,000	4,335,255,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(2,534,000)	0	0
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	(25,000,000)	0	0
Office of Homeland Security	0	(583,000)	0
Comparative transfer from:			
Fogarty International Center for International Services Branch	113,000	113,000	0
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	100,000,000	0	0
Public Health Service Emergency Supplemental Fund	88,500,000	0	0
Comparative transfer to:			
Office of the Director for program changes	(1,966,000)	(2,123,000)	0
Office of Homeland Security	(583,000)		
National Institute of Biomedical Imaging and Bioengineering	0	0	0
Subtotal, adjusted budget authority	2,525,843,000	3,981,100,000	4,335,255,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	2,525,843,000	3,981,100,000	4,335,255,000
Unobligated balance lapsing	0	---	---
Total obligations	2,525,843,000	3,981,100,000	4,335,255,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:  
FY 2002 - \$6,011,528; FY 2003 - \$6,700,000; FY 2004 - \$7,500,000  
Excludes \$6,406,961 in FY 2002 and \$8,472,311 in FY 2003 for royalties.

## Justification

### National Institute of Allergy and Infectious Diseases

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.  
Reauthorizing legislation will be submitted.

Budget Authority:

FY 2002		FY 2003 Amended		FY 2004		Increase or	
Actual		President's Budget		Estimate		Decrease	
<u>FTE's</u>	<u>BA</u>	<u>FTE's</u>	<u>BA</u>	<u>FTE's</u>	<u>BA</u>	<u>FTE's</u>	<u>BA</u>
1,236	\$2,525,843,000	1,486	\$3,981,100,000	1,586	\$4,335,255,000	100	\$354,155,000

This document provides justification for the Fiscal Year 2004 activities of the National Institute of Allergy and Infectious Diseases (NIAID), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

## INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), supports and conducts basic and applied research to understand, treat, and prevent infectious, immunologic, and allergic diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism; the emergence or re-emergence of infectious diseases such as acquired immunodeficiency syndrome (AIDS), West Nile virus, dengue, malaria, and tuberculosis, as well as the increase in asthma among children in this country.

### **Bioterrorism: Responding Through Research**

The growth of NIAID's biodefense research program is tied to a new element in the developing tapestry of public health concern over the threat of a bioterrorist attack. The horrific attacks of September 11, 2001, on the World Trade Center and Pentagon left a trail of death and disruption in their wake. Most importantly they brought home in vivid display on our television screens the simple fact that the front lines in the War on Terrorism are everywhere. This tragedy, coupled with the intentional delivery of anthrax spores through the mail to newspaper, television and government offices that made the threat of bioterrorism a reality in the U.S., have increased concern that another terrorist attack may occur at any time, anywhere around the world. The magnitude of the problem and the gravity of the situation are a grim and foreboding reminder of the presence of terrorism, biological weapons, and their potential impact not only on public health but also on the peace, prosperity and promise for the future that contemporary society makes possible.

Our nation's ability to detect and counter bioterrorism ultimately depends heavily on the state of biomedical science. As the lead agency at NIH for infectious diseases and immunology research, NIAID has developed the *NIAID Strategic Plan for Biodefense Research* and the detailed *NIAID Biodefense Research Agenda for CDC Category A Agents*, with short-, intermediate-, and long-term goals. The *Strategic Plan* and *Research Agenda* stress two overarching and complementary components: basic research into agents with bioterrorism potential and the specific and non-specific host defense mechanisms against those agents, and applied research with predetermined milestones for the development of new or improved diagnostics, vaccines, and therapies. To

further address a comprehensive biodefense research agenda, NIAID convened expert panels on: *Atopic Dermatitis and Vaccinia Immunization*; *Immunity and Biodefense*; and *Bioterrorism and its Implications for Biomedical Research: Category B and C agents*.

In FY 2002, NIAID markedly expanded and accelerated its biodefense research programs, focusing on basic research of the biology of the microbe and the properties of the host's response to infection. An essential complement to this basic research was the pursuit of an ambitious agenda of applied research to develop diagnostics, therapeutics and vaccines against agents of bioterrorist potential. In a short period of time, the Institute has generated a remarkable array of accomplishments. For example NIAID-supported scientists successfully completed a clinical trial demonstrating that the existing stockpile of smallpox vaccine (Dryvax®) can be diluted fivefold. This simple change potentially expanded the useful number of doses in the stockpile from about 15.4 million to ~ 75 million. NIAID-supported researchers also began developing a Phase I protocol for modified vaccinia Ankara (MVA), a potential 3rd generation smallpox vaccine that could be safe for individuals at high risk of complications from existing vaccines.

The need for therapeutics to address the health needs of the public in the event of a bioterrorism attack is also a top priority for the Institute. NIAID-supported scientists have demonstrated in animal model systems that the antiviral drug, cidofovir, is active against the smallpox virus. NIAID-supported researchers determined how anthrax gains entry into a cell, and demonstrated how the toxin can be effectively blocked from entering the cell, suggesting that the development of anthrax-toxin blocking compounds could be a viable therapeutic approach. NIAID will continue to expand biodefense research including research targeted at the design, development, evaluation and approval of the specific public health tools (diagnostics, therapies, vaccines) needed to control a bioterrorist-caused outbreak. A crucial element of the long-range strategic plan is to have research facilities for extramural researchers to conduct biodefense research; NIAID plans to begin construction of extramural biosafety level (BSL) 3 and 4 research facilities in FY 2003. These specialized, high-containment research laboratories, particularly when equipped for research on highly infectious agents, play an important role in developing a robust, long-term, comprehensive national biodefense research program.

### **Major International Killers: HIV/AIDS, Tuberculosis and Malaria**

The expanded efforts in area of biodefense research have not diminished the commitment of the NIAID to address the other dominant international killers – HIV/AIDS, tuberculosis and malaria. Globally, infectious diseases are the leading cause of death, killing an estimated 14.9 million people worldwide in a year.<sup>1</sup> In the less developed areas of the world, it is clear that infectious diseases alone are responsible for about one-half of all deaths recorded. Moreover, even in the industrialized and develop countries the impact of infectious diseases remains high. In the United States infectious diseases are the third leading cause of death. Leading killers among infectious microbes include the agents that cause HIV/AIDS, tuberculosis, and malaria. These three diseases continue to exact an enormous toll throughout the world. NIAID maintains a long-standing commitment to conduct and support research on these infectious diseases of global health importance. In carrying out its global health research mission, the NIAID supports intramural research programs, training and research collaborations, domestic and foreign research awards, official bilateral programs, and collaborations between international agencies and organizations. NIAID's *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis* defines, the Institute's goals and plans for fighting these devastating infectious diseases by building sustained research capability domestically and internationally and enhancing international partnerships.

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<sup>1</sup> WHO. *The World Health Report 2002*, Geneva, Switzerland.

## Emerging and Re-emerging Infectious Diseases

The scope of the NIAID research portfolio also continues to expand in response to new challenges, such as emerging and re-emerging diseases. Many biological threats facing those in the U.S. and abroad are diseases of natural origin. Time has witnessed the resurgence of cholera in the Americas, the emergence of Hantavirus in the continental U.S., new influenza viruses, the recent emergence of West Nile virus in many regions of the U.S., and transmissible spongiform encephalopathies (TSE) in the United Kingdom. Because the frequency of world travel makes the U.S. part of a global community, diseases that emerge in foreign countries are also health threats in the U.S. The advancement of knowledge through research should have enormous positive impact on our ability to diagnose, treat, and prevent these diseases.

## Other Problems in Infectious Diseases

NIAID is making rapid progress in understanding the microbes and the biological processes that underlie a broad spectrum of infectious diseases including: viral hepatitis, sexually transmitted diseases, enteric infections, Lyme disease and many others. The Institute has also made significant progress in combatting these diseases. NIAID-supported investigators have helped develop many new and improved vaccines that have saved millions of lives and prevented untold illness and disability from infectious diseases. Success stories include the development of vaccines against *Haemophilus influenzae* type b, pertussis, chickenpox, pneumococcal disease, and hepatitis A and B. NIAID will continue to support research to: identify new vaccine candidates to prevent diseases for which no vaccines currently exist; improve the safety and efficacy of existing vaccines; and design novel vaccine approaches.

Many of these infectious diseases are now exhibiting a new capacity that is becoming a critical public health problem - resistance to standard drug treatment. Microbes that cause malaria, tuberculosis, and pneumonia are evading traditional therapies. *Enterococcus faecalis* and *Staphylococcus aureus* staphylococci, are unfortunately common causes of bacterial infections in hospitalized patients. Both organisms have acquired resistance to vancomycin and methicillin thereby making these infections potentially life-threatening. By sharing their drug-resistance genes, some bacteria become deadly despite the strongest antimicrobials that are directed towards them. NIAID's research programs strive to understand how microbes develop drug resistance and to develop new strategies to control these drug-resistant infections. The development of effective vaccines that prevent these serious infections is an important element of this research strategy. The Institute's research investment has led to remarkable new insights, including a greater understanding of the molecular biology and genetics of antimicrobial resistance and the discovery and identification of novel targets for vaccines that prevent these infections in the first place.

These infectious disease challenges are arising at a time when technologies to approach them have never been more powerful. Modern biology has made genetic sequencing an everyday tool. The capability to determine the precise sequence of nucleic acids that define the genetic code of any organism is of transcendental importance and has led to a new field of research – genomics. Genomics provides NIAID-supported scientists with the genetic code of many pathogenic organisms. This information is critical in that it is leading the field of microbiology into many new targets for drugs, vaccines, and diagnostic tests. NIAID has made a significant investment in the growing field of microbial genomics and, in FY 2002, supported approximately 50 large-scale projects for sequencing the genomes of microbial pathogens and invertebrate vectors of infectious diseases. Approximately 30 of these projects have been completed, including the genomic sequences of: bacteria that cause tuberculosis, gonorrhea, chlamydia, and cholera; the parasite that causes malaria; and the mosquito that transmits malaria. The application of genomic information can reveal important aspects of the biological properties of pathogenic organisms. For example, in the case of the bacterium that causes cholera, *Vibrio cholerae*, the genome sequence has been used to identify the genes in that bacterium that enhance its virulence or ability to cause disease.

## Immune-Mediated Diseases

The past two decades of highly intense and productive research on the immune system have resulted in a wealth of new information and extraordinary growth in conceptual understanding of this complex system. These accomplishments now provide opportunities for major advances in the diagnosis, treatment, and prevention of a broad range of immune-mediated diseases, including: asthma and allergic diseases; autoimmune disorders; and rejection of transplanted solid organs, tissues, and cells.

NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals with immunologic conditions such as multiple sclerosis, type 1 diabetes, and asthma. Researchers are developing novel ways to selectively block inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as induction of immune tolerance. The NIAID-supported Immune Tolerance Network (ITN) is an international consortium consisting of approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. Since its inception, the ITN has initiated more than 21 clinical protocols in multiple disease areas, including islet transplantation for type 1 diabetes, kidney transplantation, autoimmune diseases, asthma, and allergic diseases.

For the past decade, NIAID also has focused on reducing the significant and growing burden of asthma among minority children residing in the inner cities of the U.S. The current Inner-City Asthma Study has investigated novel interventions to improve the health of children with asthma living in the inner city. One approach, called a physician feedback intervention, involves periodic status reports based on parental interviews. Another method involves an environmental intervention to identify and remove asthma triggers, such as cigarette smoke and cockroaches, from the child's home. Both interventions have reduced the need for health care and improved the quality of life of these children.

NIAID research has yielded remarkable insights into other immune-mediated diseases. NIAID-supported investigators increased understanding of the genetic susceptibility to type 1 diabetes and identified a mutant gene causing severe immunodeficiency in Native Americans. NIAID research has also led to potential therapeutic approaches. For example, NIAID-supported researchers developed a promising immune therapy for type 1 diabetes. NIAID, through its many programs (e.g., *Autoimmunity Centers of Excellence*, *Cooperative Clinical Trials in Pediatric Transplantation*, *Primary Immunodeficiency Diseases Consortium*), will continue to make outstanding contributions to the understanding of immune-mediated diseases.

In an effort to meet the challenges posed by immunologic and infectious diseases, to seize future research opportunities, and to maximize potential advances, NIAID has implemented a scientific planning process in support of basic and clinical research. The scope of NIAID's scientific vision also includes a focus on addressing health disparities, training investigators, and outreach to the Institute's stakeholders.

NIAID remains vigilant in its leadership, continuing to provide a strong science base to meet the daunting public health problems posed by infectious and immune-mediated diseases. Armed with new scientific tools and the power to exploit unprecedented scientific opportunities in immunology, microbiology, and infectious disease, NIAID is prepared to meet the challenge of these diseases through biomedical research. A commitment to the best possible research will drive the Institute's efforts to enhance our defenses against those who would attempt to harm us with bioterrorism, to develop new tools in the fights against HIV/AIDS and other infectious diseases, and to improve therapies and management of immune-mediated diseases, and as a result, improve public health both domestically and abroad.

## CONFRONTING INFECTIOUS DISEASES

### BIOTERRORISM: RESPONDING THROUGH RESEARCH

The anthrax attacks of 2001, coupled with reports that certain countries possess or are trying to acquire biological weapons, focused attention on the importance of developing an effective, nationwide biodefense capability. A key component of the plan to increase national preparedness against bioterrorism is an intensified research and product development program designed to generate, as efficiently as possible, new and improved vaccines, therapeutics, and diagnostics to protect the civilian population against agents of bioterrorism. The threat of a bioterrorist attack against civilians differs in several ways from biowarfare directed at military personnel. Civilian populations are more vulnerable to such attacks because of their diversity with regard to age and health status. Civilians, unlike military personnel, generally will not have received vaccines to prevent infections with microbes that may be used as bioweapons. Moreover, the range of pathogenic microbes that might be used in a bioterrorist attack on civilians is much broader than what might be effectively used against the military. NIAID is uniquely positioned to serve as the lead Institute for biodefense research, given its long-standing history of conducting and supporting research to combat infectious diseases.

Since the fall of 2001, NIAID has significantly expanded, accelerated, and intensified its research on microbes and toxins that could be used as biological weapons against the civilian population. NIAID is carrying out the basic research needed to understand how bacteria, viruses, and toxins cause disease and how humans and animals respond to these agents, and to translate this knowledge into drugs, vaccines, diagnostics, and other products to protect human health. At the same time, NIAID is expanding specialized research facilities and other research resources for biodefense, and to implement a comprehensive basic research and product development program in collaboration with academia, industry, and other private- and public sector organizations.

In 2002, as part of its accelerated biodefense research program, NIAID convened four expert panels within a period of seven months to assist in the development of strategic plans and research agendas that address critical needs. (1) The Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research assisted in developing the *NIAID Strategic Plan for Biodefense Research*<sup>2</sup> and the *NIAID Biodefense Research Agenda for CDC Category A Agents*<sup>3</sup>. The Strategic Plan emphasizes basic research on microbes, host defense mechanisms, and the development of drugs, vaccines, and diagnostics. The Biodefense Research Agenda articulates immediate and longer-term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, and Rift Valley fever, and Lassa virus. The agenda also addresses the research resources, facilities, and scientific manpower needed to conduct basic and applied research on these potential agents of bioterrorism. (2) The Expert Panel on Atopic Dermatitis and Vaccinia Immunization focused on the morbidity and mortality associated with administering existing smallpox vaccines to persons with eczema and other skin conditions. (3) The Expert Panel on Immunity and Biodefense addressed the immunological aspects of biodefense research, including innate and adaptive immune responses. (4) The NIAID Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research on Category B and C Agents assessed current research initiatives and goals for a diverse range of pathogens, including those that cause cholera, Typhus fever, and Yellow fever, as well as toxins that are secreted by certain microbes.

NIAID intramural and extramural investigators have made substantial progress in a short period of time, particularly in their efforts to develop vaccines and therapeutics for the most dangerous potential agents of bioterrorism. NIAID-supported scientists demonstrated that the existing

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<sup>2</sup> NIAID <http://www.niaid.nih.gov/dmid/pdf/strategic.pdf>

<sup>3</sup> NIAID <http://www.niaid.nih.gov/dmid/pdf/biotresearchagenda.pdf>

smallpox vaccine could be diluted five-fold, thereby potentially expanding the stockpile of smallpox vaccine to about 75 million doses. In addition, other supplies of vaccine have become available in recent months and the available supply of smallpox vaccine is now about 360 million doses, more than enough to vaccinate all Americans. NIAID is also testing a range of candidate vaccines in clinical and pre-clinical studies, including 3<sup>rd</sup> generation vaccines against smallpox, a 2<sup>nd</sup> generation vaccine to prevent anthrax, a DNA vaccine to prevent Ebola virus, and a new vaccine for plague. In addition, NIAID-funded scientists are developing new or improved therapeutics against several Category A agents, including smallpox, anthrax, hemorrhagic fever viruses and botulinum toxin.

## **Smallpox**

The smallpox virus is considered one of the most dangerous potential agents of bioterrorism because it is easily transmitted from person-to-person; few people carry full immunity to the virus, and no effective treatments exist. The United States discontinued routine smallpox vaccinations more than 30 years ago, and today even previously vaccinated individuals may be susceptible to infection because immunity wanes over time. Thus, the reintroduction of smallpox in the 21<sup>st</sup> century could have devastating consequences. NIAID has launched an aggressive research and development program to protect Americans against smallpox.

### *Scientific Advances in Smallpox Research*

NIAID-supported researchers demonstrated that the currently available Dryvax® smallpox vaccine can be diluted five-fold and still retain its ability to trigger the characteristic skin lesion that indicates a successful vaccine “take.” The Dryvax® vaccine is based on the use of vaccinia virus, a virus that is closely related to the cause of smallpox (*Variola*) but which does not cause the scarification, serious disease and death associated with smallpox. More than 97 percent of all clinical trial participants, none of whom had been previously vaccinated against smallpox, responded with a vaccine take. The results of the trial indicate that existing supplies of smallpox vaccine, if diluted five-fold, along with additional supplies of the smallpox vaccine being purchased, will be sufficient to vaccinate the entire U.S. population.

NIAID is also vigorously evaluating drugs for smallpox. Recently, NIAID-supported scientists developed a form of the antiviral drug cidofovir that can be administered orally. Cidofovir is of particular interest as a potential therapy for smallpox because the FDA has already approved it for the treatment of cytomegalovirus, an opportunistic infection in people with HIV/AIDS. Also, cidofovir has shown potent activity against viruses related to smallpox in test-tube studies and in animal models, and against the smallpox virus in laboratory studies.

### *A Key Scientific Question Being Addressed: Next-Generation Smallpox Vaccines*

An important goal in NIAID’s biodefense research program is to develop smallpox vaccines that are safe and effective for all individuals. The existing vaccine, which is based on the use of live, replicating vaccinia virus, can cause severe adverse reactions, including the rare possibility of death in people whose immune systems are weakened by disease, medication, or age. Also, pregnant women, very young children, and people with eczema are more susceptible to adverse reactions. The 2<sup>nd</sup> generation smallpox vaccine, currently under development and production, is derived from Dryvax® that is grown in tissue culture, not calf-skin under carefully controlled laboratory conditions. The 2<sup>nd</sup> generation vaccine is expected to be easier to manufacture and it may also have fewer side effects, although this is not yet proven.

A leading candidate for a 3<sup>rd</sup> generation vaccine is the modified vaccinia Ankara (MVA), a highly weakened form of vaccinia virus that replicates well in chick cells, but very poorly in human cells. MVA was first tested in Germany at the end of the smallpox eradication program in many

thousands of children and shown to be extremely safe. Since then MVA has been used as a vector for vaccines for the therapy of cancer and to serve as a delivery vector for other antigens, including those found in the AIDS virus. It has been used experimentally in many immunosuppressed subjects and has been shown to be safe. MVA does stimulate protective immune responses against vaccinia in animal model studies and has been shown to be immunogenic in humans. It has not been subjected to a clinical trial to establish its efficacy against smallpox because the naturally transmitted disease was eradicated just as MVA became a reality, so its effectiveness in this setting, while highly promising, remains to be demonstrated. NIAID will accelerate development of MVA vaccines, including Phase I clinical trials in FY 2003 and a Phase II clinical trial in FY 2004. An expanded initiative in FY 2004 will increase the capability for animal testing, assay development and validation, and safety and toxicity studies related to the MVA vaccine.

#### *Future Directions in Smallpox Research*

In addition to the dilution studies of Dryvax® vaccine and the clinical trials of the MVA vaccine candidates for smallpox, NIAID is initiating Phase I and II clinical trials of various concentrations of another vaccine, so called “Wetvax<sup>4</sup>,” smallpox vaccine to determine its safety, efficacy, and take rates in non-vaccinated and previously vaccinated individuals. Like Dryvax®, the “Wetvax” is a vaccine that is similar to other 1<sup>st</sup> generation smallpox vaccines. It consists of live, replicating vaccinia virus produced by scarification of the flanks of calves, a process for vaccine production that is 200 years old.

NIAID is also investigating compounds to boost or enhance immune responses to vaccines, identifying ways to reduce the incidence and severity of adverse reactions to smallpox vaccines in people with eczema, and developing new drugs against smallpox. Finally, it is recognized that orthopox viruses, like Variola, may be genetically modified or engineered to enhance their virulence and possibly escape neutralization by the immune response induced through the use of vaccinia. Basic research on the fundamental aspects of orthopox virulence and pathogenicity are being emphasized.

#### **Anthrax**

An attack using *Bacillus anthracis*, the cause of anthrax, occurred in the autumn of 2001 when anthrax spores were sent through the U.S. mail, causing 18 confirmed cases of anthrax and five deaths. Human anthrax has three major clinical forms: cutaneous, gastrointestinal, and inhalational. Even with antibiotic therapy, inhalational anthrax is often fatal (historically, a 75 percent fatality rate). Anthrax causes illness and death by releasing two potent toxins<sup>5</sup> that enter and kills cells and damages organs. The toxins remain active in the bloodstream for several days, even if antibiotics kill the bacteria that produce them.

#### *Scientific Advances in Anthrax Research*

NIAID-supported researchers have identified the biochemical process by which these toxins enter susceptible cells and kill them – eventually leading to the death of the host. This process involved a third protein produced by the bacterium. This protein, called Protective Antigen or PA binds to a protein on the cell surface termed the anthrax toxin receptor (ATR). Once this binding occurs the PA forms a protein tube that penetrates the cell membrane and permits the direct transport of the two toxins (LF and EF) into the cell cytoplasm where these two molecules exert their toxic effect and eventually kill the cell. This information has led to the development of an ingenious approach to inhibit the attachment-entry process, which could block toxin-induced damage to cells and may

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<sup>4</sup> This vaccine was produced about 40 years ago by Aventis-Pasteur and maintained in storage as a frozen product. It has retained infectivity and early studies show that it is able to induce very high rates of “takes.”

<sup>5</sup> Lethal Factor or LF and Edema Factor or EF.

form the basis of a new therapy. In addition, researchers are pursuing two other avenues. One is to identify the specific region of the ATR to which PA attaches, and screen for small molecules that have the potential to bind to PA and prevent binding and subsequent cell destruction. A second approach is to develop direct inhibitors of the two toxins.

#### *Future Directions in Anthrax Research*

In FY 2004, NIAID plans to expand research initiatives to develop new diagnostic tests and therapeutics for the anthrax bacterium. NIAID will continue an Interagency Agreement with U. S. Army Medical Research Institute of Infectious Diseases (USAMRIID) to develop and test high-priority products for anthrax in non-human primate models. NIAID will also expand its genome sequencing efforts by supporting comparative studies of different anthrax strains, including specimens obtained from victims of the 2001 anthrax attacks. Additionally, NIAID is supporting an initiative to develop a next-generation anthrax vaccine candidate through: (1) development and clinical testing of the 2<sup>nd</sup> generation anthrax vaccine based on the use of PA produced by recombinant DNA techniques to demonstrate the safety and efficacy of the PA vaccines; and (2) production and acquisition of vaccine (manufacturing scale-up and development activities that include consistency testing, product validation, licensure studies, production, and distribution).

### **Ebola**

The Ebola viruses belong to a family of viruses that causes severe and often fatal hemorrhagic fever. Under normal conditions, the Ebola viruses have been found only in Africa; none of the four strains of Ebola occur naturally in the United States. Humans become infected through contact with infected blood or other contaminated material. Once a hemorrhagic fever virus enters a human population, it can spread by person-to-person contact and no vaccine is available to prevent transmission.

#### *Scientific Advances in Research on Ebola Virus*

Basic research on Ebola virus has led to a much improved understanding of the replication of this virus. NIAID researchers discovered that the final assembly of Ebola and related viruses during the infectious cycle has some unique properties that could be exploited as a target for antiviral development.<sup>6</sup> Another research advance indicates that HIV and Ebola virus use the same, novel host protein to escape from an infected cell, providing knowledge that may aid in the development of new therapies for treating disease caused by these viruses.

#### *A Key Scientific Question Being Addressed: Experimental Ebola Vaccine to Enter Human Trials*

NIAID intramural scientists have developed a DNA-based vaccine that prevents Ebola virus infection in monkeys. A Phase I clinical trial of a candidate Ebola vaccine based on this work is planned in FY 2003. This experimental vaccine is designed to protect against several different strains of Ebola virus. The vaccine is to be administered in two stages, a “prime-boost” strategy, which tricks the immune system to respond as though a real Ebola virus infection has occurred. If the Phase I study in humans is successful, Phase II studies may be carried out in FY 2004.

#### *Future Directions in Research on Ebola*

NIAID researchers will continue basic and targeted research on hemorrhagic fever viruses to better understand how these viruses cause disease, and how to design effective vaccines, diagnostic tests

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<sup>6</sup> The Assembly of Ebola Virus Nucleocapsid Requires Virion-Associated Proteins 35 and 24 and Posttranslational Modification of Nucleoprotein Yue Huang, Ling Xu, Yongnian Sun, and Gary J. Nabel. *Molecular Cell* 2002;10:307-316.

and therapeutics. The natural reservoirs of Ebola viruses are still not known, nor is it understood how the viruses are transmitted to humans. Therefore, it is important to identify how the diseases caused by these viruses emerge under natural conditions and why some infected people develop serious disease or die, whereas others do not. NIAID studies include efforts to: (1) understand how the protein that forms the coat of Ebola allows the virus to attach to host cells, and use this information to develop therapeutics that block the process; (2) modify Ebola DNA so it can be used as the basis for new vaccines; and (3) develop and test vaccines that contain DNA from different virus strains to determine whether such a vaccines will prevent infection caused by these related, but different, viruses.

### **Other Category A Agents**

In addition to significant progress in developing candidate vaccines and therapeutics for smallpox, anthrax, and Ebola virus, NIAID-supported scientists have also achieved important progress in research on many other microbes and toxins that are bioterrorist threats. For example, scientists discovered that a mutation in a single gene of the plague bacterium, *Yersinia pestis*, aided the emergence of the “Black Death” in the 14<sup>th</sup> century. The mutation allowed the microbe to be transmitted from fleas (which feed on plague bacterium-infected rodents) to humans. NIAID scientists developed a mouse model of plague that will be used for evaluating a new vaccine, based on genetically altered DNA from the plague bacterium. NIAID investigators also made significant advances in developing a candidate vaccine that protects mice against the highly virulent tick-borne encephalitis viruses.

### **Understanding, Assessing, and Enhancing Host Immunity**

A primary component of NIAID’s mission in biodefense research is to investigate how the human immune system responds to disease-causing microbes, and use that knowledge to develop safe and effective vaccines and therapeutics. Therefore, in FY 2004, NIAID will support a range of studies designed to assess, understand, and enhance host immunity to potential agents of bioterrorism. The studies include basic studies to understand how it might be possible to enhance innate as well as adaptive immune responses to infection. NIAID-supported investigators will probe the genetic and molecular aspects of the immune response that help determine whether a person will fight off an infection or succumb to it. NIAID will support clinical trials of vaccine candidates and related immunological studies to understand why some vaccines work and some do not. Support will also be provided for initiatives to develop chemical compounds, called adjuvants, which boost and broaden the immune response to vaccines and therapeutics.

### **Research Centers, Specialized Research Facilities and Other Research Resources**

#### *Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases*

In FY 2003, NIAID will establish Regional Centers of Excellent for Biodefense and Emerging Infectious Diseases with an expansion in the number of centers planned for FY 2004. The Centers will form a nationwide network of scientific resources and expertise to significantly enhance the nation’s biodefense capabilities. Each Center will be comprised of participating universities and research institutions within a defined geographical region, will focus on specialized areas of applied research, and will establish collaborations with private industry to foster translational research. During an infectious disease emergency, whether of bioterrorism or other public health threat, the Centers will provide scientific expertise and backup laboratory support in their regions.

### **Future Directions in Biodefense Research**

In FY 2003, NIAID plans to support a total of over 40 new and expanded initiatives in biodefense research. In FY 2004, an additional 17 new and expansion initiatives are planned, encompassing the broad-based biodefense research agenda of the Institute.

In 2004, NIAID will expand the *Biodefense and Emerging Infectious Diseases Research Resources Program* to acquire, authenticate, store, and ship reagents, standardized microarrays panels, and other materials related to the study of Category A, B, and C priority pathogens. These resources will be made available to investigators and laboratories engaged in biodefense research. Other new initiatives will support the development of novel therapeutic strategies for blocking the effects of botulinum toxin, and animal models for basic and targeted research on emerging infectious diseases and biodefense.

Also in FY 2004, NIAID will expand the *Large-Scale B and T Cell Epitope Discovery Program* to understand how the two main cell types of the immune system, B and T lymphocytes, help regulate immune responses to dangerous microbes. The research will help identify how proteins and parts of proteins (epitopes) on the surfaces of B and T cells recognize viruses and bacteria. Discovery of these epitopes will facilitate the development of pathogen-specific vaccines and immunotherapeutic agents.

In addition, NIAID will establish *Cooperative Centers for Translational Research on Human Immunology* to support a centralized research infrastructure to develop, standardize, and apply appropriate technologies, reagents, and assays to the study of human immunity. Each Center will focus on a particular area of human immunity, and will facilitate translation of basic research knowledge into clinical applications.

NIAID will also expand support of the *Pathogen Functional Genomics Resource Center* to provide the research community with critical resources and reagents for conducting basic and applied research on microorganisms responsible for emerging and re-emerging infectious diseases, including potential agents of bioterrorism. NIAID will continue its support of the *Orthopoxvirus Genomics and Bioinformatics Resource Center*, a collaborative effort involving four academic centers, CDC, USAMRIID, the Defense Advanced Research Projects Agency, and the American Type Culture Collection.

Also in FY 2004, NIAID will expand its ongoing *Vaccine Treatment and Evaluation Units* to accelerate the testing of new therapeutics and vaccines within an established and efficient clinical infrastructure. Through the *Food and Waterborne Diseases Integrated Research Network*, NIAID will support the development of products to identify, prevent and treat food and waterborne diseases, such as cholera and *Escherichia coli* O157:H7 strain. Research will focus on an improved understanding of the basic biology of these agents and on the pathogenesis of infection. This basic information is essential if effective therapies, diagnostic tests and vaccines are to be developed to counter these threats.

## **MAJOR INTERNATIONAL KILLERS**

### **Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome**

HIV/AIDS infection has emerged as one of the most devastating global pandemics of infectious disease in human history. Current estimates indicate that over 40 million people are infected and over 70% of those people live in sub-Saharan Africa. In seven countries in southern Africa, it is now estimated that one in five adults is living with HIV/AIDS. During 2001, AIDS caused the deaths of approximately 3 million people worldwide, including 1.1 million women and 580,000 children under age 15<sup>7</sup>. The impact of this pandemic pervades all aspects of life in southern Africa. Schools have closed because too many teachers have already succumbed to HIV/AIDS. Hundreds

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<sup>7</sup> UNAIDS. <http://unaids.org/barcelona/presskit/report.html>

of thousands of children are being orphaned each year – significantly stressing social services. Economic growth and development have been compromised in many countries. In the 45 most affected countries, between 2000 and 2020, a projected 68 million people will die prematurely as a result of AIDS.

In the United States, the Centers for Disease Control and Prevention (CDC) estimates that 800,000 to 900,000 U.S. residents are living with HIV/AIDS and one-third are unaware of their infection. Approximately 40,000 new HIV infections occur each year in the United States, about 70 percent among men and 30 percent among women. AIDS is now the fifth leading cause of death in the U.S. among people aged 25 to 44, and continues to affect minorities disproportionately. Of all U.S. cases reported in 2001, 42 percent were among blacks, 37 percent among whites, 20 percent among Hispanics, and fewer than 2 percent among Asian/Pacific Islanders and American Indians/Alaska Natives. As of December 31, 2001, 5,408 U.S. children under the age of 13 have died of HIV/AIDS.<sup>8</sup>

Since the early 1980s, NIAID has led the government's efforts to understand the biology of HIV and discover how the immune system responds to the virus. Basic knowledge gained from these investigations has significantly enhanced the ability of NIAID to develop improved diagnostics, discover new and improved therapeutics, and design and test the safety and efficacy of candidate vaccines. NIAID also supports comprehensive research on other biomedical and behavioral prevention approaches, including drugs and vaccines to prevent mother-to-infant HIV transmission, microbicides for preventing sexual transmission of HIV, and interventions to reduce behaviors that expose people to HIV. However, despite significant gains in understanding the biology of the virus and the pathogenesis of the infection, there remains an urgent need for more effective therapies to cure the infection, including new ways to rebuild and boost immunity to HIV infection and to identify improved ways to prevent the infection including vaccine strategies that induce long-lasting, protective immunity against HIV. Research advances have progressed to the point where many innovative interventions using vaccines, drugs and other medical interventions must be tested in clinical trials; thus requiring an expansion of the infrastructure necessary to conduct clinical research, particularly in resource poor settings overseas where the pandemic is most prevalent.

#### *Scientific Advances in HIV/AIDS Research*

NIAID continues to make significant progress in understanding the biology of HIV and how the virus eludes destruction by the immune system, in translating this knowledge into more effective diagnostics, therapies, and vaccines strategies, and in conducting pre-clinical studies and clinical trials to evaluate the safety and effectiveness of treatments and vaccines.

NIAID-supported researchers recently demonstrated that the transmission of simian-HIV (SHIV) to newborn monkeys can be prevented by administering three human monoclonal antibodies that neutralize the virus. SHIV is a genetically engineered virus that combines genes from simian immunodeficiency virus (SIV) and HIV, and causes an AIDS-like illness in monkeys. This finding may lead to a new way of preventing mother-to-child transmission of HIV in humans. NIAID-funded scientists also discovered important limitations to develop effective AIDS vaccines. They found that one of eight monkeys given an experimental vaccine against SHIV, and subsequently infected with the virus, showed an increase in virus replication starting at 24 weeks after infection. The monkey was unable to control HIV infection because the virus had mutated in a way that prevented the monkey's "killer" cells, known as cytotoxic T lymphocytes (CTL), from killing the virus. As a result, the mutant virus replicated and caused disease. These new findings mean that effective AIDS vaccines must elicit a broad range of immune responses, including those mediated

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<sup>8</sup> CDC. <http://www.cdc.gov/hiv/stats/hasr1302.htm>

by CTL killer cells, so that mutant viruses will not be able to “escape” immune surveillance and cause disease.

Additionally, NIAID investigators have constructed a new candidate vaccine that contains pieces of DNA from the major genetic subtypes (clades) of HIV that occur around the world, and have tested the vaccine in monkeys. Three clades of HIV, termed A, B, and C, cause about 90 percent of all HIV infections; clade B is dominant in the Americas. Because immunity against one HIV clade may not protect against infection by another clade, NIAID researchers have been working to develop a vaccine that stimulates broad immune responses against all the major HIV subtypes. A recent study demonstrated that a candidate vaccine, which contains DNA from HIV clades A, B, and C, as well as DNA from three genes of SIV, triggered a more robust immune response in rhesus monkeys than did a vaccine that contained DNA from a single HIV clade. This pre-clinical study is an important step in the development of a broadly effective HIV vaccine for humans. A Phase I clinical trial of this multi-clade vaccine candidate is being conducted in 2003.

In efforts to develop new and improved therapies for HIV/AIDS, NIAID-supported scientists discovered a novel method for blocking HIV infection. They constructed a large protein that inhibits the entry of HIV into CD4 T cells, white blood cells that are critical for immune system function but are destroyed by HIV. The therapeutic protein prevents HIV from killing CD4 T cells by blocking the part of virus that attaches to the cells. The discovery may lead to the development of new antiviral drugs that do not induce the toxic reactions often associated with long-term, combination antiviral therapy. NIAID-funded researchers have also discovered that therapy with two protease inhibitors, drugs that help block HIV replication, can suppress HIV more effectively than a single protease inhibitor in patients who have previously failed to respond to this class of drugs.

Other important advances include the finding that mature CD4 T cells that are programmed to fight HIV are more likely to be infected with the virus than are CD4 cells programmed to fight other infections. The study confirms a long-held theory that HIV preferentially kills the cells of the immune system that are designed to fight it, thus allowing the virus to multiply and cause disease. Another study in Zambia revealed that children who are already infected with HIV, and then become infected with the measles virus, experience a temporary suppression of their HIV infection by an as-yet-unknown mechanism. These data provide the first evidence in studies of people infected with HIV that HIV replication can be suppressed by coinfection with another virus. Also, NIAID scientists have developed a method for directly measuring the number of HIV-infected white blood cells two days after the cells are exposed to the virus. The new method detects a viral protein (p24), which is labeled with a fluorescent tag, inside HIV-infected cells. The laboratory test should allow researchers to determine how human antibodies neutralize HIV, and whether a candidate vaccine has generated such neutralizing antibodies.

In addition to these research advances, NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) have announced the largest community-based, preventive HIV vaccine trial ever planned. The trial involves a collaboration between scientists from the United States and Thailand to test a prime-boost vaccine regimen in which two different vaccines are administered to stimulate a more powerful immune response. The study, to be conducted in Thailand over a period of approximately five years, will involve 16,000 volunteers.

#### *Future Directions in HIV/AIDS Research*

In FY 2003 and 2004, NIAID will continue its comprehensive research program to explore novel vaccine concepts, genetic variation of HIV and its immunological consequences, vaccine delivery methods, strategies to boost the immune response, and correlates of immune protection. NIAID intramural investigators will continue to develop and improve vaccines based on HIV genes that elicit broad, potent immune responses, including the production of antibodies that neutralize the virus and the stimulation of immune responses mediated by T cells. NIAID will continue to

support the evaluation of candidate AIDS vaccines in small animal models and non-human primates, as well as other pre-clinical studies to pave the way for clinical applications in humans. Additionally, by FY 2004 NIAID expects to support the clinical trials testing of nine new candidate vaccines for prevention, including combinations of two new vaccines aimed at stimulating different arms of the immune system; three candidate vaccines for therapeutic intervention; use of topical microbicides for prevention; and investigating the use of simpler and less expensive treatment regimens with existing drugs.

In FY 2003, NIAID will expand the *HIV Vaccine Design and Development Teams* (HVDDT) to facilitate the development of novel vaccine strategies. The HVDDT program includes multidisciplinary scientists from industry and academia focused on vaccine research through pre-clinical development to the point at which vaccine candidates can be evaluated in clinical trials. Additionally, NIAID is expanding its support of the *HIV Vaccine Trials Network* (HVTN) to implement multicenter efficacy trials of promising vaccines in the Americas, Africa, and Asia, involving over 40 clinical sites and more than 10,000 high-risk individuals. By 2004, this program will expand the clinical trial capacity in Southern Africa and Asia, as well as central laboratory resources at HVTN laboratories in the United States and satellite laboratories in South America, South Africa, and Asia.

In FY 2004, NIAID will continue to study the epidemiology and natural history of HIV/AIDS in several cohorts, the *Multicenter AIDS Cohort Study* (MACS), the *Women's Interagency HIV Study* (WIHS), and the *Women and Infants Transmission Study* (WITS). Through the *Centers for AIDS Research* (CFARs), NIAID will support multidisciplinary research in domestic and international institutions for the development of therapeutics, vaccines, and diagnostics. Support will also continue for the *Comprehensive International Program of Research on AIDS* (CIPRA) to assist developing countries in the planning and implementation of a comprehensive HIV/AIDS research and treatment agendas relevant to their populations. NIAID will continue to test candidate therapies and vaccines through several large clinical trials networks, including the *Adult AIDS Clinical Trial Groups* (ACTG), the *Pediatric AIDS Clinical Trials Group* (PACTG), and the *HIV Prevention Trials Network* (HPTN). The HPTN is a global network of clinical trial sites that explores non-vaccine strategies to prevent HIV transmission, such as the use of topical creams that kill microbes and behavioral interventions to reduce their risk of acquiring HIV.

In FY 2004, NIAID will also expand a program to stimulate research on the complications of antiretroviral therapy by supporting investigator-initiated studies on mechanisms underlying the metabolic complications of antiretroviral therapy. Other NIAID research will focus on identifying genetic variants of HIV and related viruses, as well as studies of their genomes. This information will help generate reagents for the research community for use in the development of new therapeutics and vaccines. NIAID is also renewing its support of the *National Cooperative Drug Discovery Group for Tuberculosis* (NCDDG-TB) to discover and develop new therapeutics for tuberculosis, particularly in HIV co-infected populations. In addition, NIAID will continue to support studies of other AIDS co-infections and malignancies, including hepatitis C virus, *Pneumocystis carinii*, and cancers such as Kaposi's sarcoma (KS), lymphomas, and cancers of the reproductive system and intestinal tract.

## **Tuberculosis**

### *Introduction*

Tuberculosis (TB), an ancient bacterial disease caused by *Mycobacterium tuberculosis* (Mtb), remains a devastating global health problem. An estimated one third of the world's population is

infected with *M. tuberculosis* and 16.2 million people currently have active TB disease.<sup>9</sup> TB magnifies the suffering in the world's poorest countries where malnutrition, substandard housing and minimal health care are common. Moreover, it is estimated that between 2000 and 2020, nearly 1 billion people worldwide will be newly infected, 200 million people will get sick, and 35 million people will die from TB if our ability to control this disease is not significantly improved.<sup>10</sup> It is estimated that 10-15 million people in the U.S. are currently infected with this pathogen,<sup>11</sup> with 15,989 new TB cases reported in the U.S. in 2001.<sup>12</sup> The increasing spread of this disease continues to be a public health challenge in the industrialized world due to the contributions of several forces: increased prison populations, homelessness, injection drug use, as well as increasingly crowded housing and long-term care facilities. The TB crisis is further complicated by the rise of multi-drug resistant strains and by coinfection with HIV/AIDS.

### *Scientific Advances in Tuberculosis Research*

NIAID's research efforts offer hope for better control and eventual elimination of TB. An improved understanding of how the immune system fights this formidable enemy will facilitate the development of successful vaccines, better diagnostic tests and effective therapeutic strategies. NIAID-supported researchers demonstrated that immune cells, called CD4+ T cells, help other immune cells, called CD8+ T cells, develop and maintain optimal capacity to destroy cells infected with the TB bacterium, thereby contributing to the control of infection. NIAID-supported researchers are also searching for new and improved methods for treating TB, and have identified a promising new drug for TB called Moxifloxacin. Using an animal model, investigators have determined that daily doses of the drug produced an effect comparable to isoniazid, one of the most potent drugs ever discovered to treat TB. These studies suggest that Moxifloxacin, in combination with other longer acting antibiotics, offers the potential for a shortened or more intermittent antituberculous therapy.

### *Future Directions in Tuberculosis Research*

NIAID will continue to support TB basic and applied research, adding to our fundamental base of knowledge about Mtb and the pathogenesis of TB, and leading ultimately to the development of improved diagnostic, therapeutic and prevention strategies. In FY 2004, NIAID will continue to support: the *Tuberculosis Research Materials and Vaccine Testing Program* which provides TB research reagents to investigators throughout the world; support the screening of potential TB vaccine candidates; support the discovery of new, more effective, anti-TB drugs for therapeutic and preventive use; support investigator-initiated grants; the National Cooperative Drug Discovery Groups for the Treatment of Opportunistic Infections Associated with AIDS; and establish a new program on the development of animal models for tuberculosis and aspergillosis.

## **Malaria**

### *Introduction*

Since ancient times, malaria has taken a devastating toll on people and societies. Today, more than three decades after the last effort to eradicate malaria failed, malaria still strikes an estimated 300-500 million people and causes more than 1 million deaths each year,<sup>13,14</sup> with the heaviest toll among young children in sub-Saharan Africa.<sup>15</sup> Countries with a high rate of infection are among

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<sup>9</sup>Dye *et al.* *JAMA* 282:677-686, 1999.

<sup>10</sup>WHO. WHO Fact Sheet 104, August 2002. <http://www.who.int/mediacentre/factsheets/who104/en/index.html>

<sup>11</sup>NIAID/NIH Workshop Report. Blueprint for Tuberculosis Vaccine Development. B. Bloom, ed. March 5-6, 1998.

<sup>12</sup>CDC. Reported Tuberculosis in the United States (Selected Tables), 2001. <http://www.cdc.gov/nchstp/tb>

<sup>13</sup>World Health Report 2001.

<sup>14</sup>World Health Organization Report on Infectious Diseases 2002.

<sup>15</sup>Malaria at a Glance, World Bank Report, March 2001.

the poorest in the world. In the absence of a preventive vaccine, drugs to treat malaria and insecticide impregnated bed nets are a mainstay of public health efforts to reduce the burden of this devastating disease. However, these efforts have become increasingly difficult in many parts of the world due to the emergence of drug-resistant strains of *Plasmodium falciparum* and *P. vivax*, two of the four species of human malaria<sup>16</sup>. NIAID developed a *Global Health Plan for HIV/AIDS, Malaria, and Tuberculosis* to define the Institute's goals and plans for fighting these infectious diseases by building sustained research capacity in the US as well as in malaria-endemic areas and by enhancing international partnerships. The global malaria research agenda will expand efforts on vaccine development, antimalarial drugs, diagnostics, and mosquito control methods and will also focus resources to strengthen the research capability of scientists in their own countries. NIAID is a founding member of the Multilateral Initiative on Malaria (MIM)/World Health Special Program for Research and Training in Tropical Diseases Task Force for Malaria Research Capability Strengthening in Africa. Enhancing research capability within endemic countries is also an important component within NIAID's longstanding International Centers in Tropical Diseases Research (ICTDR).

### *Scientific Advances in Malaria Research*

NIAID-supported scientists have gained a greater understanding of the emergence of resistance to a class of drugs used to treat malaria, known as antifolates. Antifolates act by inhibiting an enzyme, dihydrofolate reductase (DHFR), in the parasite, but not in humans. NIAID-supported scientists revealed that malaria parasites and humans process DHFR differently, resulting in the death of the parasite and the protection of the host's cells. Understanding how DHFR is regulated in humans and how it functions differently in the malaria-causing parasite could lead to other targets for attacking and ultimately killing this deadly pathogen.

The magnitude of the problem posed by malaria requires new approaches, including the use of vaccines for prevention and treatment. NIAID-supported researchers have sought to exploit the complex life cycle of the parasite for the development of vaccines and drugs. These efforts have been enhanced by the recent publication of the genome of *P. falciparum* and one of its vectors, *Anopheles gambiae*. In addition, NIAID-supported scientists developed a new method to detect malaria parasites in the blood that can be used in a field setting. In other studies, NIAID intramural scientists have traced *P. falciparum* strains in the world today to an ancient ancestor that existed 100,000 to 180,000 years ago and showed that the parasite is genetically more diverse than previously thought.

### *Future Directions in Malaria Research*

NIAID will continue to support malaria vaccine research and development under the *Plan for Research for Accelerated Development of Malaria Vaccines*, emphasizing: discovery and preclinical testing of new vaccine candidates; improved access to research materials; production and evaluation of candidate vaccines; and clinical research and preparation for clinical trials in endemic areas. Support will also be continued for domestic centers of excellence for tropical and parasitic diseases and for collaborative studies between U.S. and foreign scientists working in endemic areas through its International Centers for Infectious Diseases Research, Tropical Medicine Research Centers and other malaria related initiatives. NIAID's *Malaria Clinical Research and Trial Preparation* initiative will continue to support the development of clinical research and clinical trial sites in malaria endemic areas. In addition, NIAID's *Tropical Disease Translational Research Program* remains an important

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<sup>16</sup> Malaria is caused in humans by four different species: *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*. Falciparum and vivax malarias are the most common, and falciparum is the most deadly.

component of the Institute's effort to translate basic research findings on tropical diseases into product development.

## **Respiratory Diseases**

### *Introduction*

Since 1918, at least three major influenza pandemics have occurred. The worst of these, the pandemic of 1918-1919, caused an estimated 550,000 deaths in the United States, and more than 20 million deaths worldwide.<sup>17</sup> The two subsequent pandemics so called "Asian flu" in 1957 and "Hong Kong flu" in 1968 also took a heavy toll of human life. It is widely acknowledged that a new pandemic could emerge at any time. Although pandemics grab the headlines, the news is that pneumonia and influenza continue to be important causes of death in the U.S. Influenza and pneumonia are the sixth leading cause of death in the United States, killing 10,000 to 40,000 people in an average flu season. Today, acute lower respiratory infections are the third most frequent cause of death worldwide, responsible for nearly 3.5 million deaths in 1998.<sup>18</sup>

### *Scientific Advances in Respiratory Diseases Research*

Much of the illness and death caused by influenza can be prevented by annual vaccination. However, in recent years the U.S. and other countries have been plagued by shortages of influenza vaccine. NIAID rapidly responded by implementing a clinical trial to test whether giving a half dose of influenza vaccine to healthy adults would provide the same level of protection. Study results suggest that administering a half-dose of flu vaccine to healthy adults could increase the number of people vaccinated with relatively little adverse impact on the vaccine's ability to protect against infection. In other findings, NIAID researchers discovered a new flu virus protein that causes cell death. This information may help explain why some forms of influenza are more deadly and persistent than others and aid in stemming future epidemics.

### *Future Directions in Respiratory Diseases Research*

The sudden and unpredictable emergence of pandemic influenza, and its potential to cause severe health and social consequences, necessitated the development of a national plan to protect the public. NIAID served as the NIH representative on interagency working groups, convened by the National Vaccine Program Office, to aid in the preparation of a U.S. National Influenza Pandemic Preparedness and Response Plan. NIAID continues to develop and implement the biomedical research efforts called for in the plan.

A major NIAID goal is to stimulate research on more effective and accepted prophylactic and therapeutic approaches for preventing and controlling respiratory infections. NIAID will continue to support the Respiratory Pathogen Research Units (RPRU) through a contract solicitation entitled, *Basic and Clinical Approaches to Controlling Human Respiratory Pathogens*. The RPRUs form the basis of a coordinated, interactive, multi-disciplinary network for pre-clinical and clinical studies of selected human respiratory pathogens, including pneumococci, and Group A and B streptococci. Continued support will also be provided for a pneumococcal reference and resource laboratory through another contract solicitation entitled, *Respiratory Pathogens Reference Laboratory Support*. This research program provides for the development, standardization and distribution of assays and reference reagents and the measurement of bacterial antibody responses.

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<sup>17</sup> CDC. <http://www.cdc.gov/ncidod/diseases/flu/viruses.htm>

<sup>18</sup> Hoyert *et al.* Natl Vital Stat Report 47(19), 1999

## OTHER EMERGING AND RE-EMERGING INFECTIOUS DISEASES

In the last few decades, new, frightening, and unforeseen infectious disease threats have emerged, including diseases caused by multi-drug resistant *Streptococcus pneumoniae*, fatal infections (in toxic and necrotic forms) caused by *Streptococcus pyogenes* (Group A streptococcus), blood infections in newborns caused by Group B streptococcus, brain inflammation due to West Nile virus, and neurodegenerative disease caused by transmissible spongiform encephalopathies (TSE). The emergence of these infectious agents is a grim and foreboding reminder of the power, destructiveness, and endless adaptability of infectious microbes and the global importance of research to treat, prevent and control these diseases.

### West Nile Virus

#### *Introduction*

West Nile virus (WNV) belongs to a group of disease causing viruses known as flaviviruses, which are spread by insects, usually mosquitos. Most human infections from the WNV are mild, causing fever, headache and body aches, often accompanied by skin rash and swollen lymph nodes. However, the virus can cause life threatening encephalitis (inflammation of the brain) or meningitis (inflammation of the lining of the brain and spinal cord). The identification of WNV in New York in the summer of 1999 was the first time that WNV had been identified in the Americas. Until then, the virus had been found chiefly in Africa, Eastern Europe, the Middle East, and Asia. From 1999-2001, there were 149 confirmed cases of WNV in the U.S., including 18 deaths. In 2002, the number of confirmed cases and deaths increased substantially and a total of 3,519 cases and 212 deaths have so far been reported in the U.S.<sup>19</sup>

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<sup>19</sup>CDC. <http://www.cdc.gov/od/oc/media/wncount.htm>

## **Story of Discovery: Developing a Vaccine for West Nile Virus**

### **Launching the Search for a Protective Vaccine**

Faced with the potential for a serious WNV epidemic, NIAID-supported researchers took swift action to develop a vaccine that protects against infection. Basic research on newly emerging microbes has enabled rapid progress in the development of a WNV vaccine. WNV vaccine development has also benefited from the fact that WNV belongs to the group of viruses, known as flaviviruses, which have many characteristics in common. These similarities have allowed scientists to build on earlier discoveries about other flaviviruses that are closely related to WNV, including Japanese encephalitis virus (JEV), St. Louis encephalitis virus (SLEV), yellow fever virus (YFV), and dengue virus.

### **Developing Vaccines**

There has been great success in controlling yellow fever and Japanese encephalitis with well-organized vaccination campaigns centered on an efficacious vaccine. Therefore, NIH encouraged WNV vaccine development programs. Importantly, NIAID supported basic research studies discovered that hamsters, and to a lesser extent mice, were good models for West Nile disease. Researchers at the University of Texas Medical Branch, Galveston conducted a series of preliminary experiments to learn more precisely the degree of protection that candidate WN and other licensed flavivirus vaccines might have against WNV. They found that hamsters were completely protected by prototype WN vaccines, and surprisingly, at least partially protected by Japanese encephalitis and yellow fever vaccines. This new model is an important resource that could be used to test the efficacy of new vaccine candidates for WNV.

A number of vaccine approaches are being supported by NIAID. One of the earliest started in 1999, when NIAID funded a fast-track project to develop a candidate WNV vaccine with Acambis, Inc. Since then, scientists have developed a prototype vaccine that has shown promise in animal tests. The vaccine is constructed using vaccine licensed for preventing yellow fever (caused by another flavivirus) as the backbone. For the West Nile vaccine, researchers substituted the surface protein of WNV for the deleted yellow fever virus protein. This method of creating chimeric flavivirus vaccines is also being applied to developing a vaccine for dengue and JEV. The Acambis vaccine has undergone preclinical evaluations in hamsters, mice, monkeys, and horses with encouraging results. The company is moving forward with Phase I trials. Vaccine is now being produced and an investigational new drug (IND) application will be filed with the Food and Drug Administration. Trials are anticipated to begin in early 2003.

Other NIAID scientists and collaborators from the Walter Reed Army Institute of Research (WRAIR) capitalized on recent advances in recombinant DNA technology and previous research on another flavivirus, called dengue virus, to produce a new candidate WNV vaccine. The NIAID team already had tested successfully a strategy that used the new technology to replace key genes of different flaviviruses with those of dengue virus type 4 (DEN4). Unlike many flaviviruses, DEN4 does not cause disease in the brain. The resulting weakened, or attenuated, virus strains were safer for use in a vaccine but still protective. The NIAID-WRAIR research team then used this strategy to combine genes from WNV and DEN4. This hybrid virus did not infect the brain yet still stimulated a strong immune response with even a single dose. In preliminary testing in mice and non-human primates, the hybrid vaccine protected all animals against lethal WNV infection. The next steps are to conduct more comprehensive testing of this vaccine candidate in non-human primates, followed by a Phase I clinical trial in humans, estimated to start in the summer or fall of 2003. Early studies are also underway on a DNA vaccine approach and a protein vaccine approach by other NIAID-supported scientists.

### **Taking the Next Steps**

By identifying successful strategies for vaccine development, NIAID-supported studies are contributing to a major effort to slow the spread of WNV and avert a more serious public health threat from this emerging disease.

Pletnev AG, Putnak R, Speicer J, Wagar EJ, and Vaughn D: West Nile virus/dengue type 4 virus chimeras that are reduced in neurovirulence and peripheral virulence without loss of immunogenicity or protective efficacy. Proceedings of the National Academy of Sciences 99: 3036-3041, 2002.

Tesh RB, Travassos da Rose APA, Guzman H, Araujo TP, and Xiao SY: Immunization with heterologous flaviviruses protective against fatal West Nile encephalitis. Emerging Infectious Diseases 8: 245-251, 2002.

## *Future Directions in West Nile Virus Research*

NIAID will continue to participate with other federal agencies in the Interagency Task Force on West Nile Virus, established in 2002, to promote a coordinated federal response to the WNV outbreak through the development of a coordinated, broad-based plan of action. NIAID will also continue to expand and accelerate research to address all aspects of WNV, including improved diagnostics, therapeutics and vaccines. Through new programs, such as the *U.S.-based Collaborations in Emerging Viral and Prion Diseases* and *Partnerships for Development of Novel Therapeutic and Vector-Control Strategies*, NIAID will increase research on this disease and accelerate our understanding in many important areas. Through partnerships with industry, the discovery and development of novel antiviral agents against WNV will also be expanded. In addition, many programs that have been recently developed and/or expanded to address biodefense, such as the *In Vitro Antiviral Screening Program* and the *Cooperative Research for the Development of Vaccines, Adjuvants, Immunotherapeutics, and Diagnostics for Biodefense*, will support research on emerging infectious diseases such as WNV.

## **Transmissible Spongiform Encephalopathies**

### *Introduction*

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases characterized by accumulation of an abnormal form of protein called prion protein. TSEs include scrapie of sheep, Creutzfeldt-Jakob disease of humans, chronic wasting disease (CWD) of deer and elk, and bovine spongiform encephalopathy (BSE or “mad cow disease”). The epidemic of BSE that began in the United Kingdom (UK) in the 1980s has now been associated with the emergence of variant Creutzfeldt-Jakob disease (vCJD) in humans. The UK BSE epidemic resulted in the destruction of millions of cattle and, as of October 2002, 128 persons were diagnosed with definite or probable vCJD, with 117 deaths.<sup>20</sup> The appearance of CWD in deer and elk beyond its known endemic area (area where the disease was known to occur) is causing additional concern in the United States.<sup>21</sup>

### *Scientific Advances in TSE Research*

The emergence of vCJD provided the first evidence that human exposure to contaminated food products, such as animal meat, could cause TSE disease in humans. To better understand how this may have occurred, NIAID researchers examined the process by which scrapie transfers from hamsters to mice. Researchers determined that the adaptation of hamster scrapie to mice is a prolonged and subtle process, and that the early stages are very difficult to detect by current diagnostic tests. These experiments have shown evidence that species once thought to be resistant to certain TSE strains can serve as carriers of infection without becoming sick. Study results further suggest that TSE diseases may be more widespread than previously thought and highlight the importance of being vigilant in monitoring disease spread.

### *Future Directions in TSE Research*

Future NIAID-supported studies will be aimed at determining how prions cause disease, understanding how and when cross-species transmission of TSE occurs, and developing TSE therapies and diagnostic tests. NIAID will continue to support the *U.S.-based Collaboration in*

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<sup>20</sup> U.K. Creutzfeldt-Jakob Diseases Surveillance Unit. <http://www.cjd.ed.ac.uk/figures.htm>

<sup>21</sup> USDA. <http://www.aphis.usda.gov/vs/nahps/cwd/>

*Emerging Viral and Prion Disease* to establish multidisciplinary research units to develop scientific information and tools needed to control emerging viral diseases and viral-like agents, such as prions associated with TSEs in both humans and animals.

#### *Future Directions for Research on Emerging and Re-emerging Infectious Diseases*

NIAID will continue to strengthen its basic and applied research program on the multiple host, pathogen, and environmental factors that influence disease emergence and will support the development of diagnostics, vaccines, and therapies necessary to detect and control emerging and re-emerging infectious diseases. In cooperation with the Fogarty International Center, NIAID will support the *International Centers of Excellence in Clinical Research and Management Training Program* to develop certificate curricula both in clinical research and in research management for scientists and managers from less developed countries. The Program serves NIAID's long-term global health goal of building sustainable research capacity at international sites. In addition, the International Centers for Infectious Diseases Research will continue to enhance existing international research capacity for tropical pathogens that may be internationally disseminated. Furthermore, many of the programs that have been developed and expanded for biodefense are available for the study of other emerging infectious diseases.

## **OTHER PROBLEMS IN INFECTIOUS DISEASES**

### **Hepatitis C**

#### *Introduction*

Hepatitis C virus (HCV) is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. Globally, an estimated 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year. HCV is spread primarily by direct contact with human blood. The major causes of HCV infection worldwide are the use of unscreened blood transfusions and the re-use of needles and syringes that have not been adequately sterilized. No vaccine is available to prevent hepatitis C and currently available therapies are very costly.<sup>22</sup>

#### *Scientific Advance in Hepatitis C Research*

NIAID scientists have uncovered clues to how hepatitis C causes infection. Comparing the incidence and persistence of hepatitis C infection in two groups of injecting drug users, people whose blood tests revealed no evidence of previous HCV infection and people who had been infected in the past but were currently not infected, it was found that previously infected individuals were half as likely to develop new infections compared to those who had not been previously infected (12% compared to 21%, respectively). These findings suggest that humans can acquire immunity that protects against disease caused by the HCV. Other NIAID-supported researchers demonstrated that specific immune cell responses can be identified that resulted in clearance of infection and demonstrated different ways the virus becomes persistent in chronic carriers. NIAID-supported scientists also demonstrated that the outcome of hepatitis C infection could be predicted based on the viral mutations that allow the virus to escape discovery.

#### *Future Directions in Hepatitis C Research*

New Initiative: In FY 2004, NIAID will establish a hepatitis C recovery research network, a clinically based research consortia to follow patients infected with HCV for the purpose of

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<sup>22</sup> WHO. HCV Fact Sheet, October 2000.

developing a full understanding of the recovery and persistence outcomes that occur with initial HCV infection, as well as with therapy. The unfortunately all-to-common occurrence of HCV and HIV co-infection in the same individual poses an extremely difficult scientific and clinical management problem. NIAID plans to expand its efforts in the area of HCV infection in patients also infected with HIV/AIDS.

## **Sexually Transmitted Diseases**

### *Introduction*

Sexually transmitted diseases (STDs) are widespread, with 15 million new cases estimated to occur each year in the U.S.<sup>23</sup> STDs are also a critical global health problem due to their devastating impact on women and infants and their interrelationship with AIDS. The role of STDs as a risk factor for sexual transmission of HIV significantly raises the burden of this common group of infectious diseases. Recent studies indicate that the more prevalent non-ulcerative STDs (chlamydial infection, gonorrhea, bacterial vaginosis, and trichomoniasis) as well as ulcerative diseases (genital herpes, syphilis and chancroid) increase the risk of HIV transmission by at least 2- to 5-fold.<sup>24</sup> Consequences of STDs include infertility, pelvic inflammatory disease or PID (an infection of the upper female genital tract), tubal pregnancy, cervical cancer, and perinatal or congenital infections in infants born to infected mothers.

### *Scientific Advances in Sexually Transmitted Diseases*

NIAID research strives to understand the microbes that cause STDs and to apply that knowledge to develop new interventions. Toward that goal, NIAID-supported scientists recently identified a potential new cause for PID. Researchers demonstrated an association between the microorganism, *Mycoplasma genitalium*, and a tissue infection of the lining the uterus (which can progress to PID). NIAID-supported scientists also gained a greater understanding of the mechanism of infection by another sexually transmitted microbe, *Neisseria gonorrhoeae*, and the cause of gonorrhea. Researchers determined that *Neisseria gonorrhoeae* binds to different molecules on the male and female genital tract – in females, a molecule on cervical cells (called complement receptor type 3), and in males, a molecule on urethral cells (called sialoglycoprotein receptor). The results of this study may lead to new treatment and prevention strategies for gonorrhea. A better understanding of the microbes that cause STDs may also lead to more effective STD prevention approaches. NIAID-supported researchers identified a novel surface protein (Por B) on *Chlamydia trachomatis* (the microbe that causes chlamydial infections) that may provide a target for an anti-chlamydial vaccine. In animal studies, NIAID-supported scientists determined that Por B stimulates the immune system to mount an immune response that prevents the development of chlamydial infections. In addition to the identification of novel targets that may serve as potential vaccines for STD prevention, the concept that STDs can be prevented with topical antimicrobial substances (topical microbicides) ? that are applied to the vagina or rectum to kill STD pathogens transmitted by either sexual partner. In Phase II clinical trials, NIAID-supported scientists demonstrated the safety of the topical microbicides: BufferGel® and Pro 2000/5 Gel in HIV-infected men; and Carraguard (a novel vaginal microbicide) in sexually active uninfected women.

### *Future Directions in Sexually Transmitted Diseases*

NIAID will continue to support research for more effective prevention approaches to control STDs. In collaboration with GlaxoSmithKline, the Institute recently launched an efficacy trial of an

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<sup>23</sup>Cates *et al.* *Sex Trans Dis* 26 (suppl):S2-S7, 1999.

<sup>24</sup><http://www.thebody.com/sfaf/autumn00/std.html#synergy>

experimental vaccine designed to prevent genital herpes in women. The trial will enroll 7,550 women in at least 16 sites throughout the U.S. NIAID will also continue to support basic and clinical research on mechanisms of pathogenesis and immunology of bacterial and viral STDs. Continued support will be provided for: the *Sexually Transmitted Diseases Clinical Trials Group* to provide the necessary clinical trials infrastructure for clinical research on STDs, including clinical trials to evaluate diagnostics, therapeutics, vaccines, and topical microbicides; and the *Sexually Transmitted Diseases and Topical Microbicide Research Centers* to develop better approaches for the diagnosis, prevention and treatment strategies for STDs, for use both domestically and internationally. The Centers will include a focus on: basic pathogenic mechanisms of the organisms that cause STDs and other immune aspects of these diseases; the evaluation of compounds and combinations of compounds active against both STDs and HIV; and studies aimed at reducing STDs in underserved populations.

## Enteric Diseases

### *Introduction*

Infections of the gastrointestinal tract lead to diarrheal disease. In 2000 alone, it has been reported that 2.1 million people died from diarrheal diseases, with a great proportion of these cases attributed to contamination of food and drinking water. In industrialized countries, the percentage of people suffering from food-borne diseases each year is reported to be up to 30%. In the U.S., for example, about 76 million cases of food-borne diseases, resulting in 325,000 hospitalizations and 5,000 deaths, are estimated to occur each year. Among illnesses attributable to food-borne transmission, 67% are caused by viruses, 30% by bacteria, and 3% by parasites.<sup>25</sup>

### *Scientific Advances in Enteric Diseases Research*

The tremendous burden of enteric diseases requires research aimed at a better understanding of the pathogenic mechanisms employed by these bacteria. NIAID-supported researchers recently demonstrated that passage of the cholera bacterium through the human digestive tract appears to switch on key genes of the bacterium, making it up to 700 times more infectious than cholera grown in the laboratory. This heightened infectivity is maintained even after the bacteria are released into the environment, a property that likely contributes to cholera's epidemic spread. Another recent discovery has important implications for vaccine development for *Listeria monocytogenes*, another cause of food-borne illness. NIAID-supported scientists demonstrated that a vaccine based on the use of a live, attenuated bacterial variant of *L. monocytogenes* induced better protective immunity than a killed bacterial vaccine. Development of a safe and effective vaccine against rotavirus, a major cause of diarrhea in children under 2 years of age, is a high global health priority. Animal models of rotavirus disease are helpful to study disease mechanisms to provide evidence of vaccine efficacy. NIAID-supported researchers recently identified a rat model as a valuable new tool for studying rotavirus infection.

### *Future Plans in Enteric Diseases Research*

NIAID research on enteric diseases will focus on the natural history, pathogenesis and host responses to infection by enteric pathogens and will develop and test the efficacy of new enteric vaccines. Future plans include Phase I testing of Norwalk and Rotavirus vaccines and a promising attenuated *Salmonella typhi* vaccine, as well as Phase II testing of a promising attenuated *Vibrio cholerae* vaccine. New generation rotavirus vaccines, based on an attenuated bovine donor strain, are being aggressively investigated.

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<sup>25</sup> WHO. <http://www.who.int/info-fs/en/fact237.html>

## Lyme Disease

### *Introduction*

Lyme disease, an infection caused by the bacterium *Borrelia burgdorferi*, is transmitted to people by the bite of Ixodid ticks<sup>26</sup>, who in turn become infected by feeding on the white footed deer mouse or deer. The number of Lyme disease cases reported annually in the U.S. has increased 25-fold since national surveillance began in 1982. About 15,000 cases of Lyme disease are reported each year, making Lyme disease the leading cause of vector-borne illness in this country.<sup>27</sup> Manifestations of infection with *B. burgdorferi* are highly variable, ranging from no symptoms, non-specific symptoms (fever, headache, fatigue, myalgia), to chronic multi-system involvement of the skin, nerves, and joints (e.g., arthritis) for a period of years.<sup>28</sup>

### *Scientific Advances in Lyme Disease Research*

NIAID-supported researchers, using a mouse model, demonstrated that an increase in the severity of arthritis resulted from concurrent infection with *B. burgdorferi* and another agent of tick-borne disease, *Babesia microti*. In addition to studies on the influence of co-infection with other vector-borne pathogens on the severity of Lyme disease, NIAID-supported researchers determined that an immune evasion mechanism of *B. burgdorferi* contributes to the persistence of Lyme disease. These results suggest that the bacteria can avoid detection by the immune system by expressing bacterial surface components that are not recognized by antibodies. NIAID-supported scientists also determined a potential new approach for treating inflammation associated with Lyme disease and developed a new blood test for the diagnosis of Lyme disease.

### *Future Directions in Lyme Disease Research*

Lyme disease will continue to be an area of high priority for basic research, especially with regard to: the characterization and treatment of acute and chronic infection; the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment and disease severity; and the development of rapid, sensitive and specific diagnostic tests and preventive strategies. NIAID will continue supporting *Partnerships for Novel Therapeutic, Diagnostic and Vector Control Strategies in Infectious Diseases*, focusing on the development of novel treatments for human infectious diseases of high public health impact and their insect vectors, including strategies for reducing vector-borne bacterial diseases, such as Lyme disease.

## Antimicrobial Resistance

### *Introduction*

Since penicillin was first introduced in the 1940's, microbes have developed mechanisms of resistance that thwart or block the action of antimicrobial drugs. Antimicrobial resistance is growing and spreading worldwide, affecting our ability to successfully treat respiratory, diarrheal, sexually transmitted, hospital-acquired infections, and a great variety of infections caused by bacteria, fungi, and parasites. In the U.S., approximately 14,000 individuals are infected and die each year from a drug-resistant microbe acquired in the hospital setting.<sup>29</sup> Antimicrobial resistance

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<sup>26</sup> The ticks usually associated with transmission are *Ixodes scapularis* and *I. ricinus*.

<sup>27</sup> CDC. MMWR Morbidity Tables, 2001, week 51.

<sup>28</sup> CDC. <http://www.cdc.gov/ncidod/ddvbid/lyme/index.htm>

<sup>29</sup> WHO Report on Infectious Diseases 2000: Overcoming Antimicrobial Resistance. <http://www.who.int/infectious-disease-report/2000/>

has resulted in difficult to treat infections, increased hospital stays and costs, and the need for more toxic drugs.

#### *Scientific Advance in Antimicrobial Resistance Research*

Bacteria are becoming increasingly resistant to antimicrobial drugs and the transfer of resistance properties among microbes has resulted in the acquisition of resistance by previously susceptible microorganisms. Resistance can be transferred between some bacteria by small self-replicating genetic elements called plasmids. NIAID-supported researchers have identified a gene on those plasmids, named *qnr*, which encodes a protein that protects bacteria from the effects of quinolone drugs, often a “last line of defense” against serious infection. The discovery of that novel gene sheds new light on quinolone resistance in bacteria and suggests a possible target for new antibiotics. A better understanding of the molecular basis of antibiotic resistance will also aid in the development of new ways to block the process. NIAID-supported researchers recently studied the binding of six drugs to a bacterial drug-binding protein, *QacR*, which plays a key role in multi-drug recognition and in allowing some bacteria to resist the effects of antibiotics. The study provides insight into how *QacR* binds to select drugs and explains features that are likely shared among different drug-resistance proteins.

#### *Future Directions in Antimicrobial Resistance Research*

NIAID will continue to support research aimed at: identifying new diagnostic techniques, novel therapeutics, and preventive measures to minimize infection with resistant pathogens; preventing the acquisition of resistance traits; and controlling the spread of resistance factors and resistant pathogens with a focus on health care settings. In addition, through the Interagency Task Force on Antimicrobial Resistance, NIAID and other federal collaborators will develop an action plan for U.S. Government agencies to address the global problem of antimicrobial resistance.

### **The Contributions of Microbial Genomics**

The availability of genomic information has and will continue to greatly enhance our understanding of the biology of dangerous pathogens and their ability to cause disease, leading to new treatment and prevention strategies.

#### *Scientific Advances in Microbial Genomics*

NIAID has recently witnessed some extraordinary discoveries in the field of genomics research that will enhance efforts in a number of important disease areas. For example, NIAID-supported genetic studies determined that: the cholera bacterium becomes more virulent by passing through the human intestines; a gene in the microbe, *Yersinia pestis*, is required for the flea-borne transmission of plague to humans; and what the difference is between humans and the malaria parasite in the regulation of a key drug target. NIAID also supported efforts to complete the genome sequencing of *P. falciparum* and *A. gambiae*, the most lethal malaria parasite and its mosquito vector, respectively. Already, these data have proven invaluable to investigators. For example, enzymatic targets for the design of new drugs have been discovered in the *P. falciparum* sequence, and one candidate drug has moved forward for further development. The *Anopheles* genome has revealed genes whose products are involved in host seeking behavior and other activities that may be targeted for developing new malaria control interventions.

#### *Future Directions in Microbial Genomics Research*

NIAID will continue to support: *Microbial Genome Sequencing Centers* for rapid and cost-efficient production of high quality, microbial genome sequences; *Bioinformatic Resource Centers* to develop, populate, and maintain comprehensive relational databases to collect, store, display, annotate, query, and analyze genomic, functional genomic, structural and related data for

microorganisms; and *Proteomic Centers* to support studies using genomics in combination with other technologies to determine microbial protein structure and function for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics and immunotherapeutics against microorganisms. In addition, the NIAID's *Pathogen Functional Genomics Resource Center* will be expanded to conduct both basic and applied research on microorganisms responsible for emerging and re-emerging infectious diseases.

## **CONFRONTING IMMUNE-MEDIATED DISEASES**

### **Immune Tolerance**

#### *Introduction*

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated disorders, including: autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis and multiple sclerosis; asthma; allergic diseases; and rejection of transplanted solid organs, cells and tissues. Approaches to induce immune tolerance seek to selectively block or eliminate harmful immune responses while maintaining a competent immune system capable of fighting off infection. Over two decades of highly intensive and productive research in fundamental immunology have provided the knowledge base necessary to identify novel targets for tolerance induction and to apply that knowledge to the treatment of human disease. NIAID has been at the forefront in supporting basic and pre-clinical research on immune tolerance, an investment that has recently led to the ability to test multiple promising strategies in the clinical setting.

#### *Scientific Advances in Immune Tolerance Research*

Graft-versus-host disease (GVHD) is a potentially deadly complication of bone marrow transplantation in which immune cells (T cells) of the donor bone marrow perceive the recipient's tissue as being foreign and begin attacking and destroying the recipient's tissues. This attack can be prevented only if the activities of both subsets of T cells, CD4 and CD8, are blocked. Recently, NIH-supported investigators developed new strategies to inhibit the ability of these two subsets of T cells to attack and successfully prevented GVHD in a mouse model. These findings may lead to the development of strategies for the prevention of lethal GVHD in bone marrow transplant recipients.

#### *Future Directions in Tolerance Research*

In 1999, NIAID spearheaded the establishment of a unique clinical trials infrastructure, the Immune Tolerance Network (ITN), to move immune tolerance induction into the clinical setting. This international consortium of basic scientists and clinical investigators is dedicated to the clinical evaluation of novel, tolerance-inducing therapies in four areas: kidney transplantation; islet transplantation for type 1 diabetes; asthma and allergic diseases; and autoimmune diseases. One of the promising clinical trials being conducted by the ITN involves an experimental islet cell transplantation protocol for brittle, or difficult to control, type 1 diabetes. Researchers at the University of Alberta in Edmonton, Canada developed this protocol, known as the Edmonton protocol. Of the 33 patients transplanted to date through this ITN trial, 12 are currently insulin-independent. This clinical trial will serve as the baseline for introducing tolerance induction approaches in combination with this promising islet transplantation protocol induction regimens in animal models. Also, NIAID will continue to support innovative research to discover other promising molecular targets for the induction of immune tolerance and to evaluate tolerance.

### ***Story of Discovery: Immune Therapy for Type 1 Diabetes***

Type 1 diabetes is a chronic autoimmune disease that afflicts between 500,000 and one million people in the United States, usually children and young adults. Autoimmune diseases occur when the immune system attacks the body's own tissues. In type 1 diabetes, the immune system attacks and destroys the islet cells of the pancreas that secrete insulin, a hormone essential for the body's ability to use sugar from digested foods. The pancreas then produces little or no insulin, and patients must endure a difficult and life-long treatment regimen that includes multiple daily injections of insulin, multiple monitoring of blood glucose levels, and significant dietary requirements and restrictions. Furthermore, poor management of diabetes can lead to serious complications, such as blindness, kidney failure, heart disease, stroke, and foot and leg amputations.

#### **Basic and Pre-Clinical Research: Putting the Pieces Together**

Through years of research on the processes underlying autoimmune disorders, NIAID-supported scientists paved the way for the development of a new therapy for type 1 diabetes. When studies demonstrated that immune cells known as T cells were involved in the destruction of islet cells, researchers attempted to block the harmful actions of these cells with drugs that suppress the entire immune system. Unfortunately, the toxic side effects and increased risk of infection limited the use of these drugs. Developing a less toxic therapeutic approach that selectively blocks the harmful actions of the immune system while maintaining its ability to fight off infections would be a key step towards meeting the challenges posed by autoimmune reactions in type 1 diabetes. In the meantime, researchers working on novel immune therapies to prevent kidney transplant rejection developed an antibody against the CD3 complex, a cluster of molecules on the T cell surface that plays a central role in activating it to recognize and respond to toxins, bacteria, and other foreign cells. Graft rejection results when T cells recognize the transplanted organ as foreign and mount an attack against it. Studies with animal models of type 1 diabetes demonstrated that the anti-CD3 antibody could suppress the destructive T cells.

#### **Transferring Findings to Patients**

Based on the success of animal studies, NIH-supported researchers moved to test this approach in humans. They initiated a phase I trial to determine the safety of this anti-CD3 antibody in patients with new-onset type 1 diabetes. The researchers showed that administering this novel immunotherapy within 6 weeks of diagnosis of disease slowed down the loss of insulin production in 9 out of 12 young diabetic patients. The effects were still evident one year later, although the patients continued to require insulin therapy. The promising results of this preliminary study have led to a multi-center, phase II clinical trial, which is currently recruiting 80 additional patients between the ages of 7 and 27. The trial will be conducted by the Immune Tolerance Network under the co-sponsorship of NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International. Although this treatment is not a cure for type 1 diabetes, it brings us a step closer to the goal of preserving insulin production in people newly diagnosed with the disease. Greater ability to maintain the body's production of insulin will make it easier for the patients to control blood sugar levels, and improved metabolic control of diabetes will reduce the risk of developing diabetes-related complications.

## Autoimmune Diseases

### *Introduction*

Autoimmune diseases, which result when the immune system attacks the body's own tissues, can be classified into two groups: organ-specific and non-organ-specific. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Non-organ-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactions against different organs located throughout the body.

Autoimmune diseases affect an estimated 5 to 8 percent of the U.S. population (14 to 22 million people) and disproportionately afflict women. Of the approximately 2.1 million Americans suffering from rheumatoid arthritis, 1.5 million are women, and as many as 1 in 250 African American women suffer from SLE.<sup>30</sup> These chronic, disabling diseases are a major public health problem, costing over \$86 billion annually in health care expenses.<sup>31</sup>

Current treatments for many autoimmune diseases include corticosteroids, non-steroidal anti-inflammatory drugs, such as acetaminophen; immunosuppressive drugs, and radiation of the lymph nodes. While these therapeutic approaches can ameliorate the symptoms, curative or preventive therapies do not exist. Through NIAID's investments in productive basic and pre-clinical research on the underlying causes and pathogenesis of autoimmune diseases, we are now in a position to evaluate promising, immune-based therapies for the treatment and prevention of many autoimmune diseases. In addition, NIAID is committed to supporting continued research on autoimmune diseases and furthering our understanding of the role of environmental factors, genetic susceptibility, and the regulation of immune cells and biochemicals that mediate autoimmune diseases.

### *Scientific Advances in Autoimmune Diseases Research*

Severe and prolonged inflammation can lead to tissue damage, as observed in rheumatoid arthritis and multiple sclerosis. Understanding how to control inflammatory processes can aid in the design of novel approaches to manage these chronic disorders. NIAID scientists have recently shown that when a molecule known as adenosine reach excess levels outside the cells, they bind to adenosine receptors on the cell surface and initiate a chain reaction that eventually halts inflammation. Targeting adenosine and these receptors could lead to the development of new drugs and treatments for controlling inflammation in a wide range of diseases.

A group of NIAID-supported investigators have discovered the molecular basis for the ability of antihistamines, which are normally used to alleviate allergy symptoms, to reduce the severity of autoimmune diseases in animal models. They demonstrated that activity of H1R, a signaling protein that is blocked by antihistamines, is required for reactions. When H1R signaling is blocked, the damage caused by the immune system is reduced. This information may assist scientists in designing new strategies for managing autoimmune diseases.

### *Future Directions in Autoimmune Diseases Research*

Through the establishment of the Autoimmunity Centers of Excellence (ACEs) in 1999, NIAID has been instrumental in bringing together basic and clinical researchers from multiple medical

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<sup>30</sup> *Arthritis Rheum* 41:778, 1998.

<sup>31</sup> American Autoimmune Related Diseases Association. July 7, 1999 Press Release. [http://www.aarda.org/press\\_release7.html](http://www.aarda.org/press_release7.html)

disciplines to conduct collaborative projects on autoimmune diseases, including pilot clinical trials of promising immune-based therapies. The ACEs are presently enrolling participants for two pilot clinical trials: the effect of antibody directed against regulatory cell surface molecules on B cells as treatment for systemic lupus erythematosus, and combination drug regimen of albuterol and Copaxone<sup>®</sup> (glatiramer acetate) for multiple sclerosis. By expanding the ACEs in FY 2004, NIAID will continue to support basic, preclinical, and clinical research to accelerate the development and evaluation of promising therapies for autoimmune diseases.

The Immune Tolerance Network is also developing clinical trials of tolerance induction approaches for autoimmune diseases, including antibody against the stimulatory CD154 molecules on T cells for the treatment of multiple sclerosis, and antibody against the CD52 molecules on T cells for the treatment of type 1 diabetes. The principle behind antibody-mediated therapy is that the binding of antibodies to these specific molecules on the surface of targeted immune cells can alter or suppress the activities of those immune cells.

Through the Stem Cell Transplantation for Autoimmune Diseases Consortium, NIAID is developing clinical trials to assess the efficacy of hematopoietic stem cell (HSC) transplantation in treating several severe autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and scleroderma. HSCs, which are generated in the bone marrow, give rise to and continually replenish our blood cells, such as red blood cells, platelets, and immune cells. The rationale behind HSC transplantation for autoimmune diseases is to destroy the dysfunctional immune cells that attack the body's own tissues and to generate a new, properly functioning immune system.

## **Asthma and Allergic Diseases**

### *Introduction*

Asthma and allergic diseases combined represent the 6<sup>th</sup> leading cause of chronic illness and disability in the United States. Asthma afflicts approximately 14 million Americans,<sup>32</sup> and disproportionately affects children. According to a recent study, approximately 50 percent of Americans have positive skin tests to at least one of ten allergens that contribute to allergic illnesses, including ragweed, cat, house dust mite, German cockroach, and peanut.<sup>33</sup> Chronic allergic conditions significantly decrease quality of life and productivity for millions of Americans, and account for over \$14 billion in health care costs. NIAID has been at the forefront of discoveries leading to the characterization of asthma and allergic diseases as immunologic disorders and is now vigorously pursuing the translation of basic knowledge into the development of more effective treatment and prevention strategies.

### *Scientific Advances in Asthma and Allergic Diseases Research*

Significant advances have been made recently in the discovery of genes and proteins that play a critical role in the development of asthma. Using mouse models that mimic human asthma, NIH-supported scientists have identified a family of genes, called *Tim*, that is associated with the development of airway hyperreactivity and susceptibility to asthma. Another group of NIH-supported scientists have shown that lacking a protein called T-bet results in airway inflammation and asthma-like changes in the lung structure. These advances in our understanding of the genetic basis of asthma will provide new opportunities and insight into prevention and treatment.

In the area of allergic diseases research, NIH-supported scientists recently designed and created a molecule, called GE2, that can bind to and cross-link two receptors that control the release of histamine and other mediators of allergy by cells of the immune system. One of the receptors

<sup>32</sup> CDC. MMWR Seoptember 6, 2002, 51(35): 781-784.

<sup>33</sup> Matricardi *et al.* *J Allergy Clin Immunol* 110:381-387, 2002

stimulates the release and the other inhibits it, but the inhibitory action results only when activation of the two receptors is coupled. GE2 binding blocked histamine release and allergic inflammation, demonstrating that this newly designed protein could be a model for new treatments of allergic reactions.

In 2001, NIAID and the National Institute of Environmental Health Sciences (NIEHS) completed the Inner City Asthma Study, a five-year project that evaluated the effectiveness of two asthma interventions among children ages 5 to 11 with moderate to severe asthma. The physician feedback intervention provided primary care physicians with up-to-date information on recent asthma symptoms, medication, and health care utilization. The environmental intervention involved home-based education to reduce exposure to environmental triggers, including environmental tobacco smoke, cockroaches, house dust mites, molds, furry pets, and rodents. A total of 941 patients were recruited and evaluated for a 1-year intervention period plus an additional year of follow-up. The environmental intervention increased the number of symptom-free days by 2 to 4 weeks and reduced the number of unscheduled medical visits. These improvements correlated with reduction in cockroach and house dust mite allergen levels. The physician feedback intervention resulted in a 20% decrease in unscheduled medical visits.

#### *Future Directions in Asthma and Allergic Diseases Research*

NIAID will continue to support innovative basic and clinical research focused on elucidating the molecular and cellular immune mechanisms involved in asthma and allergic diseases, and developing the next generation of therapeutic agents and prevention strategies. The Immune Tolerance Network is currently supporting a clinical trial of DNA-ragweed allergen treatment for allergic rhinitis (hay fever), and will be pursuing other clinical trials involving tolerance induction approaches for asthma and various allergic diseases.

Asthma disproportionately affects minority children, particular those residing in the inner city. In children under the age of 18, the prevalence of asthma in African Americans was 7.4 percent, compared to 5.0 percent in white children. To combat this disproportionate burden of asthma among inner-city children, NIAID established the Inner City Asthma Consortium in FY 2002 to evaluate promising immune-based strategies for the treatment of asthma in this population. In FY 2004, the Consortium will be expanded to incorporate natural history studies of asthma. Such studies will examine the natural progression of disease, i.e., the course of disease over time unaffected by treatment, including the identification of key risk factors for disease development.

## **Transplantation**

### *Introduction*

For millions of Americans suffering from illnesses such as kidney failure, liver disease, coronary heart disease, and end-stage lung disease, the transplantation of failing organs, tissues, and cells can reverse the devastating outcomes of disease. Today, transplantation procedures are performed using over 25 different organs and tissues, and first year graft survival rates exceed 80 percent. Despite these successes, immune-mediated graft rejection and the critical shortage of donor organs remain as two major limiting factors. In 2001, there were approximately 78,000 patients on the waiting lists for solid organ transplants, but only 24,110 transplants were performed. In an effort to address the problem of organ shortage, NIAID supports programs to improve donor registries and increase organ donation. To combat the obstacle of graft rejection, NIAID supports a broad range of basic and pre-clinical research on immunology and tolerance induction, and the clinical evaluation of promising new therapies to improve long-term graft survival.

## *Scientific Advances in Transplantation Research*

Chemokines are biological molecules that control the movement of white blood cells to sites of inflammation, and CCR5 and CCR2 are chemokine receptors found on the surface of these white blood cells. NIAID intramural scientists recently discovered that patients with small changes in the genes for these receptors have lower risk of kidney transplant rejection. These genetic differences may be influencing the risk of rejection by affecting the level of immune activity against the foreign kidney mediated by these receptors. With increased understanding of the role of such genetic factors, we will be better equipped to develop new approaches to improving the outcome of organ transplantation.

## *Future Directions in Transplantation Research*

Through the Immune Tolerance Network, NIAID is committed to developing new strategies to selectively block immune responses against the graft. Currently, the ITN is conducting two clinical trials using such strategies for kidney transplantation - a combined bone marrow/kidney transplant protocol for multiple myeloma patients with end-stage renal disease, and a novel T cell-depleting antibody for tolerance induction.

Kidney transplantation accounts for 58 percent of all solid organ transplant procedures and is the treatment of choice for end-stage renal disease.<sup>34</sup> In order to coordinate multi-center clinical trials of new immunosuppressive drugs and biologicals to enhance long-term kidney graft survival, NIAID established the Cooperative Clinical Trials in Adult Kidney Transplantation (CCTAT) in 1991 and the Cooperative Clinical Trials in Pediatric Kidney Transplantation (CCTPT) in 1994. The CCTAT is supporting a pilot study of kidney transplantation in HIV-positive patients who have developed end-stage renal disease as a consequence of antiviral therapy. The CCTPT is examining the causes of lower patient and graft survival in pediatric kidney transplant recipients, and evaluating the safety and efficacy of various immunosuppressive therapies in the pediatric population.

## ***Primary Immunodeficiency Diseases***

### *Introduction*

Primary immunodeficiency diseases, almost all of which are rare, are caused by intrinsic defects in the cells of the immune system, often due to inherited genetic defects. These diseases are distinct from secondary immunodeficiency diseases, such as AIDS, which are due to another illness or agent. The hallmark of primary immunodeficiency diseases is increased susceptibility to infection, but they can also be associated with anemia, malabsorption and diarrhea, low platelet counts, malignancies of lymphoid organs, arthritis, and autoimmune phenomena. Over 80 different forms of primary immunodeficiency diseases afflict approximately 500,000 Americans.<sup>35, 36</sup> The major goal of NIAID-supported research on primary immunodeficiency diseases is to expand the genetics knowledge base in order to better understand the causes, improve the diagnosis, and develop protective and curative treatments.

### *Scientific Advances in Primary Immunodeficiency Diseases Research*

Severe combined immunodeficiency disease (SCID) is characterized by a complete loss of functional immune cells and, hence, extreme susceptibility to infection. Although rare in the general population, SCID affects 1 out of 2,000 newborns among the Navajo and Apache Native Americans.<sup>37</sup> NIH-supported investigators determined that a mutation in the gene for a protein

<sup>34</sup> United Network for Organ Sharing. Critical Data. <http://www.unos.org>

<sup>35</sup> CDC. *Vital Health Statistics*, Series 13, No. 148, September 2000

<sup>36</sup> Report of a WHO Scientific Group. *Clin Exp Immunol* 109 (Suppl. 1): 1-28, 1997

<sup>37</sup> Li et al, *J Immunol* 168: 6329-6329, 2002

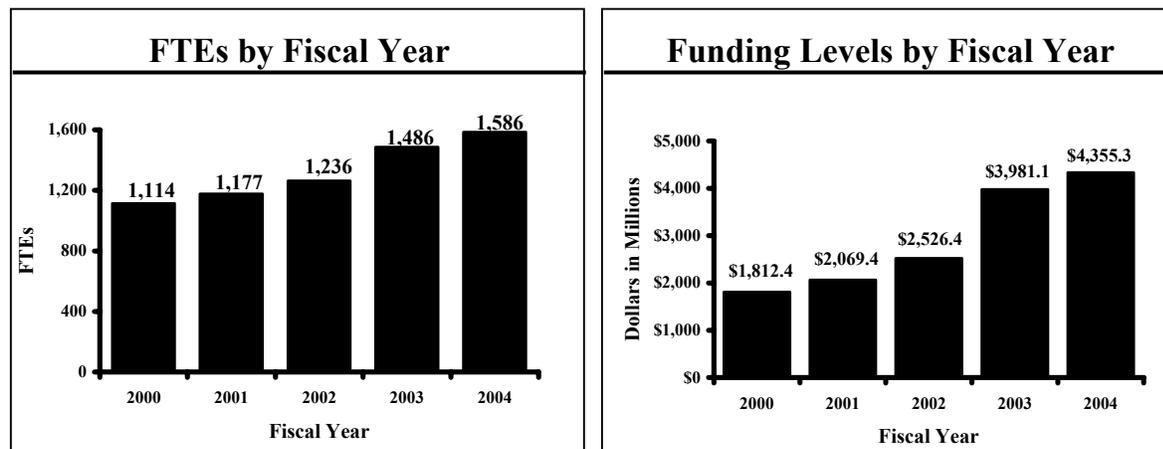
called Artemis, which normally helps repair chromosomal breaks, causes SCID. This research resulted in the development of a simple and definitive test for the mutant gene that will immediately benefit perinatal diagnosis and the detection of carriers.

*Future Directions in Primary Immunodeficiency Diseases Research*

In order to advance our understanding of these devastating diseases, NIAID plans to establish a Primary Immunodeficiency Diseases Consortium (PIDC) to enhance coordination of research efforts and facilitate collaborations aimed at the development of novel diagnostics, disease models, and treatment approaches. In addition, the PIDC will establish and maintain a primary immunodeficiency diseases registry, which will make available to the research community information on the clinical characteristics and prevalence of these diseases. The wealth of knowledge gained from these programs will provide opportunities to design and develop novel strategies for the treatment and prevention of these rare diseases.

## Budget Policy

The Fiscal Year 2004 budget request for the NIAID is \$4,335,255,000, including AIDS, an increase of \$354,155,000 and 8.9 percent over the FY 2003 level. A five-year history of FTEs and Funding Levels for NIAID are shown in the graphs below. The increase in FTEs in FY 2004 is to support the continued expansion of the biodefense research effort. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.



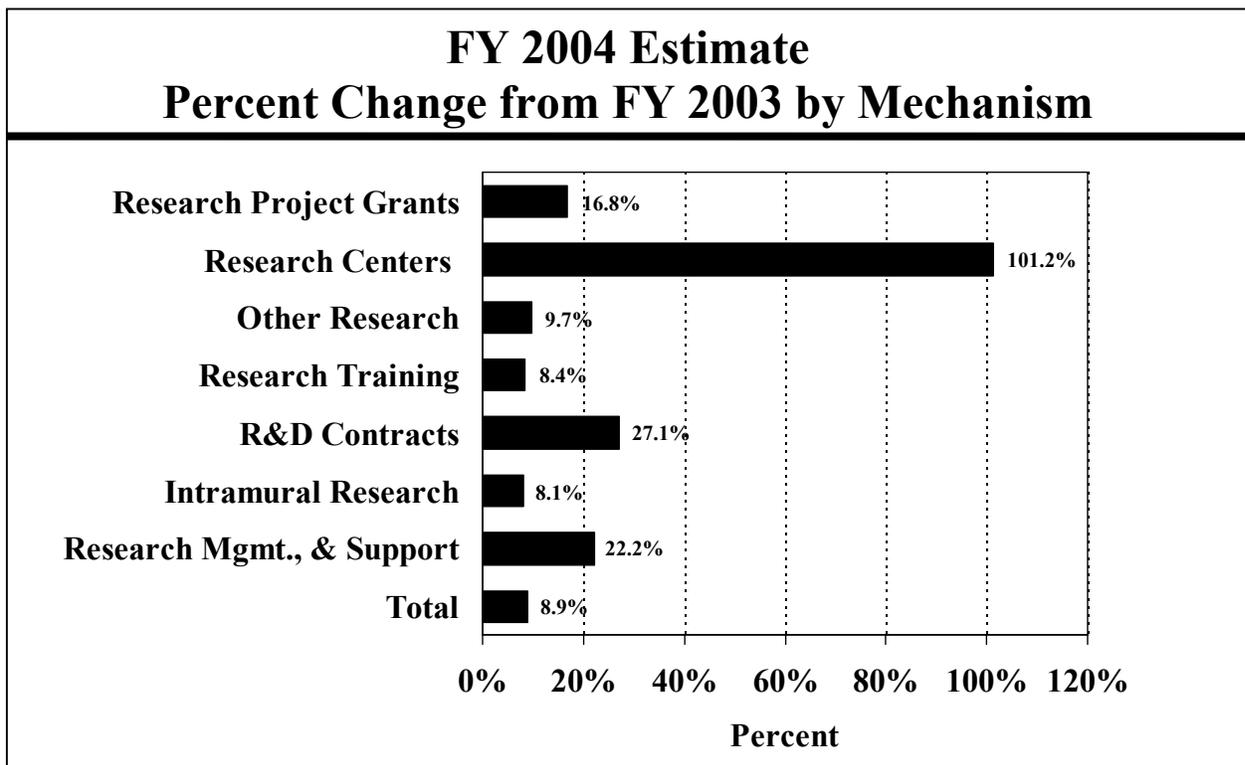
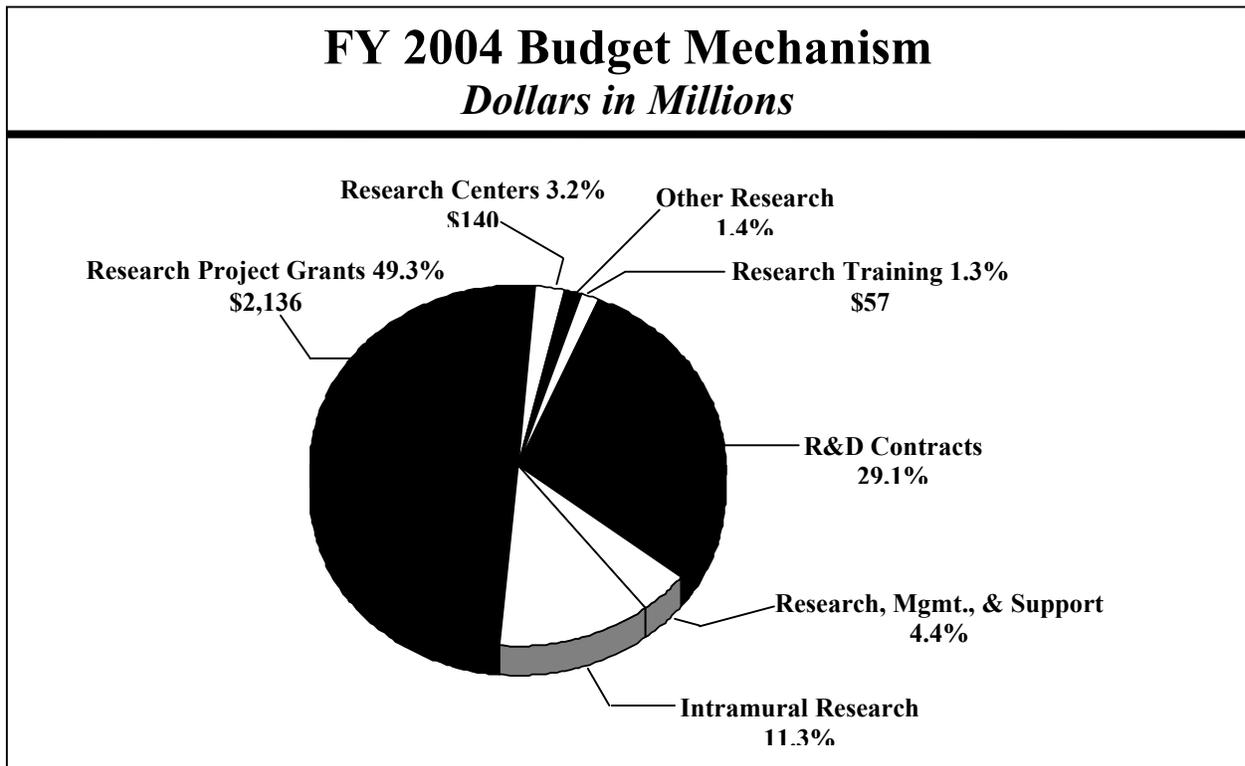
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The NIAID provided an average cost increase for competing RPGs of 2.6 percent in FY 2004. However, the average cost comparison with FY 2003 is skewed because of the cost of biodefense challenge grants in fiscal years 2003 and 2004.

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NIAID will support 1,251 pre- and postdoctoral trainees in full-time training positions, an increase of 74 compared to FY 2003. This increase is the result of providing support for training in biodefense research. Stipend levels for NRSA trainees will increase by 4.0 percent over Fiscal Year 2003 levels for predoctoral fellows, and from 4-1 percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 32 research centers, 374 other research grants, including 322 clinical career awards, and 285 R&D contracts. The R&D contracts mechanism also includes support for 56 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs and \$1,645,000 for the Best Pharmaceuticals for Children's Act. Intramural Research and Research Management and Support receive increases of 1.8 percent over FY 2003 for non-biodefense related research. The additional increases in these areas are the result of conducting and supporting biodefense research.

Included as part of the increase for NIAID in FY 2004 is \$250,250,000 to support the Administration's initiative to develop biomedical tools to detect, diagnose, prevent, and treat infections by biological agents that could serve as possible weapons.

The mechanism distribution by dollars and percent change are displayed below:



**NATIONAL INSTITUTES OF HEALTH**  
National Institute of Allergy and Infectious Diseases

Budget Mechanism - Total

MECHANISM	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects:						
Noncompeting	2,521	\$1,103,909,000	2,812	\$1,187,093,000	3,040	\$1,330,657,000
Administrative supplements	(90)	10,302,000	(60)	12,000,000	(60)	12,000,000
Full funded	0	0	0	0	68	122,802,000
Single year	1,067	354,206,000	1,442	541,680,000	1,614	570,214,000
Subtotal, competing	1,067	354,206,000	1,442	541,680,000	1,682	693,016,000
Subtotal, RPGs	3,588	1,468,417,000	4,254	1,740,773,000	4,722	2,035,673,000
SBIR/STTR	222	60,095,000	259	88,131,000	292	100,834,000
Subtotal, RPGs	3,810	1,528,512,000	4,513	1,828,904,000	5,014	2,136,507,000
Research Centers:						
Specialized/comprehensive	23	27,439,000	28	64,185,000	32	134,696,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	1,500,000	0	1,500,000	0	1,500,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	3,666,000	0	4,168,000	0	4,347,000
Subtotal, Centers	23	32,605,000	28	69,853,000	32	140,543,000
Other Research:						
Research careers	272	32,237,000	310	38,279,000	322	42,111,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	1,005,000	0	1,058,000	0	1,103,000
Other	52	11,535,000	52	15,189,000	52	16,587,000
Subtotal, Other Research	324	44,777,000	362	54,526,000	374	59,801,000
Total Research Grants	4,157	1,605,894,000	4,903	1,953,283,000	5,420	2,336,851,000
Research Training:	FTEPs		FTEPs		FTEPs	
Individual awards	153	6,162,000	163	6,814,000	174	7,516,000
Institutional awards	919	39,474,000	1,014	45,432,000	1,077	49,120,000
Total, Training	1,072	45,636,000	1,177	52,246,000	1,251	56,636,000
Research & development contracts (SBIR/STTR)	234 (0)	489,938,000 (0)	251 (0)	992,899,000 (0)	285 (0)	1,262,789,000 (0)
Intramural research	FTEs		FTEs		FTEs	
Intramural research	726	299,775,000	735	452,168,000	735	488,975,000
Research management and support	510	84,600,000	751	155,504,000	851	190,004,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		375,000,000		0
Total, NIAID	1,236	2,525,843,000	1,486	3,981,100,000	1,586	4,335,255,000
(Clinical Trials)		(463,019,000)		(585,781,000)		(604,092,000)

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Allergy and Infectious Diseases**

**Budget Authority by Activity**  
**(dollars in thousands)**

ACTIVITY	FY 2002		FY 2003		FY 2004		Change	
	Actual		Amended President's Budget		Estimate			
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
<u>Extramural Research:</u> Allergy, Immunology, and Infectious Diseases		\$2,141,468		\$3,373,428		\$3,656,276		\$ 282,848
Subtotal, Extramural research		2,141,468		3,373,428		3,656,276		282,848
Intramural research	726	299,775	883	452,168	883	488,975	0	36,807
Res. management & support	510	84,600	603	155,504	703	190,004	100	34,500
Cancer Control & Prevention	0	0	0	0	0	0	0	0
<b>Total</b>	<b>1,236</b>	<b>2,525,843</b>	<b>1,486</b>	<b>3,981,100</b>	<b>1,586</b>	<b>4,335,255</b>	<b>100</b>	<b>354,155</b>

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Allergy and Infectious Diseases**

**Summary of Changes**

2003 Amended President's Budget		\$3,981,100,000	
2004 Estimated Budget Authority		4,335,255,000	
Net change		354,155,000	
CHANGES	2003 Amended President's Budget Base		Change from Base
	FTEs	Budget Authority	FTEs Budget Authority
A. Built-in:			
1. Intramural research:			
a. Within grade increase		\$95,562,000	\$1,273,000
b. Annualization of January 2003 pay increase		95,562,000	753,000
c. January 2004 pay increase		95,562,000	1,469,000
d. One extra day of pay		95,562,000	368,000
e. Payment for centrally furnished services		60,500,000	1,210,000
f. Increased cost of laboratory supplies, materials, and other expenses		296,106,000	4,489,000
Subtotal			9,562,000
2. Research Management and Support:			
a. Within grade increase		59,265,000	994,000
b. Annualization of January 2003 pay increase		59,265,000	469,000
c. January 2004 pay increase		59,265,000	914,000
d. One extra day of pay		59,265,000	228,000
e. Payment for centrally furnished services		20,800,000	416,000
f. Increased cost of laboratory supplies, materials, and other expenses		75,439,000	1,134,000
Subtotal			4,155,000
Subtotal, Built-in			13,717,000

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Allergy and Infectious Diseases**

**Summary of Changes--continued**

CHANGES	2003 Amended President's Budget Base			
	Change from Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,812	\$1,199,093,000	228	\$143,564,000
b. Competing	1,442	541,680,000	240	151,336,000
c. SBIR/STTR	259	88,131,000	33	12,703,000
Total	4,513	1,828,904,000	501	307,603,000
2. Research centers	28	69,853,000	4	70,690,000
3. Other research	362	54,526,000	12	5,275,000
4. Research training	1,177	52,246,000	74	4,390,000
5. Research and development contracts	251	992,899,000	34	269,890,000
Subtotal, extramural				657,848,000
6. Intramural research	<u>FTEs</u> 735	452,168,000	<u>FTEs</u> 0	36,807,000
7. Research management and support	751	155,504,000	100	34,500,000
8. Cancer control and prevention	0	0	0	0
9. Construction		375,000,000		(375,000,000)
Subtotal, program		3,981,100,000		354,155,000
Total changes			100	367,872,000

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Allergy and Infectious Diseases**

**Budget Authority by Object**

	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
<b>Total compensable workyears:</b>			
Full-time employment	1,486	1,586	100
Full-time equivalent of overtime & holiday hours	6	6	0
Average ES salary	\$0	\$0	\$0
Average GM/GS grade	10.9	10.9	0.0
Average GM/GS salary	\$64,269	\$65,555	\$1,286
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	\$72,287	\$73,732	\$1,445
Average salary of ungraded positions	92,266	93,950	1,684
OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	\$65,758,000	\$74,228,000	\$8,470,000
11.3 Other than Full-Time Permanent	36,998,000	40,394,000	3,396,000
11.5 Other Personnel Compensation	3,864,000	4,331,000	467,000
11.7 Military Personnel	3,417,000	3,710,000	293,000
11.8 Special Personnel Services Payments	15,131,000	15,812,000	681,000
<b>Total, Personnel Compensation</b>	<b>125,168,000</b>	<b>138,475,000</b>	<b>13,307,000</b>
12.1 Personnel Benefits	28,099,000	31,476,000	3,377,000
12.2 Military Personnel Benefits	1,559,000	1,712,000	153,000
13.0 Benefits for Former Personnel	0	0	0
<b>Subtotal, Pay Costs</b>	<b>154,826,000</b>	<b>171,663,000</b>	<b>16,837,000</b>
21.0 Travel & Transportation of Persons	7,940,000	8,775,000	835,000
22.0 Transportation of Things	1,277,000	1,410,000	133,000
23.1 Rental Payments to GSA	3,417,000	3,554,000	137,000
23.2 Rental Payments to Others	4,200,000	4,574,000	374,000
23.3 Communications, Utilities & Miscellaneous Charges	9,292,000	10,583,000	1,291,000
24.0 Printing & Reproduction	976,000	1,058,000	82,000
25.1 Consulting Services	976,000	1,065,000	89,000
25.2 Other Services	114,402,000	129,899,000	15,497,000
25.3 Purchase of Goods & Services from Government Accounts	335,054,000	375,158,000	40,104,000
25.4 Operation & Maintenance of Facilities	14,856,000	16,356,000	1,500,000
25.5 Research & Development Contracts	1,039,485,000	1,105,619,000	66,134,000
25.6 Medical Care	3,719,000	4,101,000	382,000
25.7 Operation & Maintenance of Equipment	6,167,000	6,989,000	822,000
25.8 Subsistence & Support of Persons	0	0	0
<b>25.0 Subtotal, Other Contractual Services</b>	<b>1,514,659,000</b>	<b>1,639,187,000</b>	<b>124,528,000</b>
26.0 Supplies & Materials	55,458,000	61,198,000	5,740,000
31.0 Equipment	36,006,000	39,747,000	3,741,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	2,193,029,000	2,393,486,000	200,457,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	20,000	20,000	0
44.0 Refunds	0	0	0
<b>Subtotal, Non-Pay Costs</b>	<b>3,826,274,000</b>	<b>4,163,592,000</b>	<b>337,318,000</b>
<b>Total Budget Authority by Object</b>	<b>3,981,100,000</b>	<b>4,335,255,000</b>	<b>354,155,000</b>

**NATIONAL INSTITUTES OF HEALTH**  
**National Institute of Allergy and Infectious Diseases**

**Salaries and Expenses**

OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
<b>Personnel Compensation:</b>			
Full-Time Permanent (11.1)	\$65,758,000	\$74,228,000	\$8,470,000
Other Than Full-Time Permanent (11.3)	36,998,000	40,394,000	3,396,000
Other Personnel Compensation (11.5)	3,864,000	4,331,000	467,000
Military Personnel (11.7)	3,417,000	3,710,000	293,000
Special Personnel Services Payments (11.8)	15,131,000	15,812,000	681,000
<b>Total Personnel Compensation (11.9)</b>	<b>125,168,000</b>	<b>138,475,000</b>	<b>13,307,000</b>
Civilian Personnel Benefits (12.1)	28,099,000	31,476,000	3,377,000
Military Personnel Benefits (12.2)	1,559,000	1,712,000	153,000
Benefits to Former Personnel (13.0)	0	0	0
<b>Subtotal, Pay Costs</b>	<b>154,826,000</b>	<b>171,663,000</b>	<b>16,837,000</b>
Travel (21.0)	7,940,000	8,775,000	835,000
Transportation of Things (22.0)	1,277,000	1,410,000	133,000
Rental Payments to Others (23.2)	4,200,000	4,574,000	374,000
Communications, Utilities and Miscellaneous Charges (23.3)	9,292,000	10,583,000	1,291,000
Printing and Reproduction (24.0)	976,000	1,058,000	82,000
<b>Other Contractual Services:</b>			
Advisory and Assistance Services (25.1)	527,000	500,000	(27,000)
Other Services (25.2)	114,402,000	129,899,000	15,497,000
Purchases from Govt. Accounts (25.3)	188,610,000	207,210,000	18,600,000
Operation & Maintenance of Facilities (25.4)	9,611,000	10,586,000	975,000
Operation & Maintenance of Equipment (25.7)	6,167,000	6,989,000	822,000
Subsistence & Support of Persons (25.8)	0	0	0
<b>Subtotal Other Contractual Services</b>	<b>319,317,000</b>	<b>355,184,000</b>	<b>35,867,000</b>
Supplies and Materials (26.0)	55,393,000	61,126,000	5,733,000
<b>Subtotal, Non-Pay Costs</b>	<b>398,395,000</b>	<b>442,710,000</b>	<b>44,315,000</b>
<b>Total, Administrative Costs</b>	<b>553,221,000</b>	<b>614,373,000</b>	<b>61,152,000</b>

## NATIONAL INSTITUTES OF HEALTH

### National Institute of Allergy and Infectious Diseases

#### SIGNIFICANT ITEMS IN SENATE APPROPRIATIONS COMMITTEE REPORTS

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

#### Item

***Advanced Vaccine/Device Combination*** — The Committee is aware of new vaccine/device delivery systems that could increase vaccine efficacy, use far less vaccine, and require fewer doses. The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) is currently conducting research and development on vaccine/device combinations to improve the performance of vaccines against weaponized organisms, including anthrax, plague, and staphylococcus enterotoxin B. The Committee encourages NIAID to work with USAMRIID on this effort. (p. 117)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is committed to the development of vaccines and other products to protect U.S. civilians against potential agents of bioterrorism, including anthrax, plague, and staphylococcus enterotoxin B. To help meet significantly intensified and accelerated goals in biodefense research and product development, NIAID has expanded its long-standing, productive relationship with the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) on a broad range of projects, including the development of diagnostics, drugs, and vaccines against microbes and toxins that could be used as biological weapons. Additionally, NIAID is supporting research to develop delivery devices and systems that enhance the performance of vaccines against a range of infectious diseases. Although the specific item described in the Committee's report, the development of a vaccine/device combination to improve the performance of vaccines against weaponized organisms, is not currently the focus of NIAID-USAMRIID collaboration, an Interagency Agreement (IAA) between NIAID and USAMRIID is written broadly enough to allow such collaborations, if needed.

NIAID and USAMRIID are working together to evaluate therapeutics and vaccines against potential agents of bioterrorism such as anthrax and plague, as well as viruses related to smallpox in non-human primate models. This collaboration is designed to develop standardized laboratory and clinical isolates, strains, and specimens of infectious agents that have the potential to be used as bioterrorist agents. For example, NIAID has provided funds to USAMRIID to scale up the synthesis of experimental therapeutic agents for smallpox and to evaluate the drugs in animal models (mice and monkeys). One high-priority antiviral drug, cidofovir, was shown to be effective against monkey pox, a relative of smallpox virus that causes disease in monkeys. Also, through an IAA with USAMRIID, NIAID supported studies to develop blood tests to determine whether a candidate vaccine against anthrax stimulates protective immunity against the most serious, inhaled form of anthrax.

NIAID has established a new IAA with USAMRIID to support additional collaborations in biodefense research and development. An important goal of this collaborative effort is to develop medical countermeasures and interventions that will be suitable for use in both military and

civilian populations. Under this IAA, NIAID and USAMRIID will collaborate on the construction of a new research facility at Ft. Detrick, Maryland, scheduled to begin in FY 2003 and to include Biosafety Level (BSL) 2, 3, and 4 laboratories. BSL-3 and BSL-4 laboratories are specifically designed to contain the most dangerous pathogenic microbes and allow researchers to conduct the necessary basic and targeted research under conditions that are safe for scientists and the general public.

In FY 2003, NIAID will engage in specific biodefense projects with USAMRIID and other Department of Defense (DoD) components that include: (1) a Phase I clinical trial to assess whether a new, second-generation vaccine against anthrax, based on a modified form of the anthrax toxin (rPA), is safe and can stimulate strong immune responses; (2) determining ways that collaborations with DoD can best be conducted for developing countermeasures against staphylococcus enterotoxin B; and (3) activities to scale up the manufacture of a DoD candidate vaccine against plague. In addition, NIAID intramural scientists are collaborating with USAMRIID to accelerate research on the development of rodent models of plague transmission, and to develop a vaccine that can protect against multiple strains of Ebola virus. In another collaboration, NIAID and USAMRIID investigators are testing a hybrid vaccine composed of pieces of a weakened tick borne encephalitis virus (TBEV) combined with a dengue virus backbone. This candidate vaccine was developed to provide resistance to the highly virulent, closely related, select agent TBEVs.

NIAID is also supporting several projects to develop new methods of vaccine delivery, which include oral, intranasal, inhaled, and trans-cutaneous modes of administration. A new intranasal influenza vaccine is one example of this research. Also, a research initiative entitled *Vaccine Delivery Systems and Platform Technologies* is on the NIAID List of High Priority Products for Biodefense for FY 2003. This list is used to inform extramural scientists who are applying for research support about priority areas and, in FY 2003, includes new research initiatives on: *Biodefense and Emerging Infectious Diseases; In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense; Clinical Trials for Antiviral Therapies; and Cooperative Research for the Development of Vaccines, Adjuvants, Immunotherapeutics, and Diagnostics for Biodefense.*

#### Item

***Asthma, Allergic Diseases, and Drug Allergy*** — The Committee encourages the NIAID to continue its efforts on asthma and expand its research into the area of drug allergy. Penicillin allergy alone causes 400 deaths each year in this country. The Committee encourages the NIAID, in collaboration with other Institutes as appropriate, to implement a program that will begin to address this need. (p. 117)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains deeply committed to the support of research to improve the diagnosis, treatment, and prevention of asthma and allergic diseases, including drug allergy. For example, in FY 2003, the *Immune Tolerance Network*, the NIAID-established international consortium dedicated to the clinical evaluation of therapies to induce immune tolerance, will expand its support for clinical trials in asthma and allergic diseases. In addition, in a newly initiated pediatric research program, NIAID intramural researchers will seek to develop a non-invasive, painless method to monitor airway inflammation in children, which will facilitate studies of the efficacy of new anti-inflammatory therapies for the management of pediatric asthma. Furthermore, in FY 2004, NIAID plans to fund a new research

program, *Immune System Development and the Genesis of Asthma*, to stimulate research into how early life changes in immune function may lead to the development of asthma.

To develop new and more effective therapies for asthma and allergic diseases, including allergies to medications, it will be essential to understand the underlying mechanisms of the immune responses that mediate these diseases. To this end, NIAID researchers have made significant scientific advances in understanding the genetic basis and immunologic mechanisms of allergic diseases that will provide new avenues for research on allergy prevention and treatment. For example, NIAID-supported researchers have successfully suppressed allergic reactions in a humanized mouse model, using genetic engineering techniques to block allergen-sensitive receptors. In addition, NIAID-supported scientists have isolated and verified the critical role played by certain suppressor molecules in taming allergic reactions in a mouse model. These results could form the basis for developing new therapeutic approaches for decreasing the severity of allergic diseases and reactions, including drug allergies.

In the future, NIAID researchers will continue efforts to better understand the basic mechanisms of asthma and allergic diseases and to develop novel immune-based therapies. For example, NIAID intramural researchers will study healthy individuals who exhibit immunological tolerance to commonly found airborne allergens to gain a better understanding of how allergic sensitization works. In addition, in FY 2003, NIAID will re-compete its long-standing *Asthma and Allergic Diseases Research Centers* program that supports basic and clinical research on asthma and allergic diseases, such as drug allergies. Furthermore, in FY 2003, NIAID will participate in planning a meeting, sponsored by the International Life Sciences Institute-Health and Environmental Science Institute, to identify and address the barriers to progress for research on immune-mediated drug reactions. The planning committee includes members from National Institutes of Health Institutes, other government agencies, academia, and industry.

#### Item

***Asthma Research and Management*** — The Committee is very pleased with the NIAID's leadership regarding asthma research and management. The Committee recognizes the role the Institute has played in the Inner-City Asthma Study and the importance of this effort concerning morbidity and mortality among underserved populations, particularly children. The Committee encourages the NIAID to continue to improve its focus and effort on asthma management, especially as it relates to children. The Committee also encourages 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 encourages the Institute to expand research into the role that infections and vaccines may play in the development of asthma. (p. 117)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to improving the diagnosis, treatment, and prevention of asthma, particularly for inner-city children so disproportionately affected by this disease. The Institute supports a diverse portfolio of research on asthma through its extra- and intramural programs, including cooperative research centers, demonstration and education projects, contracts, and investigator-initiated grants. For example, in FY 2003, NIAID will build on the success of the *National Cooperative Inner-City Asthma Study* (NCICAS), the first multi-site cooperative research program focused on reducing

asthma severity in inner-city minority children, by initiating a follow-up of the study participants to determine whether the effects of the intervention have persisted for the five years since the study was completed.

NIAID continues its efforts to improve asthma treatment and management. For example, in FY 2002, the Institute launched the *Inner-City Asthma Consortium*, a network of basic scientists and clinical investigators, to evaluate the safety and efficacy of promising immune-based therapies to reduce asthma severity in inner-city children. In FY 2003, this Consortium will be expanded to incorporate natural history studies aimed at understanding the natural progression of asthma and identifying critical risk factors for disease onset and severity. In addition, NIAID supports demonstration and education research projects that address asthma in medically underserved, predominantly inner-city Hispanic and African American populations. Preliminary results from the *Inner-City Asthma Study* (ICAS), launched in FY 1996 by NIAID and the National Institute of Environmental Health Sciences, suggest that environmental intervention to reduce home allergen levels is associated with a reduction in asthma symptoms.

The NCICAS intervention, through a collaboration with the Centers for Disease Control and Prevention, is being implemented in 23 inner-city health care delivery sites throughout the country, and will reach approximately 6,000 children. NIAID-funded researchers have translated the asthma risk assessment tool developed for the NCICAS into a form suitable for use by community health organizations. A key element of the intervention is the Child Asthma Risk Assessment Tool (CARAT), an instrument that enables caregivers to systematically analyze the asthma risks for a child and to develop an intervention strategy based on the risk profile. In FY 2003, NIAID plans widespread distribution of the CARAT as well as a link to a repository of information related to the NCICAS asthma intervention on the NIAID web site (<http://www.niaid.nih.gov/default.htm>). This will enable caregivers of children with asthma, as well as voluntary health organizations, to develop individually tailored educational, behavioral, and environmental interventions that complement traditional medication-based asthma management strategies.

Understanding the immune mechanisms that cause and exacerbate asthma, including the role of viral and bacterial infections, is a high priority for NIAID. For example, two of the 13 currently funded NIAID *Asthma and Allergic Diseases Research Centers* (AADRCs) focus exclusively on the role of viral infections in asthma development, progression, and severity. Four other centers include projects to examine the cellular and molecular mechanisms underlying the association between asthma and infections. In FY 2003, NIAID will re-compete the *Asthma and Allergic Diseases Research Centers* program to advance insights into the pathobiology of asthma, including the role of viral and bacterial infections. In addition, in FY 2004, NIAID will launch a new program, *Immune System Development and the Genesis of Asthma*. The mechanisms underlying the effects of bacteria and viruses on the developing immune system will be an important focus of the program.

#### Item

**Eye Diseases** — The Committee encourages the Institute to collaborate with the NEI on research involving eye-related viruses and infectious diseases. (p. 117)

#### Action to be taken

The study of eye-related viruses and infectious diseases continues to be a priority for the National Institute of Allergy and Infectious Diseases (NIAID). Infections of the eye remain a major cause of blindness around the globe. For example, trachoma, caused by the organism *Chlamydia trachomatis*, is the most common cause of preventable blindness and affects millions of people worldwide. To address this issue, NIAID researchers are working on the development of a

vaccine against trachoma and have made progress in understanding immunity against *Chlamydia* infection in animal models.

NIAID continues to collaborate with the National Eye Institute (NEI) on studies that address infectious eye diseases. For example, NIAID and NEI intramural researchers are collaborating on studies of Human Immunodeficiency Virus (HIV)-infected persons with cytomegalovirus retinitis. Observations from this research have contributed to the 2002 U.S. Public Health Service/Infectious Disease Society of America *Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus*. In addition, researchers of the NIAID *Adult AIDS Clinical Trials Group* work closely with investigators in the NEI-supported *Studies of Ocular Complications of AIDS* on HIV-related eye disease.

#### Item

**Food Allergy** — An estimated 7 million individuals suffer from food allergies in the United States, with up to 6 percent of all children under the age of three experiencing these potentially life-threatening allergies. The Committee urges the NIAID to implement a program to stimulate more research in this area. (p. 117)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID), through its extra- and intramural programs, remains committed to improving the diagnosis, treatment, and prevention of food allergies. For example, in FY 2003, NIAID will re-compete its *Asthma and Allergic Diseases Research Centers Program*. This long-standing program supports both basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases, including food allergies.

Additional NIAID-supported research to address food allergies focuses on: gaining a better understanding of safe and effective methods to block allergic responses to food; developing mouse models to study immune responses to allergens and to determine if novel agents will block the allergic response to food; and human studies of immune tolerance induction approaches and of the effectiveness of oral administration of allergens to induce tolerance for food allergies. The *Immune Tolerance Network* (ITN), an NIAID-established international consortium dedicated to the clinical evaluation of novel immune tolerance-inducing therapies, also is conducting research designed to block the allergic response. If these ITN-supported clinical trials show promise, they may be extended to test the effectiveness of this approach for the treatment of food allergies. Furthermore, NIAID recently participated in two conferences, organized by the Environmental Protection Agency, to identify approaches to determine the risk of allergic reactions associated with the ingestion of bioengineered foods.

Eosinophilic gastroenteritis is an inflammatory disease of the gut that is often associated with multiple severe food allergies. As such, it is a valuable model being used by NIAID intramural scientists to examine the immunological responses to food allergens. For example, NIAID researchers are completing a Phase I/II study of a monoclonal antibody as a therapy for eosinophilic gastroenteritis. In addition to providing data on therapeutic potential, it is expected that this study will yield insight into the inflammatory mechanisms present in food allergy.

In FY 2003, NIAID will convene a panel of experts to identify key knowledge gaps and opportunities for research to prevent and reduce the severity of food allergies. In addition, NIAID intramural researchers will continue their efforts to understand how immunomodulatory therapies work and can be applied to the prevention and treatment of food allergies.

#### Item

**Hemophilia** — The Committee supports the NIAID's efforts to ensure access for persons with

hemophilia to clinical trials for improving treatment of HIV and complications of hemophilia, including hepatitis C (HCV). The Committee, in particular, is encouraged by the NIAID's leadership in supporting research related to liver disease progression and response to HCV treatment among HIV/HCV co-infected persons with hemophilia, and it urges the Institute to continue its efforts in this area. (p. 117)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) encourages the participation of people with hemophilia in its extra- and intramural research studies, including clinical trials for Human Immunodeficiency Virus (HIV) infection and its sequelae. For example, NIAID has worked with the National Hemophilia Foundation (NHF) to promote the inclusion of hemophiliacs infected with HIV in clinical trials through the NIAID *Adult AIDS Clinical Trials Group* and the NIAID *Pediatric AIDS Clinical Trials Group*.

NIAID remains committed to supporting research targeted to the HIV-infected hemophiliac population, including research on co-infection with hepatitis C virus (HCV). To this end, in FY 2003, the Institute will continue funding research to examine liver disease progression and its relationship to HCV genomic variability in HIV-infected hemophiliacs.

#### Item

**Hepatitis C** — The Committee encourages the NIAID to support the virology and immunology portions of the NIDDK's HALT-C clinical trial. The HALT-C trial is a multi-center, randomized, controlled study designed to determine if using interferon over several years will suppress the hepatitis C virus, prevent progression to cirrhosis, prevent liver cancer, and reduce the need for liver transplantation. In addition, the Committee understands that limited clinical trials in Europe have partially validated the premise that the most effective way to eliminate the hepatitis C virus is to initiate an aggressive treatment at the inception of the virus. The Institute is encouraged to collaborate with the NIDDK and the Centers for Disease Control and Prevention to establish and validate treatment guidelines for use with individuals with acute hepatitis C at its inception. (p. 118)

#### Action to be taken

Research to address the diagnosis, prevention, and treatment of hepatitis C virus (HCV) remains a high priority for the National Institute of Allergy and Infectious Diseases (NIAID). NIAID has co-sponsored the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) *Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial* since its inception in FY 2000, and will continue this support in FY 2003. NIAID-supported research in this trial will focus on understanding the virological and immunological responses to HCV infection and how they affect recovery and disease progression.

NIAID actively collaborates with other National Institutes of Health (NIH) Institutes, Centers and Offices in planning and conducting HCV-related research. For example, in June 2002, NIAID joined NIDDK, the NIH Office of Medical Applications of Research, and other NIH Institutes and Centers in sponsoring the second NIH Consensus Development Conference on the Management of Hepatitis C. This conference was also co-sponsored by the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Department of Veterans Affairs. The consensus development conference examined the current state of knowledge regarding the treatment and management of HCV infection and identified directions for future research. In FY 2003, NIAID plans to co-sponsor a new NIDDK research program, *Hepatitis C: Natural History, Pathogenesis, Therapy, and Prevention*. This initiative is intended to identify the mechanisms responsible for the acute and chronic injury caused by HCV, define the factors that determine the course and long-term outcome of chronic infection, and establish the basis for resistance to current therapeutic regimens.

NIAID intramural research also focuses on the immunology and biology of HCV. One goal of this work is to determine the factors that contribute to disease variability and severity. For example, because genetic differences in the virus are believed to play an important role in the pathogenicity of this virus, NIAID scientists are studying viral gene changes in recently infected individuals as well as those on interferon therapy. These studies of individuals with recent HCV infection have revealed that certain viral gene patterns observed early in infection are predictive of the outcomes of HCV infection. In addition, patients with chronic HCV infection who received interferon therapy exhibited distinct viral gene patterns that allowed researchers to categorize them into groups based on their response to therapy. These findings may be useful in predicting the outcome of interferon therapy early in the course of treatment and in formulating treatment guidelines for HCV infection.

NIAID also supports the *Hepatitis C Cooperative Research Centers Program* to design and conduct clinical studies in special populations disproportionately affected by HCV, such as African Americans, with the goal of increasing understanding of how HCV infection progresses. This research could lead to new and improved diagnostics, vaccines, and therapies. In addition, the Institute currently is supporting a Phase I clinical trial to study the safety of a polyclonal antibody that may prevent HCV reinfection following liver transplant. Through the *Adult AIDS Clinical Trials Group* and the *Pediatric AIDS Clinical Trials Group*, NIAID also supports clinical studies in populations co-infected with Human Immunodeficiency Virus (HIV) and HCV to evaluate the interactions of HCV and HIV diseases and evaluate treatments for HCV.

Recently, NIAID-supported researchers have published promising results regarding HCV. Reports suggest that when chimpanzees were vaccinated with a DNA vaccine, viral persistence and the severity of subsequent HCV infection were diminished. Based on this observation, a team of NIAID investigators demonstrated, by screening the blood of injection drug users, that patients previously infected with HCV were less susceptible to new infections than those who had never been infected. This suggests that humans can acquire immunity against HCV and that vaccines could be a viable approach to reducing HCV-associated liver disease. In addition, NIAID-supported researchers are studying the earliest phases of HCV infection and the wide variation in immune response in a group of health care workers following accidental needlestick exposure. This research is providing new insights into how the immune system clears HCV infection and how the virus may become persistent in chronic carriers.

#### Item

***Inflammatory Bowel Disease*** — The Committee continues to note with interest a scientific research agenda for Crohn’s disease and ulcerative colitis (collectively known as inflammatory bowel disease) titled “Challenges to Inflammatory Bowel Disease (IBD).” This report identifies strong linkages between the functions of the immune system and IBD. The Committee is aware of the NIAID’s research partnerships with the IBD community, and it encourages the Institute to expand 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. 118)

#### 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, in FY 2002, NIAID established a new research program, *Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection*” Research projects supported under this program will identify and validate the role of pathogens in chronic diseases, with several studies addressing IBD. Also, in FY 2002, the Institute established a new program, the *Pathogen Functional Genomics Center Resource*, to support the genetic characterization of organisms responsible for disease in humans, including *Helicobacter pylori*, which has been linked to the development of

IBD. Knowledge gained from this program will facilitate the development of improved diagnostics, vaccines, and treatments for IBD.

NIAID intramural researchers continue their investigations of IBD, including both basic studies of the immunology of IBD as well as clinical studies of the safety and efficacy of new immune-based therapies for Crohn's Disease and ulcerative colitis. Furthermore, NIAID scientists are conducting research on the effects of these new therapies on the immune system. This research may reveal targets for novel therapeutics. For example, NIAID scientists recently completed a study of an immune-based therapy, anti-interleukin-12 antibody, in patients with Crohn's disease and are preparing to analyze and report the results.

Additional NIAID research focuses on identifying the genetic and immune-modulated factors that may contribute to the development of IBD. For example, the NIAID *Multiple Autoimmune Diseases Genetics Consortium* (MADGC) serves as a repository of genetic and clinical data and specimens from families affected by more than one distinct autoimmune disease. The MADGC, which will be renewed in FY 2004, provides researchers with specimens, such as DNA and cell samples, to aid in the identification of the genes involved in the development of IBD and other autoimmune diseases. In addition, in FYs 2003 and 2004, NIAID plans to renew and expand, respectively, the *Autoimmunity Centers of Excellence* (ACEs), in cooperation with the National Institute of Diabetes and Digestive and Kidney Disorders, the National Institute of Arthritis and Musculoskeletal and Skin Disorders, and the National Institutes of Health Office of Research on Women's Health. Emphasizing a multidisciplinary approach, the ACEs facilitate collaborative basic and clinical studies of multiple autoimmune diseases, including both single and multiple site pilot clinical trials of immunomodulatory therapies, including those for IBD.

NIAID continues to expand its IBD research agenda to include studies of the environmental factors and infectious agents that may be associated with the various forms of IBD, including Crohn's disease and ulcerative colitis. For example, in FY 2002, NIAID funded research to identify microbial agents, such as *Mycobacterium paratuberculosis* (Map), which may be involved in the development of IBD. In addition, the NIAID Enteric Pathogens Research Unit contract supports tissue acquisition from both IBD patients and healthy individuals. Researchers are culturing these tissues and identifying the microbial agents that are present. The Enteric Pathogens Research Unit will be expanded and re-competed in FY 2003 under the title, *Food and Waterborne Diseases Integrated Research Network*. The Network will support integrated research programs to develop products to identify, prevent, and treat food- and waterborne diseases, including investigations of the potential transmission of Map from animals to humans.

#### Item

**Juvenile Diabetes** — The Committee is aware that the Immune Tolerance Network is investigating methods to create and maintain tolerance to transplanted insulin-producing islet cells in recipients with juvenile diabetes. The Committee understands that the goal of this investigation is to eliminate the need for patients to undergo long-term immunosuppressive therapy after transplantation. The Committee encourages the NIAID to continue and expand this area of research, including developing additional protocols focused on islet cell transplantation into individuals with juvenile diabetes. (p. 118)

#### 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 juvenile diabetes. Two major NIAID clinical research programs have been established to evaluate the safety and efficacy of promising immune-based therapeutic approaches for many immune-mediated diseases, including type 1 diabetes. Through the NIAID *Autoimmunity Centers of Excellence* (ACE), a research program cosponsored by the National Institute of Diabetes and Digestive and

Kidney Diseases (NIDDK), the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), multiple sites are conducting pilot clinical trials to test novel strategies for the treatment of juvenile diabetes. For example, a recently completed ACE pilot study of patients with new-onset type 1 diabetes tested whether a certain antibody would be effective in blocking the harmful action of T cells, the white blood cells involved in the destruction of pancreatic islet cells. Administering a two-week course of this immunotherapy slowed the destructive process that causes the deterioration of insulin production, with the effects still evident one year later. In light of these promising results, a larger, multicenter, Phase II clinical trial, involving 80 patients, is being conducted. NIAID will renew and expand in FYs 2003 and 2004, respectively, the ACE program, to continue basic, preclinical, translational, and clinical studies to identify and test novel immune therapies for multiple autoimmune diseases.

The second major NIAID clinical research program, the *Immune Tolerance Network* (ITN), is an NIAID-established international, collaborative research consortium co-sponsored by the NIDDK and the Juvenile Diabetes Research Foundation International (JDRFI). The ITN focuses on the design, clinical development, and evaluation of novel immune tolerance-inducing therapies for multiple immune-mediated disorders, including autoimmune diseases such as type 1 diabetes. A key ITN research goal with respect to transplanted pancreatic islets is to selectively block the immune responses that lead to the destruction of transplanted islet cells while maintaining a competent immune system capable of preserving immunity against infectious agents.

Currently, the ITN is conducting an experimental islet cell transplantation protocol for type 1 diabetes, developed by researchers at the University of Alberta in Edmonton, Canada, and known as the "Edmonton Protocol." The ITN trial is assessing the safety and efficacy of this treatment regimen as well as expanding the capacity for islet cell preparation and clinical transplantation at nine sites in the United States, Canada, and Europe. Results of this international multicenter trial will establish the baseline success rate for islet cell transplantation and facilitate the development of new ITN-supported islet cell transplant trials designed to direct the immune response more selectively. In FY 2003, the ITN plans to initiate enrollment in two clinical studies to evaluate the potential for specific antibodies to induce tolerance to transplanted islet cells.

NIAID actively continues its collaborations with other NIH Institutes, Offices, and Centers (ICs) to promote type 1 diabetes research. For example, NIAID, NIDDK, and the National Institute of Child Health and Human Development (NICHD) co-sponsor the *Type 1 Diabetes TrialNet*, a consortium of clinical centers and core support facilities to enable rapid and efficient testing of additional promising new strategies, including vaccines, to prevent type 1 diabetes or to delay disease progression. The ITN and TrialNet jointly will conduct studies to evaluate new regimens to induce immune tolerance to transplanted pancreatic islet cells. Also, in FY 2002, NIAID and NIDDK renewed and expanded the ongoing *Non-Human Primate Immune Tolerance Cooperative Study Group* to continue studies of promising approaches for the induction of immune tolerance in clinically relevant large animal models. To date, investigators have demonstrated long-term graft acceptance in both kidney and islet transplantation in these animal models. Based on the outcome of these studies, the ITN and TrialNet may evaluate immune tolerance induction approaches deemed promising in human trials.

NIAID, in collaboration with other NIH ICs, continues to support several other large, multidisciplinary programs to address type 1 diabetes. For example, under the program *Innovative Grants on Immune Tolerance*, established in FY 2000, NIAID, NIDDK, and the National Heart, Lung, and Blood Institute (NHLBI) support novel research on the mechanisms underlying immune response and the development of approaches to block or eliminate, selectively, the body's harmful immune responses. These studies could significantly increase the understanding of the mechanisms that induce long-lived immune tolerance, leading to new treatment and prevention strategies for human immune-mediated diseases. In FY 2004, NIAID

plans to renew the Innovative Grants on Immune Tolerance program. In addition, in FY 2001, NIAID, NIDDK, NICHD, ORWH, and JDRFI established the *Centers for Prevention of Autoimmune Diseases* to conduct basic research on the development of new targets and approaches to prevent autoimmune diseases and to evaluate these novel approaches in pilot clinical studies. Type 1 diabetes is a major focus of this research program. NIAID, in conjunction with several other ICs and the JDRFI, also supports the *International Histocompatibility Working Group* to identify the variations in immune response genes that may account for the increased susceptibility of certain individuals to immune-mediated diseases including juvenile diabetes.

NIAID collaborates closely with NIDDK to co-sponsor a variety of type 1 diabetes research programs. For example, the programs *Gene Therapy Approaches for Diabetes and its Complications*, which is also supported by NHLBI, and *Gene Transfer Approaches to Enhance Islet Transplantation* support research on the development of novel gene therapy approaches for the treatment of type 1 diabetes. Other programs foster collaborations between researchers, including the *Innovative Partnerships in Type 1 Diabetes Research* program, which supports interdisciplinary collaborations between type 1 diabetes researchers and researchers with expertise in other fields to provide valuable insight into type 1 diabetes. In addition, the *Bench to Bedside Research on Type 1 Diabetes and its Complications* program supports partnerships between basic and clinical biomedical researchers to translate advances in understanding the molecular basis of type 1 diabetes into new therapies. The *Consortium for Identification of Environmental Triggers of Type 1 Diabetes* supports research to identify infectious agents, dietary factors, or other environmental agents that are associated with increased risk of type 1 diabetes when the onset of diabetes occurs at a very early age.

#### Item

**Primary Immune Deficiency Diseases** — The Committee also understands that the NIAID intends to establish a cooperative consortium of investigators to address clinical and pre-clinical research questions on PI, including the molecular and cellular characterization of patients with novel phenotypes, and the development of new models, novel diagnostics, and new treatment approaches, such as gene therapy. The Committee urges the NIAID to move ahead aggressively with this initiative. In addition, the Committee would like to see the NIAID's current research project that is testing a new screening method for underserved populations replicated in other urban centers. Finally, the Committee continues to support greater involvement by the NIAID in the Jeffrey Modell Foundation's national campaign for physician education and public awareness of these diseases. (p. 118)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID), through its extra- and intramural programs, remains committed to the study of primary immunodeficiency diseases. For example, the NIAID Laboratory of Host Defenses conducts a wide range of research on primary immunodeficiencies, including chronic granulomatous disease, severe combined immune deficiency (SCID), and leukocyte adhesion deficiency. This research includes clinical studies of novel gene therapies, such as lentivirus vectors.

In July 2002, NIAID issued a new Request for Proposals to establish a *Primary Immunodeficiency Diseases Consortium*, in collaboration with the National Institute of Child Health and Human Development (NICHD). The Consortium is designed to advance understanding of primary immunodeficiency diseases by providing scientific leadership and mentoring, facilitating collaborations, and coordinating research efforts. The Consortium will solicit and make awards for pilot or small research projects to investigate these diseases and will establish and maintain a primary immunodeficiency disease registry. This registry will provide

data to the research community about the clinical characteristics and prevalence of these diseases, as well as information to patients about approved research studies. Awards for the program are anticipated in FY 2003.

About 500,000 Americans are afflicted with primary immunodeficiencies and it is estimated that another 500,000 may remain undiagnosed. In FY 2000, the NIAID, in collaboration with NICHD and the National Cancer Institute, began a project at the Mount Sinai School of Medicine and the Metropolitan Hospital in New York to determine, using a new screening method, if the occurrence of primary immunodeficiencies in medically underserved minority populations is underdiagnosed. The results from this study are being analyzed to determine the effectiveness of the screening method and to develop approaches to expand the study to other urban centers.

In addition to conducting and supporting research on primary immunodeficiency diseases, the Institute works in partnership with organizations, such as the Jeffrey Modell Foundation (JMF) and the Immune Deficiency Foundation, to increase awareness and educate the public and medical professionals about these rare diseases. For example, NIAID has developed informational booklets about primary immune deficiency diseases, such as chronic granulomatous disease, for distribution to patients and their families and to physicians. In addition, NIAID clinicians give lectures to the clinical community about primary immunodeficiencies and participate in scientific meetings and conferences, some of which are supported by the JMF. NIAID will continue to meet and collaborate with organizations with an interest in primary immunodeficiency diseases to promote physician education and public awareness.

#### Item

***Temporomandibular Joint Disorders*** — The Committee urges NIAID to incorporate the autoimmune and inflammatory processes involved in temporomandibular diseases and disorders into its research portfolio. The collection of tissue samples from TMJ patients and people without TMJ disease has been suggested as part of a patient registry, to determine whether inflammatory mediators, growth factors, cytokines and other cell and molecular factors affecting immunity may differ between people with and without TMJ disease. (p. 119)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad range of investigator-initiated basic and clinical research that focuses on the molecular and cellular processes of inflammation. In addition, NIAID-supported researchers study the interactions of the neural and immune systems in health and disease. While the etiology and natural course of temporomandibular joint disorders (TMJ) remain unclear, an understanding of these processes and systems may provide insight into the inflammation and pain associated with TMJ disorders.

NIAID continues to participate in the Temporomandibular Joint Disorders Interagency Working Group (TJDIWG), led by the National Institute of Dental and Craniofacial Research. The TJDIWG facilitates communication and collaboration among the National Institute of Neurological Disorders and Stroke; National Institute of Nursing Research; National Institute of Arthritis and Musculoskeletal and Skin Diseases; National Heart, Lung, and Blood Institute; and the National Institutes of Health Office of Research on Women's Health, as well as the Agency for Health Care Research and Quality, the U.S. Food and Drug Administration, and the Centers for Disease Control and Prevention.

#### Item

***Transplantation*** — The Committee is aware of the wide gap between the supply of and demand

for transplanted organs. The Institute is encouraged to expand research on organ transplantation, including the development of artificial organs, hepatocyte transplantation, xenotransplantation, live-donor liver transplantation, split liver transplantation, and other research focuses as appropriate. (p. 119)

#### Action to be taken

Despite the successes of transplantation, immune-mediated graft rejection and the critical shortage of donor organs remain important concerns for the millions of Americans who suffer from illnesses such as kidney failure, liver disease, coronary heart disease, and end-stage lung disease. 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. NIAID does not support research on the development of artificial organs, hepatocyte transplantation, and split liver transplantation.

To address the problem of graft rejection, NIAID supports a broad range of basic and pre-clinical research on immunology and tolerance induction, including approaches to selectively block or eliminate harmful immune responses while maintaining an immune system that can fight off infection. In addition, the Institute supports clinical research to evaluate promising new therapies to improve long-term graft survival. For example, NIAID-supported investigators have developed new methods for stopping certain cells from eliciting harmful immune responses in mouse models of bone marrow transplantation. These findings could lead to the development of strategies to prevent lethal graft-versus-host disease in bone marrow transplant recipients. In addition, NIAID extramural researchers are developing new diagnostic methods to improve the matching of donors and recipients. For instance, they have compared methods of tissue typing for bone marrow transplantation and demonstrated that DNA-based typing is more effective than the more commonly used antibody-based method. These results may lead to significant improvements in the number of successful bone marrow transplants. Also, NIAID intramural scientists are continuing their efforts to understand the role that genetic factors play in the immune response during kidney transplantation. With this knowledge, novel approaches to improve transplant outcomes will be possible.

Examples of NIAID support for clinical research on solid organ, tissue, and cell transplantation include the *Cooperative Clinical Trials in Pediatric Kidney Transplantation* (CCTPT) program, established in 1994, to conduct multicenter clinical trials in pediatric kidney transplant recipients to evaluate: (1) novel approaches to prevent acute and chronic graft rejection; (2) modifications of immunosuppressive drug regimens to mitigate unwanted side effects, such as growth retardation; and (3) pre-transplant immunotherapy to improve the medical status of patients who are on the kidney transplant waiting list. In FY 2003, the CCTPT will initiate a clinical trial to investigate whether treatment with intravenous immunoglobulin, a drug used to boost the immune system, can improve long-term graft acceptance in certain pediatric kidney transplant candidates. Also, the *Immune Tolerance Network* (ITN), an NIAID-established international consortium of approximately 80 basic and clinical researchers at over 40 institutions around the world, is conducting clinical trials on a novel immunosuppressive therapy in live-donor kidney transplantation as well as mechanistic studies of long-term liver transplant recipients. NIAID will continue to solicit proposals for ITN transplantation clinical trials in FY 2003.

NIAID supports a number of research projects focusing on the immune response to xenotransplanted organs. In addition, the Institute funds research to develop methods for the rapid identification and treatment of infectious diseases that are spread across species barriers.

NIAID also represents the National Institutes of Health (NIH) on the Secretary's Advisory Committee on Xenotransplantation (SACX). The SACX, chartered in July 1999, addresses the full range of complex scientific, medical, social, and ethical issues and the public health concerns raised by xenotransplantation, including ongoing and proposed protocols, and makes recommendations to the Secretary on policy and procedures. The recommendations of the Committee facilitate the efforts of the Department of Health and Human Services to develop an integrated approach to addressing emerging public health issues in xenotransplantation.

NIAID actively collaborates with other NIH Institutes, Centers, and Offices to further transplantation research. For example, in FY 2002, under the NIAID and National Institute of Diabetes and Digestive and Kidney Disorders research program, *Gene Transfer Approaches to Enhance Islet Transplantation*, NIAID made several new awards to explore the use and feasibility of this new technology for genetic modification of islet cells to enhance engraftment and graft survival. Also, in FY 2003, NIAID and the Office of Laboratory Animal Welfare will sponsor a *Non-Human Primate Transplantation Techniques Workshop* for investigators who conduct non-human primate transplantation research. The workshop will address transplantation techniques and other issues regarding this specialized pre-clinical research area. In collaboration with the National Center for Minority Health and Health Disparities, NIAID also will continue to support demonstration and education research projects to increase minority participation in organ donor registries, including the Legacy Donor Registry in Louisiana and the Minority Community Outreach on Organ Donation and Transplantation at the Hope Heart Institute in Washington.

In FY 2004, NIAID will launch the *Clinical Trials in Organ Transplantation* program, a new multicenter initiative to evaluate novel therapies for preventing graft rejection and prolonging transplant graft survival in kidney, liver, and heart transplantation. In addition, in FY 2004, the Institute will establish the *Genomics of Transplantation* program to identify genetic factors that play a role in responsiveness to immunosuppressive therapies, graft survival and rejection, and immune responses during transplant rejection.

#### Item

***Tuberculosis*** —Tuberculosis continues to account for more deaths worldwide than any other infectious disease and for over a quarter of all preventable adult deaths. The Committee commends the NIAID for its aggressive program of tuberculosis research, and it encourages a greater emphasis on the development of a vaccine, as noted by the NIAID's "Blueprint for Tuberculosis Vaccine Development." (p. 119)

#### Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains deeply committed to the development of diagnostics, therapeutics, and vaccines for tuberculosis (TB). NIAID continues to follow the strategy outlined in the *Blueprint for Tuberculosis Vaccine Development* by supporting programs such as *TB Vaccine Testing and Research Materials* and the *Tuberculosis Research Unit* (TBRU). These contracts facilitate the translation of basic research into vaccines and therapeutics by providing researchers around the world with valuable resources. *TB Vaccine Testing and Research Materials*, which will be re-competed in FY 2004, provides investigators with research materials and supports the screening of vaccine candidates in animal models. The TBRU conducts clinical trials of new TB diagnostic, therapeutic, and preventive strategies and serves as a repository for clinical samples that are distributed to researchers.

NIAID invests heavily in basic research on TB, with the belief that this research will yield the knowledge to develop better diagnostics, therapeutics, and vaccines. This investment is already producing new vaccine and drug candidates. For example, the NIAID *Vaccine Treatment and Evaluation Units* (VTEU) will soon conduct clinical trials of a new TB vaccine, which was developed with NIAID support. Also, NIAID-supported researchers have recently gained valuable

insight into how the cells of the immune system fight infection by *Mycobacterium tuberculosis* (Mtb), the bacterium that causes TB. These findings may facilitate the development of more successful vaccines against Mtb and may lead to a better understanding of why patients with AIDS develop TB more rapidly than healthy individuals. Other investigators supported by NIAID are sequencing the genome of *Mycobacterium smegmatis*, a bacterium similar to Mtb that is a useful model for laboratory studies. In FY 2003, NIAID will expand its basic TB research portfolio with new programs such as *New Animal Models for TB and Invasive Aspergillus (IA) – Post Genomic Research*, which supports the development of new animal models to study the pathogenesis of TB and to identify novel targets for diagnostics, therapeutics, and vaccines.

The NIAID intramural research program also conducts a wide range of basic research to address TB. Intramural investigators are studying the mechanisms by which Mtb causes disease as well as the mechanisms by which Mtb lays dormant in the host (latency). NIAID scientists also are examining how humans and other animal hosts defend themselves against Mtb infection. In addition, NIAID investigators are studying the DNA of Mtb isolated from thousands of TB patients with different manifestations of the disease, i.e., in and outside the lungs. This information will be useful in determining if different Mtb genes are involved in the different forms of the disease.

NIAID sponsors a broad range of programs to translate basic research into clinical strategies. In FY 2002, the NIAID *Millennium Vaccine Initiative – Novel Vaccines for Tuberculosis and Malaria* facilitated the development of new vaccines in developing countries by increasing collaboration between industry and the public sector. The NIAID *International Collaborations in Infectious Disease Research* program supports the development and testing of new diagnostic methods in international settings where TB is endemic. The NIAID-supported *Tuberculosis Antimicrobial Acquisition and Coordinating Facility* (TAACF) collects and maintains a database of novel antimicrobial agents against TB. The candidate therapeutics from TAACF are then tested for ability to inhibit Mtb growth through the NIAID *Tuberculosis Drug Screening* contract. Also, the NIAID *National Cooperative Drug Discovery Groups for TB* program, which will be renewed in FY 2004, supports the development of novel antimicrobial agents against TB at five sites across the United States. In addition, NIAID continues to support the Small Business Innovative Research (SBIR) and Challenge Grant programs to develop, through collaborations with industry, new TB diagnostics, therapeutics, and vaccines. Also, NIAID intramural investigators continue to develop novel antimicrobial agents against Mtb and study the mechanisms by which current TB therapeutics cure Mtb infection.

NIAID continues its collaborations with other National Institutes of Health (NIH) Institutes to improve the understanding of basic TB biology. In FY 2002, NIAID co-sponsored with the National Heart, Lung, and Blood Institute (NHLBI) the *Response to the Presidential Vaccine Initiative – Overcoming the Tuberculosis Latency Challenge* program to examine the mechanisms underlying persistent, asymptomatic TB infection. NIAID also co-sponsored the NHLBI program *Genetic Aspects of Tuberculosis in the Lung* to stimulate genetic research on TB using new technologies. In addition, NIAID partnered with the National Institute of General Medical Sciences to establish and support the *Mtb Structural Genomics Consortium*, a global consortium of 128 laboratories in 12 countries to determine and analyze the structures of Mtb proteins. The partnership has thus far succeeded in solving the structures of 20 Mtb proteins. This information will be useful in the development of vaccines and therapeutics.

In addition to its trans-NIH collaborations, NIAID endeavors to foster scientific communication and collaboration at the international level. NIAID program staff serves as consultants and liaisons to international TB groups and coordinates international scientific meetings on TB. For example, NIAID was the Secretariat and co-sponsor of the 4<sup>th</sup> World Congress on Tuberculosis held in Washington, DC, in June 2002.

**NATIONAL INSTITUTES OF HEALTH  
National Institute of Allergy and Infectious Diseases**

**Authorizing Legislation**

	PHS Act/ Other Citation	U.S. Code Citation	2003 Amount Authorized	2003 Amended President's Budget	2004 Amount Authorized	2004 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
Infectious Diseases	Section 41B	42§285	Indefinite	\$3,928,854,000	Indefinite	\$4,278,619,000
National Research Service Awards	Section 487(d)	42§288	a/	52,246,000	b/	56,636,000
<b>Total, Budget Authority</b>				<b>\$3,981,100,000</b>		<b>\$4,335,255,000</b>

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

b/ Reauthorizing legislation will be submitted.

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**Appropriations History**

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation <sup>1/</sup>
1995	<sup>2/</sup> \$542,864,000	\$535,847,000	\$535,847,000	\$535,847,000 <sup>3/</sup>
Rescission				(648,000)
1996	557,354,000 <sup>2/</sup>	1,169,628,000	549,246,000 <sup>3/</sup>	1,169,628,000
Rescission				(676,000)
1997	584,362,000 <sup>2/</sup>	1,256,149,000	595,016,000 <sup>3/</sup>	1,257,794,000 <sup>4/</sup>
1998	634,272,000 <sup>2/</sup>	1,339,459,000	1,359,688,000	1,351,655,000
1999	703,723,000 <sup>2/5/</sup>	1,470,460,000	1,540,102,000	1,570,102,000
Rescission				(1,039,000)
2000	789,156,000 <u><sup>2/</sup></u>	1,714,705,000	1,786,718,000	1,803,063,000
Rescission				(5,025,000)
2001	935,166,000 <sup>2/</sup>	2,062,126,000	2,066,526,000	2,069,388,000
Rescission				(1,084,000)
2002	2,355,325,000	2,337,204,000	2,375,836,000	2,535,778,000
Rescission				(1,239,000)
2003	3,983,693,000			
2004	4,335,255,000			

<sup>1/</sup> Reflects enacted supplementals, rescissions, and reappropriations.

**NATIONAL INSTITUTES OF HEALTH**  
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**Detail of Full-Time Equivalent Employment (FTEs)**

OFFICE/DIVISION	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
Office of the Director	181	239	294
Division of Allergy, Immunology, and Transplantation	37	55	70
Division of Microbiology and Infectious Diseases	73	160	177
Division of Extramural Activities	112	167	180
Division of Acquired Immunodeficiency Syndrome	107	130	130
Division of Intramural Research	726	735	735
<b>Total</b>	<b>1,236</b>	<b>1,486</b>	<b>1,586</b>
FTEs supported by funds from Cooperative Research and Development Agreements	(1)	(1)	(1)
FISCAL YEAR	Average GM/GS Grade		
2000	10.9		
2001	10.8		
2002	10.9		
2003	10.9		
2004	10.9		

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**Detail of Positions**

GRADE	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
ES-6	0	0	0
ES-5	0	0	0
ES-4	0	0	0
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	0	0	0
Total - ES Salary	\$0	\$0	\$0
GM/GS-15	59	69	71
GM/GS-14	136	160	169
GM/GS-13	135	159	177
GS-12	160	188	211
GS-11	138	162	168
GS-10	3	4	4
GS-9	87	103	111
GS-8	52	61	66
GS-7	76	89	100
GS-6	51	60	66
GS-5	13	16	19
GS-4	13	15	18
GS-3	6	7	7
GS-2	7	8	8
GS-1	4	5	5
Subtotal	940	1,106	1,200
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	20	20	20
Senior Grade	13	13	13
Full Grade	10	10	10
Senior Assistant Grade	1	1	1
Assistant Grade	1	1	1
Subtotal	46	46	46
Ungraded	362	426	455
Total permanent positions	966	1,137	1,213
Total positions, end of year	1,348	1,586	1,693
Total full-time equivalent (FTE) employment, end of year	1,263	1,486	1,586
Average ES level			
Average ES salary			
Average GM/GS grade	10.9	10.9	10.9
Average GM/GS salary	\$62,337	\$64,269	\$65,555

**NATIONAL INSTITUTES OF HEALTH**  
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**New Positions Requested**

	FY 2004		
	Grade	Number	Annual Salary
ADMINISTRATIVE ASSISTANT	7	2	37,420
ADMINISTRATIVE OFFICER	13	1	78,936
ADMINISTRATIVE OFFICER	12	1	66,380
CONTRACT SPECIALIST	13	2	78,936
CONTRACT SPECIALIST	12	5	66,380
CONTRACT SPECIALIST	11	2	55,386
CONTRACT SPECIALIST	9	1	45,774
GRANTS FINANCIAL ANALYST	12	1	66,380
GRANTS MANAGEMENT SPEC	9	2	45,774
GRANTS MANAGEMENT SPEC	11	3	55,386
GRANTS MANAGEMENT SPEC	12	5	66,380
GRANTS MANAGEMENT SPEC	13	2	78,936
GRANTS MANAGEMENT SPEC	14	1	93,279
GRANTS TECHNICAL ASST. (OA)	6	1	33,674
GRANTS TECHNICAL ASST. (OA)	7	2	37,420
HEALTH SCIENCE ADMINISTRATOR	AD	3	93,279
HEALTH SCIENCE ADMINISTRATOR	15	1	109,720
HEALTH SCIENCE ADMINISTRATOR	14	3	93,279
HEALTH SCIENCE ADMINISTRATOR	13	5	78,936
HEALTH SCIENCE ADMINISTRATOR	12	3	66,380
HEALTH SCIENCE ADMINISTRATOR	6	2	33,674
MATHEMATICAL STATISTICIAN	13	2	78,936
MEDICAL OFFICER	AD	3	93,279
MEDICAL OFFICER	15	1	109,720
MEDICAL OFFICER	14	1	93,279
MEDICAL OFFICER	13	1	78,936
OFFICE AUTOMATION CLERK	4	3	26,999
OPERATIONS RES. ANALYST	14	1	93,279
OPERATIONS RES. ANALYST	12	1	66,380
PROCUREMENT TECHNICIAN	8	1	41,443
PROGRAM ANALYST	14	1	93,279
PROGRAM ANALYST	13	2	78,936
PROGRAM ANALYST	12	2	66,380
PROGRAM ANALYST	11	1	55,386
PROGRAM ANALYST	9	1	45,774
PROGRAM ANALYST	7	1	37,420
PROGRAM MANAGEMENT OFFICER	13	1	78,936
PROGRAM MANAGEMENT OFFICER	14	1	93,279
PURCHASING TECHNICIAN	9	2	45,774
PURCHASING TECHNICIAN	7	2	37,420
RESEARCH ASSOCIATE	14	1	93,279
RESEARCH ANALYST	13	1	78,936
RESEARCH ANALYST	12	1	66,380
RECORDS MGMT. TECH (OA)	8	2	41,443
SECRETARY	9	2	45,774
SECRETARY	8	2	41,443
SECRETARY	7	4	37,420
SECRETARY	6	3	33,674
SECRETARY	5	3	30,208
TECH TRANSFER SPECIALIST	12	4	66,380
TRAINING COORDINATOR	13	1	78,936
<b>Total Requested</b>		<b>100</b>	