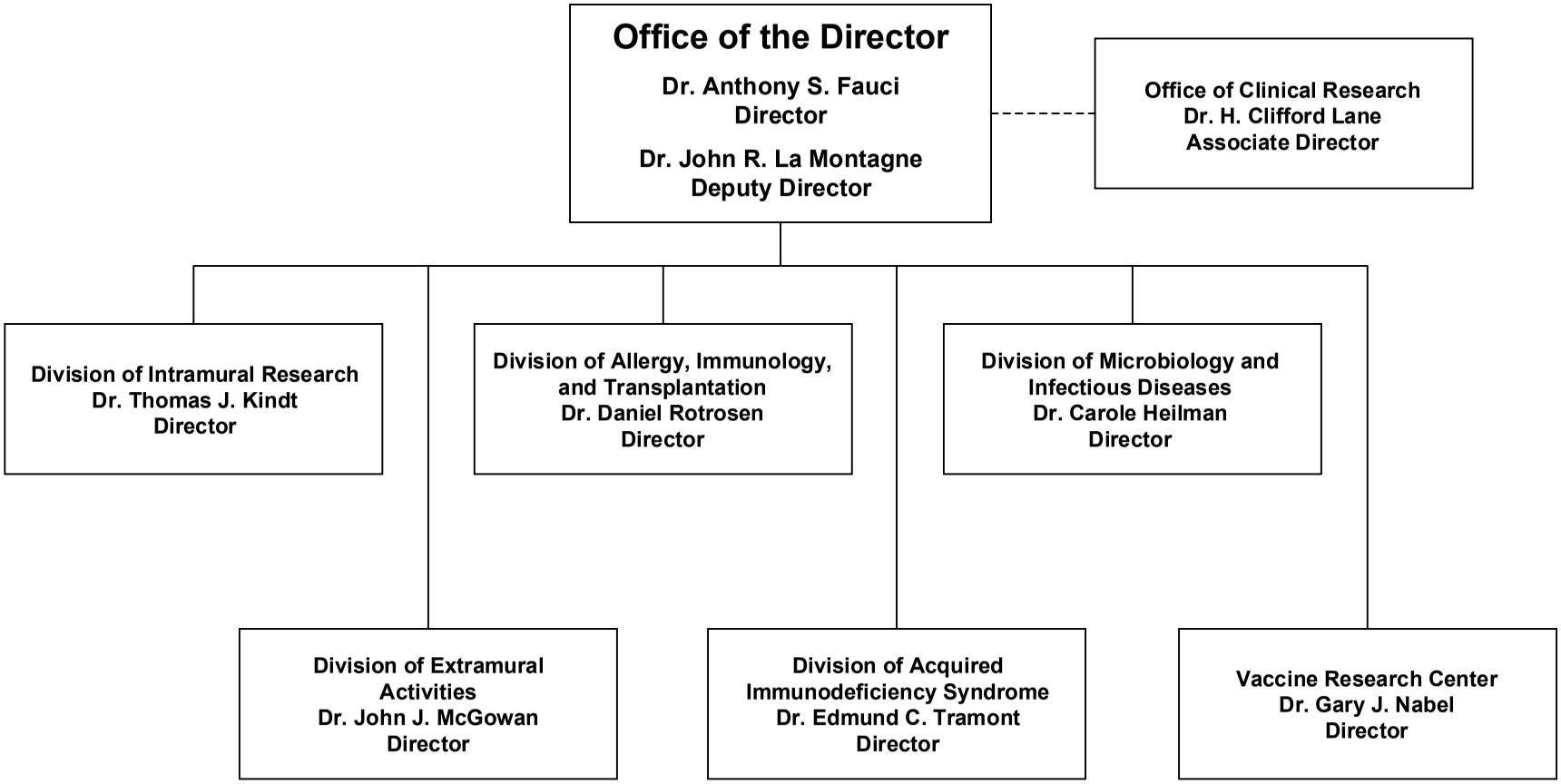
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

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



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 [$2,372,278,000] *$3,959,054,000.* Provided, that [the Director may transfer up to $25,000,000] $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 Institutes' efforts to prevent and alleviate these diseases.

[Department of Labor, Health and Human Services, Education and Related Agencies Appropriations Act for Fiscal Year 2002 (P.L. 107-116)].

National Institutes of Health

National Institute of Allergy and Infectious Diseases
Amounts Available for Obligation 1/

Source of Funding	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Appropriation	$2,043,208,000	$2,372,278,000	$3,950,148,000
Enacted Rescission	(1,084,000)	(1,239,000)	---
Subtotal, Adjusted Appropriation	2,042,124,000	2,371,039,000	3,950,148,000
Comparable adjustment for legislative proposal for accrued retirement costs	7,299,000	7,907,000	8,906,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(387,000)	---	---
HHS for the Office of Human Research Protection	(426,000)	---	---
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	---	(25,000,000)	---
Comparative transfer to:			
National Institute of Biomedical Imaging and Bioengineering	(532,000)	---	---
Comparative transfer from:			
Office of the Director for the Academic Research Enhancement Award program	3,139,000	---	---
National Cancer Institute for research activities	---	---	40,325,000
National Cancer Institute for Dale and Betty Bumpers Vaccine Research Center	18,171,000	---	---
Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis	---	100,000,000	---
Public Health Service Emergency Supplement Fund	---	88,500,000	---
Subtotal	2,069,388,000	2,542,446,000	3,999,379,000
Unobligated Balance, start of year 2/	0	---	---
Revenue from 2/	0	---	---
Unobligated Balance, end of year) 2/	0	---	---
Subtotal, adjusted budget authority	2,069,388,000	2,542,446,000	3,999,379,000
Unobligated balance, lapsing	---	---	---
Total obligations	2,069,388,000	2,542,446,000	3,999,379,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2001 - $32,277,421; FY 2002 - $22,407,000; FY 2003 - $23,406,000.
Excludes $9,254,727 in FY 2001 and $3,536,004 in FY 2002 for royalties.

FY 2003 Justification Narrative

National Institute of Allergy and Infectious Diseases

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

Budget Authority:

	2001 Actual	2002 Appropriation	2002 Current Estimate	2003 Estimate	Increase or Decrease
Current Law BA	$2,062,089,000	$2,535,778,000	$2,534,539,000	$3,990,473,000	$1,455,934,000
Accrued Costs	7,299,000	7,907,000	7,907,000	8,906,000	999,999
Proposed Law BA	2,069,388,000	2,543,685,000	2,542,446,000	3,999,379,000	1,456,933,000
FTE	1,177	1,295	1,295	1,524	229

This document provides justification for the Fiscal Year 2003 activities of the National Institute of Allergy and Infectious Diseases (NIAID), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2003 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR).

The President's appropriations request of $3,999,379,000 for this account includes current law adjusted by assuming Congressional action on the proposed Managerial Flexibility Act of 2001.

Introduction and Summary

NIAID is the component of NIH responsible for the support and conduct of research that strives to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives. Although enormous progress has been made during the last century in reducing the toll of infectious diseases, infectious diseases continue to exact a heavy toll of life in the United States. Infectious diseases remain the third leading cause of death in the United States and the leading cause of death for people under age 45 around the world.[1] The progress that has been achieved is due to the important contribution of basic and clinical research, which has led to vaccines that effectively prevent illness and disease, new diagnostic tests, and a myriad of therapeutic agents.

One of the great challenges of infectious diseases is that infectious disease problems are global in distribution. This simple fact has two important consequences. The first is that infections that

[1] JAMA 1996 Jan 17;275(3): 189-93, "Trends in Infectious Diseases Mortality in the United States," Pinner RW, Teutsch SM, Simonsen L, Klug LA, Graber JM, Clarke MJ, Berkelman RL.

appear in one location around the world can easily be transported to another part of the globe. Many emerging and re-emerging infectious diseases have been identified in the last ten years. A recent example of this phenomenon occurred with the introduction of West Nile Virus (WNV) in the New York City area two years ago. This mosquito-borne infection occurs normally in Eastern Africa, the Middle East and Central Asia. Since its introduction in New York the virus has rapidly spread north and south along the Atlantic coast and was detected as far west as the Mississippi River by September, 2001. The emergence of a new viral infection in the New York City area was a clear signal that there is a potential for any new infectious disease to become established in the United States. It is essential that a vigilant and proactive research enterprise be maintained so that the needed diagnostic tests, vaccines and therapeutic agents can be effectively developed. As the human population grows and international commerce and trade expand, these reintroductions are inevitable. A second and equally important consequence of this pattern of emergence and re-emergence is that it is essential to pursue research on these problems with a global view in mind. The only way to mitigate the impact of the all to familiar emergence and reemergence of infectious diseases is to develop a research program infrastructure that enhances and facilitates international collaboration and research.

To these two problems must be added the enormous challenge of bioterrorism. The tragic events of September 11, 2001, and the subsequent intentional release of anthrax spores through the mail have radically transformed the NIAID and the research programs it supports. The NIAID has supported research on the most likely agents of bioterrorism (smallpox, anthrax, plague and tularemia) for several years and much progress has been made during that time, such as the identification of an antiviral drug that can be used to treat orthopox infections (variola or vaccinia) and the development of a new vaccine to prevent anthrax. Since September 11, 2001, the NIAID has begun to rapidly expand its efforts in support of research on possible agents of bioterrorism. The goals of this markedly expanded research effort are to develop the countermeasures that will be needed to respond and control the release of agents of bioterrorism. It is clear that if this effort is to be successful in generating the vaccines, therapeutics, and diagnostic tests that will be needed to counter bioterrorist attack, a comprehensive and substantial increase in resources will be needed. This includes a marked increase in the number of laboratories equipped for research on these highly infectious agents, biosafety level 3 and biosafety level 4 laboratories (BSL-3 and BSL-4). It is clear that significant and enduring changes in infectious disease and immunology research capabilities will be needed for these efforts to be successful.

For many years, NIAID has supported and conducted research on diseases that transcend national boundaries. While HIV/AIDS, malaria, and tuberculosis have gained the most attention as global health scourges and necessarily receive intense attention from NIAID, many other diseases such as acute respiratory infections and diarrheal diseases, which both rank among the top ten causes of death worldwide, also fall into the category of global health concerns and are active areas of NIAID research.

Other infectious diseases on which NIAID focuses are “emerging diseases,” that is, previously unknown human pathogens (e.g., Hanta viruses and Ebola virus), and “re-emerging diseases,” that is, old public health enemies that once again are posing serious public health threats (e.g., tuberculosis) and diseases that have posed ongoing health problems in developing countries that are re-emerging in the U.S. (e.g., West Nile Virus). The Institute also focuses on a class of re-emerging diseases that recently has become of even greater consequence to our National interest

– infectious diseases that might be spread deliberately by bioterrorists. Importantly, because many global health threats, resurgent endemic diseases, and other serious infectious diseases increasingly are becoming resistant to existing antimicrobial drugs, research on resistance will remain an important component of NIAID's portfolio.

Because vaccination historically has been the most effective means to combat infectious diseases, vaccinology is a cornerstone of the NIAID research portfolio. In the 53 year history of the Institute, NIAID-supported research has been instrumental in the development of many new and improved vaccines, such as those against hepatitis A and B, *Haemophilus influenzae* type b, pertussis, typhoid, varicella, and pneumococcal disease. The Institute continues to focus on vaccine development, incorporating the rapidly evolving science base in pathogen genomics, immunology, and microbiology. The increased emphasis on research to develop countermeasures to protect against bioterrorist attacks will also increase markedly institute-supported efforts in genomic research. Additional microbial sequences are required. These data sets must be complemented by research efforts in proteomics and informatics. The Institute also is pursuing vaccines that target mucosal surfaces, which serve as entry sites for many pathogens, and is exploring the development of new adjuvants, substances that boost the immune response to vaccines. In addition, NIAID is pursuing vaccines to protect against potential bioterrorism agents, prevent chronic diseases with infectious origins, and avert autoimmune diseases and other immune-mediated conditions.

Over the past few years, NIAID researchers have been exploiting the rapid and accurate methods now available for sequencing genomes. NIAID scientists have been involved in generating the complete genomic sequences of many medically important pathogens, including *Mycobacterium tuberculosis*, *Chlamydia trachomatis*, and *Borrelia burgdorferi*. Many other microbe sequencing projects are currently underway. Importantly, the analysis and application of genomic data, a process termed functional genomics, has been transformed over the past few years by the development of new tools such as microarray and DNA "chip" technologies, which enable an investigator to delineate the functional expression of genes. This information holds great promise for facilitating studies of disease pathogenesis and drug resistance and, ultimately, for accelerating vaccine and drug development.

The past two decades of focused research on the immune system have resulted in major strides in understanding the mechanisms that underlie a range of immune-mediated diseases such as asthma, allergic diseases, and autoimmune diseases. These advances in conceptual understanding now provide realistic opportunities for significant improvement of the diagnosis, treatment, and prevention of many immune-mediated diseases. Perhaps the most promising development is our increasing understanding of tolerance induction—the blocking of specific immune responses. Through tolerance induction it may be possible, for example, to prevent graft rejection in transplant patients without the use of immunosuppressive drugs that have substantial side effects. Tolerance induction also holds great promise for treatment of other immune-mediated conditions such as asthma and autoimmunity.

Much of NIAID's research addresses health disparities that exist in the United States. For many years, NIAID has recognized the existence of differential risks and susceptibilities among populations for infectious and immunologic diseases, and has attempted to mitigate such disparities through research on improved therapies, vaccines, and other interventions. Research on HIV treatment and prevention research, hepatitis C virus, asthma, and autoimmunity are just a

few examples of the Institute's efforts to address conditions that disproportionately affect minority communities and/or women. In addition, NIAID continues a long-standing commitment to the training of minority investigators and support of such investigators as they become involved in biomedical research.

CONFRONTING INFECTIOUS DISEASES

A UNIQUE AND TERRIBLE THREAT

Bioterrorism

The threat of bioterrorism became a reality in the United States with the intentional delivery of anthrax spores through the mail to newspaper, television, and government offices. The anthrax attacks have dramatized the vulnerability of the United States population to such events. Five deaths due to inhalation anthrax have been recorded in the United States since September 2001. Thousands of people were placed on antibiotic therapy and many buildings have had to be decontaminated. The economic costs of the attack have not yet been accounted, but are likely to be in the hundred's of millions of dollars. Most importantly, the experience has vividly illustrated that there is no substitute for accurate information on therapeutic options and other medical interventions to guide the response to the problem. The magnitude of the problem and the gravity of the situation are a grim and foreboding reminder of the presence of biological weapons and their potential impact on public health. The importance of meeting this public health challenge is clear. The capability to detect and counter terrorism depends to a substantial degree on the relevant medical science and basic research.

Scientific Advances in Bioterrorism

Many years of research on anthrax fortuitously offered hope of improved treatment options just as the disease became the focus of a biological terrorism attack gripping the United States. NIAID-supported scientists have pinpointed the protein receptor on the cell to which anthrax attaches in order to gain entry. In normal circumstances, the anthrax toxin, also called protective antigen or PA, attaches itself to the cell receptor, creates a hole in the cell membrane, and becomes the conduit for two other toxins – the lethal factor or LF and the edema factor or EF. The NIAID-supported researchers who identified the anthrax toxin receptor (ATR), then demonstrated in the laboratory that a synthetic, soluble version of ATR can work as a decoy or sponge to absorb the toxin before it attaches to the ATR on the cells, thereby effectively blocking entry of the toxin into cells and protecting the cells from destruction. A second team of NIAID-supported scientists determined the structure of LF and learned how LF attaches to its target molecule on the cell surface, inserts LF and EFf into the cell thereby disrupting cell processes and eventually leading to cell death. By understanding how LF works at the molecular level, we now have the information needed for rational, or targeted, drug design.

A Key Scientific Question Being Answered

In the near-term, a bioterrorist attack involving smallpox would require the utilization of stores of the existing smallpox vaccine to protect those at immediate risk. Results of NIAID's initial smallpox vaccine dilution study, showed not only that the long-stored vaccine had maintained its potency, but also that 70 percent of people who received a single dose of the vaccine diluted to

one-tenth of the standard strength (1:10 dilution) mounted a sufficient immune response. Based on those results, the Institute initiated a larger, multi-site dilution study to determine the best strategy for optimal use of available Dryvax vaccine. This study, which enrolled over 680 people, evaluated three different doses (undiluted, 1:5, 1:10) of Dryvax. Researchers studied the ability of the various vaccine formulations to stimulate a scab, or "take," at the vaccination site and to produce neutralizing immune responses in the blood. Those participants who did not develop a scab in seven to nine days after vaccination were revaccinated with the same vaccine dose they received the first time. By that strategy, researchers hope to learn which vaccine dose given in a single injection elicits the desirable response among the largest number of people and whether "boosters" can increase the take rate on a population basis. The data will be important in guiding the use of the remaining stockpile of smallpox vaccine, if needed.

Future Directions in Bioterrorism

NIAID has significantly accelerated bioterrorism research in the wake of the recent anthrax attacks. To expand and build on existing programs, the Institute has developed a comprehensive program designed to sustain research aimed at developing biomedical tools to detect, diagnose, prevent, and treat infection by biological agents that could serve as potential weapons. The program is articulated in NIAID's "Bioterrorism-Related Research Agenda." The initial focus of this research effort is on the agents identified in the threat list, specifically those identified in Category A (smallpox, anthrax, plague, tularemia, viral hemorrhagic agents and botulism). A major component of this research program is to enhance the Nation's capability to do research on these agents. This will require that additional high containment research facilities (BSL-3 and BSL-4) will need to be constructed and accessible to government-supported scientists.

A primary objective of this research program is to attract the long-term interest and support of industry and academia in the efforts needed to develop effective bioterrorism countermeasures. NIAID's program will facilitate this through the use of all available funding mechanisms with a focus on developing ten Extramural Centers of Research Excellence for Bioterrorism and Emerging Infections, expanding the availability of biosafety level 3 and 4 laboratories, expanding investigator-initiated and Institute-initiated grants and contracts and Intramural research, and initiating challenge grants to industry and academia.

The bioterrorism research program is designed to maximize the efforts of industry, academia, and federal researchers in ways that will provide synergy to the discovery process, and accelerate the development of new and safer vaccines, therapeutic agents, and improved diagnostic tests. The plan consists of four, broad interconnected efforts:

- Expand basic research to accelerate understanding and knowledge of the physiology and genetics of potential bioterrorism agents, the immune system function and response to each potential agent, and the pathogenesis of each disease.
- Accelerate discovery and development of the candidate products that could become the next generation vaccines, therapeutic agents, and diagnostic tests by leveraging the knowledge and understanding gained through basic research.
- Expand clinical research on newly discovered and developed products to test for safety and effectiveness of potential next-generation vaccines, therapeutic agents, and diagnostic tests.

- Expand research infrastructure to enable biomedical research efforts on pathogenic microbes, including potential bioterrorism agents.

NIAID will convene a Blue Ribbon Panel on Bioterrorism-Related Research in February 2002 to obtain advice and input on the Bioterrorism-Related Research Agenda. The Panel will assess the current state of research related to bioterrorism, as outlined in the agenda, and make recommendations regarding priorities and implementation.

In FY 2003, NIAID will expand on existing bioterrorism-related initiatives, including the many initiatives started in FY 2002, by launching a broad range of initiatives to accomplish the following milestones:

- Establish the first four to seven of what will be ten Extramural Centers of Excellence for Bioterrorism and Emerging Infections. These centers will be based regionally and will form the heart of the extramural research activities in their geographical areas. Each center will provide support to researchers by making available specialized equipment and tools, including biosafety level 3 and/or 4 laboratories; providing specialized knowledge and expert advice; and conducting specialized training.
- Conduct genomic sequencing and annotation of ten to twenty-five microbial pathogens that are potential bioterrorism agents.
- Establish and expand a library of databases containing genomic sequences and proteomic analyses of pathogens that are potential bioterrorism agents. The information in this library will enhance development efforts for new vaccines, therapeutic agents, and diagnostic reagents that can be used to combat and diagnose the diseases caused by these pathogens. This library of genetic sequences will also enable the development and production of DNA microarrays and similar detection/scanning tools to quickly identify and differentiate between pathogenic strains.
- Launch challenge grants to industry and academia to attract their long-term interest and support in research aimed at developing biomedical tools to combat, detect and diagnose the diseases by these pathogens.
- Broaden the support for clinical trials of next-generation vaccines and therapeutic agents through expansion of the Vaccine Trial Evaluation Units (VTEU), specialized laboratory support, and regulatory/monitoring oversight of clinical trials. This expansion will allow more clinical trials and a wider range of clinical trials to be conducted, safely and effectively.
- Complete Phase II and start Phase III clinical trials for next-generation smallpox vaccines.
- Conduct Phase I/II clinical trials of next-generation anthrax vaccines.
- Conduct Phase I clinical trials for an Ebola vaccine.

MAJOR INTERNATIONAL KILLERS

In recognition of the magnitude of the disease burden caused by just three diseases, in FY 2001, the Institute developed an "NIAID Global Health Research Plan for HIV/AIDS, Malaria and Tuberculosis." The plan builds on and extends the Institute's on-going extramural and intramural research programs relating to those diseases.

Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS)

The HIV pandemic continues to rage around the world. UNAIDS estimates that, by the end of 2001, roughly 40 million people will be living with HIV, some 5 million people worldwide will have been infected with HIV in that year, and about 68 percent and 16 percent of those disease transmissions will have occurred in sub-Saharan Africa and South-East Asia, respectively.[2] In seven countries in southern Africa, at least one in five adults is living with HIV.[3] Moreover, HIV also continues to have a profound effect on children, with approximately 2.7 million below the age of fifteen expected to be living with the disease by December 2001.[4] The enormity of the global HIV/AIDS epidemic clearly necessitates attention on the development of inexpensive prevention measures as well as affordable treatments for those who are already infected. The development of a safe and effective vaccine represents the world's best hope for arresting the spread of HIV.

In the U.S., the number of deaths due to HIV/AIDS has declined substantially in the last decade due primarily to the introduction of antiretroviral drugs. When used in combinations termed highly active antiretroviral therapy or HAART, these drugs can decrease the amount of virus in the body to virtually undetectable levels. But the prolongation of the lives of infected individuals has resulted in more individuals living with the disease. According to the CDC, roughly 800,000 to 900,000 residents in the U.S. are living with HIV/AIDS, with about one third unaware of their HIV positive status. New infections continue at roughly 40,000 per year, with more than half occurring in individuals younger than 25 years of age. HIV/AIDS also continues to disproportionately affect minorities, notably African Americans. In fact, African Americans make up almost 38 percent of all AIDS cases reported in this country, even though they represent an estimated 12 percent of the total U.S. population.[5, 6]

Advances in HIV/AIDS Research

In a recent clinical study, scientists sought to determine the feasibility of reducing the daily regimen of anti-HIV drugs, termed highly active antiretroviral therapy or HAART, to a regimen permitting brief drug-free periods, referred to as intermittent therapy. Such a regimen would be beneficial because the anti-HIV drugs often produce a range of adverse side effects and are expensive. In this pilot study, the participants received repeated cycles of 7 days on HAART followed by 7 days off HAART. This regimen was effective in maintaining the suppression of

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[2] UNAIDS, "AIDS Epidemic Update: December 2001," Joint United Nations Programme on HIV AIDS/ World Health Organization, Geneva, 2001
[3] UNFPA Facts About HIV/AIDS http://www.unfpa.org/aids/facts.htm
[4] op cit UNAIDS
[5] CDC HIV/AIDS Surveillance Report, year-end edition, Vol.12, No.2
[6] CDC HIV/AIDS Among African Americans. Available at: http;/www.cdc/gov/hiv/pubs/facts/afam.htm.

viral replication in the blood. Importantly, there was no evidence for the development of resistance to the anti-HIV drugs used in the regimen. Presently, larger clinical trials are underway to measure the efficacy of short cycle intermittent therapy.

There also is progress toward an AIDS vaccine. In a recent study, NIAID-supported scientists demonstrated that a new HIV DNA vaccine, used in combination with a vaccina virus booster, is capable of protecting rhesus monkeys from disease. All vaccinated animals remained clinically healthy while nearly all of the unvaccinated ones developed clinical AIDS several weeks after challenge with virus. In another HIV DNA vaccine study, investigators demonstrated that a DNA vaccine combined with an adjuvant (a substance that enhances the immune-stimulating properties of a vaccine) also prevented the onset of clinical AIDS in rhesus monkeys. A vaccine that does not prevent HIV infection, but slows the course of disease may not only benefit vaccinated individuals, but also could decrease the spread of disease because sufficient lowering of the viral load in HIV-infected individuals has been shown to decrease the transmissibility of the virus. Both HIV DNA vaccine candidates are progressing toward phase I human trials.

Future Directions in HIV/AIDS Research

NIAID will continue to support HIV/AIDS research through several large clinical networks including the adult and pediatric AIDS Clinical Trials Groups, the HIV Prevention Trials Network, the HIV Vaccine Trials Network, the Women's Interagency HIV Study, and the Multicenter AIDS Cohort Study. While the Institute is committed to increasing minority participation in all of its studies, the latter two, designed to study HIV/AIDS in women and homosexual or bisexual men, respectively, are currently being expanded to increase the number of minority participants. The goal is to address new questions that are relevant to these populations. Also, NIAID will continue to support the Comprehensive International Program of Research on AIDS (CIPRA), which is intended to provide support for developing countries to plan and implement a comprehensive HIV/AIDS prevention and treatment research agenda relevant to their populations, and to provide infrastructure to conduct such research. Research on topical microbicides, a particularly important focus for preventing HIV/AIDS in women, will be sustained through renewal of preclinical and clinical initiatives. In addition, the Institute will continue to conduct HIV vaccine research and development at its Dale and Betty Bumpers Vaccine Research Center (VRC) located on the NIH campus. The VRC recently began enrolling patients in a clinical trial of the first vaccine candidate developed at the facility.

New Initiative: In FY 2003, NIAID anticipates launching a new initiative to enhance preclinical discovery and development of topical microbicides, and to facilitate translation of these preclinical studies into pilot clinical studies.

New Initiative: Both the HIV Vaccine Design and Development Teams (HVDDTs) and the HIV Vaccine Trials Network (HVTN) will be expanded in FY 2003. The HVDDTs are designed to advance vaccine concepts to the clinical testing stage; the HVTN is the Institute's flagship program for conducting pre-clinical and clinical HIV vaccine research throughout the world.

Tuberculosis (TB)

Tuberculosis has a devastating impact globally, with an estimated 8.4 million new cases and approximately 2-3 million deaths.[7] One third of the world is infected with Mycobacterium tuberculosis and 16.2 million people have tuberculosis disease.[8] In the United States, a total of 16,377 new cases were reported to the CDC from the 50 States and the District of Columbia during 2000. Approximately 78 percent of these TB cases involved racial and ethnic minorities.[9] Although the number of cases and deaths due to tuberculosis in the United States has declined since 1992 due to Federal budget support and a renewed emphasis on tuberculosis therapy, prevention, and control[10], the tuberculosis crisis has intensified with the emergence of tuberculosis caused by drug resistant M. tuberculosis strains.[11]

Scientific Advances in TB Research

Vaccines are one of the most powerful of all medical interventions for the prevention of many life-threatening diseases. Despite the success of vaccines in preventing many infections, the current BCG (Bacillus Calmette-Guerin) vaccine provides protection against tuberculosis but does so only to varying degrees. In response to the need for a more potent vaccine against tuberculosis, NIH-supported researchers constructed a candidate BCG vaccine that produces an *M. tuberculosis* protein, the 30-kDa major secretory protein. Guinea pigs vaccinated with the modified BCG were protected better against tuberculosis than animals vaccinated with the unmodified BCG. This demonstrates that the existing vaccine against tuberculosis, BCG, can be improved by bioengineering, and this approach may lead to new candidate vaccines for humans.

Future Directions in TB Research

NIAID's active TB research programs will continue in FY 2003, including intramural investigations and the multidisciplinary Tuberculosis Research Unit. Genomic and post genomic research efforts are fueling the pipeline of candidate drugs and vaccines.

New Initiatives: In FY 2003, NIAID will fund one new initiative and expand another on animal models for use in TB research. The new initiative focuses on development of new animal models for use in testing new diagnostics and drugs. The lack of adequate animal models has been a rate-limiting step for further development of treatment interventions. The expanded initiative, using established TB mouse models of infection, would provide a resource for rapid screening of compounds for in vivo activity and bioavailability and for evaluating the therapeutic efficacy of promising antituberculous compounds. These testing resources are critical to entering new agents into the drug development pipeline. Development of improved animal models would be another facet of the initiative.

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[7] World Health Organization (WHO). Global Tuberculosis Control. World Health Report 2001. Geneva, Switzerland, 2001.
[8] Dye *et al. JAMA* 282:677-686, 1999.
[9] Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States, 2000, Atlanta, GA, October 2, 2001. http://www.cdc.gov/nchstp/tb
[10] Institute of Medicine (U.S.) Ending Neglect: The Elimination of Tuberculosis in the United States. L. Geiter, ed.: pp 23-50. National Academy Press, Washington, D.C., 2000.
[11] Espinal *et al. NEJM* 344:1294-1303, 2001.

Malaria

Malaria has taken a devastating toll on society, in terms of morbidity, mortality, and economic loss. The WHO estimates that about 300 million cases of clinical malaria and over 1 million deaths occur annually.[12,13] Approximately 60 percent of malaria deaths occur in the poorest 20 percent of the total global population.[14] It has been estimated that economic losses due to malaria amount to $12 billion per year, and a reduction of economic growth of African countries of up to 1.35 percent per year.[15]

The increase in the malaria parasite's resistance to prevailing drugs has significantly contributed to failure to control the disease. In addition, changing epidemiological and ecological patterns, increased resistance of mosquitoes to standard insecticides, and a lack of sustainability of existing control measures have driven the incidence of malaria upwards.[16]

Scientific Advances in Malaria Research

Malaria is caused by plasmodium parasites that are transmitted by a group of mosquitoes in the genus *Anopheles*. The life cycle of the malaria parasite is complex and includes reproduction in the infected person's red blood cells (RBCs). Scientists have known for more than two decades that the growth of the malaria parasite in RBCs is accompanied by increased uptake of nutrients by these cells. However, neither the mechanism of uptake nor the exact role of the malaria parasite in this process had been elucidated. Recently, NIH scientists, using a method for determining electrical conductance within a cell, termed "whole-cell voltage clamping," determined that malaria parasites induce the opening of a new channel though the surface of the RBC, which potentially serves a role in parasite nutrient acquisition. This advance provides a potential target for vaccine or drug development against malaria.

Future Directions in Malaria Research

Research on malaria is a high priority for NIAID and is supported through both extramural and intramural channels including Tropical Diseases Research Units, International Collaborations in Infectious Diseases Research, and Tropical Medicine Research Centers. In FY 2003, as a result of an earlier initiative, NIAID will support three new International Centers of Excellence in Research which will foster independent research capacity and collaborative U.S. partnerships. NIAID will continue its efforts to understand the ecology and biology of insect vectors, including the *Anopheles* mosquito, and to develop and create the infrastructure for testing novel control strategies. In addition, in FY 2003, NIAID will support a contract to operate a facility for the testing of malaria vaccines in phase I clinical trials in adult human subjects.

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[12] *Weekly Epid Rec* 74:265-272, 1999.
[13] WHO Statistical Information Service (WHOSIS)
[14] Malaria at a Glance, World Bank Report, March 2001.
[15] Malaria at a Glance, World Bank Report, March 2001.
[16] WHO Fact Sheet. No. 94, October 1998. http://www.who.int/inf-fs/en/fact094.html

Story of Discovery: Determining the Genetic Cause of Drug-Resistant Malaria

Falling Behind in the Battle with Drug Resistance

Since the discovery of the malaria parasite and its transmission by mosquitoes at the end of the 19th century, public health officials have focused on eradicating malaria with a combination of drug treatment and mosquito control strategies. The introduction of the drug chloroquine and the insecticide DDT in the 1940s set the stage for a worldwide effort to eliminate malaria. But early successes in this endeavor were soon overshadowed by the phenomenon known as resistance--the ability of organisms to develop strains that are impervious to specific threats to their existence. Not only did strains of mosquitoes become resistant to DDT, but chloroquine-resistant strains of *Plasmodium falciparum*, the most deadly species of malaria parasite, also emerged. Chloroquine resistance first appeared in Southeast Asia and South America in the late 1950s, and emerged in Africa by the late 1970s. The rates and geographical distribution of resistance as well as the rates of infection and death from *P. falciparum* continue to increase. Today, nearly all regions where *P. falciparum* malaria is endemic have chloroquine-resistant strains. This has forced the replacement of chloroquine with newer agents that have more severe side effects and are more expensive, but some countries cannot afford those alternatives.

Tracking the Resistance Gene in the Laboratory

Since the mid-1980s, NIH investigators have been leading research efforts to find the *P. falciparum* gene or genes responsible for resistance to chloroquine and to develop methods to genetically manipulate *P. falciparum*. Through those efforts, researchers identified a region of DNA on the parasite's seventh chromosome that appeared to be involved in chloroquine resistance. In 2000, after years of searching this particular stretch of DNA, the researchers reported a gene, called *pfcrt*, that contained tiny mutations in several chloroquine-resistant strains of *P. falciparum*. One specific mutation, known as *pfcrt* T76, was present in all resistant strains. Then, the team was able to convert chloroquine-sensitive parasites to resistant ones by introducing a mutated *pfcrt* gene. Although NIH investigators were confident that the *pfcrt* gene plays a central role in chloroquine resistance, they needed field tests to determine whether the same mutations responsible for resistance in the laboratory also were responsible for the failure of patients to respond to chloroquine treatment.

Confirming Findings in the Field

Recently, collaborating teams of laboratory and clinical researchers in the United States and Mali conducted studies confirming that the mutations responsible for resistance in the laboratory also are responsible for the failure of chloroquine treatment Clinical investigators in Mali tested blood samples from patients in two villages before and after chloroquine treatment. The first of several field studies found that the *pfcrt* T76 mutation was present in all samples from patients who remained infected after treatment or who were resistant to treatment, confirming the laboratory finding that this *pfcrt* mutation in *P. falciparum* confers resistance to chloroquine. The investigators also found, however, that some patients whose samples carried the *pfcrt* T76 mutation cleared the *P. falciparum* organism after treatment. Further, other investigators discovered a link between chloroquine resistance and the mutation of another *P. falciparum* gene,

known as *pfmdr* 1. But this link is much weaker than that between resistance and the *pfcrt* T76 mutation. These additional findings suggest that although the *pfcrt* mutation is responsible for chloroquine resistance, other factors, such as partial immunity to malaria and other genetic mutations in the parasite, also may play a role in modulating responsiveness to the drug.

Using New Knowledge for Public Health

The correlation between the presence of the *pfcrt* T76 mutation and post-treatment infection has many implications for public health efforts against malaria. The finding suggests that the *pfcrt* T76 mutation could be used to identify the prevalence of chloroquine resistance in a population. Moreover, the knowledge may help researchers restructure chloroquine to renew its effectiveness. In addition, further research on the role that partial immunity plays in eliminating chloroquine-resistant *P. falciparum* infection may prove useful to investigators who are trying to develop a malaria vaccine.

Respiratory Diseases

Acute lower respiratory tract infections are ubiquitous throughout the world, and are the third most frequent cause of death, responsible for about 3.5 million deaths. In the United States, pneumonia and influenza are the sixth leading causes of death, responsible for 3.7 percent of all deaths.[17] Despite their significance as pathogens, these infections remain a challenge to accurately diagnose and prevent. Delineation of the mechanism of pathogenesis and virulence factors for many microbial agents that cause respiratory disease may provide insight into new diagnostic and prevention strategies.

Scientific Advances in Respiratory Diseases Research

Understanding the basis of the virulence of the influenza virus will aid in the prevention of outbreaks of influenza in the future. NIAID-supported scientists recently offered new insights into the virulence of Hong Kong H5N1 influenza A virus, a lethal avian influenza virus that was transmitted directly to humans from chickens and was responsible for the deadly outbreak of influenza in Hong Kong in 1997. Key to the virus's virulence was a small genetic change in one of several genes involved in replication of the virus. The results provide information that may be useful in understanding the emergence of future viruses with pandemic potential.

In other findings, NIAID-supported investigators gained new clues to how the influenza virus gains entry into the cell. Influenza virus enters and infects cells by a mechanism that involves the fusion of viral and host cell membranes. A peptide (protein fragment) on the surface of the virus facilitates the fusion process. The researchers developed a system to determine the detailed structure of an influenza fusion peptide using an artificial membrane. Understanding the viral fusion process will allow researchers to more specifically target new antiviral therapies for influenza and other viruses that use membrane fusion as their means of infecting cells.

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[17] Hoyert *et al. Natl Vital Stat Report* 47(19), 1999.

Future Directions in Respiratory Diseases Research

New Initiative: In FY 2003 NIAID will fund a new initiative, the "Partnerships for Novel Approaches to Controlling Infectious Disease." New classes of vaccines are needed for influenza and would impact significantly on public health. Development of novel cross-protective influenza vaccines is likely to benefit from the kind of academic/industry/government collaboration this initiative is designed to foster and will be targeted under the initiative.

New Initiative: In FY 2003, NIAID will renew and expand the Respiratory Pathogens Research Unit and Reference Laboratory. This initiative supports clinical and translational research on bacterial carriage, progression to lower respiratory tract disease, mixed bacterial/viral infections, and optimization of the immune response to candidate vaccines. The research program also will support assay and diagnostics development, immunology and pathogenesis studies, and provide a resource facility for standardization and provision of key assays and reagents.

PROBLEMATIC TROPICAL DISEASES

Ebola

The Ebola virus, considered to be a potential bioterrorism weapon, is one of a group of viruses that causes hemorrhagic fever in monkeys and humans. It is an extremely virulent pathogen that kills up to 90 percent of infected individuals. The prevailing scientific view is that Ebola is maintained in an as yet unidentified animal species native to the African continent and is transmitted to humans though contact with that species. Of the four known strains of the Ebola virus—Zaire, Sudan, Ivory Coast, and Reston—the Zaire strain is responsible for the most human deaths.[18] This strain of Ebola virus kills quickly, giving the body little time to develop natural immunity. No effective antiviral therapy is currently available. An effective vaccine against Ebola virus is therefore urgently needed and offers the best hope for preventing this dreaded disease.

Scientific Advances in Ebola Research

NIAID intramural scientists have developed a new, DNA-based vaccine that prevents Ebola virus infection in monkeys. Unlike traditional vaccines, typically made from viral proteins, the DNA vaccine delivers DNA that enters a cell and uses that cell's machinery to create new viral proteins. Researchers believe this strategy might better trick the immune system into thinking a real viral infection has occurred. To create a vaccine against multiple strains of Ebola virus, the scientists combined genes responsible for the production of surface proteins from each strain, and another virus structural protein that is common to all strains. The response to the DNA vaccine was then boosted by an injection with an adenovirus vector that also makes the surface protein, but may better deliver the gene to specialized cells of the immune system. When this prime-boost immunization strategy was tested in monkeys, all test animals exhibited strong anti-Ebola immune responses and survived subsequent exposure to lethal doses of Ebola Zaire virus. Further, the vaccinated monkeys remained symptom-free, with no detectable virus in their blood for the duration of the study. This first primate model of immune protection against Ebola virus

[18] WHO. Ebola hemorrhagic fever fact sheet no. 103, December 2000. http://www.who.int/inf-fs/en/fact 103.html

is allowing NIAID scientists to design a vaccine that prevents the disease in humans. NIAID plans to conduct a Phase I clinical trial on the Ebola vaccine in FY 2003.

Dengue

Dengue, a mosquito-borne viral infection, has emerged as an international public health concern. The dengue virus causes two diseases—dengue fever and dengue hemorrhagic fever. Globally, there are an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of dengue hemorrhagic fever. Dengue fever can cause severe aches and pains, headaches, and high fever. Dengue hemorrhagic fever is a more serious, often fatal, illness that includes internal hemorrhaging and dramatic loss of blood pressure. Four closely related types of dengue virus (Dengue virus types 1-4) each cause the full spectrum of dengue disease in humans.[19] The spread of dengue is associated with the ever-increasing geographic distribution of the dengue viruses and their mosquito vectors and an increase in the number of individuals in urban areas.[20]

Scientific Advances in Dengue Research

A vaccine would aid the effort to combat dengue and dengue hemorrhagic fever. NIAID-supported scientists tested the recombinant candidate vaccine against dengue, in 20 human volunteers. They found that the vaccine is well tolerated, safe, and generates an immune response against type-4 dengue virus. The vaccine candidate not only shows promise as a vaccine against type-4 dengue virus, but serves as a basis for creating a vaccine that protects against all four types of dengue virus. The high degree of immune response and very mild symptoms generated by this vaccine are encouraging.

Leishmaniasis

Parasites of the genus *Leishmania* cause several distinct diseases in humans, each of which have a range of clinical manifestations. These include cutaneous leishmaniasis, a form of leishmaniasis that causes disabling and disfiguring skin sores, and visceral leishmaniasis (also known as kala-azar), an often fatal form that attacks internal organs such as the liver and spleen. An estimated 12 million people worldwide are affected by *Leishmania* infection (leishmaniasis),[21] and 350 million people live in areas where they may be exposed to the parasite.[22] The type of *Leishmania* that infects humans undergoes a critical stage of development within the sandfly, the insect that transmits the parasite through its bite. Researchers had identified genes involved in the development of *Leishmania* from noninfective to highly infective forms, but the molecular mechanisms involved in the initiation and regulation of this vital step had not yet been defined.[23]

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[19] CDC. Dengue and dengue hemorrhagic fever fact sheet. http://www.cdc.gov/ncidod/dvbid/dengue/facts.htm
[20] WHO. Dengue and dengue hemorrhagic fever fact sheet no. 117, November 1998. http://www.who.int/inf-fs/en/fact117.html

[21] WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases. http://who.int/emc-documents/surveillance/docs/whocdscsrisr2001.html/Leishmania
[22] http://www.cdc.gov/ncidod/dpd/parasites/leishmania/factsht_leishmania.htm
[23] Coulson *et al*. *Mol Biochem Parasitol* 40:63, 1990.

Scientific Advances in Leishmaniasis Research

NIAID-supported scientists recently discovered that a compound called tetrahydrobiopterin (H_4B), which is produced by an enzyme called pteridine reductase 1 (PTR1), plays an important role in the development of *Leishmania* into an infectious form. The scientists made this discovery by observing that mice infected with genetic mutants of *Leishmania* that cannot produce high levels of H_4B had greater number of lesions and higher number of parasites in their bodies. The investigators hypothesize that, by controlling the activity of PTR1, *Leishmania* parasites can keep H_4B levels high, thus limiting the severity of disease and keeping the host alive. This ensures transmission of the parasites to other hosts. A better understanding of the *Leishmania* life cycle may lead to new treatments that are less toxic and more effective than the current first-line drug therapy.

From earlier studies, scientists had determined that proteins in the saliva of the sandfly increase the efficiency of transmission of the *Leishmania* parasite.[24] Recently, NIH scientists characterized several of the salivary gland proteins and demonstrated that a vaccine containing one of these proteins can protect mice from Leishmania infection. These results suggest that the sandfly salivary gland proteins may serve as viable candidates for a vaccine against Leishmania.

Future Directions in Tropical Disease Research

Intramural research on Ebola, Leishmania, and other tropical diseases will continue. To further confront the challenges in tropical medicine and international health more effectively, NIAID established the International Centers for Tropical Disease Research (ICTDR) in 1991, a program which will continue in FY 2003. This program incorporates Institute-supported intramural and extramural tropical disease research centers into an interactive network focused on tropical infectious disease problems. NIAID-supported investigators will conduct basic, clinical, and field research that seeks to discover and develop vaccines, drugs, and vector-control methods to prevent and treat tropical diseases. Toward this end, NIAID provides support for research to be conducted at sites in endemic areas where scientists can gain access to populations of patients, microbial pathogens, and invertebrate vectors.

New Initiative: Filariasis and Schistosomiasis, two tropical diseases caused by worms (helminths), pose major public health threats in the developing world. In FY 2003 NIAID will renew and expand an initiative to provide access to parasite research materials that are difficult to produce in individual laboratories, train investigators in helminth research techniques and parasite life cycle maintenance, and support the application of molecular biological/genomic technology to the study of these parasites.

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[24] Titus *et al. Science* 239:1306-1308, 1988.

OTHER PROBLEMS IN INFECTIOUS DISEASE

Escherichia coli and Enteric Diseases

An estimated 76 million people experience food-borne illnesses each year in the United States.[25] Many types of bacteria can cause attacks of diarrhea or foodborne illnesses. Escherichia coli, an organism present in soil, water, and vegetation, and a major component of the normal intestinal flora, can also cause serious illness. One strain, *E. coli O157:H7*, causes an estimated 73,000 cases of infection and 61 deaths in the United States each year.[26] Infection with *E. coli O157:H7* leads to diarrhea and hemolytic uremic syndrome, which can be especially problematic in young children, the elderly and those with decreased immune function. Other enteric pathogens include Campylobacter, Cryptosporidium, Cyclospora, Listeria, Salmonella, Shigella, Vibrio and Yersinia. Although there appears to be much regional variation in the incidence of foodborne illnesses, the incidence of these illnesses declined during 1999 compared with 1996, primarily as a result of decreases in campylobacteriosis and shigellosis.[27]

Scientific Advances in E. coli and Enteric Pathogens Research

In an effort to understand differences between pathogenic and non-pathogenic strains of *E. coli*, NIAID-supported scientists compared the sequenced genomes of pathogenic *E. coli* O157:H7 and a non-pathogenic strain of *E. coli*. Investigators found that 70 percent of the genome of *E. coli* O157:H7 was identical to the non-pathogenic strain. In addition, the genome of *E. coli* O157:H7 was about 30 percent larger than the non-pathogenic strain. The additional DNA in *E. coli O157:H7* includes genes that code for virulence factors. The identification of virulence genes may aid in the design of new therapies and vaccines.

Future Directions in E. coli and Enteric Pathogens Research

In FY 2003, NIAID is planning to recompete the Enteric Pathogens Research Unit. Activities in this contract will promote continued progress in understanding the pathogenesis and developing treatments and preventive strategies for diarrheal diseases.

Hepatitis

The vast majority of cases of hepatitis, or inflammation of the liver, are caused by one of five viruses, called hepatitis A, B, C, D, and E. All of these viruses can cause acute disease with symptoms lasting many weeks including yellowing of the skin and eyes, dark urine, extreme fatigue, nausea, vomiting and abdominal pain. Of these viruses, Hepatitis C virus (HCV) is the most common chronic blood-borne infection in the United States. Chronic infection with hepatitis virus may result in liver cirrhosis or cancer. Worldwide, an estimated 170 million people are chronically infected with HCV, and 3 to 4 million people are newly infected each year.[28] It is estimated that 10 to 20 years from now, 165,900 deaths will occur from liver disease,

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[25] http://www.cdc.gov/ncid/dbmd/diseaseinfo/foodborneinfections_t.htm
[26] http://www.cdc.gov/ncidod/dbmd/diseaseinfo/escherichiacoli_t.htm
[27] http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4910a1.htm#fig1
[28] WHO. Hepatitis C fact sheet no. 164, October 2000. http://www.who.int/inf-fs/en/fact164.html

27,000 deaths from liver cancer and $10.7 billion will be expended to cover hospital costs.[29] HCV more heavily affects minority populations and persons living in poverty, and the racial disparity is compounded by the fact that African Americans have a uniquely poor response to HCV therapies.

Scientific Advances in Hepatitis Research

Efforts to design better drugs to treat HCV have been hampered by the lack of cell culture systems robust enough to actually study the dynamics of HCV replication in the laboratory. NIAID-supported researchers now have developed a model cell culture system having high enough levels of HCV replication to enable study of the dynamics of HCV replication. They established this model system by identifying mutations in a region of the HCV genome that codes for a protein called NS5A, which significantly enhances the replication efficiency of HCV. The researchers validated the model by demonstrating that interferon, a substance currently licensed as a therapy for HCV, could significantly inhibit the viral replication seen in the system. In addition to the value of the model, the identification of mutations in the NS5A protein, which affect the ability of the virus to replicate, may aid in the development of an HCV attenuated vaccine (a vaccine containing weakened virus that normally does not cause disease but triggers an immune response that protects against the disease-causing virus).

Future Directions in Hepatitis Research

The work of NIAID's extramural Hepatitis C Cooperative Research Centers, the intramural investigations of the basis for variations in responses to HCV therapy, and other on-going hepatitis research will continue in FY 2003.

New Initiative: Under a new FY 2003 initiative, "Partnerships for Novel Approaches to Controlling Infectious Diseases," which will facilitate collaboration among government, academia, and industry, investigators will identify key steps of HBV replication and host interactions as targets for the development of new classes of drugs against chronic Hepatitis B. (This initiative also is mentioned under Respiratory Diseases above.)

West Nile Virus

West Nile Virus (WNV) has emerged in recent years in North America, presenting a threat to public health. The most serious manifestation of WNV in humans is fatal encephalitis (inflammation of the brain). WNV, a virus commonly found in Africa, West Asia, and the Middle East, has been most recently found in North America. In the United States, WNV has occurred in Connecticut, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Florida, Georgia, Virginia, Ohio, and the District of Columbia *through July 2001*.[30] Over 20 cases of severe disease, including 2 deaths due to WNV were reported in 2000 in the United States.[31]

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[29] Wong *et al*. *Am J. Public Health* 90:1562-1569, 2000.
[30] CDC. http://www.cdc.gov/ncidod/dvbid/westnile/index.htm
[31] CDC. http://www.cdc.gov/ncid/dvbid/westnile/q&a.htm

Scientific Advances in West Nile Virus Research

NIH-supported researchers have developed a hamster model of WNV encephalitis in which infected animals show signs of encephalitis 6 days after infection, and about 50-70 percent of the animals succumb to infection. This animal model will provide an inexpensive, readily available means to study pathogenesis and test diagnostics, vaccines, and therapies.

Future Directions in West Nile Virus Research

Research under several on-going and new initiatives is relevant to West Nile Virus including the International Centers of Excellence in Research, which supports efforts to understand the ecology and biology of insect vectors; the Partnerships for Novel Approaches to Controlling Infectious Disease, which will evaluate the impact and effectiveness of vector control products; and the International Collaboration in Infectious Disease Research.

Lyme Disease

Lyme disease, an infection caused by the bacterium *Borrelia burgdorferi*, is transmitted to people by deer ticks and western black-legged ticks. The disease is an inflammatory disease that affects multiple organ systems. Over 16,000 cases of Lyme disease were reported in 1999, making it the leading cause of vector-borne infectious illness in this country.[32] Complications of untreated early-stage disease include 40-60 percent joint disease, 15-20 percent neurologic disease, 8 percent inflammation of the heart, and 10 percent or more are hospitalized.[33]

Scientific Advances in Lyme Disease Research

Most patients can be successfully treated with antibiotic therapy when diagnosed in the early stages of Lyme disease; however, some patients develop chronic infection. Recently, NIAID investigators evaluated the efficacy of antibiotic therapy on chronic Lyme disease. Data from two clinical trials provide evidence that intensive antibiotic therapy is not more effective than placebo in improving chronic Lyme disease symptoms. These findings, coupled with the knowledge of treatment of other chronic infectious diseases caused by persistent bacteria, suggest that it is unlikely that a longer course of antibiotic therapy or different antibiotic combinations would further improve chronic symptoms. Thus, patients can be spared a costly, ineffective treatment associated with side effects.

Future Directions in Lyme Disease Research

Researchers will characterize the patients in the studies on Lyme disease as thoroughly as possible to learn more about the mechanisms involved in chronic Lyme disease. The role that autoimmune reactions (immune system reactions against the body's own tissues) may play in persistent symptoms also is under investigation. Knowledge gained from these continuing studies could lead to more effective approaches for treatment of chronic Lyme disease.

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[32] CDC. http://www.cdc.gov/ncidod/dvbid/lyme/index.htm
[33] CDC. http://www.cdc.gov/od/oc/media/fact/lyme.htm

Antimicrobial Resistance

Antimicrobial resistance is growing and spreading worldwide, affecting our ability to successfully treat respiratory, diarrheal, sexually transmitted, healthcare-associated, and a great variety of other infections caused by viruses, bacteria, fungi, and parasites. Antimicrobial resistance has resulted in difficult to treat infections, increased hospital stays and costs, and the need to use more toxic drugs. In the United States alone, approximately 14,000 individuals are infected and die each year from a drug-resistant microbe acquired in a hospital setting.[34] Of the bacteria that cause hospital-acquired infections, 70 percent are resistant to at least one of the drugs most commonly used to treat these infections.[35] Significant increases have occurred in hospital-acquired antimicrobial resistant infections in intensive care unit patients in the United States in the five years prior to January 1999. Methicillin-resistant *Staphylococcus aureus* increased by 40 percent to 53.5 percent, methicillin resistant coagulase staphylococci increased by 4 percent to 88.2 percent, and vancomycin resistant enterococci increased by 40 percent to 24.7 percent.[36] Of the *Mycobacterium* tuberculosis isolates in 2000, 8 percent were resistant to isoniazid (a commonly prescribed tuberculosis drug).[37] Resistance to chloroquine, the mainstay anti-malaria drug, is crippling control efforts, especially in Africa.[38] Novel and innovative research approaches and concepts are needed to advance the field of study and develop new diagnostic, therapeutic, or preventive approaches.

Scientific Advances in Antimicrobial Resistance Research

NIAID-supported researchers working to understand mechanisms of antimicrobial resistance identified a regulatory pathway that controls resistance to beta-lactamase antibiotics (antibiotics structurally related to penicillin) in *S. aureus*. Specifically, they discovered that, in the presence of the antibiotic, resistance is modulated in a multi-step pathway involving at least two proteins, a "DNA-binding repressor protein" and a "sensor-transducer protein" that interact to turn on and off genes and cause other proteins to be made. Understanding the fundamental processes involved in antimicrobial resistance within microbes forms an important basis for the development of prevention and treatment interventions.

Future Directions in Combating Antimicrobial Resistance

New Initiative: In FY 2003, in an effort to expand the understanding of factors affecting the development of resistant pathogens and the spread of resistance genes, NIAID will support a new initiative for research on innovative approaches to combat antibiotic resistance. To lay the basis for development of new diagnostic, therapeutic or preventive approaches, NIAID will support studies to enhance the understanding of antimicrobial resistance, the effect of resistance mutations on microbial fitness, microbial ecology, innovative molecular diagnostics, and the impact of variations in antimicrobial use patterns that may affect the emergence and spread of resistance.

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[34] WHO. Report on Infectious Diseases 2000: Overcoming Antimicrobial Resistance.
[35] Unpublished data from CDC, 2000. Atlanta, GA. August 2001.
[36] CDC. The National Nosocomial Infections Surveillance System Semiannual Report. June 2000.
[37] CDC. Surveillance Reports. Reported Tuberculosis in the United States, 2000. http://www.cdc.gov/nchstp/tb
[38] Trape *et al. CR Acad Sci III* 321:689-697, 1998.

The Promise of Microbial Genomics

Infectious diseases caused by human pathogens are the leading cause of death for persons under age 45 worldwide.[39] Determining the complete genetic make-up of microbial pathogens will greatly accelerate the identification of genes embedded in the genetic code that underlie the basis of infectious diseases. Identifying these genes will provide a more profound understanding of the mechanisms of pathogenesis and this, in turn, will lead to new, more effective, and inexpensive ways to diagnose, treat, and prevent disease. Advances in DNA sequencing technology have allowed scientists to rapidly, efficiently, and cost-effectively sequence genomes of pathogenic microorganisms. In addition, new technologies employing advances in miniaturization, robotics, and fabrication are providing new tools for research on microbial genomes, once they have been sequenced. High density arrays of microbial DNA segments ("gene chips" and microarrays) are being used to determine how gene expression varies under different conditions, at different stages of infection, and in different isolates of the organism, as well as to discover new drug and vaccine targets.

Scientific Advances in Microbial Genomics

The progress and success of microbial genomics have been a critical achievement for biomedical research. In FY 2001, NIAID-supported researchers published the complete genomic sequence of five bacterial pathogens including *Escherichia coli* O157:H7 (causes bloody diarrhea and kidney failure), *Salmonella typhimurium* (causes food-borne diseases and gastritis), *Ureaplasma urealyticum* (causes non-gonococcal urethritis), *Streptococcus pneumoniae* (causes pneumonia, bacteremia, meningitis, and middle ear infection) and *Streptococcus pyogenes* (causes strep throat, rheumatic fever, and "flesh-eating" disease). The sequence information for *E. coli* O157:H7 has revealed genome sequences that may contribute to the organism's virulence. This new information will provide leads to better ways to diagnose, treat, and prevent *E. coli* O157:H7 infections. The sequence information of *S. pyogenes* has revealed numerous encoded virulence factors and factors responsible for the adaptability of the organism as a human pathogen. The *S. pyogenes* sequence will aid in understanding the physiology and pathogenesis of streptococcal diseases and may lead to improved prevention and treatment of these diseases. After sequencing the genome of *S. pyogenes*, NIH scientists used a high-throughput, whole-genome strategy to identify eleven Group A streptococcus genes that are present in all strains examined from worldwide sources. Sequencing of these genomes has revealed the existence of novel genes and proteins, and such information will greatly aid in the development of vaccines and drugs against these pathogens.

Significant progress has been made in the sequencing of several other bacterial genomes by NIAID. Although not yet published, manuscripts are in preparation for the complete genome sequence of *Haemophilus ducreyi* (the etiologic agent of chancroid), *Mycobacterium tuberculosis* (the etiologic agent of tuberculosis), *Neisseria gonorrhoeae* (the cause of gonorrhea, a sexually-transmitted disease), *Enterococcus faecalis* (a cause of hospital-acquired infections), and *Staphylococcus aureus* (a cause of bacterial infection of the blood and inflammation of the inner heart).

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[39] WHO. Report on Infectious Diseases, Removing Obstacles to Healthy Development, Geneva, Switzerland, 1999.

NIAID is also supporting the genomic sequencing of several pathogens that are considered to be potential biological weapons: *Bacillus anthracis* (anthrax, Ames strain) with the Office of Naval Research and the Department of Energy; *Yersinia pestis* (plague); *Brucella suis* with DARPA; *Clostridium perfringens* (soft tissue infections and enteric diseases); *Burkholderia mallei* (glanders); *Rickettsia typhi* (typhus) with DARPA; and *Coxiella burnetii* (Q fever) with DARPA.

Future Directions in Microbial Genomics

NIAID is expanding and re-prioritizing its genomic sequencing efforts to focus on pathogens that could be used as weapons of bioterrorism. NIAID will promote research in proteomics, which takes advantage of the availability of microbial genome sequence data to conduct functional analyses of genes and the corresponding proteins and their interactions within each microbial genome. In addition, microbial genomics will be used together with the human genome sequence to better understand the host immune response and an individual's susceptibility to pathogens. Enhanced understanding of the biology of pathogens and the ability of pathogens to cause disease is expected to accelerate the pace of research on infectious disease and lead to new strategies for prevention and treatment.

New Initiative: Significant progress in DNA sequencing technology has increased the capacity to sequence microbial genomes and invertebrate vectors rapidly in an efficient and cost-effective way. Capitalizing on that opportunity presented by this capacity, in FY 2003, NIAID will support the Network for Large-Scale Sequencing of Microbial Genomes to establish high-throughput, efficient, cost-effective centers for the rapid sequencing of human microbial pathogens and invertebrate vectors. The focus of this effort will be pathogens and vectors that could serve as weapons or delivery mechanisms of bioterrorism.

Other Future Directions in Controlling Infectious Diseases

In FY 2003, NIAID will renew support for an initiative on Clinical Trials for Antiviral Therapies. Under this initiative, scientists will conduct clinical trials of therapies for treatment of severe acute and chronic human viral infections of public health importance including those for non-HIV viral diseases that are not a high priority for the pharmaceutical industry and those for rare viral diseases and diseases in special populations.

New Initiative: In FY 2003, NIAID's antiviral screening program will be renewed and expanded to support cell-based systems to evaluate compounds for their biological specificities in antiviral activity and cytotoxicity. This important initiative serves as a tool of discovery for new drugs.

New Initiative: In FY 2003, NIAID will fund an initiative to study the role of "mixed infections" on colonization, virulence, and the host immune response. Understanding the complex relationship between pathogens and normal flora, as well as the interactions among pathogens themselves, could lead to improved strategies to prevent or treat complications of infections.

CONFRONTING IMMUNE-MEDIATED DISEASES

Immune Tolerance

Immune tolerance is the selective blocking or prevention of harmful immune responses. Advances in our understanding of immune tolerance and how to induce tolerance are poised to dramatically improve our ability to treat and prevent a broad range of immune-mediated diseases including autoimmune diseases (such as Type I diabetes, rheumatoid arthritis, and multiple sclerosis); asthma and allergic diseases; and graft rejection in kidney, pancreas, heart, lung, bone marrow, and cell transplantation.

Scientific Advances in Tolerance Research

An NIAID-supported investigator and colleagues induced donor-specific immune tolerance in miniature swine through pre-transplant gene therapy. The transplant recipient's bone marrow cells were temporarily removed and genetically modified to express the donor's MHC molecules (cell surface molecules that are the target of the immune response). Once these cells were re-introduced, the animals then received a kidney from the donor and only a twelve-day course of immunosuppressive medications. Most of the animals receiving the donor-MHC expressing bone marrow cells maintained the kidney graft for more than three years with no evidence of chronic graft rejection, while control animals rejected their kidney transplants within two months. This is the first demonstration of durable immune tolerance to a solid organ graft in a large animal model using gene-transfer of MHC molecules and a short course of immunosuppression.

Future Directions in Tolerance Research

In 1999, NIAID established the Immune Tolerance Network (ITN), an international consortium of more than 70 basic scientists and clinical investigators, to test promising tolerogenic treatment in three clinical areas: transplantation, autoimmunity, and asthma/allergy. In FY 2000, the ITN began accepting proposals and will have completed five full review cycles by January 2002. In the first stage, ITN received more than 135 concepts and 45 were accepted for submission as full proposals. To date, 16 clinical trials have been approved for implementation in all three clinical areas. NIAID will continue to support the ITN in FY 2003.

Autoimmune Diseases

Autoimmune diseases result when a body's immune system attacks the body's own tissues. Examples of autoimmune diseases include Type 1 diabetes, multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, and systemic lupus erythematosus. Type I diabetes afflicts 300,000 to 500,000 Americans, 120,000 of whom are less than 20 years of age.[40] Multiple sclerosis afflicts approximately 250,000 to 350,000 Americans.[41] An estimated 832,000 Americans suffer from inflammatory bowel disease.[42] Rheumatoid arthritis afflicts

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[40] Diabetes in America, 2nd Edition, NIH, NIDDK, NIH publication no. 95-1468, p.1, 1995.
[41] *Ann Neurol* 31:333, 1992.
[42] Stonnington *et al*. *Gut* 28:402-409, 1987; and Gollop *et al*. *Gut* 29:49-56, 1988.

approximately 2.1 million Americans (1.5 million women and 600,000 men).[43] At least 239,000 Americans are diagnosed with, or suspected of having Systemic Lupus Erythematosus (SLE).[44] Incremental advances in our understanding of these chronic and debilitating diseases provide hope for new strategies to interrupt or prevent the self-reactive response leading to autoimmune disease. Autoimmune diseases tend to be far more prevalent in women than men, and even more prevalent in African-American women. As many as 1 in 250 young African American women suffer from SLE.[45]

Scientific Advances in Autoimmune Diseases Research

In autoimmune diseases such as rheumatoid arthritis, chronic inflammation causes serious injury to many tissues and organs. A key cellular molecule that controls inflammation within cells of the immune system is a molecule known as nuclear factor kappa B (NFκB). An NIAID-supported investigator and others analyzed the molecular structure of regulatory molecules that affect the activation of NFκB, and designed a synthetic molecule to inhibit its activation. The synthetic molecule prevented inflammation in two mouse models of inflammatory disease. These findings may aid in the development of new therapeutic approaches for the treatment of autoimmune diseases and other inflammatory diseases.

Another new strategy for the treatment of autoimmune diseases may result from delineation of the mechanism of action of the anti-inflammatory properties of intravenous immunoglobulin (IVIG). IVIG, a product containing antibodies harvested from human blood, has well recognized anti-inflammatory properties. However, it was not clear how IVIG elicits these effects. Recently, an NIAID-supported investigator and colleagues determined that the anti-inflammatory properties of IVIG are mediated through an inhibitory pathway triggered by an antibody-binding receptor called Fc gamma receptor IIB (FcRIIB). These receptors, located on the surface of macrophages (specialized immune cells that engulf and destroy antibody-coated cells), bind the antibodies in IVIG. As a result, protection is provided against inflammation. Manipulation of this inhibitory receptor pathway may lead to the development of new treatments for immune-mediated diseases, including some autoimmune disorders.

Future Directions in Autoimmune Diseases Research

In FY 2003, NIAID will support new and ongoing clinical trials of promising immune therapies for multiple autoimmune diseases through renewal of the Autoimmunity Centers of Excellence and on-going trials under the ITN (see Immune Tolerance above). Center led multidisciplinary, interactive research projects will be focused on elucidation of the basic mechanisms of autoimmunity, understanding self tolerance and/or immune modulation in autoimmune disease, and an integrated clinical component for piloting of novel immunotherapies. Clinical trials on treatments for three autoimmune diseases -- Type 1 diabetes, multiple sclerosis, and systemic lupus erythematosus -- will continue into FY 2003 under the ITN.

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[43] *Arthritis Rheum* 41:778, 1998.
[44] *Arthritis Rheum* 41:778, 1998.
[45] *Arthritis Rheum* 41:778, 1998.

Asthma and Allergic Diseases

Asthma and allergic diseases are the sixth leading cause of chronic disease in the United States. Approximately one out of every five Americans, is reactive to at least one of eight selected allergens known to contribute to allergic illness.[46] Asthma prevalence, morbidity and mortality have been increasing steadily over the past 20 years in the United States. Based on the Behavioral Risk Factor Surveillance System (BRFSS) survey, an estimated 14.6 million adults in the United States had current asthma in 2000, and the overall prevalence of asthma among adults was 7.2 percent.[47] In 1998, approximately 1 million children less than 5 years of age and 2.9 million children 5-17 years of age had physician-diagnosed asthma and had an episode of asthma.[48] Chronic sinus disease is frequently associated with asthma, and the incidence of sinusitis in asthmatic subjects ranges from 40-75 percent.[49]

Scientific Advances in Asthma and Allergic Diseases Research

Exposure to many indoor allergens, such as house dust mites, may lead to allergic sensitization, a process whereby the body is primed to mount a strong immune response upon re-exposure to an allergen. Such sensitization increases the risk of developing allergies and asthma. Paradoxically, NIH-supported scientists have discovered that high levels of cat allergen in the home decrease the risk of sensitization to that allergen, apparently because of the particular way the immune system responds to cat allergen. They found that high levels of cat allergen prompted children's immune systems to make IgG, a class of antibody that does not cause an allergic response, as opposed to allergy-inducing IgE antibodies. Elucidating the factors that regulate IgG and IgE production may aid in the development of new prevention strategies and more effective allergy and asthma treatments.

NIAID-supported scientists determined that a gene abnormality for cystic fibrosis (CF), characterized by mucous membrane abnormalities in the lungs, may be responsible for the development of chronic sinusitis, a disease that is frequently associated with asthma. CF occurs only when individuals inherit two mutant copies of the cystic fibrosis transmembrane regulator (CFTR) gene. An NIH-supported investigator and colleagues discovered that individuals who inherit only a single copy of a mutant CFTR gene are highly predisposed to develop chronic sinusitis. Mutations in the CFTR gene may account for about 1 in 15 cases of chronic sinusitis. Future research efforts that focus on CFTR gene alterations may prove critical for the development of new prevention strategies and more effective treatments for chronic sinusitis.

Future Directions in Asthma and Allergic Diseases Research

In FY 2003, NIAID will continue to support innovative, multidisciplinary basic and clinical research focused on new approaches for the diagnosis, treatment and prevention of asthma and allergic diseases. Major emphasis will be placed on human clinical studies of patients with

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[46] NHANES II, the second National Health and Nutrition Examination Survey – *J Allergy Clin Immunol* 1987, 80: 669-679, 1987.
[47] CDC. *MMWR* August 17, 2001, 50: 682-686.
[48] CDC. National Health Interview Survey, 1997-1998.
[49] Spector *et* al. J *Allergy Clin Immunol* 102:S107-S144, 1998; and http://www.aaaai.org/public/fastfacts/statistics.stm

asthma or allergic diseases. Studies will further elucidate the molecular and cellular immune mechanisms involved in the pathogenesis of asthma and allergic diseases and will lead to the development of the next generation of therapeutic agents and prevention strategies. In addition, clinical trials relating to cat allergy/asthma and to ragweed allergen will continue in FY 2003 under the ITN (see Immune Tolerance above).

New Initiative: In FY 2003, NIAID will expand the capacity of the Inner City Asthma Consortium which was established in FY 2002 to explore and evaluate promising new strategies for the treatment of asthma among minority children residing in the inner city. This consortium of basic scientists and clinical investigators will conduct clinical studies to elucidate the immunopathogenesis and natural history of asthma in this population.

Transplantation

The principal goal of transplantation is the physical and functional replacement of failing organs, tissues, and cells. In 1999, 22,953 organ transplants were performed in the United States, including 13,372 kidneys, 4,954 livers, 2,198 hearts, 435 pancreata, 956 lungs, 48 heart-lung combinations, and 911 combined kidney-pancreas.[50] Transplanted bone marrow and stem cells from bone marrow increasingly are used to treat a variety of diseases. The success of organ transplantation depends on the availability of donated organs and accurate matching of donor and recipient human leukocyte antigen (HLA). Organ transplantation represents a key health disparity for African Americans. African Americans are less likely to find suitable donors and tend to remain longer on transplant waiting lists. Also, current knowledge of relevant HLA typing in minority populations is incomplete.

Scientific Advances in Transplantation Research

An NIAID-supported investigator and colleagues evaluated the efficacy of cord blood transplantation versus bone marrow transplantation in patients with acute leukemia, lymphoma, and aplastic anemia. Their investigation revealed that recipients of cord blood hematopoietic stem cells (HSC) have a significantly lower risk of both acute and chronic Graft vs. Host Disease, when compared to recipients of bone marrow HSC from HLA-identical siblings. This investigation suggests that cord blood transplantation is safer and less costly alternative to bone marrow transplantation for certain forms of leukemia and lymphoma.

A primary reason for graft failure or transplant rejection is the recipient's vigorous immune response to the graft. Acute rejection is currently monitored by analyzing needle biopsies of the transplanted organ to identify vascular damage and /or the presence of T cells. Researchers recently demonstrated that they could detect signs of immune rejection of a transplanted kidney by measuring, in patient urine samples, two RNAs (molecules that are precursors to proteins) that appear to play a role in transplant rejection. The researchers found that the expression of these proteins was higher in urine samples from patients undergoing an episode of acute rejection, which was confirmed by needle biopsy, than in samples from patients with no evidence of acute rejection. Refinements of this diagnostic test are expected to increase the accuracy of diagnosis

[50] United Network for Organ Sharing (UNOS), Critical Data.

and allow transplant recipients to be monitored non-invasively and more frequently to predict acute graft rejection and institute appropriate therapy before irreversible injury occurs.

Future Directions in Transplantation Research

In FY 2003, NIAID will renew the Cooperative Clinical Trials in Pediatric Transplantation to evaluate drugs and biologicals to improve graft survival and function in children. Through this clinical research program, new therapeutic regimens to enhance long-term graft survival will be evaluated, the underlying mechanisms of actions of the agents will be evaluated, diagnostic tests to predict graft rejection will be developed, and surrogate/biomarkers for acute and chronic rejection will be developed. Also, under the ITN (see Immune Tolerance above) trials related to kidney transplantation and islet cell transplantation will continue into FY 2003. Also, work on HLA typing by the International Histocompatibility Working Group will continue.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases are caused by intrinsic defects in cells of the immune system and are often due to inherited genetic defects. The hallmark of a primary immunodeficiency disease is increased susceptibility to infection. Approximately 500,000 Americans are afflicted with primary immunodeficiencies, 5,000 to 10,000 of whom are severely affected. Approximately 500,000 persons are believed to remain undiagnosed.[51] The number of hospitalizations for primary immunodeficiencies for 1998 was 9000.[52]

Scientific Advances in Primary Immunodeficiency Diseases Research

Chronic Granulomatous Disease (CGD) is an inherited primary immunodeficiency disease characterized by a defect in a specific white blood cell, the phagocyte, which renders the affected individual susceptible to bacterial and fungal infections. While immune therapy and antibiotics are the first line of treatment to prevent infections in patients with CGD, for patients with chronic illness and debilitation, transplantation of stem cells derived from the bone marrow of a matched donor also has been utilized. This treatment is suboptimal, however, as it requires toxic levels of radiation to eliminate immune cells in the patient's bone marrow prior to replacement with donor-matched cells. Recently, NIH scientists developed a new transplantation regimen for CGD patients that involves chemotherapy but does not require the use of radiation, and demonstrated its effectiveness as an alternative treatment for CGD. This advance should lead to increased life expectancy for chronically ill CGD patients who require transplantation.

Future Directions in Primary Immunodeficiency Diseases Research

New Initiative: Building on the Primary Immunodeficiency Diseases Registry that the Institute established in 1998, NIAID will establish a cooperative consortium of investigators called the Primary Immune Deficiency Disease Consortium to address clinical and preclinical research questions in primary immunodeficiency diseases, including the molecular and cellular characterization of patients with novel phenotypes and the development of new models, novel

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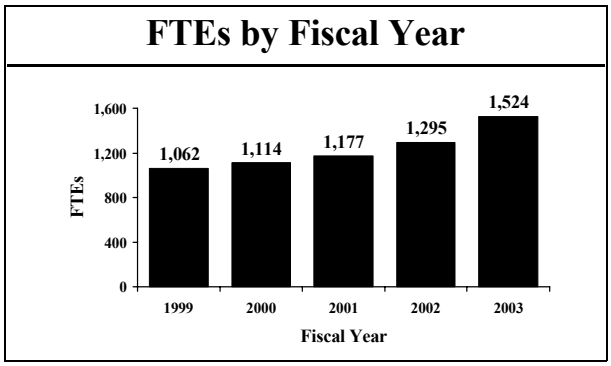
[51] Stiehm, Immunologic Disorders in Infants and Children, Primary Immunodeficiency Diseases: Report of a WHO Scientific Group, 1996; and *Clin Exp Immunol 1* (Supp. 99): 1-24, 1995.

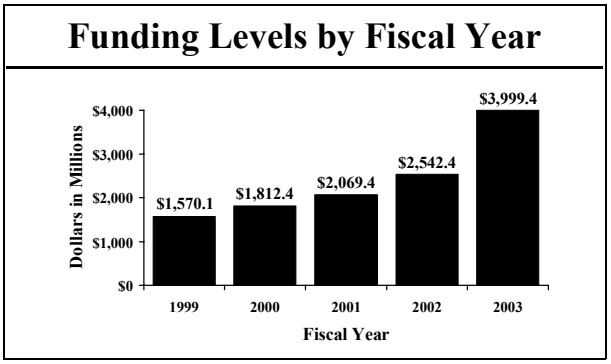
[52] Vital Health Statistics, series 13, no. 148, National Hospital Discharge Survey, September 2000.

diagnostics, and new treatment approaches. The Consortium will utilize and expand the current registry, which serves as a unique resource to this research community.

Budget Policy

The Fiscal Year 2003 budget request for the NIAID is $3,999,397,000, including AIDS, an increase of $1,456,933,000 and 57.3 percent over the FY 2002 level.





A five year history of FTEs and Funding Levels for NIAID are shown in the graphs below. Note that Fiscal Years 2000 and 1999 are not comparable for the Managerial Flexibility Act of 2001 legislative proposal.

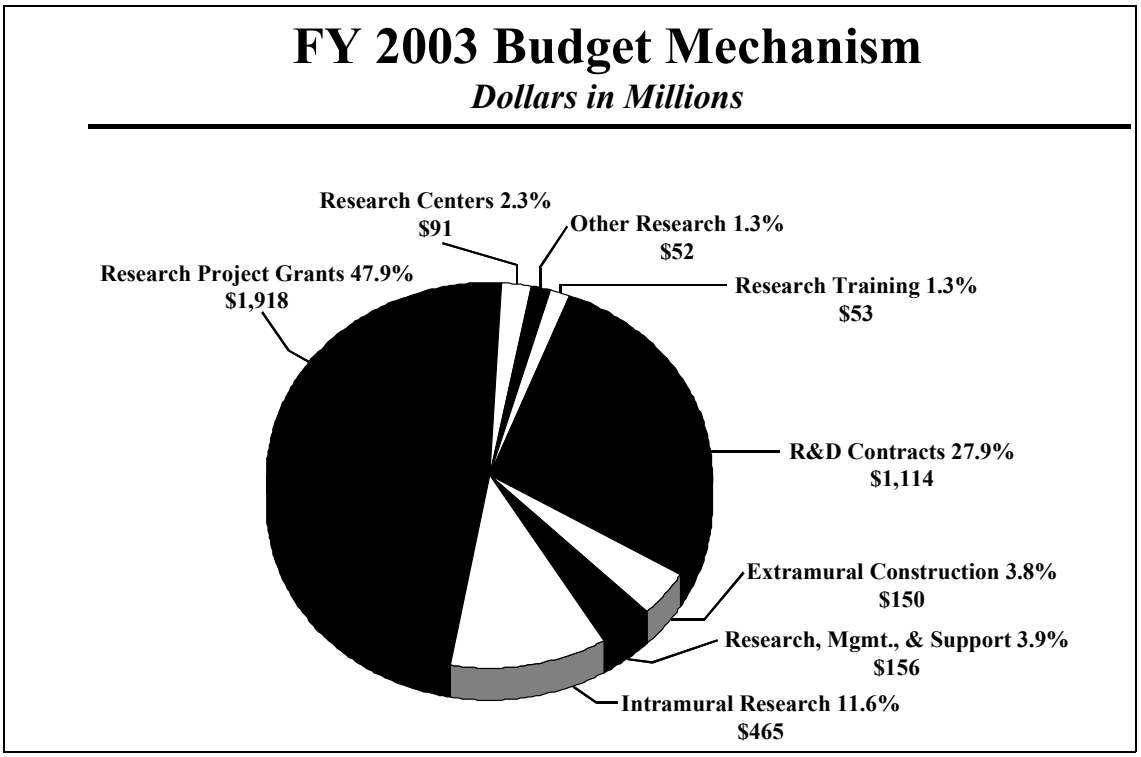
One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The Fiscal Year 2003 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index (BRDPI), estimated at 4.0 percent. The NIAID provided an average cost increase of 4.0 percent in FY 2003. However, the average cost comparison with FY 2002 is skewed because of the cycling of large clinical trial grants like the Pedatric AIDS Clinical Trials Group, and the new bioterrorism grants. Noncompeting RPGs will be funded at committed levels which include increases of 3.0 percent on average for recurring direct costs.

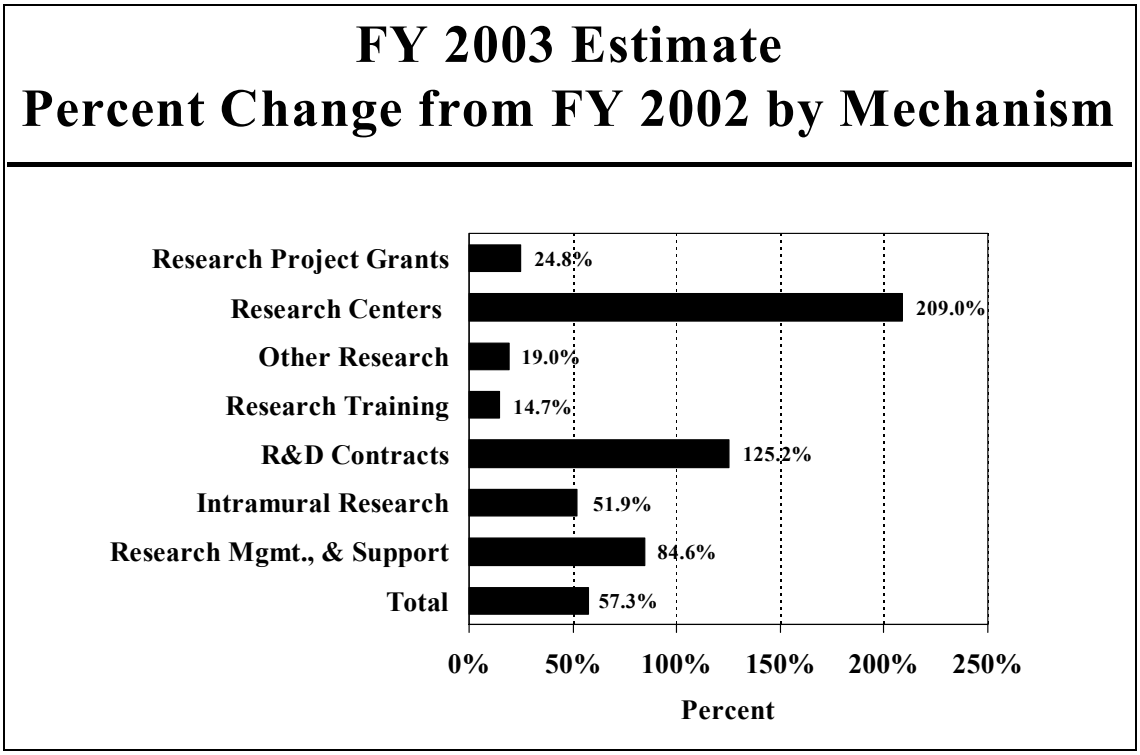
Future promises for advancement in medical research rest in part with new investigators with new ideas. In the Fiscal Year 2003 request, NIAID will support 1,179 pre- and postdoctoral trainees in full-time training positions, an increase of 110 compared to FY 2002. This increase is the result of providing support for training in bioterrorism research. Stipend levels for NRSA trainees will increase by 4.0 percent over Fiscal Year 2002 levels.

The Fiscal Year 2003 request includes funding for 33 research centers, 349 other research grants which includes 301 clinical career awards, and 295 R&D contracts. The R&D contracts mechanism also includes support for 28 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs. Intramural Research and Research Management and Support receive increases of 9.0 percent over FY 2002 for non-bioterrorism related research. The additional increases in these areas are the result of conducting and supporting bioterrorism research.

Included as part of the increase for NIAID in FY 2003 is $1,195,021,000 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. Additionally, the FY 2003 President's budget request will allow NIAID to continue our FY 2002 support of $25 million for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

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





NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
TOTAL - Current Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	2,471	$990,590,000	2,557	$1,078,985,000	2,557	$1,078,985,000	2,748	$1,218,659,000
Administrative supplements	(94)	54,653,000	(60)	12,000,000	(60)	12,000,000	(60)	12,000,000
Competing:								
Renewal	303	102,239,000	292	134,932,000	292	134,932,000	273	141,282,000
New	562	200,593,000	662	249,884,000	662	249,884,000	928	448,525,000
Supplements	19	6,043,000	28	9,405,000	28	9,405,000	28	9,848,000
Subtotal, competing	884	308,875,000	982	394,221,000	982	394,221,000	1,229	599,655,000
Subtotal, RPGs	3,355	1,354,118,000	3,539	1,485,206,000	3,539	1,485,206,000	3,977	1,830,314,000
SBIR/STTR	182	45,215,000	204	52,393,000	204	52,393,000	259	88,131,000
Subtotal, RPGs	3,537	1,399,333,000	3,743	1,537,599,000	3,743	1,537,599,000	4,236	1,918,445,000
Research Centers:								
Specialized/comprehensive	23	20,197,000	27	24,529,000	27	24,529,000	33	85,600,000
Clinical research	-	0	-	0	-	0	-	0
Biotechnology	-	1,500,000	-	1,500,000	-	1,500,000	-	1,500,000
Comparative medicine	-	0	-	0	-	0	-	0
Research Centers in Minority Institutions	-	2,929,000	-	3,356,000	-	3,356,000	-	3,692,000
Subtotal, Centers	23	24,626,000	27	29,385,000	27	29,385,000	33	90,792,000
Other Research:								
Research careers	245	28,885,000	265	32,640,000	265	32,640,000	301	38,945,000
Cancer education	-	0	-	0	-	0	-	0
Cooperative clinical research	-	0	-	0	-	0	-	0
Biomedical research support	-	0	-	0	-	0	-	0
Minority biomedical research support	-	1,202,000	-	1,384,000	-	1,384,000	-	1,523,000
Other	41	9,248,000	41	10,006,000	41	10,006,000	48	11,923,000
Subtotal, Other Research	286	39,335,000	306	44,030,000	306	44,030,000	349	52,391,000
Total Research Grants	3,846	1,463,294,000	4,076	1,611,014,000	4,076	1,611,014,000	4,618	2,061,628,000
Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards	146	5,266,000	146	5,793,000	146	5,793,000	161	6,645,000
Institutional awards	923	37,113,000	923	40,825,000	923	40,825,000	1,018	46,840,000
Total, Training	1,069	42,379,000	1,069	46,618,000	1,069	46,618,000	1,179	53,485,000
Research & development contracts	185	240,963,000	207	495,907,000	207	494,668,000	295	1,114,078,000
(SBIR/STTR)	-	(0)	-	(0)	-	(0)	-	(0)
	FTEs		FTEs		FTEs		FTEs	
Intramural research	695	245,282,000	755	297,995,000	755	297,995,000	761	455,756,000
Research management and support	482	70,171,000	540	84,244,000	540	84,244,000	763	155,526,000
Cancer prevention & control	-	0	-	0	-	0	-	0
Construction		0		0		0		150,000,000
Total, NIAID	1,177	2,062,089,000	1,295	2,535,778,000	1,295	2,534,539,000	1,524	3,990,473,000
(Clinical Trials)		(371,468,000)		(420,302,000)		(420,302,000)		(646,525,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
TOTAL - Accrued Costs for Retirement and Health Benefits
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting								
Administrative supplements								
Competing:								
Renewal								
New								
Supplements								
Subtotal, competing	0	0	0	0	0	0	0	0
Subtotal, RPGs	0	0	0	0	0	0	0	0
SBIR/STTR								
Subtotal, RPGs	0	0	0	0	0	0	0	0
Research Centers:								
Specialized/comprehensive								
Clinical research								
Biotechnology								
Comparative medicine								
Research Centers in Minority Institutions								
Subtotal, Centers	0	0	0	0	0	0	0	0
Other Research:								
Research careers								
Cancer education								
Cooperative clinical research								
Biomedical research support								
Minority biomedical research support								
Other								
Subtotal, Other Research								
Total Research Grants								
Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards								
Institutional awards								
Total, Training								
Research & development contracts (SBIR/STTR)								
	FTEs		FTEs		FTEs		FTEs	
Intramural research	0	4,306,000	0	4,586,000	0	4,586,000	0	5,426,000
Research management and support	0	2,993,000	0	3,321,000	0	3,321,000	0	3,480,000
Cancer prevention & control	0	0	0	0	0	0	0	0
Construction				0		0		0
Total, NIAID	0	7,299,000	0	7,907,000	0	7,907,000	0	8,906,000
(Clinical Trials)		(0)		(0)		(0)		(0)

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
TOTAL - Proposed Law
Budget Mechanism

MECHANISM	FY 2001 Actual		FY 2002 Appropriation		FY 2002 Current Estimate		FY 2003 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount	No.	Amount
Research Projects:								
Noncompeting	2,471	$990,590,000	2,557	$1,078,985,000	2,557	$1,078,985,000	2,748	$1,218,659,000
Administrative supplements	(94)	54,653,000	(60)	12,000,000	(60)	12,000,000	(60)	12,000,000
Competing:								
Renewal	303	102,239,000	292	134,932,000	292	134,932,000	273	141,282,000
New	562	200,593,000	662	249,884,000	662	249,884,000	928	448,525,000
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Subtotal, RPGs	3,537	1,399,333,000	3,743	1,537,599,000	3,743	1,537,599,000	4,236	1,918,445,000
Research Centers:								
Specialized/comprehensive	23	20,197,000	27	24,529,000	27	24,529,000	33	85,600,000
Clinical research	-	0	-	0	-	0	-	0
Biotechnology	-	1,500,000	-	1,500,000	-	1,500,000	-	1,500,000
Comparative medicine	-	0	-	0	-	0	-	0
Research Centers in Minority Institutions	-	2,929,000	-	3,356,000	-	3,356,000	-	3,692,000
Subtotal, Centers	23	24,626,000	27	29,385,000	27	29,385,000	33	90,792,000
Other Research:								
Research careers	245	28,885,000	265	32,640,000	265	32,640,000	301	38,945,000
Cancer education	-	0	-	0	-	0	-	0
Cooperative clinical research	-	0	-	0	-	0	-	0
Biomedical research support	-	0	-	0	-	0	-	0
Minority biomedical research support	-	1,202,000	-	1,384,000	-	1,384,000	-	1,523,000
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Training:	FTTPs		FTTPs		FTTPs		FTTPs	
Individual awards	146	5,266,000	146	5,793,000	146	5,793,000	161	6,645,000
Institutional awards	923	37,113,000	923	40,825,000	923	40,825,000	1,018	46,840,000
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Research & development contracts	185	240,963,000	207	495,907,000	207	494,668,000	295	1,114,078,000
(SBIR/STTR)	-	(0)	-	(0)	-	(0)	-	(0)
	FTEs		FTEs		FTEs		FTEs	
Intramural research	695	249,588,000	755	302,581,000	755	302,581,000	761	461,182,000
Research management and support	482	73,164,000	540	87,565,000	540	87,565,000	763	159,006,000
Cancer prevention & control	-	0	-	0	-	0	-	0
Construction		0		0		0		150,000,000
Total, NIAID	1,177	2,069,388,000	1,295	2,543,685,000	1,295	2,542,446,000	1,524	3,999,379,000
(Clinical Trials)		(371,468,000)		(420,302,000)		(420,302,000)		(646,525,000)

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Budget Authority by Activity 1/
(dollars in thousands)

ACTIVITY	FY 2001 Actual		FY 2002 Estimate		FY 2003 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Allergy, Immunology, and Infectious Diseases		$1,746,636		$2,152,300		$3,379,191		1,226,891
Subtotal, extramural research		1,746,636		2,152,300		3,379,191		1,226,891
Intramural research	695	249,588	755	302,581	761	461,182	6	158,601
Research managament and support	482	73,164	540	87,565	763	159,006	223	71,441
Total	1,177	2,069,388	1,295	2,542,446	1,524	3,999,379	229	1,456,933

1/ Please see the following tables for the crosswalk from current law to proposed law to reflect the administration's proposal for full accrued retirement and health benefits.

National Institutes of Health

National Institute of Allergy and Infectious Diseases

2001 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2001 Actual Current Law	2001 Additional Accrual Costs	2001 Actual Proposed Law
Extramural Research:			
Allergy, Immunology, and Infectious Diseases	$1,746,636	$0	1,746,636
Subtotal, extramural resarch	1,746,636	0	1,746,636
Intramural Research	245,282	4,306	249,588
Research management and support	70,171	2,993	73,164
Total	2,062,089	7,299	2,069,388

National Institutes of Health

National Institute of Allergy and Infectious Diseases

2002 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2002 Current Estimate Current Law	2002 Additional Accrual Costs	2002 Appropriation Proposed Law
Extramural Research:			
Allergy, Immunology, and Infectious Diseases	$2,152,300	$0	$2,152,300
Subtotal, extramural resarch	2,152,300	0	2,152,300
Intramural Research	297,995	4,586	302,581
Research management and support	84,244	3,321	87,565
Total	2,534,539	7,907	2,542,446

National Institutes of Health

National Institute of Allergy and Infectious Diseases

2003 Crosswalk for Accrued Retirement and Health Benefit Costs
(Dollars in thousands)

	2003 Estimate Current Law	2003 Additional Accrual Costs	2003 Estimate Proposed Law
Extramural Research:			
Allergy, Immunology, and Infectious Diseases	$3,379,191	$0	$3,379,191
Subtotal, extramural research	3,379,191	0	3,379,191
Intramural Research	455,756	5,426	461,182
Research management and support	155,526	3,480	159,006
Total	3,990,473	8,906	3,999,379

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Summary of Changes

2002 Estimated budget authority				$2,542,446,000
2003 Estimated budget authority				3,999,379,000
Net change				1,456,933,000
	2002 Current Estimate Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$84,082,000		$1,112,000
b. Annualization of January 2002 pay increase		84,082,000		1,022,000
c. January 2003 pay increase		84,082,000		1,640,000
d. Payment for centrally furnished services		49,786,000		4,481,000
e. Increased cost of laboratory supplies, materials, and other expenses		172,034,000		3,839,000
f. Accrued costs for retirement and health benefits		4,586,000		840,000
Subtotal				12,934,000
2. Research Management and Support:				
a. Within grade increase		50,054,000		869,000
b. Annualization of January 2002 pay increase		50,054,000		590,000
c. January 2003 pay increase		50,054,000		976,000
d. Payment for centrally furnished services		8,105,000		729,000
e. Increased cost of laboratory supplies, materials, and other expenses		26,085,000		1,451,000
f. Accrued costs for retirement and health benefits		3,321,000		159,000
Subtotal				4,774,000
3. Cancer Prevention and Control:				
a. Within grade increase		0		
b. Annualization of January 2002 pay increase		0		
c. January 2003 pay increase		0		
d. Payment for centrally furnished services		0		
e. Increased cost of laboratory supplies, materials, and other expenses		0		
f. Accrued costs for retirement and health benefits		0		
Subtotal				0
Subtotal, Built-in				17,708,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Summary of Changes--continued

CHANGES	2002 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,557	1,090,985,000	191	139,674,000
b. Competing	982	394,221,000	247	205,434,000
c. SBIR/STTR	204	52,393,000	55	35,738,000
Total	3,743	1,537,599,000	493	380,846,000
2. Centers	27	29,385,000	6	61,407,000
3. Other research	306	44,030,000	43	8,361,000
4. Research training	1,069	46,618,000	110	6,867,000
5. Research and development contracts	207	494,668,000	88	619,410,000
Subtotal, extramural				1,076,891,000
	FTEs		FTEs	
6. Intramural research	755	302,581,000	6	158,601,000
7. Research management and support	540	87,565,000	223	71,441,000
8. Construction		0	-	150,000,000
Subtotal, program		2,542,446,000		1,456,933,000
Total changes			229	1,474,641,000

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Budget Authority by Object

	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease
Total compensable workyears:				
Full-time employment	1,295	1,295	1,524	229
Full-time equivalent of overtime and holiday hours	6	6	6	0
Average ES salary	$139,850	$139,850	$143,486	$3,636
Average GM/GS grade	10.8	10.8	10.8	0.0
Average GM/GS salary	$62,534	$62,534	$64,160	$1,626
Average salary, grades established by act of July 1, 1944 (42 U.S.C. 207)	$69,620	$69,620	$72,961	$3,341
Average salary of ungraded positions	$117,380	$117,380	$123,014	$5,634

	OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Estimate	FY 2003 Estimate	Increase or Decrease
	Personnel Compensation:				
11.1	Full-Time Permanent	$62,826,000	$62,826,000	$78,174,000	$15,348,000
11.3	Other than Full-Time Permanent	26,105,000	26,105,000	32,752,000	6,647,000
11.5	Other Personnel Compensation	3,513,000	3,513,000	4,367,000	854,000
11.8	Special Personnel Services Payments	11,627,000	11,627,000	14,674,000	3,047,000
11.9	**Total Personnel Compensation**	**104,071,000**	**104,071,000**	**129,967,000**	**25,896,000**
12.1	Personnel Benefits	24,685,000	24,685,000	30,834,000	6,149,000
12.1	Personnel Benefits, Accrued Retirement Costs	5,380,000	5,380,000	6,142,000	762,000
13.0	Benefits for Former Personnel	0	0	0	0
	Subtotal, Pay Cost, Current Law	**128,756,000**	**128,756,000**	**160,801,000**	32,045,000
	Subtotal, Pay Cost, Proposed Law	**134,136,000**	**134,136,000**	**166,943,000**	**32,807,000**
21.0	Travel and Transportation of Persons	5,038,000	5,038,000	7,698,000	2,660,000
22.0	Transportation of Things	867,000	867,000	1,397,000	530,000
23.1	Rental Payments to GSA	7,498,000	7,498,000	9,533,000	2,035,000
23.2	Rental Payments to Others	850,000	850,000	1,081,000	231,000
23.3	Communications, Utilities and Miscellaneous Charges	6,983,000	6,983,000	11,952,000	4,969,000
24.0	Printing and Reproduction	540,000	540,000	760,000	220,000
25.1	Consulting Services	327,000	327,000	481,000	154,000
25.2	Other Services	24,389,000	24,389,000	39,920,000	15,531,000
25.3	Purchase of Goods and Services from Government Accounts	161,399,000	161,399,000	232,956,000	71,557,000
25.3	Accrued Retirement Costs	2,527,000	2,527,000	2,764,000	237,000
25.4	Operation and Maintenance of Facilities	11,943,000	11,943,000	20,156,000	8,213,000
25.5	Research and Development Contracts	471,037,000	469,798,000	1,284,184,000	814,386,000
25.6	Medical Care	1,805,000	1,805,000	3,035,000	1,230,000
25.7	Operation and Maintenance of Equipment	4,214,000	4,214,000	6,389,000	2,175,000
25.8	Subsistence and Support of Persons	0	0	0	0
25.0	**Subtotal, Other Contractual Services, Current Law**	**675,114,000**	**673,875,000**	**1,587,121,000**	**913,246,000**
25.0	**Subtotal, Other Contractual Services, Proposed Law**	**677,641,000**	**676,402,000**	**1,589,885,000**	**913,483,000**
26.0	Supplies and Materials	31,871,000	31,871,000	54,834,000	22,963,000
31.0	Equipment	20,626,000	20,626,000	40,179,000	19,553,000
32.0	Land and Structures	3,000	3,000	4,000	1,000
33.0	Investments and Loans	0	0	0	0
41.0	Grants, Subsidies and Contributions	1,657,632,000	1,657,632,000	2,115,113,000	457,481,000
42.0	Insurance Claims and Indemnities	0	0	0	0
43.0	Interest and Dividends	0	0	0	0
44.0	Refunds	0	0	0	0
	Subtotal, Non-Pay Costs, Current Law	**2,407,022,000**	**2,405,783,000**	**3,829,672,000**	**1,423,889,000**
	Subtotal, Non-Pay Costs, Proposed Law	**2,365,984,000**	**2,364,745,000**	**3,758,433,000**	**1,393,688,000**
	Total Budget Authority by Object, Current	**2,535,778,000**	**2,534,539,000**	**3,990,473,000**	**1,455,934,000**
	Total Budget Authority by Object, Proposed	**2,543,685,000**	**2,542,446,000**	**3,999,379,000**	**1,456,933,000**
	Total Accrued Retirement Costs	**7,907,000**	**7,907,000**	**8,906,000**	**999,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Salaries and Expenses

OBJECT CLASSES	FY 2002 Appropriation	FY 2002 Current Estimate	FY 2003 Estimate	Increase or Decrease
Personnel Compensation:				
Full-Time Permanent (11.1)	$62,826,000	$62,826,000	$78,174,000	$15,348,000
Other Than Full-Time Permanent (11.3)	26,105,000	$26,105,000	32,752,000	6,647,000
Other Personnel Compensation (11.5)	3,513,000	$3,513,000	4,367,000	854,000
Special Personnel Services Payments (11.8)	11,627,000	$11,627,000	14,674,000	3,047,000
Total Personnel Compensation (11.9)	**104,071,000**	**104,071,000**	**129,967,000**	**25,896,000**
Civilian Personnel Benefits (12.1)	24,685,000	24,685,000	30,834,000	6,149,000
Accrued Costs of Retirement Benefits (12.1)	5,380,000	5,380,000	6,142,000	762,000
Benefits to Former Personnel (13.0)	0	0	0	0
Subtotal, Pay Costs, Current Law	**128,756,000**	**128,756,000**	**160,801,000**	**32,045,000**
Subtotal, Pay Costs, Proposed Law	**134,136,000**	**134,136,000**	**166,943,000**	**32,807,000**
Travel (21.0)	5,038,000	5,038,000	7,698,000	2,660,000
Transportation of Things (22.0)	867,000	867,000	1,397,000	530,000
Rental Payments to Others (23.2)	850,000	850,000	1,081,000	231,000
Communications, Utilities and		0		
Miscellaneous Charges (23.3)	6,983,000	6,983,000	11,952,000	4,969,000
Printing and Reproduction (24.0)	540,000	540,000	760,000	220,000
Other Contractual Services:		0		
Advisory and Assistance Services (25.1)	327,000	327,000	481,000	154,000
Other Services (25.2)	24,389,000	24,389,000	39,920,000	15,531,000
Purchases from Govt. Accounts (25.3)	36,505,000	36,505,000	49,565,000	13,060,000
Accrued Retirement Costs (25.3)	2,527,000	2,527,000	2,764,000	237,000
Operation & Maintenance of Facilities (25.4)	11,943,000	11,943,000	20,156,000	8,213,000
Operation & Maintenance of Equipment (25.7)	4,214,000	4,214,000	6,389,000	2,175,000
Subsistence & Support of Persons (25.8)	0	0	0	0
Subtotal, Other Contractual Services, Current Law	**77,378,000**	**77,378,000**	**116,511,000**	**39,133,000**
Subtotal, Other Contractual Services, Proposed Law	**79,905,000**	**79,905,000**	**119,275,000**	**39,370,000**
Supplies and Materials (26.0)	31,847,000	31,847,000	54,792,000	22,945,000
Subtotal, Non-Pay Costs, Current Law	**123,503,000**	**123,503,000**	**194,191,000**	**70,688,000**
Subtotal, Non-Pay Costs, Proposed Law	**126,030,000**	**126,030,000**	**196,955,000**	**70,925,000**
Total, Administrative Costs, Current Law	**252,259,000**	**252,259,000**	**354,992,000**	**102,733,000**
Total, Accrued Costs	**7,907,000**	**7,907,000**	**8,906,000**	**999,000**
Total, Administrative Costs, Proposed Law	**260,166,000**	**260,166,000**	**363,898,000**	**103,732,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

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

Item

[Asthma] -- The Committee is pleased with NIAID's leadership regarding asthma research and management and 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 urges the Institute to continue to improve its focus and effort on asthma management, especially as it relates to children. (p. 64)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to the diagnosis, prevention, and treatment of asthma, including its effects on children. For example, NIAID's Asthma and Allergic Diseases Research Centers program conducts basic and clinical research to examine the causes, prevention, and treatment of asthma. The knowledge gained from this program, which was renewed in FY 2001, will provide a basis for the design of improved asthma therapeutic and prevention strategies.

In 1991, NIAID established the National Cooperative Inner-City Asthma Study (NCICAS), the first multi-site cooperative research program designed to reduce asthma severity among inner-city minority children. Building on this effort's success, NIAID has collaborated with the Centers for Disease Control and Prevention to launch a new project to disseminate and put into practice the NCICAS asthma intervention. The 4-year program will be implemented nationwide through 23 community health organizations and will target low-income children with moderate to severe asthma who reside in the inner city. This collaboration is expected to benefit more than 6,000 disadvantaged children. In addition, NIAID supports demonstration and education research projects that address asthma in medically underserved, predominately inner-city Hispanic and African American populations. Furthermore, the NIAID and the National Institute of Environmental Health Sciences cosponsor the Inner City Asthma Study (ICAS), which evaluates the effectiveness of physician education and comprehensive environmental intervention on asthma symptoms in inner-city children. The ICAS program includes a component, co-funded by the Environmental Protection Agency, to determine the influence of airborne particulate matter and co-pollutants on asthma severity. Results from ICAS are expected in early FY 2002.

In FY 2002, NIAID will establish a new clinical research program, the Inner City Asthma Consortium, to evaluate the safety and efficacy of promising immune-based asthma therapies, as well as studies of the immunopathogenesis of asthma in inner-city children. In addition, in FY 2002, NIAID's Immune Tolerance Network plans to evaluate tolerance induction strategies for

the treatment of asthma. In FY 2003, the Institute will re-compete the Asthma and Allergic Diseases Research Centers program with an increased focus on the identification of risk factors that contribute to asthma development in early childhood.

Item

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

Action to be taken

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

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

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

Treatment of autoimmune diseases remains another area of NIAID's focus. Through the Autoimmunity Centers of Excellence (ACE), established in 1999, NIAID will evaluate the efficacy of potential therapies for multiple immune diseases including systemic lupus erythematosus (SLE), lupus nephritis, and multiple sclerosis through the conduct of basic and clinical research. The ACEs are co-sponsored by NIDDK, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the NIH ORWH. Final planning is in progress for clinical trials to study the efficacy of a stem cell therapy approach using adult stem cells for the treatment of multiple sclerosis, scleroderma, and SLE through the Clinical Trials Network for Stem Cell Transplantation in Autoimmune Diseases, which was established by NIAID in FY 2001. Under the Hyperaccelerated Award Mechanisms in Immune Disease Trials, NIAID supports mechanistic studies associated with clinical trials of immunotherapies for immune-mediated diseases, including autoimmune diseases. In FY 2003, NIAID will support new and

ongoing clinical trials of immune therapies for multiple autoimmune diseases through the autoimmunity centers of excellence.

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

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

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

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

Item

[Diabetes] -- The Committee commends the Institute for its work in implementing juvenile diabetes research. The Committee is pleased with the progress of the Collaborative Network for Clinical Research on Immune Tolerance and particularly with the research successes involved with transplantation of insulin-producing cells, and urges NIAID to enhance efforts in this area. The Committee requests that the Director of the Institute be prepared to provide a status of efforts to develop a vaccine to prevent juvenile diabetes at the fiscal year 2003 appropriations hearing. (p. 64)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues its long-standing commitment to research on juvenile diabetes. The Institute has made progress in the work of the Collaborative Network for Clinical Research on Immune Tolerance, now referred to as the Immune Tolerance Network (ITN).

One of the first clinical trials conducted by the ITN was the "Edmonton Protocol," an experimental islet cell transplantation protocol for brittle type 1 diabetics. The initial study, conducted by the University of Alberta, resulted in insulin independence for 17 patients. The ITN trial will further assess the safety and efficacy of this treatment regimen and expand the capacity for islet cell preparation and clinical transplantation at 10 sites in the United States, Canada, and Europe. Results of this international, multi-center trial will establish the "baseline" success rate for islet cell transplantation and facilitate the development of new tolerogenic ITN-supported islet cell transplant trials. Another ITN clinical trial includes the use of a specific antibody to treat type 1 diabetes. In addition to continuing the ITN studies on immune tolerance as a treatment regimen for juvenile diabetes, in FY 2001, NIAID in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Heart, Lung, and Blood Institute (NHLBI) co-sponsored an initiative, "Innovative Research on Immune Tolerance." This initiative supports pilot research projects on the molecular mechanisms and applications of antigen-specific immune tolerance.

In addition to research involving tolerance induction approaches for the treatment of juvenile diabetes, NIAID will continue to support additional research on approaches for the treatment of this disease. In FY 2002, in response to the Request for Applications (RFA) "Gene Therapy Approaches for Diabetes and Its Complications", NIAID, NIDDK, and NHLBI will co-fund research on the development of novel gene therapy approaches for the treatment of type 1 diabetes. In FY 2002, NIAID and NIDDK will co-sponsor the RFA "Gene Transfer Approaches to Enhance Beta-Cell Transplantation" to support the development of gene transfer approaches to enhance transplantation of beta cells and islet cells and potentially interrupt the recurrent autoimmune destruction of the islet cells.

NIAID, in collaboration with other NIH Institutes and Centers (ICs) continues its efforts to support the development of vaccines to prevent autoimmune diseases, including type 1 diabetes. Vaccines for autoimmune diseases will be distinct from the vaccines given to prevent infectious diseases. Unlike vaccines against infectious diseases, they will "turn off" a destructive immune response that is directed at the body's own tissues. In FY 2001, NIAID and the National Institute of Child Health and Human Development (NICHD) cosponsored the NIDDK-initiated Type 1 Diabetes TrialNet, a consortia of clinical centers and core support facilities to enable rapid and efficient testing of additional promising new strategies, including vaccines, to prevent or delay progression of type 1 diabetes. In the future, candidate interventions, including vaccines, resulting from pilot clinical studies supported by the Cooperative Study Group for Autoimmune Disease Prevention [established by NIAID, NIDDK, NICHD, the NIH Office of Research on Women's Health (ORWH) and the Juvenile Diabetes Research Foundation International (JDRF) in FY 2001] may be evaluated through the ITN, the Autoimmunity Centers of Excellence, and TrialNet.

NIAID participates with NIDDK and NICHD to support diabetes prevention through non-vaccine interventions. The Diabetes Prevention Trial-Type 1 is a multi-site, cooperative clinical trial to prevent type 1 diabetes in first-degree relatives of patients with type 1 diabetes using a non-vaccine approach. One arm of this trial enrolled high-risk subjects but ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which is testing the effectiveness of oral insulin to prevent the development of disease, is continuing to enroll participants, and is expected to be completed in 2004. In FY 2001, NIAID established the Cooperative Study Group for Autoimmune Disease Prevention to conduct basic research for the development of new targets and approaches to prevent autoimmune diseases and to evaluate novel approaches in pilot and clinical studies.

NIAID will continue research on juvenile diabetes in a cooperative and collaborative manner through partnerships to enhance research. Through the NIH Autoimmune Diseases Coordinating Committee (ADCC), established in FY 1998 at the request of Congress and chaired by NIAID, collaboration among the many NIH Institutes, private groups, and other federal agencies interested in autoimmune diseases, including juvenile diabetes, is fostered to facilitate the development of coordinated research plans. The first report of the ADCC was published in FY 2001. The NIH ADCC plans to present a comprehensive strategic and collaborative research plan for autoimmune diseases to Congress in Spring 2002.

In FY 2000, NIAID partnered with other NIH Institutes and Centers and the JDRF in the International Histocompatibility Working Group, which focuses on the role of human leukocyte antigen (HLA) genes in autoimmune diseases. Further understanding of HLA in juvenile diabetes will aid in improving the ability to predict, diagnose, and treat this and other immune-mediated diseases. To further strengthen ongoing efforts in diabetes research, NIAID will co-sponsor a RFA in FY 2002 with NIDDK titled "Innovative Partnerships in Type 1 Diabetes Research" to provide access to specialized expertise or technologies, and to facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. Support will be provided for collaborative research partnerships between independent principal investigators with expertise in different aspects of type 1 diabetes. In FY 2002, NIAID and NIDDK will co-sponsor the RFA "Bench to Bedside Research on Type 1 Diabetes and its Complications" to support partnerships between clinical and basic researchers to translate advances in the understanding of the molecular basis of type 1 diabetes into new therapies for the prevention, treatment, and cure of this disease.

Building upon these partnerships, NIAID will co-sponsor a meeting with the NIH Office of Rare Diseases, the NIH ORWH, and the American Autoimmune Related Diseases Association in FY 2002, on "Animal Models in Autoimmunity." This meeting will bring together clinical researchers and animal model experts to discuss models in autoimmunity, including type 1 diabetes, and continues NIAID's expanded focus on translational research (translation of findings in animal models of disease to human disease).

Item

[Food Allergies] -- Approximately seven million Americans suffer from food allergies. Every year, roughly 30,000 people receive emergency room treatment due to the ingestion of allergenic foods and an estimated 150 people die from anaphylactic shock caused by a food allergy. The Committee encourages NIAID to enhance efforts in this area through all available mechanisms,

as appropriate, including convening a panel of expert to review current basic and clinical research efforts and development of a research agenda. (p. 64)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to supporting basic and clinical research to improve the diagnosis, prevention, and treatment of food allergy.

Basic research on food allergy is focused on gaining a more complete understanding of the immune response to allergens. For example, in the intramural program, scientists are conducting research to define, at the molecular level, the complex sequence of events that result in allergic responses. This includes research on the identification and characterization of stimuli that regulate allergic disease. NIAID intramural scientists are also developing laboratory techniques required to understand how immunomodulatory therapies work and can be applied. These efforts may be applicable to improving the diagnosis and treatment of food allergies.

NIAID extramural research in this area includes support for studies of safe and effective methods of blocking allergic responses to food. For example, NIAID supports research to develop mouse models of food allergy, which can be used to test the effectiveness of novel agents designed to block the allergic response. Other related studies in humans are underway to determine the effectiveness of orally administered allergens in the induction of immune tolerance (the selective blocking or prevention of harmful immune responses) to specific allergens. Moreover, the Immune Tolerance Network, co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Foundation International, is supporting clinical trials of tolerance induction by blocking responses to allergens. If the results of these trials are promising, similar tolerance induction trials may be designed to test the effectiveness of this approach for food allergies.

In FY 2003, the Institute plans to convene a panel of experts to identify key gaps and opportunities in food allergy research. In addition, in FY 2003, NIAID will re-compete its Asthma and Allergic Diseases Research Centers program. This long-standing program is designed to support basic and clinical research on asthma and allergic diseases, including food allergies.

Item

[Hemophilia] -- The Committee encourages NIAID to continue its efforts with the National Hemophilia Foundation to ensure people with hemophilia have access to and opportunities to participate in research for improving treatment of HIV and complications of hemophilia including hepatitis C. (p. 65)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to research targeted to the HIV-infected hemophiliac population, including research on co-infection with hepatitis C. In April 2000, NIAID, in conjunction with the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute, issued a Request for

Applications (RFA) entitled "Treatment of HIV and Associated Complications in Hemophiliacs." This initiative supports clinical research to understand mechanisms of pathogenesis and to test therapeutic concepts, focusing on the short and long-term outcomes of antiretroviral therapy, protective resistance to HIV-infection, non-progression to AIDS, and co-infection with hepatitis C. In response to this RFA, in July 2001, NIAID awarded a grant to study hepatitis C virus genomic variability in HIV infected hemophiliacs.

NIAID has supported efforts to enhance participation of hemophiliacs in research activities. NIAID has worked for several years with the National Hemophilia Foundation to provide the opportunity for the inclusion of hemophiliacs co-infected with HIV in clinical trials through the adult and pediatric AIDS Clinical Trials Group (ACTG) sponsored by the Institute.

Item

[Hepatitis C] -- The Committee urges NIAID to work with other Institutes and Centers and with public health organizations to promote liver wellness and prevention on hepatitis C, especially among African Americans. (p. 65)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a strong commitment to improving minority health. Continued research is focused on addressing the health disparity associated with hepatitis C in African-Americans. NIAID supports six Hepatitis C Cooperative Research Centers devoted to understanding the infection and disease process so as to identify new and better approaches to prevention and treatment. Trials are underway to understand the differential response to treatment, and the immunologic and genetic differences between African-Americans and Caucasians.

NIAID actively works with other Institutes in pursuing research in the area of hepatitis. The Institute provides support for the National Institute of Diabetes and Digestive and Kidney Disease's Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, which focuses on means of prevention of cirrhosis and liver cancer in hepatitis C patients. The trial will evaluate the safety and efficacy of a specific modified interferon that allows for longer retention of the drug in the body for the treatment of chronic hepatitis C in patients who failed to respond to previous treatment with interferon. This effort will aid in understanding the virus and the host immune response and their association with recovery and disease progression.

NIAID's intramural division is supporting research on the study of the natural history of chronic hepatitis C infection, including the mechanism that leads to the transition from asymptomatic infection to chronic infection and recovery in response to therapy. Current research also includes delineating immune system cell differences that lead to chronic infection or recovery from infection. Other research focuses on viral components that are predictive of disease outcome. In the future, NIAID will launch studies that focus on types of genetic mutations that help the hepatitis C virus evade the immune system and on the types of antibodies produced during the early immune response. Understanding these phenomena will allow the development of new tools for hepatitis C treatment and prevention.

In addition to NIAID's role in the scientific study of hepatitis, the Institute plays a role in the dissemination of information on hepatitis. NIAID maintains general information about HCV on its website. NIAID will continue to organize meetings and workshops such as the second consensus development conference on the management of hepatitis C in FY 2002.

Item

[Inflammatory Bowel Disease] -- The Committee continues to note with interest a scientific research agenda for Crohn's disease and ulcerative colitis, collectively known as inflammatory bowel disease, entitled "Challenges in Inflammatory Bowel Disease (IBD)". This report identifies linkages between the functions of the immune system and IBD. The Committee is aware of NIAID's research partnership with the IBD community and encourages the Institute to enhance its support of research focused on the immunology of IBD as well as the interaction of genetics and environmental factors in the development of the disease. (p. 65)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) provides a broad range of basic and clinical research support for inflammatory bowel disease (IBD). NIAID supports collaborative basic and clinical research on multiple autoimmune diseases, including IBD, in single-site and multi-site pilot clinical trials of immunomodulatory therapies through the Autoimmunity Centers of Excellence, established in 1999. In the future, NIAID plans to develop trials of investigational treatments for ulcerative colitis.

NIAID's research agenda includes support for research on the interaction of environmental factors and genetics in the development of disease, as well as the immunology of IBD. The role of environmental and infectious agents in the development of autoimmune diseases was explored in two recent research solicitations in which NIAID participates. Research projects were funded to study the immune mechanisms by which microorganisms normally found in the gut can stimulate a chronic inflammatory response in the gut of genetically susceptible animal models. Studies are underway to extrapolate these findings to human disease. NIAID will fund applications in FY 2002 in response to the Request For Applications, “Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection.” These grants will identify and validate the role of pathogens in chronic diseases, including IBD. In addition, NIAID recently established a new functional genomics resource center to support the genetic characterization of organisms responsible for disease in humans including agents that may be involved in chronic diseases such as IBD.

The interaction of genetics in the development of IBD is promoted through the Multiple Autoimmune Diseases Genetics Consortium, which was established by NIAID in 1999 to serve as a repository of genetic and clinical data from families affected by more than one distinct autoimmune disease. Provision of clinical information and specimens, including DNA and cell samples, to investigators through this consortium will aid in support of studies on the genetics and etiology of IBD and other autoimmune diseases. Further, NIAID is beginning to bank genetic material that will aid in the discovery of IBD susceptibility genes and their correlation with disease activity, immune system effects, and response to treatments.

Another area of NIAID's focus is the association between the immune system and IBD. The NIAID, the National Institute of Dental and Craniofacial Research, and the Crohn's and Colitis Foundation of America co-sponsored the research initiative, "Innovative Research in Human Mucosal Immunity," to promote exploratory and innovative investigations in this important area. NIAID's continued research focused on immunology has resulted in the development of a promising new therapy. NIAID is currently evaluating the safety and efficacy of this novel, immune-based therapy in patients with Crohn's Disease. NIAID will continue to focus studies on the immunology of IBD and the effect of new therapies on the immune system in an effort to reveal targets for further therapy improvements and innovations. In addition, NIAID plans to renew and expand the Autoimmunity Centers of Excellence in FY 2003 to support basic research on new and ongoing clinical trials of immune therapies for multiple autoimmune diseases, including IBD.

Item

[Primary Immune Deficiency Diseases] -- More than 70 primary immune deficiency diseases have been identified to date. These diseases, which impair the body's immune system, strike most severely at children, many of whom do not survive beyond their teens or early twenties. The Committee continues to be pleased with NIAID's commitment to addressing the medical and other problems caused by primary immunodeficiencies, including the primary immune deficiencies clinical registries program. The Committee urges NIAID to continue to support this program and enhance research efforts with respect to these diseases through all available mechanisms, as appropriate, including gene therapy, bone marrow transplantation, and cord blood transplantation. The Committee also urges the Institute to continue to work with the primary immune deficient community and the Centers for Disease Control and Prevention on a national education and awareness campaign and a primary immune deficiency surveillance program.

The Committee looks forward to learning the results of NIAID-sponsored research concerning the impact of primary immunodeficiencies among urban minority populations. (p. 65**)**

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support a broad range of basic and clinical research related to primary immunodeficiencies (PIs). The focus of NIAID's research program on PIs is to understand the causes and immune mechanisms leading to the development of PIs, to expand the genetics knowledge base in order to improve diagnosis, facilitate genetic counseling and decision-making for affected individuals, and to provide protective and curative treatments, including bone marrow transplantation and gene therapy.

As noted by the Committee, NIAID, through a contract to the Immune Deficiency Foundation (IDF), maintains a registry of clinical information on United States residents affected by eight different PIs: chronic granulomatous disease; Hyper-IgM Syndrome; Severe Combined Immunodeficiency Disease (SCID); X-linked agammaglobulinemia; Wiskott-Aldrich Syndrome; common variable immunodeficiency; leukocyte adhesion deficiency; and DiGeorge Syndrome.

In addition to the activities outlined above, the Institute works in partnership with other Federal agencies and non-governmental organizations such as the Jeffrey Modell Foundation to increase awareness and to educate the public and medical community about PIs.

NIAID, along with National Cancer Institute (NCI), and the National Institute of Child Health and Human Development (NICHD), initiated a research project to test a new screening procedure to determine if PIs are under-diagnosed in large, urban Hispanic and African American populations. This study is ongoing. Importantly, the grant is also supporting the development of educational materials targeted at minority health care providers to increase awareness of these diseases in those with primary responsibility for care for minority populations.

In FY 2001, NIAID, the NIH Office of Rare Diseases, NICHD, NCI, the IDF, and the Jeffrey Modell Foundation organized a meeting entitled "Gene Therapy for Primary Immunodeficiency Diseases." This meeting brought together leaders from several complementary research communities to explore the need for and challenges associated with clinical trials in this area.

In FY 2001, NIAID, together with NICHD and NCI, convened a meeting of a non-Federal, expert advisory panel on PIs. Discussions focused on current gaps in knowledge, impediments to physician investigators, ways to overcome obstacles, potential approaches to enhance utilization of the NIAID-supported primary immune diseases registry, and research opportunities.

In FY 2001, NIAID participated in a meeting on "Applying Genetics and Public Health Strategies to Primary Immunodeficiency Diseases," convened by the CDC. In FY 2003, NIAID intends to establish a cooperative consortium of investigators to address clinical and pre-clinical research questions on PIs, 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 consortium will utilize and expand the current registry of primary immunodeficiency disease patients, which serves as a unique resource to this research community.

Item

[Rhinosinusitis] -- Rhinosinusitis affects approximately 33 million Americans, yet its cause remains unclear. Recent studies have suggested that the trigger in the development of sinusitis, accompanied by benign polyps in one or more sinus, is fungus or fungi that circulate in the environment. Many people may be exposed to the same fungi, yet some do not develop rhinosinusitis or sinus polyps. NIAID is encouraged to support research to determine the factors that sensitize a patient to fungus or which generate a fungus-specific immune response through all available mechanisms, as appropriate. (p. 66)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports research to evaluate the role of fungi in chronic sinusitis. Studies are ongoing to discover why some individuals mount an immune response to fungi, whether fungal antigens induce specific inflammatory responses, and if there is a correlation between expression of sinusitis and immune responses to fungi, such as chronic sinusitis and asthma. In addition, NIAID is supporting research to determine whether anti-fungal agents reduce the severity of sinusitis (and of asthma). These

studies will further our understanding of whether specific fungi contribute to the development of sinusitis and if the immune response to the fungal antigens plays a role in the induction of sinusitis.

If the immune response to fungal antigens is shown to be critical to the development of sinusitis, future NIAID research may focus on ways to block the immune response in order to prevent and treat sinusitis. The Institute will continue to support investigator-initiated research and program projects on the relationship between fungi and sinusitis (rhinosinusitis).

Item

[Sjogren's Syndrome] -- NIAID has taken a leadership role in the NIH Autoimmune Diseases Coordination Committee (ADCC), which is vital to the coordination and promotion of autoimmune research. The Committee is encouraged to pursue critical statistics and epidemiology in Sjogren's and other autoimmune diseases that will expand knowledge and lead to new avenues for research. NIAID is encouraged to enhance its research support into the immunological aspects of Sjogren's syndrome through all available mechanisms, as appropriate, including ensuring the submission of high quality proposals in this area. (Pg. 66)

Action Taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains deeply committed to the prevention, diagnosis, and treatment of autoimmune diseases, including Sjögren's syndrome. As part of this effort, NIAID has the lead role in coordinating autoimmune diseases research with other National Institutes of Health (NIH) Institutes and offices, Federal partners and private organizations that are members of the NIH Autoimmune Diseases Coordinating Committee (ADCC). In Spring 2002, the NIH ADCC plans to present a comprehensive strategic and collaborative research plan for autoimmune diseases to Congress. It is anticipated that the plan will address the need for epidemiological studies and better data on the incidence and prevalence of autoimmune diseases, including Sjögren's syndrome.-

NIAID has worked to enhance research on Sjögren's syndrome through a broad portfolio of basic and clinical research on autoimmune diseases. NIAID-supported research for autoimmune diseases includes support for immunological aspects of autoimmune diseases. NIAID's research portfolio includes programs such as the recently established Cooperative Study Group for Autoimmune Disease Prevention co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Child Health and Human Development, the NIH Office of Research on Women's Health (ORWH) and the Juvenile Diabetes Research Foundation International, as well as the Autoimmunity Centers of Excellence co-sponsored by NIDDK, the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the NIH ORWH. NIAID also supports the Immune Tolerance Network, which is developing clinical trials involving tolerance induction approaches for multiple autoimmune diseases. Much of the research underway in these programs is focused on gaining a better understanding of the general immune mechanisms involved in autoimmune diseases. As such, this information potentially will be beneficial in the development of therapeutic approaches to treating multiple autoimmune diseases, including Sjögren's syndrome.

Item

[Vaccine Safety] -- The Committee encourages NIAID, in coordination with NICHD and NIEHS, to enhance research to evaluate the long-term safety of vaccines for children and vaccine ingredients including the potential connection to diabetes, autism, ADD/ADHS, SIDS and pediatric brain tumors. The Committee requests that the Director of the Institute be prepared to provide a progress report at the fiscal year 2003 appropriations hearing. (p. 66)

Action to be taken

Vaccines remain among the most powerful tools for disease prevention. The National Institute of Allergy and Infectious Diseases (NIAID) remains a leader in the discovery and testing of new and improved vaccines and will continue to nourish this field. Efforts to improve the safety and efficacy of existing vaccines as well as to ensure the safety of new vaccines are critical to NIAID's vaccine research program.

In addition to NIAID's mission to conduct and support research leading to new and improved vaccines, NIAID has also initiated several studies focused on several newly-identified immunization safety concerns. For example, NIAID supports several studies evaluating the potential impact of thimerosal in vaccines, the potential risk of intussusception with rotavirus vaccine, and the relationship of immunization and diabetes mellitus.

NIAID is evaluating vaccine-derived exposure levels of mercury. One study is underway to determine if vaccines containing thimerosal significantly affect the levels of mercury found in the blood, hair, and stool of children 6 months of age or younger. In addition, the NIAID has partnered with the National Institute of Environmental Health Sciences to cosponsor a study in infant monkeys to examine the pharmacokinetics and tissue distribution of thimerosal, ethyl mercury, and methyl mercury after intramuscular injection.

NIAID is exploring the possible link between the rotavirus vaccine and intussusception using an animal model. In addition, epidemiological studies are being conducted to determine if the rotavirus vaccine had an impact on the incidence of intussusception in the United States.

NIAID is also supporting studies to determine if vaccination history is a risk factor for type 1 diabetes and other autoimmune diseases in a cohort of children through the Diabetes and Autoimmune Study in the Young (DAISY), a long-term program supported by the National Institute of Diabetes and Digestive and Kidney Diseases and NIAID.

Another avenue of research designed to enhance vaccine safety involves the Vaccine Immunology Basic Research Centers Program, funded in FY 1999. Through this program, NIAID supports research on cell-mediated immunity (immune protection provided by the direct action of immune cells) in children. This research will provide information that will help design and improve vaccines for children.

In addition, NIAID, in collaboration with the Centers for Disease Control and Prevention, requested that the Institute of Medicine (IOM) establish an independent expert committee to review hypotheses regarding the relationship between specific vaccines and alleged adverse events. This committee is helping to assess some of the safety issues identified above and others. Specifically, this committee reviews the state of knowledge regarding a particular immunization safety concern and communicates the results to providers and the public. In 2001, the committee met to review 1) measles-mumps-rubella vaccine and autism, 2) thimerosal-containing vaccines

and neurodevelopmental disorders, and 3) multiple immunizations and immune dysfunction. Public input has been sought for the recommendation of future topics. The committee will continue to review important topics related to vaccine safety.

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

Item

[Asthma research and management] -- The Committee is pleased with NIAID's leadership regarding asthma research and management. The Committee recognizes the role that NIAID has played with the Inner City Asthma Study and the importance of this effort concerning morbidity and mortality among underserved populations, particularly children. The Committee urges NIAID to continue to improve its focus and efforts on asthma management, particularly as it relates to children. (p. 140)

Action to be taken

Please see response to House page 64.

Item

[Crohn's disease] -- The Committee notes with interest and concern NIAID's report titled "Crohn's Disease – Is There a Microbial Etiology?" The report findings show that Crohn's disease may have an infectious etiology. The Committee shares NIAID's concern that if it is proven that *Mycobacterium avium* subspecies *paratuberculosis* is the cause of Crohn's disease, the impact upon the public health could be enormous because of the prevalence of this mycobacteria on farms and in standing water. The Committee urges the NIH to consider designating Crohn's as an "emerging infectious disease" and encourages the NIAID to establish a formal Crohn's disease program specifically for research into an infectious cause of Crohn's disease. (p. 141)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) remains committed to supporting research on inflammatory bowel disease (IBD), including Crohn's disease. As the Committee notes, in December 1998, NIAID sponsored the workshop: Crohn's Disease – Is There a Microbial Etiology? The workshop participants recommended that further basic and clinical research be conducted in order to answer the question of whether *Mycobacterium avium* subspecies *paratuberculosis* (Map) is a causal agent of Crohn's disease. NIAID will continue to pursue the potential association between Map and the onset of Crohn's disease as well as the autoimmune aspects of the disease.

Since the workshop, NIAID has initiated studies in several of the research areas identified by the workshop participants. For example, NIAID is supporting several pilot studies to assess various technologies to isolate Map from the gut of Crohn's patients and healthy individuals. In addition, work has begun at the NIAID-funded Enteric Pathogens Research Unit on tissue acquisition from Crohn's patients and controls. Samples will be cultured for Map and one type of *Escherichia coli*, two organisms thought to be potential etiologic agents of Crohn's disease.

NIAID has supported additional research to investigate a possible infectious cause of Crohn's disease. In FY 1999, the NIAID participated in two trans-National Institutes of Health solicitations for research on the role of environmental and infectious agents in the pathogenesis of autoimmune diseases. Research projects were funded to study the immune mechanisms by which microorganisms normally found in the gut can stimulate a chronic inflammatory response in the gut of genetically susceptible animal models. Studies are underway to extrapolate these findings to human disease.

In FY 2002, NIAID will fund applications received in response to the Request for Applications "Infectious Etiology of Chronic Diseases: Novel Approaches to Pathogen Detection" co-sponsored by NIAID, the National Cancer Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, and the NIH Office of Research on Women's Health. These grants will identify and validate the role of pathogens in chronic diseases, including IBD. In addition, the Institute recently established a functional genomics resource center to support the genetic characterization of organisms responsible for disease in humans, including agents that may be involved in chronic diseases.

In other studies, investigators supported by NIAID are focusing on the analysis of the influence of genetics on autoimmune diseases, including IBD. In FY 1999, the NIAID established the Multiple Autoimmune Diseases Genetics Consortium to collect clinical information, and DNA and cell samples for genetic studies from families who have members with more than one autoimmune disease, including IBD. Clinical information and specimens will be available to investigators to support studies of the genetics and etiology of these diseases.

The association between the immune system and IBD is another area of NIAID's focus. In FY 2000, awards for projects related to IBD were made in response to the research initiative, Innovative Research in Human Mucosal Immunity, co-sponsored by NIAID, the National Institute of Dental and Craniofacial Research, and the Crohn's and Colitis Foundation of America. The goal of the initiative is to promote exploratory and innovative investigations in this important area.

In FY 2003, the NIAID intends to renew and expand the Autoimmunity Centers of Excellence to support basic research and new and ongoing clinical trials of immune therapies for multiple autoimmune diseases, including IBD.

Item

[Hemophilia] -- The Committee encourages NIAID to continue its efforts with the National Hemophilia Foundation leadership to ensure that persons with hemophilia have access to and opportunities to participate in research for improving treatment of HIV and complications of hemophilia, including hepatitis C. (p. 141)

Action to be taken

Please see response to House page 65.

Item

[Hepatitis C vaccine development] -- The Committee encourages increased priority on research that will accelerate the development of a hepatitis C vaccine. The development of an effective vaccine would be greatly assisted by research that studies the mechanisms that lead to recovery from initial infection, the mechanism that leads to the transition from asymptomatic infection to chronic infection and recovery in response to therapy. The Committee is aware that the NIAID has conceptually approved research in this field encompassed by a project titled Hepatitis C: Recovery Research Network. The Committee urges that adequate funding be made available to initiate this project. As part of that effort, the Committee urges the Institute to evaluate early treatment or treatment within the first year of infection. (p. 141)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a broad portfolio of research on modes of disease transmission, pathogenesis, and disease progression in individuals infected with hepatitis C virus (HCV). The goals of this program are to develop more effective treatments and prevention strategies, including a vaccine against hepatitis C.

As noted by the Committee, in 2000, the Institute released a Request for Proposals (RFP) titled the "Hepatitis C Research Recovery Network (HC RRN)." The intent of this proposal was to identify the virologic, immunologic and genetic factors involved in recovery from hepatitis C virus (HCV) infection. In addition, the contract was intended to examine such areas as: factors associated with infection, the natural history including the severity of infection and early persistent infection, and the ability of early treatment to enhance the recovery outcome. Regrettably, only one proposal was submitted, and that proposal was not selected for funding after going through the peer review process. NIAID is considering the possibility of restructuring the initiative in a way that would encourage more proposals.

Prevention and treatment of hepatitis C are a focus of NIAID's research. In the Fall of 2000, NIAID re-competed and expanded the HCV Cooperative Research Centers program. The network unites basic and clinical researchers investigating hepatitis C infection and the disease process so as to identify new and better means of prevention and treatment. As part of the expansion, largely unexplored questions, such as why African Americans respond less well to the current standard of care, and unresolved issues, such as how disease persists unnoticed in the body for decades, were added to the ongoing studies. The HCV Cooperative Research Centers will retain a coordinated, multidisciplinary approach, fostering collaboration among scientists in virology, immunology, cell and tissue biology, pathogenesis, animal studies, clinical investigation and allied research.

In addition to the studies conducted through the HCV Cooperative Research Centers, NIAID is providing support for an important HCV clinical study led by the National Institute of Diabetes and Digestive and Kidney Diseases: the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. This is a randomized controlled trial to evaluate the safety and efficacy of long-term treatment with a specific modified interferon that allows for longer retention of the drug in the body in patients who failed to respond to previous interferon treatment. NIAID is also conducting ancillary studies to identify the virological and immunological responses associated with either recovery or disease progression.

Vaccine development for hepatitis C remains primarily in the research and development phase. In the NIAID intramural program, scientists have made several strides toward this goal. For example, they have prepared a standardized viral inoculum that will be distributed to the scientific community for use in testing vaccine candidates in chimpanzees. Further, NIAID intramural scientists have been refining the chimpanzee as an animal model of HCV while, concurrently, working on a replacement animal model of the disease. In other studies with chimpanzees, NIAID intramural scientists developed and tested candidate DNA vaccines for HCV. The candidate vaccines did not prevent infection, but modified the course of infection. In collaborative studies, NIAID intramural scientists are genetically manipulating HCV with the goal of generating a form of the virus capable of replicating both in tissue culture as well as in the chimpanzee. Achievement of this goal would be an important step toward the development of both live and inactivated HCV vaccines.

In FY 2002, NIAID will continue to fund research aimed at understanding host and viral components of recovery and persistence outcomes, resistance to infection and mechanisms of protective immunity to HCV infections in animal models and humans. In addition, the Institute will continue to support preclinical vaccine development for HCV. In the future, vaccine candidates resulting from basic research programs will be moved forward for testing in established clinical trials networks.

Item

[Inflammatory bowel disease (IBD)] -- The Committee is aware of 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. 141)

Action to be taken

Please see response to House page 65.

Item

[Population mixing] -- The Committee urges the NIAID, in cooperation with the Department of Defense, to develop a plan for studying population mixing, which is an unusual mixing of people in relatively isolated rural areas. In such situations, a variety of infectious viruses and bacteria may trigger an unusual and rare reaction that affects children in susceptible populations. The Committee hopes that this study will contribute to a greater understanding of this important possible cause of childhood cancers. This will benefit communities around the Nation such as Fallon, Nevada, which has experienced an outbreak of childhood acute lymphocytic leukemia (ALL). (p. 142)

Action to be taken

NOTE: Language on population mixing was included in the National Institute of Allergy and Infectious Diseases (NIAID) section of the Senate Report. The National Cancer Institute (NCI) conducts research on childhood cancers and examines factors, such as population mixing, which may have an association with the incidence of childhood cancers.

An expert panel was convened on February 15, 2001 in Reno, Nevada by the Nevada State Health Officer to evaluate and investigate observed excess occurrences of acute lymphocytic leukemia (ALL) in Fallon, Nevada. The expert panel, made up of representatives from the National Cancer Institute (NCI), Centers for Disease Control and Prevention (CDC), the University of Minnesota Cancer Center, and the University of California, Berkeley School of Public Health, discussed the theory of population mixing as a possible explanation for excess ALL cases in Fallon. The panel reviewed the state health department's investigation of ALL that had been diagnosed in the Fallon area and considered possible follow-up actions and priorities by the Nevada Health Division.

An additional activity related to the study of the theory of population mixing is planned. A workshop, "Epidemiological Approaches to Testing the Population Mixing Hypothesis," will be conducted by the NCI on March 27, 2002. The workshop was originally scheduled for Sept. 15, 2001. Invited experts will work to identify epidemiological approaches to test the population-mixing hypothesis for clustering of ALL using analytical studies. The goal of the workshop is to propose a set of viable strategies to test the hypothesis including potential study populations, biological correlates, and study designs for follow-up epidemiologic studies. The results of the workshop will be summarized and shared with leadership of the Department of Health and Human Services involved in childhood cancer research and with the investigator community.

Item

[Primary immunodeficiencies (PI)] -- The Committee continues to be pleased with NIAID's strong commitment to addressing the medical and other problems caused by primary immunodeficiencies. In particular, the Committee looks forward to learning the results of the NIAID-sponsored research concerning the impact of PI among urban minority populations and seeing the research replicated on a larger scale throughout the country. Building on past collaborations with nonprofit groups, the Committee encourages NIAID to move aggressively in all research areas, including cutting-edge research related to gene therapy, bone marrow transplantation, and cord blood transplantation. The Committee also continues to be pleased with NIAID's PI clinical registries program, and urges the NIAID to continue to support this important initiative. The Committee also encourages the Institute to work with the PI community and the Centers for Disease Control and Prevention on a national surveillance program. Finally, the Committee urges NIAID to continue to remain actively and meaningfully involved in the national education and awareness campaign for PI sponsored by the Jeffrey Modell Foundation and to expand its role in fiscal year 2002. (p. 142)

Action to be taken

Please see response to House page 65.

Item

[Prostatitis research] -- The Committee strongly urges the formation of prostatitis research centers under the direction of infectious disease specialists as separate and distinct entities from the urological centers. (p. 142)

Action to be taken

NOTE: Language on prostatitis research was included in the National Institute of Allergy and Infectious Diseases (NIAID) section of the Senate Report. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) conducts research on prostatitis. The response provided here was developed by NIDDK.

The NIDDK's prostatitis research program has grown substantially, increasing nearly three-fold between FY 1997 and FY 2001. The program includes both clinical and basic research addressing questions about diagnosis, prognosis, cause and treatment of this terrible problem. At the forefront of clinical research is NIDDK's Chronic Prostatitis Collaborative Research Network (CPCRN), which has already developed and validated a questionnaire being used by the wider research community to assess accurately symptom severity and quality of life. The network is documenting symptoms, possible risk factors, medical histories, treatments, and the results of blood, prostate fluid, semen, and urine tests. Two new clinical sites were added in FY 2001 to help recruit patients, especially minorities, and in FY 2002, NIDDK will extend funding for the CPCRN for an additional year so that centers may plan and conduct more clinical trials.

A recent NIDDK initiative will expand the pool of prostate researchers and increase the use of novel technologies and innovative approaches in prostate research as part of the Institute's Prostate Research Novel Exploratory Teams (Prostate Research NET).

Item

[Rhinosinusitis] -- Chronic rhinosinusitis affects approximately 33,000,000 Americans, yet its cause remains unclear. Recent studies have suggested that the trigger is fungus or fungi that circulate in the environment. Many healthy, normal people may be exposed to the same fungi, yet do not develop rhinosinusitis or sinus polyps. The Institute is urged to support studies to determine the factors that sensitize an individual to fungus or which generate a fungus-specific immune response. (p. 142)

Action to be taken

Please see response to House page 66.

Item

[Temporomandibular joint disorders (TMJ)] -- The Committee urges NIAID to put a greater focus in its research portfolio on TMJ patients and autoimmune and inflammatory processes. 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. 142)

Action to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) participates in the Temporomandibular Joint Disorders Interagency Working Group (TMDIWG), which is led by

the National Institute of Dental and Craniofacial Research (NIDCR). The TMDIWG facilitates communication and collaboration among agencies that have an interest in understanding temporomandibular joint (TMJ) and associated disorders. In addition to NIDCR and NIAID, the group has representatives from the National Institute of Neurological Disorders and Stroke, the National Institute of Nursing Research, the National Institute of Arthritis and Musculoskeletal Disorders, the National Center for Complementary and Alternative Medicine, the National Heart, Lung, and Blood Institute, the NIH Office of Research on Women's Health, the Agency for Healthcare Research and Quality, the Food and Drug Administration, and the Centers for Disease Control and Prevention.

NIAID supports a broad range of investigator-initiated research focused on the molecular and cellular processes of inflammation. Further, NIAID-supported investigators study the interactions of the neural and immune systems in health and disease. An understanding of these systems may provide insight into inflammation and pain related to TMJ disorders.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2001 Amount Authorized	2002 Estimate	2003 Amount Authorized	2003 Budget Estimate 1/
Research and Investigation	Section 301	42§241	Indefinite	$2,495,828,000	Indefinite	$3,945,894,000
National Institute of Allergy and Infectious Diseases	Section 417B	42§285	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	46,618,000	b/	53,485,000
Total, Budget Authority				2,542,446,000		3,999,379,000

a/ Funding provided under the Departments of Labor, Health and Human Services, Education, and Related Agencies Appropriations Act for fiscal year 2002, (P.L. 107-116).
b/ Reauthorizing legislation will be submitted.

1/ Reflects proposed transfer from the National Cancer Institute

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Appropriation History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1994	$1,065,583,000	$1,065,583,000	$1,065,583,000	$1,063,704,000
1995 2/	542,864,000	535,847,000	535,847,000	535,847,000 3/
Rescission				(648,000)
1996	557,354,000 2/	1,169,628,000	549,246,000 3/	1,169,628,000
Rescission				(676,000)
1997	584,362,000 2/	1,256,149,000	595,016,000 3/	1,257,794,000 4/
1998	634,272,000 2/	1,339,459,000	1,359,688,000	1,351,655,000
1999	703,723,000 2/5/	1,470,460,000	1,540,102,000	1,570,102,000
Rescission				(1,039,000)
2000	789,156,000 2/	1,714,705,000	1,786,718,000	1,803,063,000
Rescission				(5,025,000)
2001	935,166,000 2/	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	3,999,379,000			

1/ Reflects enacted supplementals, rescissions and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $569,000.
4/ Excludes enacted administrative reductions of $575,000
5/ Reflects an increase of $1,683,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
Office of the Director	171	189	252
Division of Allergy, Immunology, and Transplantation	30	41	56
Division of Microbiology and Infectious Diseases	66	81	170
Division of Extramural Activities	104	110	166
Division of Acquired Immunodeficiency Syndrome	111	119	119
Division of Intramural Research	695	755	761
Total, NIAID	1,177	1,295	1,524
Statutorily-ceiling exempt FTEs not included above	(1)	(1)	(1)

Funds to support these FTEs are provided by Cooperative Research and Development

FISCAL YEAR	Average GM/GS Grade
1999	10.7
2000	10.9
2001	10.8
2002	10.8
2003	10.8

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
Detail of Positions

GRADE	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
ES-6	1	0	0
ES-5	2	2	2
ES-4	2	2	2
ES-3	0	0	0
ES-2	0	0	0
ES-1	0	0	0
Subtotal	5	4	4
Total - ES Salary	$668,500	$419,550	$430,458
GM/GS-15	66	71	76
GM/GS-14	116	132	162
GM/GS-13	123	141	183
GS-12	140	163	215
GS-11	130	150	169
GS-10	1	1	1
GS-9	69	75	87
GS-8	42	44	50
GS-7	73	80	101
GS-6	41	43	54
GS-5	17	17	24
GS-4	26	29	35
GS-3	5	8	8
GS-2	7	7	7
GS-1	6	6	6
Subtotal	862	967	1,178
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	17	17	17
Senior Grade	12	12	12
Full Grade	10	10	10
Senior Assistant Grade			
Subtotal	40	40	40
Ungraded	327	355	373
Total permanent positions	876	969	1,124
Total positions, end of year	1,234	1,366	1,590
Total full-time equivalent (FTE) employment,end of year	1,177	1,295	1,524
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$133,700	$139,850	$143,486
Average GM/GS grade	10.8	10.8	10.8
Average GM/GS salary	$59,784	$62,534	$64,160

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
New Positions Requested

	FY 2003		
	Grade	Number	Annual Salary
ADMINISTRATIVE ASSISTANT	7	4	35,584
ADMINISTRATIVE OFFICER	13	2	75,058
ADMINISTRATIVE OFFICER	12	2	63,119
ANIMAL CARETAKER	4	1	25,674
BIOLOGIST	AD	5	88,699
BIOLOGIST	12	6	63,119
BIOLOGIST	13	4	75,058
BIOLOGIST	14	4	88,699
BIOLOGIST	11	6	52,663
BIOLOGIST	9	1	43,525
BUDGET ANALYST	14	1	88,699
BUDGET ANALYST	12	2	63,119
CHEMIST	14	2	88,699
CHEMIST	AD	1	88,699
CHEMIST	11	1	52,663
CHEMIST	12	1	63,119
CLERICAL ASSISTANT (OA)	5	1	28,727
CLERICAL ASSISTANT (OA)	6	1	32,022
CLERICAL ASSISTANT (OA)	7	1	35,584
COMMITTEE MGMT. OFFICER	12	1	63,119
COMMITTEE MGMT. OFFICER	13	1	75,058
COMPUTER SCIENTIST	AD	1	88,699
COMPUTER SPECIALIST	13	1	75,058
COMPUTER SPECIALIST	12	4	63,119
CONTRACT SPECIALIST	7	1	35,584
CONTRACT SPECIALIST	14	1	88,699
CONTRACT SPECIALIST	13	2	75,058
CONTRACT SPECIALIST	12	5	63,119
CONTRACT SPECIALIST	11	2	52,663
CONTRACT SPECIALIST	9	1	43,525
FILE CLERK	5	1	28,727
GRANTS FINANCIAL ANALYST	12	2	63,119
GRANTS MANAGEMENT SPEC	9	2	43,525
GRANTS MANAGEMENT SPEC	11	3	52,663
GRANTS MANAGEMENT SPEC	12	5	63,119
GRANTS MANAGEMENT SPEC	13	2	75,058
GRANTS MANAGEMENT SPEC	14	1	88,699
GRANTS TECHNICAL ASST. (OA)	6	2	32,022
GRANTS TECHNICAL ASST. (OA)	7	4	35,584
GRANTS TECHNICAL ASST. (OA)	8	1	39,409
GRANTS TECHNICAL ASST. (OA)	9	1	43,525
HEALTH SCIENCE ADMINISTRATOR	AD	3	88,699
HEALTH SCIENCE ADMINISTRATOR	15	1	104,336
HEALTH SCIENCE ADMINISTRATOR	14	3	88,699
HEALTH SCIENCE ADMINISTRATOR	13	5	75,058
HEALTH SCIENCE ADMINISTRATOR	12	2	63,119
HEALTH SCIENCE ADMINISTRATOR	11	2	52,663
HEALTH SCIENCE ADMINISTRATOR	6	2	104,336

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases
New Positions Requested (Continued)

	FY 2003		
	Grade	Number	Annual Salary
HEALTH EDUCATION SPECIALIST	14	1	88,699
HEALTH EDUCATION SPECIALIST	13	1	75,058
HEALTH EDUCATION SPECIALIST	12	5	63,119
MATHEMATICAL STATISTICIAN	13	2	75,058
MEDICAL OFFICER	AD	5	88,699
MEDICAL OFFICER	15	2	104,336
MEDICAL OFFICER	14	2	88,699
MEDICAL OFFICER	13	1	75,058
MICROBIOLOGIST	AD	3	88,699
MICROBIOLOGIST	15	2	104,336
MICROBIOLOGIST	14	3	88,699
MICROBIOLOGIST	13	8	75,058
MICROBIOLOGIST	12	1	63,119
MICROBIOLOGIST	11	2	52,663
MICROBIOLOGIST	9	1	43,525
NURSE	14	2	88,699
NURSE	13	5	75,058
NURSE	12	2	63,119
OFFICE AUTOMATION CLERK	4	5	25,674
OPERATIONS RES. ANALYST	14	2	88,699
OPERATIONS RES. ANALYST	12	2	63,119
PERSONNEL MANAGEMENT SPECIALIST	14	1	88,699
PERSONNEL MANAGEMENT SPECIALIST	13	1	75,058
PERSONNEL MANAGEMENT SPECIALIST	12	3	63,119
PROCUREMENT TECHNICIAN	8	2	39,409
PROGRAM ANALYST	14	2	88,699
PROGRAM ANALYST	13	3	75,058
PROGRAM ANALYST	12	3	63,119
PROGRAM ANALYST	11	3	52,663
PROGRAM ANALYST	9	2	43,525
PROGRAM ANALYST	7	2	35,584
PROGRAM MANAGEMENT OFFICER	13	1	75,058
PROGRAM MANAGEMENT OFFICER	14	2	88,699
PURCHASING TECHNICIAN	9	3	43,525
PURCHASING TECHNICIAN	7	4	35,584
RESEARCH ASSOCIATE	14	1	88,699
RESEARCH ANALYST	13	1	75,058
RESEARCH ANALYST	12	1	63,119
RECORDS MGMT. TECH (OA)	7	1	35,584
RECORDS MGMT. TECH (OA)	8	1	40,569
SECRETARY	9	1	43,525
SECRETARY	8	2	39,409
SECRETARY	7	4	35,584
SECRETARY	6	6	32,022
SECRETARY	5	5	28,727
STATISTICIAN (HEALTH)	12	2	63,119
TECH TRANSFER SPECIALIST	13	1	75,058
TECH TRANSFER SPECIALIST	12	3	63,119
TRAINING COORDINATOR	13	1	75,058
VETERINARIAN	14	2	78,265
Total Requested		229	