

Chapter 1

Introduction

The National Institutes of Health (NIH) is one of the world's foremost biomedical research centers. As an agency of the U.S. Department of Health and Human Services, NIH is the federal entity in charge of health research. NIH's mission to support biomedical research is achieved through its 27 institutes and centers.

The National Institute of Allergy and Infectious Diseases (NIAID) is one of the leading institutions at NIH. For more than 50 years, NIAID has supported research in immunology, allergy, and infectious diseases with the aim of understanding, treating, and ultimately preventing those diseases (<http://www.usmedicine.com/article.cfm?articleID=122&issueID=20>). To meet the challenges of the new millennium and take advantage of unprecedented scientific opportunities, the institute has developed a strategic research plan for the 21st century focused on four major areas:

- Immune-mediated diseases, including allergy and asthma
- HIV/AIDS
- Global health and emerging infectious diseases
- Vaccines

In its mission to reduce the burden of human disease, NIAID is committed to encouraging and supporting accelerated translation of biomedical discoveries into new treatments on a global scale, especially in the areas of HIV/AIDS, tuberculosis, and malaria (www.niaid.nih.gov/publications/globalhealth/global.pdf).

Immune-Mediated Diseases. The burden of immune-mediated diseases is staggering. In the United States, these conditions result in direct and indirect costs that exceed US\$100 billion. Autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis, together affect approximately 5% of the U.S. population. At least 7% of American children are asthmatic, and more than 1 in 5 individuals in the United States are affected by allergies. In addition, immune-mediated graft rejection remains a significant obstacle to the potentially life-saving transplantation of organs. Recent advances in basic and clinical immunology, many accomplished with NIAID funding and support, hold

great promise for developing new treatments for individuals with immune-mediated diseases.

Among the most exciting areas of inquiry—and a major goal for the treatment of immune-mediated disorders—is the induction of immune tolerance; that is, selectively blocking (for a specific antigen) harmful immune responses while leaving protective immune responses intact. By inducing immune tolerance, it may be possible to prevent graft rejection in transplant patients without the long-term use of immunosuppressive drugs that dampen protective immune responses as well as destructive ones, thereby placing patients at increased risk of infection and malignancies.

The ability to block the immune response selectively also holds great promise for the treatment of many other immune-mediated conditions, including autoimmune diseases and asthma and allergic diseases. NIAID has developed a multifaceted research effort in immune tolerance. In autumn 1999, NIAID established the Immune Tolerance Network (ITN) in collaboration with the Juvenile Diabetes Foundation International and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (<http://www.usmedicine.com/article.cfm?articleID=122&issueID=20>).

HIV/AIDS. Acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), is one of the greatest threats to global health and one of the most destructive scourges in human history. Since the beginning of the HIV pandemic, an estimated 58 million people worldwide have been infected with HIV, of whom approximately 22 million have died. In the United States, approximately 800,000 to 900,000 people are living with HIV/AIDS; 430,000 deaths among people with AIDS had been reported to the Centers for Disease Control and Prevention by the end of 1999.

The global HIV-infected population continues to expand: in 2000 alone, there were 5.3 million new infections worldwide, half of which occurred among people younger than 25 years of age. In the United States, the rate of new HIV infections has reached an unacceptable plateau of 40,000 per year, with minority communities

disproportionately affected (<http://www.usmedicine.com/article.cfm?articleID=122&issueID=20>).

Although potent combinations of anti-HIV drugs (highly active antiretroviral therapy, or HAART) have reduced the number of AIDS deaths and new AIDS cases in many Western countries, the utility of these medications is limited by their substantial cost, toxicities, complicated and disruptive dosing regimens, and the development of drug resistance. Therefore, an important NIAID research priority is the development of new, less toxic therapies to control HIV replication and boost, rebuild, or replace immunity lost in HIV infection. Other methods of preventing HIV transmission, such as education, behavior modification, and the social marketing and provision of condoms, have also proved effective, both in the United States and in developing countries such as Uganda, Senegal, and Thailand. To build on these successes, NIAID recently launched the international *HIV Prevention Trials Network (HPTN)* to develop and test promising non-vaccine strategies to prevent the spread of HIV. The HPTN, a collaborative effort with the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, includes research sites in the United States and countries in Latin America, Europe, Africa, and Asia. The institute recently launched the *HIV Vaccine Trials Network (HVTN)*, an international network to develop and test preventive HIV vaccines. The HVTN will conduct all phases of clinical trials, from evaluating candidate vaccines for safety and ability to stimulate immune responses to testing the efficacy of vaccines. In addition to sites in the United States, HVTN sites are located in sub-Saharan Africa, Asia, Latin America, and the Caribbean. The network's international sites are critical in helping to identify vaccines appropriate for those regions hit hardest by AIDS.

Global Health and Emerging Infectious Diseases. The NIAID research program is predicated on the view that we live in an interconnected, global community; indeed, the institute's international research programs span the globe. As a nation, the interest of the United States in global health stems both from humanitarian concerns and what has been called "enlightened self-interest." An area's poor health status can have a profound negative impact on its social and economic development and frequently contributes to political instability.

The globalization of health problems—and their relevance to the United States—was brought emphatically to the attention of the public and policymakers by the AIDS epidemic. In the past few years, global health problems, particularly those related to emerging infectious diseases, are being recognized at the highest levels. For example, in 2000 the United Nations Security Council for the first time devoted an entire session to a health issue—AIDS in Africa—recognizing the enormous threat that the disease poses to the security not

only of that continent but also to that of the world. Despite many important advances in prevention and therapy, infectious diseases remain a leading impediment to global health. The World Health Organization (WHO) estimates that 1,500 people die each hour from an infectious disease. Half of these deaths occur in children under 5 years of age, and most of the rest are working adults who frequently are breadwinners and parents.

Adding to the burden of endemic infectious diseases are newly recognized diseases (e.g., HIV, Nipah virus) and the re-emergence of well-known diseases (e.g., tuberculosis, malaria) that have become increasingly problematic because of drug resistance, social conditions, and other factors. In addition, the international community now faces the specter of a new kind of emerging disease: one deliberately spread by a bioterrorist. These and other emerging disease threats are an important focus of NIAID efforts to improve global health. The NIAID's research efforts in this regard are directed toward three broad goals:

- Strengthening basic and applied research on the multiple host, pathogen, and environmental factors that influence the emergence of disease
- Supporting the development of diagnostics, vaccines, and therapies necessary to detect and control infectious diseases
- Maintaining and expanding the national and international scientific expertise required to respond to health threats

Many of the challenges posed by emerging infectious diseases lend themselves to research in a relatively new field: genomics. The sequencing of the entire human genome and the anticipated assignment, over the next few years, of function to the estimated 60,000 to 100,000 human genes will have an enormous impact on all of medicine, including our understanding of the host response to microbial pathogens. Parallel with the *Human Genome Project*, the many projects under way to sequence microbial pathogens will be a critical component of 21st-century strategies for developing diagnostics, therapeutics, and vaccines for endemic as well as emerging pathogens. The first microbial sequencing project, *Haemophilus influenzae*, was completed in July 1995 with extraordinary speed. Using newly developed techniques, investigators used a "shotgun" approach to sequence thousands of fragments of the bacterium's genome. Special computer programs read these sequences and stitched them together by comparing overlapping sequences. The result was the complete DNA sequence containing all of the genetic information of this bacterium. Encouraged by this success, NIAID has funded projects to sequence the full genomes of many medically important microbes, including the bacteria that cause tuberculosis, gonorrhea, chlamydia, and cholera, as well as individual chromosomes of important organisms such as the malaria parasite, *Plasmodium falciparum*. Many

of these microorganisms have been completely sequenced and are now being annotated and analyzed. Currently, the NIAID-funded researchers deposit the sequence data in specialized and public databases such as *GenBank*, operated by the National Center for Biotechnology Information, where they can be accessed by anyone through the Internet. Access to the sequence data, before they are published in peer-reviewed journals, enables the broader research community to jump-start and accelerate its experimental studies.

Vaccine Development. Vaccination has been recognized as the greatest public health achievement of the 20th century, and vaccine research has long been a vital part of the NIAID research portfolio. 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 (<http://www.usmedicine.com/article.cfm?articleID=122&issueID=20>). The rapidly evolving science base in pathogen genomics, immunology, and microbiology will facilitate further progress in developing new or improved vaccines. The use of currently available and future technologies in the 21st century promises to bring about a renaissance in an already vital field. In particular, the availability of the genomic sequences of major microbial pathogens will make it easier to identify a wide array of new antigens for vaccine targets.

Vaccines that target mucosal surfaces, such as those in the intestine or respiratory tract, are of great importance, because many pathogens gain entry to the host via mucosal sites. Vaccines administered orally, nasally, or transdermally are easy to administer and therefore have potentially great utility in developing countries and for mass immunization programs. The development of new adjuvants, which boost the immune response to vaccines, is another important area of research that has progressed rapidly in recent years.

In addition to the development of vaccines against classic infectious diseases, vaccines are being investigated to fight potential agents of bioterrorism, chronic diseases with infectious origins, and autoimmune diseases and other immune-mediated conditions.

Addressing Health Disparities. Much of the NIAID research effort is aimed at the health disparities that exist in the United States, as well as at the growing gap in health status between developed and developing countries. One example of this is the development of vaccines to prevent infectious diseases that disproportionately affect the poor, both in the United States and abroad. Other research addresses conditions that exact a significant toll in minority communities, such as research on HIV treatment and prevention, hepatitis C, and asthma, as well as tissue typing and other transplantation research and research into certain autoimmune diseases. In addition, NIAID has a long-standing commitment to increasing the number of minority investigators involved in

biomedical research and to education and outreach activities. As part of a broad NIH effort to eliminate health disparities, NIAID has developed a strategic plan for addressing health disparities in the new millennium. As discussed in this plan, NIAID will continue to strengthen its efforts to help eliminate health disparities due to infectious and immunologic diseases.

1.1 Primary NIAID Research Areas in Microbiology and Infectious Diseases (Non-HIV/AIDS)

NIAID is continuing its support of research in microbiology and infectious diseases primarily through the Division of Microbiology and Infectious Diseases (DMID). In general, DMID supports research to control and prevent diseases caused by virtually all human infectious agents except HIV/AIDS (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>).

Major research areas in microbiology and infectious diseases supported by NIAID include:

- **Bacteriology and Mycology.** Research areas in basic bacteriology and mycology include molecular structure and functions, genetics, biochemical composition, and physiologic and biochemical processes. Studies on infectious human pathogens would extend basic insights to identify candidate antigens for vaccines and drug targets and to examine mechanisms of infections, pathogenicity, and virulence. Areas of particular interest include tuberculosis, streptococci, pneumonia, hospital-caused nosocomial infections, fungal/opportunistic infections, antibiotic resistance, bacterial sexually transmitted diseases, and bacterial diarrheas (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>).
- **Biodefense.** As concern grows about the use of biological agents as weapons in acts of terrorism and war, the U.S. federal agencies are evaluating and accelerating measures to protect the public from health consequences of such an attack. The ability of the U.S. government to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science in general and the support NIAID is providing to the NIH's biodefense efforts and those of other federal agencies by funding and conducting research ranging from basic biology of pathogenic microorganisms (including those that could be intentionally introduced) and their interactions with the human immune system to preclinical and clinical evaluation of new diagnostics, therapeutics, and vaccines. One of the integral components of NIAID's Biodefense

- Program is its Biodefense Vaccine and other Biologicals Product Development Section (BVBPD), which is responsible for overseeing the creation, implementation, and execution of research focusing on the development of vaccines and other biological products (<http://www3.nih.gov/about/organization/dmid/overview/>).
- **Drug Development.** NIAID maintains an extensive drug development program that supports research at three levels: drug discovery (which encompasses the pathogenesis of the disease and identifying, characterizing, and screening the target on the pathogen); pre-clinical evaluation by testing drug candidates in models of human infections; and clinical trials evaluating new therapies. For most human pathogens, there are resources for identifying and validating the pathogen target and for developing the assay. For selected viruses and other pathogens, such as tuberculosis, hepatitis B and C, and the NIAID biodefense priority pathogens, there are additional resources for acquiring compounds, screening them, performing *in vitro* and *in vivo* assays, evaluating efficacy in animals and conducting preliminary drug exposure studies, and performing safety testing and pharmacokinetic/pharmacodynamic analyses. In addition, NIAID is involved in multiple public-private partnerships—arrangements that innovatively combine skills and resources from institutions in the public and private sectors to advance drug development (<http://www3.nih.gov/about/organization/dmid/overview/>).
 - **Emerging and Re-emerging Infectious Diseases.** Despite remarkable advances in medical research and treatment, infectious diseases remain among the leading causes of death worldwide, resulting, in part, from the emergence of new infectious diseases, the re-emergence of old infectious diseases, and the persistence of intractable diseases, sometimes as the result of drug resistance. In addition, the finding that chronic diseases may develop as consequences of acute illness, the challenge of opportunistic infections, and the discovery of viral infections associated with malignancies are presenting new challenges to the scientific community. As a result, NIAID is continuing its support to basic and clinical research—in particular microbial genomics—to better understand the pathogenesis, microbiology, and epidemiology of emerging and re-emerging infectious diseases with the goal of developing more effective diagnostics, vaccines, and therapeutics (<http://www3.nih.gov/about/organization/dmid/overview/>).
 - **Global Health Research.** A 2002 WHO report on the impact of infectious diseases on public health identifies the following leading infectious diseases with the highest mortality rates: respiratory diseases (pneumonia, influenza), diarrheal diseases, AIDS, malaria, measles, and tuberculosis (<http://www.who.int/infectious-diseases-report/2002/>).

report/2002/). Recognizing that infectious diseases spread without regard to national boundaries, NIAID will continue to make international research in infectious diseases a high priority by supporting research aimed at all aspects of infectious pathogens that present, or potentially present, a significant public health threat—research ranging from basic biology and pathology to vaccine development and improved diagnostics. One fundamental part of the NIAID international program is its emphasis on strengthening research capacity for infectious diseases in endemic areas. To achieve this goal, NIAID participates in a number of international partnerships, including the establishment of research programs in tropical medicine, country-to-country bilateral agreements, and interagency agreements with the U.S. Agency of International Development (USAID), the Centers for Disease Control and Prevention (CDC), the National Aeronautics and Space Administration (NASA), and the Department of State, as well as multilateral programs with WHO, the United Nations Children's Fund (UNICEF), the Global Alliance for Vaccines and Immunization (GAVI), and the Multilateral Initiative on Malaria (MIM) (<http://www3.nih.gov/about/organization/dmid/overview/>).

- **Microbial Genomics.** One important area of interest for NIAID is funding of research projects to sequence the full genomes of medically important microorganisms. Genome sequencing can make it easier to define targets for vaccine and drug development, identify mutations that contribute to drug resistance, help trace microbial evolution, and provide information for forensic studies by differentiating among strains of organisms (<http://www3.nih.gov/about/organization/dmid/overview/>).
- **Parasitology.** NIAID continues its support of research on human parasites using biochemical, genetic, and immunologic approaches to identify protective and diagnostic antigens and to develop more effective drugs. In addition, studies on insect vectors will help control the transmission of pathogens, such as malaria, that are responsible for inflicting significant morbidity and mortality worldwide. Because parasitic and other tropical diseases are international health problems, the NIAID support extends to clinical trials in regions where these infections are endemic through the Tropical Medicine Research Centers and the International Collaboration in Infectious Diseases Research programs (<http://www3.nih.gov/about/organization/dmid/overview/>).
- **Respiratory Diseases.** NIAID's Respiratory Diseases Program is aimed at supporting research on effective diagnosis, prevention, and treatment of respiratory infections. This includes developing vaccines and treatments, understanding the long-term health impact that respiratory pathogens have in various populations, stimulating basic research on the pathogenesis, immunity,

and structural biology of these pathogens, and developing better diagnostics (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>). To this end, major areas of interest remain research on influenza and severe acute respiratory syndrome (SARS).

- *Vaccine Development for Sexually Transmitted Infections.* Sexually transmitted infections (STIs) represent a critical global health priority because of their devastating impact on women and infants and their interrelationships with HIV/AIDS. The NIAID research funding is aimed at vaccine development as well as clinical, epidemiologic, and behavioral investigations to identify strategies for primary and secondary prevention of STIs and conditions associated with them. Such conditions include pelvic inflammatory disease (PID), infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infections, and the spread of HIV. NIAID is also supporting research on topical microbicides in an effort to prevent further spreading of STIs by funding basic product development and clinical research (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>).
- *Vaccine Development.* One goal of primary importance to NIAID is the development of new and improved vac-

cines and strategies for vaccine delivery for the entire spectrum of infectious agents: viruses, bacteria, parasites, and fungi. To this end, since 1981, NIAID has been supporting a program for the accelerated development of new vaccines using advances in molecular biology, immunology, genetics, and epidemiology. An important part of these efforts is to conduct studies on vaccine safety through clinical trials sponsored by NIAID (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>).

- *Virology.* NIAID continues its long-standing support of basic and applied research in virology ranging from vaccine development and gene therapy to drug target identification, as well as the study of virus-host interactions, especially those involved in pathogenesis and immune evasion. Basic information derived from these studies is being used to control the impact of significant viral diseases, such as polio, rabies, diseases caused by herpesviruses, emerging viral infections, and viruses important for biodefense, as well as to develop crucial public health tools, such as antiviral therapeutics (<http://www3.niaid.nih.gov/about/organization/dmid/overview/>).