VI.
National Institute of Allergy and Infectious Diseases

INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) can trace its origin back to the Laboratory of Hygiene established by the Department of the Treasury on Staten Island, New York, in 1887. The Laboratory of Hygiene evolved into the National Microbiological Institute, which was renamed the National Institute of Allergy and Infectious Diseases. After the dissolution of the Office of International Research, of the National Institutes of Health (NIH), in 1968, NIAID assumed responsibility for the Office's International Centers for Medical Research and Training (ICMRT) Program. NIAID subsequently assumed lead NIH responsibility for research on influenza (1974), sexually transmitted diseases (STDs) (1974), and human immunodeficiency virus (HIV) (1986).

NIAID's organization into six Divisions is similar to that of other NIH Institutes, which also carry out and fund research. The Institute's Division of Intramural Research (DIR) and its Vaccine Research Center (VRC) are responsible for research conducted in NIAID's laboratories. The three extramural Divisions fund research outside the NIH: the Division of Microbiology and Infectious Diseases; the Division of Allergy, Immunology, and Transplantation; and the Division of AIDS (acquired immunodeficiency syndrome) (DAIDS). The Division of Extramural Activities is responsible for groups convened by NIAID to provide initial review of grant proposals; administrative management of external awards; and secretariat support to the National Advisory Allergy and Infectious Diseases Council.

NIAID is the third largest component of the NIH, the research arm of the U.S. Public Health Service (PHS), a domestic agency. Authority for the NIH to conduct international research was formally defined in the PHS Act of 1963, which limited studies to "international research of health and welfare of U.S. populations." The PHS Act of 1988, the "AIDS" Act, expanded this authority to training, technology, and institutional strengthening in HIV/AIDS and related areas. In fiscal year 1994 (FY 94), NIAID was, for the first time, given a specific mandate for research on tropical disease. NIAID uses the following six mechanisms to conduct international research: (1) intramural collaboration with DIR and VRC; (2) awards for foreign research; (3) awards for domestic research with foreign components; (4) bilateral programs; (5) interagency agreements; and (6) multilateral activities.

Division of Intramural Research

DIR consists of 18 Laboratories. The Laboratories are concentrated on the NIH campus, Bethesda, Maryland, but some are located in Rockville and Frederick, Maryland, and at the Rocky Mountain facilities in Hamilton, Montana.

The 18 Laboratories are as follows: Laboratory of Allergic Diseases; Laboratory of Cellular and Molecular Immunology; Laboratory of Clinical Investigation; Laboratory of Host Defenses; Laboratory of Human Bacterial Pathogens; Laboratory of Immunogenetics; Laboratory of Immunology; Laboratory of Immunopathology; Laboratory of Immunoregulation; Laboratory of Intracellular Parasites; Laboratory of Infectious Diseases; Laboratory of Microbial Structure and Function; Laboratory of Molecular Microbiology; Laboratory of Parasitic Diseases; Laboratory of Persistent Viral Diseases; Laboratory of Viral Diseases; Rocky Mountain Operations Branch; and Rocky Mountain Microscopy Branch.

The Dale and Betty Bumpers VRC formally opened in FY 00. VRC was established by former President Bill Clinton to facilitate research in vaccine development. The Center represents a partnership among NIAID, the National Cancer Institute (NCI), the Office of AIDS Research, and other components of the NIH. The initial focus of the VRC is on HIV/AIDS vaccines, but the ultimate goal is to improve global human health through the rigorous pursuit of effective vaccines for human diseases.

DIR and VRC consist of tenured scientists, tenured clinicians, tenure-track scientists, non-tenured scientists (one-third from foreign countries), and a support staff of non-scientists. During FY 00, the largest national groups of foreign scientists receiving short-term research training at NIAID were from Japan (45), China (33), France (22), Germany (22), Italy (19), Canada (17), Korea (17), India (16), the United Kingdom (13), Brazil (12), Australia (9), Russia (8), and Spain (8). Other countries and areas represented were Albania, Algeria, Argentina, Austria, Bangladesh, Belgium, Bulgaria, Colombia, Croatia, the Czech Republic, Denmark, Ethiopia, Gabon, Hungary, Ireland, Israel, Jordan, Mali, Mexico, Morocco, the Netherlands, New Zealand, Peru, the Philippines, Portugal, Romania, Slovakia, South Africa, Sweden, Switzerland, Thailand, Turkey, Ukraine, and Taiwan. The personnel in this Division constitute the majority of NIAID staff but only about 10% of the NIAID budget.

Extramural Research

NIAID support for extramural research is the primary source of funding for civilian investigators in U.S. universities and research institutions in the areas of HIV and AIDS, STDs, tropical diseases, tuberculosis, and development and evaluation of human vaccines. Extramural research accounts for about 90% of the NIAID funding but only 10% of staff positions.

In contrast to most domestic research agencies, NIAID allows foreign investigators to apply directly for investigator-initiated research grants and, under certain circumstances, to respond to solicited Program Announcements (PAs), Requests for Applications (RFAs), and Requests for Proposals (RFPs). The rivalry for investigator-initiated grants and other awards, however, has be-

come so competitive that direct application is not viable for most overseas scientists. The more effective strategy for foreign scientists is to identify a U.S. collaborator with experience and success in writing applications for NIH grants. The U.S. partner can then submit the collaborative proposal to the NIH. If peer review finds the proposal to be competitive, NIAID provides funds to the U.S. institution to carry out both the domestic and foreign components of the proposal. In research areas such as international tropical diseases, vaccine evaluation, and AIDS, proposals for research in resource-poor settings often do not compete successfully in the general grants pool. To fulfill its research mission, NIAID therefore develops special funding mechanisms, reserves funds, and solicits applications that compete against each other for available funds in these areas.

The Division of Microbiology and Infectious Diseases supports four special international programs:

1. The Tropical Disease Research Unit (TDRU) awards support multidisciplinary centers of research excellence in the United States.

2. The Tuberculosis Prevention and Research Unit (TBRU) supports a U.S. university to coordinate a network of domestic and international centers for research on this reemerging disease.

3. The International Collaboration in Infectious Disease Research (ICIDR) Program provides funding to U.S. institutions to link with institutions in developing countries.

4. Tropical Medicine Research Center (TMRC) awards are direct funding to outstanding institutions located in the tropics.

During FY 97, NIAID initiated three Emerging Viral Diseases Centers (EVCs), and the Institute supports six Viral Hepatitis Research Centers, as part of the Emerging and Reemerging Infectious Diseases Research Initiative.

In 1987, DAIDS (NIAID) launched the International Collaboration in AIDS Research (ICAR) Program, modeled after the ICIDR Program. The ICAR awards were succeeded by the more focused Preparing for AIDS/HIV Vaccine Evaluation (PAVE) linkage awards. DAIDS supports an International AIDS Vaccine Master Contract, which makes HIVNET (HIV Network) awards to U.S. institutions to carry out specific HIV/AIDS intervention or prevention projects in the United States or in developing countries. In July 2000, NIAID split the HIVNETs into HIV/AIDS Prevention Trial Units (HPTUs) and HIV Vaccine Trial Units (HVTUs), each of which constitutes global networks devoted to evaluation of a number of prevention modalities and vaccine candidates.

To more closely coordinate and monitor international research activities, NIAID established the International Centers for Tropical Disease Research (ICTDR) Network in 1992. The ICTDR Network consists of (1) the NIAID Office of Tropical Medicine and International Research; (2) the Laboratory of Parasitic Diseases; (3) ICIDR, TDRU, and TMRC participants; and (4) U.S. institutions receiving substantial NIAID support for research in tropical medicine. The ICTDR Network convenes each spring in an open scientific meeting in Bethesda, Maryland, for coordination, exchange, and identification of research needs and opportunities.

Bilateral Activities

NIAID's country-to-country activities run the gamut from direct scientist-to-scientist collaboration to formal agreements at NIAID, the NIH, PHS, and the presidential level. NIAID participates in bilateral agreements with Brazil, China, Croatia, Finland, France, Georgia, Germany, India, Israel, Italy, Japan, Mongolia, Poland, Russia, Slovenia, South Africa, and Taiwan. For some of these agreements, extrabudgetary funds are available from the U.S. Agency for International Development (USAID), the U.S. Department of State, or the Special Foreign Currency (Public Law 480) Program, but most are implemented with regular NIAID resources.

Interagency Agreements

It has become increasingly common for agencies to combine resources to carry out joint programs. This strategy has been particularly common with USAID, which frequently uses the resources within the U.S. Government to carry out its international activities. Other examples include participation by the Laboratory of Immunoregulation and DAIDS (NIAID) in an agreement with the Centers for Disease Control and Prevention (CDC) for Projet SIDA in the Democratic Republic of the Congo (former Zaire) and NIAID participation in the International Cooperative Biodiversity Group Program, which is managed by the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC), NIH. In addition, NIAID and the National Aeronautics and Space Administration are engaged in an ongoing dialogue to identify projects of mutual interest.

Multilateral Activities

Infectious diseases, including AIDS, are the major causes of preventable death and disease throughout the world. New knowledge and research advances made possible by NIAID research, therefore, are important for the global prevention, treatment, and control of these conditions. The World Health Organization (WHO) is the lead United Nations agency in health. NIAID scientists and awardees participate extensively in WHO advisory committees and steering committees in tropical diseases, infectious diseases, AIDS, and immunology. NIAID laboratories or programs also serve as WHO Collaborating Centers: (1) Epidemiology of Asthma and Allergic Diseases (Division of Allergy, Immunology, and Transplantation); (2) Microbial Vector Research (Laboratory of Viral Diseases); and (3) AIDS Reagent Center (DAIDS).

NIAID also has a close working relationship with the Regional Office of WHO for the Americas and the Pan American Sanitary Bureau, which is the health component of the Organization of American States. Both components function as the Pan American Health Organization, located in downtown Washington, D.C. NIAID is also a member of the consortium of United Nations agencies (e.g., WHO and the United Nations International Children's Emergency Fund) and other organizations participating in the Global Alliance for Vaccines and Immunization.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

HIV/AIDS

In FY 99, NIAID decided to phase out the domestic and international HIVNET prevention program. NIAID nearly doubled the available funding and established the global HIV/AIDS Prevention Trials Network (HPTN) and the global HIV/AIDS Vaccine Trials Network (HVTN).

HIV/AIDS Prevention Trials Network. Family Health International, Durham, North Carolina, coordinates the domestic and international HIV/AIDS Prevention Trial Centers (HPTCs). The purpose of the HPTN is to support a global network of field sites in which prevention research protocols can be implemented. The HPTN prevention research agenda includes projects in reducing mother-to-infant and perinatal HIV transmission, microbicides, behavioral change, reduction of substance abuse, control of STDs, and community-based studies. The 14 international sites and participating institutions are as follows:

- Brazil—University of California, Los Angeles, and Federal University of Rio de Janeiro;
- China—Johns Hopkins University, Baltimore, Maryland, and the National Center for AIDS Prevention and Control, Beijing;
- India—(1) Brown University, Providence, Rhode Island, and the YGMR Foundation, Chennai, and (2) Johns Hopkins University, Baltimore, and the ICMRT National AIDS Research Institute, Pune;
- Malawi—Johns Hopkins University, Baltimore, Queen Elizabeth Hospital, Blantyre, and Lilongwe General Hospital;
- Peru—University of Washington, Seattle, and Cayetano Heredia Peruvian University, Lima;
- Russia—University of North Carolina, Chapel Hill, and St. Petersburg University;
- South Africa—South African Medical Research Council, Durban;
- Tanzania—Harvard School of Public Health, Boston, Massachusetts, and Muhimbili Medical Center, Dar es Salaam;
- Thailand—Johns Hopkins University, Baltimore, and Chiang Mai University;
- Uganda—(1) Columbia University, New York City, New York, and Uganda Viral Research Institute, Kampala, and (2) Johns Hopkins University, Baltimore, and Makerere University, Kampala;
- Zambia—the University of Alabama, Birmingham, and University Teaching Hospital, Lusaka; and
- Zimbabwe—the University of California, San Francisco, and the National Family Planning Council, Harare.

HIV/AIDS Vaccine Trials Network. The University of Washington, Seattle, will be the coordinator of the domestic and international HIV/AIDS Vaccine Trial Center (HVTCs). Coordination involves a leadership group that includes the Core Operations Center for administrative, technical, and operational support; the Statistical and Data Management Center; and the Central Laboratory. The nine domestic HVTCs are located at (1) the University of Alabama, Birmingham; (2) Harvard University, Boston; (3) Johns Hopkins University, Baltimore; (4) the University of Maryland, Baltimore; (5) the University of Rochester, New York; (6) St. Louis University, Missouri; (7) San Francisco Health Department, California; (8) Vanderbilt University, Nashville, Tennessee; and (9) Fred Hutchinson Cancer Research Center and the University of Washington, Seattle.

Eight international HVTN sites will be located at (1) Hospital Escola São Francisco de Assisi, Rio de Janeiro, Brazil (affiliated with the University of Rochester, New York); (2) Guangxi Health and Epidemic Center, Nanning, China (affiliated with Johns Hopkins University, Baltimore); (3) Cornell-GH-ESKIO, National Laboratory and Research Institute, Port-au-Prince, Haiti (affiliated with Vanderbilt University School of Medicine, Nashville); (4) the ICMRT National AIDS Research Institute, Pune, India (affiliated with Johns Hopkins University); (5) IMPACTA-Cayetano Heredia Peruvian University, Lima (affiliated with the University of Washington, Seattle); (6) South African Medical Research Council, Durban; (7) Chiang Mai University, Thailand (affiliated with Johns Hopkins University); and (8) Medical Research Foundation of Trinidad and Tobago, Port of Spain (affiliated with the University of Maryland, Baltimore). In addition to the established international sites, the HVTN has the flexibility to move rapidly into other study locations.

University of California/Los Angeles International Center for AIDS Research. The Center has been active in HIV/AIDS research and training activities in Brazil, Cambodia, Myanmar, Peru, Russia, Thailand, and Vietnam.

International Clinical Trials. NIAID supports the University of Minnesota, Minneapolis, to coordinate the Esprit Study in Argentina, Australia, Denmark, Germany, Greece, Israel, the Netherlands, Norway, Portugal, Spain, Sweden, Thailand, and the United Kingdom. The Esprit Study is a randomized, controlled, phase III clinical trial that compares treatment with escalating doses of interleukin 2 (IL-2) plus antiretroviral drugs versus therapy with antiretroviral drugs alone, in HIV-positive patients with counts of CD4-positive T cells higher than 350/mm3.

Epidemiology. The University of Hawaii, Manoa, is conducting studies on the molecular epidemiology of strains of human immunodeficiency virus type 1 (HIV-1) from Papua New Guinea and Vietnam.

Natural History. The Laboratory of Immunoregulation (NIAID), the University of Washington, Seattle, the University of Alabama, Birmingham, the Institute of Clinical Research, Montreal, Quebec, San Raffaele Institute, Milan, Italy, and the University of Geneva, Switzerland, reported that the qualitative nature of the primary immune response to HIV-1 infection is a prognosticator of disease progression independent of initial plasma viremia.

Opportunistic Infections. Stanford University, California, San Matteo Polyclinic, Pavia, Italy, and the University of Zimbabwe, Harare, studied the geographic and demographic differences in the frequency of human cytomegalovirus (CMV) gB genotypes in HIV-positive populations in Italy, Zimbabwe, and the United States. In Italy, gB3 levels were higher in intravenous drug users than in homosexuals; gB4 levels were higher overall in Italian patients; and gB2 levels were higher in both intravenous drug users in Italy and heterosexuals in Zimbabwe.

NCI (NIH), New York University, New York City, North Shore University Hospital, Manhasset, New York, George Washington University, Washington, D.C., the University of Maryland, Baltimore, and Specialty Laboratories, Santa Monica, and Immune Response Corporation, Carlsbad, California, are using specimens from blood donors in India to examine the association between serum antibodies to herpesvirus type 8 (HHV-8) and various malignant diseases in populations from Jamaica and elsewhere in the Caribbean, Southeast Asia, Uganda, and the United States.

Dartmouth Medical College, Lebanon, New Hampshire, coordinates a study of the epidemiology of disseminated *Mycobacterium avium* complex infections in Finland, Kenya, Trinidad and Tobago, and the United States.

The University of Cincinnati, Ohio, Johns Hopkins University, Baltimore, the University of Washington, Seattle, Seoul National University, Korea, and the University of Witwatersrand, Johannesburg, South Africa, determined that, although serological positivity for *Pneumocystis carinii* is worldwide, reaction to higher-weight proteins is less frequent in Mexico and the United States than in Africa. This finding suggests the presence of antigenically different *P. carinii* organisms.

Pathogenesis. Investigators at the University of Minnesota, Minneapolis, Beth Israel Hospital, Boston, Massachusetts, the University of Pittsburgh, Pennsylvania, California Regional Primate Center, Davis, the University of California, San Diego, Northwestern University Medical School, Chicago, Illinois, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany, and the University of Amsterdam, the Netherlands, are studying the sexual transmission of simian immunodeficiency virus (SIV) and HIV-1. They found that both viruses replicated predominantly in CD4-negative T cells and persisted in latent T cells after antiretroviral therapy. Latent and chronically infected cells derived from this population, therefore, pose challenges to eradicating infection and developing an effective vaccine.

Virology. Aaron Diamond AIDS Research Center, New York City, New York, has NIAID support to study HIV variation and cross-clade recognition of cytotoxic T lymphocytes (CTLs) in Africa, China, Thailand, and South America.

Harvard School of Public Health, Boston, Hôpital Bichat, Paris, France, the French Institute for Cooperative Research in Development, Montpellier, France, Popa University, Iasi, Romania, and Cheikh Anta Diop University, Dakar, Senegal, are documenting V3 peptide serology in specimens from sub-Saharan Africa and Europe, in an effort to correlate their serology with their genotype.

Vaccines. Emory University, Atlanta, Georgia, Institut Pasteur, Paris, France, and the University of Zhrich, Switzerland, are evaluating measles, yellow fever, and modified vaccinia viruses as vectors for candidate AIDS vaccines.

Antimicrobial Drug Resistance

Bacterial Diseases. Rockefeller University, New York City, New York, is coordinating a 21-country, multicenter study of the molecular typing of methicillin-resistant *Staphylococcus aureus* and *Enterococcus* in Argentina, Brazil, Bulgaria, Chile, China, Colombia, the Czech Republic, Denmark, Hungary, Iceland, Italy, Japan, Mexico, Poland, Portugal, Spain, the United States, Uruguay, and Taiwan.

Emerging and Reemerging Infectious Diseases

Bacterial Diseases. Johns Hopkins University, Baltimore, the University of Alabama, Birmingham, the International Center for Diarrheal Disease Research of Bangladesh, Dhaka, and the University of Göteborg, Sweden, studied enterotoxin-specific immunoglobulin E (IgE) responses in Bangladeshi, Swedish, and U.S. patients after infection with or immunization against diarrhea-causing enteric pathogens. The investigators found that levels of IgE in Bangladeshi patients, on average, were more than 89 times higher than those in Swedish patients and 34 times higher than those in U.S. patients.

Washington University, St. Louis, Missouri, is investigating the importance of *Helicobacter pylori* gene transfer in the development of resistance to metronidazole and clarithromycin in previously unstudied populations in China and India.

Louisiana State University, Baton Rouge, the National Institute of Infectious Diseases, Tokyo, Oshima Seishoen National University, Kagawa, and Osaka University Medical School, Japan, and Catholic University of Korea, Seoul, are studying the genomic diversity and global distribution of genotypes of *Mycobacterium leprae* from specimens collected from around the world.

Diagnostic Tests. The University of Texas Medical Branch, Galveston, Louisiana State University, Baton Rouge, and the Australian Rickettsial Reference Laboratory, Geelong, developed and evaluated a recombinant antigen specific for *Rickettsia felis*. This finding makes it possible to differentiate *R. felis* from *R. typhi,* the classic agent that causes flea-borne typhus fever.

Vector Biology. Yale University, New Haven, Connecticut, and the National Institute of Health, Bogotá, Colombia, are investigating the genetics and biogeography of sand fly disease vectors in Brazil, Colombia, Costa Rica, and Panama.

Viral Diseases. The University of Notre Dame TDRU, South Bend, Indiana, is conducting a comparative analysis of Cache Valley virus isolates from Canada, Mexico, and Panama in an effort to determine immunogenic epitopes.

The Laboratory of Infectious Diseases (NIAID), CDC, Eastern Virginia Medical School, Norfolk, Baylor College of Medicine, Houston, Texas, the University of Melbourne, Australia, Sapporo University School of Medicine, Japan, and M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia, participate in the International Calciviridae Study Group of the International Committee on Taxonomy of Viruses.

The University of Texas Medical Branch, Galveston, the Mexico-U.S. Commission for the Prevention of Foot and Mouth Disease and Other Exotic Animal Diseases, Mexico City, and the National Depository for Animal Emergency Sanitation, Palo Alto, California, and Tuxtla, Mexico, identified four major genetic and antigenic lineages among isolates of eastern equine encephalitis virus from North, Central, and South America.

In August 2000, scientists at the NIAID Vaccine Center identified a protein on the surface of Ebola virus isolates from the Democratic Republic of the Congo that is primarily responsible for the virus' pathogenicity. They discovered that deletion of the mucin domain of the virus blocked its ability to kill cells. This finding raises the possibility of developing inhibitors of glycoprotein-mediated cytotoxicity in an effort to reduce the severity of this disease, which is usually fatal.

The U.S. Department of Agriculture (USDA), St. Jude Children's Research Hospital, Memphis, Tennessee, Queen Mary Hospital and the University of Hong Kong, Hong Kong, and the Institute of Virology, Beijing, China, and the National Veterinary Research Hospital, Anyang, Korea, charac-

terized the pathogenicity of members of the newly established H9N2 influenza virus lineages in Asia.

Researchers at Montreal General Hospital, Quebec, and Cayetano Heredia Peruvian University, Lima, explored the immunologic basis for the observation that measles vaccines are less effective in the tropics. They found definite differences in immune responses after immunization, particularly a marked and diffuse activation of subsets of peripheral blood mononuclear cells in Peruvian children. The finding suggests that subclinical immune responses may interfere with the normal effect of measles vaccination. The researchers also reported that susceptibility of pregnant women to rubella predicted susceptibility to measles, raising the possibility that obstetric clinics should consider the routine administration of rubella–measles vaccine rather than monovalent rubella vaccine.

The University of Texas Medical Branch, Galveston, studied the genetic relatedness of isolates of St. Louis encephalitis virus from the Americas, as part of an effort to elucidate mechanisms this virus uses to survive adverse seasons. Previous studies during 1952–1989 in the San Joaquin Valley, California, had shown a high degree of homogeneity, but this study using current methods demonstrated considerable genomic variation with evidence of geographic spread. Some isolates in Florida, for example, were similar to isolates from Mexico and Panama, and other Florida isolates were similar to those in Maryland.

The University of California, Berkeley, and Charles University, Prague, Czech Republic, have studied the prevalence and genotypic analysis of the recently identified TT virus and determined that it does not seem to be associated with blood transfusion or intravenous substance abuse. The scientists are working to determine whether infection with the virus is associated with clinical disease in humans.

In August 2000, NIAID made a fast-track Small Business Innovative Research grant to OraVax, Boston, Massachusetts, to support the development of a chimeric vaccine against West Nile virus, a recent import to the northeastern United States from the Middle East.

CDC, the University of Massachusetts, Worcester, Globio Corporation, Beverley, Massachusetts, and the Department of Health, Taipei, Taiwan, used the new denKEYTM assay kit to detect dengue virus in human sera collected during the febrile phase of infection in Puerto Rico, Thailand, and Taiwan.

Hepatitis C Virus

Special Programs

In FY 00, NIAID recompeted and expanded the existing Hepatitis C Cooperative Research Centers Program. The number of Centers expanded from four to six. The network is applying the tools of genome analysis and other advanced technologies in a multidisciplinary fashion.

The six Hepatitis C Cooperative Research Centers are at Ohio State University, Columbus; Stanford University, California; the University of Southern California, Los Angeles; University of Tennessee Health Science Center, Memphis; the University of Texas Medical Branch, Galveston; and the University of Washington, Seattle.

Tropical Medicine

International Collaboration in Infectious Diseases Research Program. In its 20th year in FY 00, the ICIDR Program provides support to U.S. institutions to carry out collaborative research in infectious diseases in tropical countries. Current ICIDR projects are located at the following sites:

- Brazil—Enteric Infections: Impact and Outcome, University of Virginia, Charlottesville; Schistosomiasis: Host Genetics, State University of New York (SUNY), Buffalo; and Tuberculosis Control, Johns Hopkins University, Baltimore;
- Chile—Hantavirus: Ecology and Disease, University of New Mexico, Albuquerque;
- Egypt—Hepatitis E: Epidemiology, University of Maryland, Baltimore;
- Gabon, the Gambia, and Ghana—Severe Malaria in Children, Michigan State University, East Lansing;
- Kenya—Lymphatic Filariasis, Case Western Reserve University, Cleveland, Ohio; Severe Malaria in Children, Michigan State University, East Lansing; Malaria Vectors, Tulane University, New Orleans, Louisiana; and Urinary Schistosomiasis, Case Western Reserve University, Cleveland;
- Mexico—Dengue Fever, Colorado State University, Fort Collins; and Drug-Resistant Tuberculosis, Stanford University, Palo Alto, California;
- Papua New Guinea—Lymphatic Filariasis, Case Western Reserve University, Cleveland;
- Peru—*Taenia solium* Cysticercosis, Johns Hopkins University, Baltimore;
- South Africa—Infectious Diarrhea/Micronutrients, New England Medical Center, Boston, Massachusetts;
- Tanzania—Tuberculosis, Epidemiology, Immunology, Harvard University, Boston, Massachusetts;
- Thailand—Hepatitis C Epidemiology, Johns Hopkins University, Baltimore; and

Venezuela—Dengue Fever Pathogenesis, University of Massachusetts, Worcester.

Tropical Diseases Research Units. The TDRU Program consists of domestic grant awards to U.S. institutions to support multidisciplinary, targeted research on helminthic and protozoan human pathogens. The four TDRUs are located at the following sites:

- University of California, San Francisco—Anti-Parasitic Chemotherapy: Targeting Cysteine Proteases;
- University of Georgia, Athens—*Trypanosoma cruzi* Vaccine Discovery;
- University of Notre Dame, South Bend, Indiana—Malaria Control by Genetic Manipulation; and
- University of Virginia, Charlottesville—Adherence Blocking Vaccine for Amebiasis.

Tropical Medicine Research Centers. TMRCs are multidisciplinary centers of excellence located in or near the tropics that are directly funded by NIAID. The current four TMRCs are at the following sites:

- Brazil—Tropical Diseases, Pathogenesis, Therapy, Federal University of Bahia, Salvador;
- China—Emerging Helminthiases, Institute of Parasitology, Shanghai; and
- Mali—Malaria Epidemiology and Entomology, National School of Medicine, Bamako.

Human Immune Response to Malaria in Endemic Areas. NIAID supports three cooperative agreements to fund clinical studies designed to further the understanding of immunity to *Plasmodium falciparum* or *P. vivax* in humans in endemic areas. The three current sites and lead institutions are

(1) Cameroon—Georgetown University, Washington, D.C.; (2) Indonesia—the Naval Medical Research Center, Bethesda, Maryland; and (3) Kenya—Case Western Reserve University, Cleveland.

Malaria Clinical Research and Trial Preparation Sites. NIAID supports two research contracts for clinical and field-based research on malaria and transmission and pathogenesis of malaria in endemic settings. The two current contracts are for sites in Ghana, at Noguchi Memorial Institute for Medical Research, Legon, and in Mali, at the National School of Medicine, Bamako, through the University of Maryland Center for Vaccine Development, Baltimore.

Malaria Research Reagent and Reference Services. In FY 00, NIAID established and funded the Malaria Research Reagent and Reference Resource Center through a contract with the American Type Culture Collection, Manassas, Virginia. In collaboration with the Multilateral Initiative on Malaria, WHO, and other groups, the Resource Center provides research reagents to the international malaria research community, coordinates international studies, and conducts training courses.

The National Polytechnic Institute, Mexico City, Mexico, collaborated with the Laboratory of Parasitic Diseases (NIAID), Institut Pasteur, Paris, and the University of the Mediterranean, Marseilles, France, and the University of Kyoto, Japan, in identifying a domain of *P. falciparum* that mediates adhesion to chondroitin sulfate A and serves as a receptor for human placental infection.

The Naval Medical Research Institute, Rockville, Maryland, and Gorgas Memorial Laboratory, Panama City, Panama, are collaborating with the U.S. Naval Medical Research Unit No. 3, Jakarta, in the study of onset of acquired immunity to malaria in nonimmune populations in Indonesia.

Michigan State University, East Lansing, is responsible for a multicountry ICIDR involving Gabon, the Gambia, Ghana, Kenya, and Uganda that is examining the clinical aspects of malaria in children. Active projects include (1) a multicenter, prospective, observational study of intraleukocytic and intraerythrocytic pigment as prognostic features in African children with malaria and (2) a "dose-finding" phase II study of pentoxifylline in children with cerebral malaria.

The Laboratory of Parasitic Diseases (NIAID), the U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia, and the Naval Medical Research Center Detachment, Lima, Peru, developed a polymerase chain reaction (PCR) assay based on the orthologue of *P. falciparum* CG4, which is very sensitive (100%) but not particularly specific (58%) in detecting chloroquine sensitivity of *P. vivax* in Guyana, Indonesia, and Peru.

The Laboratory of Parasitic Diseases (NIAID) and Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, and Federal University of Minas Gerais, Belo Horizonte, Brazil, are exploring the biological and phylogenetic relationships between various avian circumsporozoite proteins and malarias in different parts of the world. The scientists determined that strains of *Plasmodium inui* from Brazil, Indonesia, and the Philippines are similar but that they are not closely related to other *Plasmodium* species that cause quartan malaria.

Onchocerciasis. Researchers at the Onchocerciasis Control Program, Ouagadougou, Burkina Faso, the Swiss Tropical Institute, Basel, Case Western Reserve University, Cleveland, and the Papua New Guinea Institute of Medical Research, Madang, investigated why Melanesians with "α-thalassemia have increased susceptibility to uncomplicated malaria as young children. In the Abalem-speaking tribal group that has high prevalence of "-thalassemia, the researchers discovered the mutation responsible for erythrocyte Duffy-antigen negativity on the FY*A allele, They also found that populations with heterozygotes deficient for this allele had a higher prevalence of vivax malaria. They suggest that *P. vivax* is involved in the selection of this erythroid polymorphism and that the mutation would ultimately comprise a protection against severe *P. falciparum malaria,* mediated by "α-thalassemia and *P. vivax*.

Tuberculosis

Special Programs

NIAID supports a contact award to manage the TBRU, a consortium of institutions in Brazil, Uganda, and the United States, which identifies research needs, opportunities, and priorities and develops appropriate protocols. These institutions then compete against each other and other applicants to carry out the protocols. In FY 99, NIAID recompeted the TBRU for an additional 8 years with more of a focus on the development of new or improved drugs and treatment regimens and on vaccine discovery and evaluation.

Other Programs

Therapy. Case Western Reserve University, Cleveland, Duke University Medical Center, Durham, North Carolina, University of Arkansas Medical Center, Little Rock, Federal University of Espirito Santo, Vitória, Brazil, the National Institute of Mental Health and Neuroscience, New Delhi, India, Ewha Women's University Hospital, Seoul, Korea, and Makerere University, Kampala, Uganda, are investigating the importance of drug tolerance to the outcome of therapy for tuberculosis.

Immunology

Immune Tolerance Network. In October 1999, NIAID in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIH) and the Juvenile Diabetes Association launched the Collaborative Network on Immune Tolerance, which is coordinated by the University of Chicago, Illinois. The network consists of nearly 40 research institutions in the United States and six international sites in Australia, Canada, Germany, Italy, Switzerland, and the United Kingdom. The priority areas include the use of "toleragenic" approaches to improve the success of kidney transplants; transplantation of human pancreatic islet cells to treat juvenile type 1 (insulin-dependent) diabetes mellitus; and desensitization and vaccines for asthma, allergic diseases, and autoimmune disorders.

International Histocompatibility Working Group. Starting in September 2000, NIAID is leading an initiative to catalog a cluster of nearly 220 genes constituting the human leukocyte antigen (HLA) gene complex. The working group consists of a network of nearly 200 laboratories in 70 countries coordinated by the Fred Hutchinson Cancer Research Center, Seattle, Washington.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Argentina

AIDS. Five Argentine hospitals are participating in the Vanguard Study Group: the Italian Hospital, J. A. Fernandez Hospital, the Clinical Hospital, the Central Foundation for Infectious Diseases, and the University of Buenos Aires, Buenos Aires. Preliminary phase II results in Argentina indicate that, in this setting, IL-2 therapy is well tolerated and increases the count of CD4-positive T cells without significant changes in plasma levels of HIV RNA.

Viral Diseases. The University of Nevada, Reno, and the National Institute of Human Viral Diseases, Pergamino, Argentina, are working on the pathogenesis of South American Hantaviruses. With CDC and Scripps Research Institute, La Jolla, California, the scientists studied the genetic diversity and geographic distribution of Junin virus in central Argentina.

Australia

AIDS. In FY 00, NIAID made a new award to the University of New South Wales, Sydney, to lead a consortium of Australian universities and research organizations in the production of a DNA vaccine that contains both HIV genes and specific stretches of DNA that directly stimulate immune responses. Administration of this vaccine will be followed by a booster vaccine that also contains immunity-enhancing genes, in a fowlpox delivery system.

Bacterial Diseases. CDC, the University of Alabama, Birmingham, Johns Hopkins University, Baltimore, and Queensland Health Department, Brisbane, have molecularly characterized and identified a globally distributed lineage of serotype 12F *Streptococcus pneumoniae* that was responsible for invasive disease in Australia, Maryland, and Texas.

Parasitic Diseases. In FY 00, NIAID made a new foreign grant award to the Walter and Eliza Hall Institute of Medical Research, Sydney, to identify genes associated with host response to *Leishmania major.* A second foreign award deals with adherence of red blood cells infected with malarial parasites.

Immunology. NIAID supports a foreign grant award to an investigator at the Walter and Eliza Hall Institute of Medical Research, Melbourne, on the regulation of tolerance versus immunity.

Austria

AIDS. Harvard Medical School and School of Public Health and Dana-Farber Cancer Research Institute, Boston, Massachusetts, University of Texas M. D. Anderson Cancer Center, Bastrop, Memorial Sloan-Kettering Cancer Center, New York City, New York, and the Institute of Applied Microbiology, Vienna, found that human neutralizing monoclonal antibodies of the IgG1 subtype protected macaque monkeys against mucosal challenge with infection with chimeric simian–human immunodeficiency virus.

Immunology. The Laboratory of Immunogenetics (NIAID), University of Vienna Medical School, and Sandoz Research Institute, Vienna, found that the occurrence of IgG and reactivity of high-affinity IgE receptors (FceRI") define an autoimmune-mediated subentity of chronic urticaria and provide a basis for the development of new diagnostic procedures and, perhaps, therapeutic strategies for this disease.

Bangladesh

University of Virginia/Charlottesville TDRU. The TDRU and the International Center for Diarrheal Diseases Research (ICDDR), Bangladesh, are conducting field studies of immunity to amebiasis in Bangladesh. With Johns Hopkins University School of Public Health, Baltimore, they found that acquired immunity to amebiasis is associated with mucosal IgA antibody against adherence lectin of *Entamoeba histolytica* in Bangladeshi children.

Bacterial Diseases. Johns Hopkins University, Baltimore, and the ICDDR/Bangladesh are collaborating in studies of the epidemiology of *Vibrio cholerae* in Bangladesh. With California State University, Monterey Bay, and the National Aeronautics and Space Administration's Ames Research Center, Moffett Field, California, they have used remote sensing data to track temporal patterns of cholera cases. In a study by New England Medical Center, Boston, Massachusetts, and the ICDDR/Bangladesh, the investigators reported that sunlight was a significant inducer of the *V. cholerae* prophage that induces cholera enterotoxin. This finding suggests that sunlight-induced transmission of the cholera enterotoxin bacteriophage may be part of a natural mechanism for the origination of new toxigenic strains of *V. cholerae*.

Barbados

Immunology. Johns Hopkins University, Baltimore, ALK Laboratory, Denmark, and the University of the West Indies, Bridgetown, found that specific antibodies to *Blomia tropicalis* are a good predictor of the severity of asthma in Barbados.

Belgium

AIDS. Allegheny University of the Health Sciences, Philadelphia, Pennsylvania, the University of Maryland, Baltimore, and Free University of Brussels are collaborating in the phase I, open, uncontrolled evaluation of an HIV Tat toxoid vaccine candidate for therapeutic use in HIV-positive persons and for prevention in HIV-negative persons.

Bacterial Diseases. Louisiana State University, Baton Rouge, Colorado State University, Fort Collins, and Institut Pasteur, Brussels, are measuring the immune response and protective effect of recombinant DNA vaccine candidates against leprosy in mice.

Mycotic Diseases. The Janssen Research Foundation, Beerse, provides the NIAID Mycoses Study Group and the NIAID AIDS Cooperative Treatment Groups with antimycotic drugs used in clinical trials on the diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis.

Belize

Parasitic Diseases. In FY 00, NIAID funded a new grant to the University of California, Davis, in response to the FIC solicitation for proposals for research on the Ecology of Infectious Disease, which will evaluate the environmental determinants of malaria in Belize.

Botswana

Harvard School of Public Health/Boston HVTU. This new HVTU is collaborating with Brown University, Providence, Rhode Island, and the National Health Laboratory, Gaborone, to conduct phase I, II, and III clinical trials of HIV vaccines in the United States and Botswana.

AIDS. Before the HVTU award, Harvard School of Public Health and Harvard AIDS Institute, Boston, and the National Health Laboratory, Gaborone, were conducting a genomic analysis of HIV-1 transmission in Botswana. The researchers have developed a profile of the most frequent HLA class I alleles that might be relevant to an HLA-based design for an HIV vaccine for use in Botswana. In FY 00, Harvard School of Public Health also received a new award to identify HLA-restricted CTL epitopes of clade C of HIV-1, the dominant strain in Botswana.

Brazil

University of Pittsburgh/Pennsylvania HIVNET. In FY 00, the HIVNET involved collaboration with Federal University of Rio de Janeiro to perform studies of descriptive epidemiology, natural history, and prevention of HIV in a cohort of high-risk, homosexual men in Rio de Janeiro.

Natural history. HIV-1 serotypes B and BN are both common in Brazil. Prospective studies of patients with HIV-1 B or BN serotype in Brazil suggest that infection with HIV clade B is associated with more rapid disease progression, indicating that minor differences in the V3 loop of the B clade virus may be important in prognosis.

Prevention. With Johns Hopkins University School of Medicine, Baltimore, the HIVNET determined that the seminal load was not suppressed in patients treated with antiretroviral therapy who do not adhere to the medication protocol.

University of Rochester/New York HVTU. This HVTU is collaborating with Federal University of Rio de Janeiro to achieve the following goals: (1) discover and evaluate novel immunogens designed to stimulate neutralizing antibodies against primary HIV isolates; (2) evaluate vaccine candidates designed to induce high levels of CTL activity and other responses; (3) investigate approaches to improvement of mucosal immunity; (4) develop replicating bacterial and viral vectors; (5) assess different routes of vaccine administration; (6) develop new immunologic assays; and (7) study the impact of host factors and viral variation on vaccine efficacy.

University of California/Los Angeles HPTU. In addition to the University of Rochester HVTU, NIAID made an HPTU award to the University of California, Los Angeles, to collaborate with a network of clinical sites in Rio de Janeiro, Belo Horizonte, and Pôrto Alegre, in the conduct of phase I, II, and III trials of HIV prevention, with an emphasis on perinatal and heterosexual HIV transmission.

Johns Hopkins University/Baltimore ICIDR. NIAID made a new ICIDR award to Johns Hopkins University in FY 99 to collaborate with the University of Pittsburgh, Pennsylvania, and Federal University of Rio de Janeiro on two innovative approaches to the treatment and control of tuberculosis.

State University of New York/Rochester ICIDR. In FY 99, NIAID renewed the ICIDR to continue collaboration with Federal University of Minas Gerais, Belo Horizonte. The study is focusing on host genetic correlates in schistosomiasis.

University of Texas Medical Branch/Galveston ICIDR. In FY 00, the ICIDR, CDC, and FIOCRUZ, Belo Horizonte, conducted parallel cellular and isotypic, immunologic assessment of susceptibility and resistance to *Schistosoma mansoni*.

University of Virginia/Charlottesville ICIDR. The ICIDR involving Federal University of Ceará, Fortaleza, and Federal University of Rio Grande do Norte, Natal, was successfully recompeted in FY 99 for research on chronic diarrhea and the interaction between infection and nutrition.

Leishmaniasis. With the University of Rochester, New York, the ICIDR completed a 10-year prospective study of the epidemiology and natural history of *Leishmania chagasi* infection in northeastern Brazil. The study demonstrated that persons who developed asymptomatic, self-resolving *L. chagasi* infection in childhood did not develop visceral leishmaniasis during this period, suggesting that they had become immune.

Nutritional status. With Columbia University, New York City, New York, the ICIDR assessed vitamin A nutritional status in children and HIV-positive adults from Brazil and children in the Marshall Islands. For the Brazilian children and HIV-positive adults, retinol-binding protein is a good surrogate measure for retinol. The scientists detected considerable vitamin A deficiency, but it is difficult to determine whether this condition was due to nutritional deficiency or infection. They concluded that reduced serum vitamin A levels, even within the normal range, correlated with impaired intestinal function and that administration of vitamin A, perhaps combined with zinc, may contribute to improving intestinal function and growth, which in turn may help to break the "vicious cycle" of diarrhea and enteric infections, malnutrition, and impaired development.

Case Western Reserve University/Cleveland TBRU. Federal University of Espirito Santo, Vitória, is an overseas site for the TBRU. During FY 00, Federal University of Espirito Santo participated in a multicountry project showing that phenotypic tolerance of antituberculosis drugs was not specific for any particular drug, appeared after prolonged drug exposure, and might be an important outcome of tuberculosis therapy.

Federal University of Bahia/Salvador TMRC. This direct award to Federal University of Bahia, Salvador, supports multidisciplinary research in leishmaniasis and Chagas' disease, often in collaboration with other Brazilian and U.S. institutions.

Leishmaniasis. With the University of Iowa, Iowa City, and the University of Virginia, Charlottesville, the TMRC has studied the familial aggregation of *L. chagas*i infection in northern Brazil and gathered preliminary information that the outcome of infection may, at least in part, be genetically determined.

Schistosomiasis. With Harvard Medical School, Boston, and Johns Hopkins University School of Medicine, Baltimore, the TMRC studied human immune responses to four vaccine candidate antigens (paramyosin, IrV-5, Sm23, and triose phosphate isomerase) against *Schistosoma mansoni* in

human subjects from an endemic area of Brazil.

Trypanosomiasis. The TMRC completed a retrospective study of patients treated with available drugs for acute Chagas' disease 14–30 years previously. The investigators found that patients with no cardiac alterations (cured) had stronger proliferative responses against *Trypanosoma cruzi* parasite antigens than those with heart disease.

Bacterial Diseases. The University of California, Berkeley, and FIOCRUZ, Salvador, Bahia, developed a "proof of concept" oral vaccine against enteropathogenic *Escherichia coli* expressed in a *Salmonella typhi* 21A vector.

Cornell University Medical College, New York City, New York, the University of California, Berkeley, and Goncalo Moniz FIOCRUZ Research Center and the Secretary of Health for Bahia, Salvador, investigated a large urban outbreak of leptospirosis with a high mortality rate (15%) due primarily (87%) to *Leptospira interrogans serovar copenhageni*. The condition was frequently confused with dengue fever.

Corixa Corporation, Seattle, Washington, and the Medical School of Itajuba, Minas Gerais, have cloned a *Mycobacterium tuberculosis* gene that encodes a purified protein derivative protein, which elicits strong tuberculosis-specific, delayed-type hypersensitivity.

In FY 00, NIAID awarded a new collaborative agreement to Corixa Corporation, Seattle, to collaborate with Federal University of Bahia, Salvador, to incorporate identified mycobacterial antigens into a recombinant tuberculosis vaccine.

Parasitic Diseases. Infectious Diseases Research Institute, the University of Washington, and Corixa Corporation, Seattle, Cornell University Medical College, New York City, and Instituto Butantan, São Paulo, have identified and characterized LeIF, a recombinant *Leishmania* protein. This protein induces an IL-12–mediated type 1 helper T cell (TH1) cytokine profile that may have potential as a therapeutic or prophylactic vaccine antigen or both when used in combination with other leishmanial antigens.

Cornell University Medical College, New York City, and Professor Edgard Santos University Hospital, Salvador, carried out a randomized, double-blind study of stibogluconate plus human granulocyte–macrophage colony-stimulating factor (GM-CSF) versus stibogluconate alone in patients with cutaneous leishmaniasis. The scientists found that, in 70% of patients receiving GM-CSF, the lesions healed within 40 days of therapy, compared with 10% of the control group.

Viral Diseases. The University of California, Berkeley, the Ministry of Health, Managua, Nicaragua, and FIOCRUZ, Rio de Janeiro, have used restriction site–specific PCR to develop a rapid test for subtyping dengue virus serotypes 1–4 and are using it to identify viruses circulating in Brazil, El Salvador, Guatemala, and Nicaragua.

University of Colorado Health Sciences Center, Denver, and Federal University of Bahia, Salvador, compared the relationship between HHV-8 and Kaposi's sarcoma in Brazilian and U.S. patients with or at risk for Kaposi's sarcoma. The levels of seroprevalence were similar in all groups, but anti–HHV-8 antibody titers were higher in patients with Kaposi's sarcoma than in HHV-8–positive patients without the disease.

Immunology. In a study at University of Virginia Health Sciences Center, Charlottesville, and Medical School of Ribeiro Preto, São Paulo, levels of IgE antibody against mites were higher than levels of IgE antibody against *Ascaris lumbricoides* roundworms, in a group of Brazilian children with asthma, rhinitis, or both.

Medical College of Wisconsin and the Veterans Affairs Medical Center, Milwaukee, University of Texas Southwestern Medical Center, Dallas, the University of São Paulo, and Federal University of Mato Grosso do Sul, Campo Grande, have started the first steps in defining the role of T cells in the autoimmunity observed in patients with pemphigus foliaceus (fogo selvagem), a disease seen only in Brazil.

Burkina Faso

Parasitic Diseases. The Laboratory of Parasitic Diseases (LPD) (NIAID), Washington University, St. Louis, Missouri, AMRAD-ICT Diagnostics, Sydney, Australia, and the Onchocerciasis Control Program, Ouagadougou, collaborated on the conduct of field trials to evaluate the sensitivity and specificity of a rapid-format antibody test to diagnose onchocerciasis at several sites in West Africa. The test was easy to perform, produced visual readout results in 15 minutes, was sensitive and specific for onchocerciasis, and differentiated onchocerciasis from other filarial and helminthic infections.

Investigators at Case Western Reserve University, Cleveland, the University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program, Ouagadougou and BouakJ, Côte D'Ivoire, developed a diethylcarbamazine patch test that is useful in detecting *Onchocerca volvulus* recrudescence in a sentinel population of children and young adults living in an onchocerciasis-free area created by the program.

Cambodia

AIDS. The University of California, Los Angeles, and Family Health International, Phnom Penh, reported on HIV surveillance in Cambodia for 1999.

Bacterial Diseases. Dana-Farber Cancer Research Institute, Brigham and Women's Hospital, and the Center for Blood Research, Boston, Massachusetts, and the Cambodian Health Committee and Institut Pasteur, Phnom Penh, discovered that IL-10–producing T cells suppressed immune responses in anergic patients with tuberculosis.

Cameroon

Georgetown University/Washington, D.C., ICIDR. NIAID supported this ICIDR for 5 years to collaborate with the University of YaoundJ to study malaria in women and children in Cameroon. The ICIDR is being phased out, but in FY 00, work continued through the new Malaria and Host Response award to Georgetown University and regular NIH sources.

The ICIDR evaluated the importance of angiogenic factors, such as angiogenin, in remodeling placental micro-architecture in low-birth-weight neonates born to *P. falciparum*–positive mothers.

Compared with control subjects who were not pregnant, both primigravidae and multigravidae women were more susceptible to malaria infection during the second trimester of pregnancy. This susceptibility coincided with decreased T-cell but not B-cell responses to mitogens, reduction of T-cell

proliferative response to some mitogen peptides, and decreased interferon g production.

Georgetown University/Washington, D.C., Malaria and Host Response Collaborative Research Award. In FY 00, NIAID made a new award that will continue Georgetown University's collaboration with the University of Yaoundé. The joint research will focus on the effect of TH2 bias on immunity to malaria in Cameroon. The project will monitor changes in antimalarial immune responses throughout pregnancy and compare them with changes in immune status after pregnancy. The scientists will also conduct a prospective study of infants born to women with malarial infection of the placenta. Both studies will be performed in Yaoundé, where malaria levels are low, and in Ngali, a rural village with high rates of malaria transmission throughout the year.

AIDS. New York University, New York City, is studying the immunologic relatedness between and among HIV-1 clades collected in Cameroon. During FY 00, NIAID expanded this research to include determination of the evolution and properties of HIV/SIV clades in specimens collected from various sites in Cameroon. NIAID made a new award in FY 00 to Aaron Diamond AIDS Research Center, New York City, New York, to study SIVrcm and related primate lentiviruses in Cameroon and elsewhere in West Africa.

Family Health International, Durham, North Carolina, and the Ministry of Health, Yaoundé, carried out a double-blind, placebo-controlled trial in female commercial sex workers who were provided with an educational program, condoms, and STD treatment. The study showed that the vaginal film impregnated with nonoxynol 9 did not reduce new HIV infections or gonorrheal and chlamydial infections in this population.

Parasitic Diseases. The University of Massachusetts, Amherst, and Smith College, Northampton, Massachusetts, New York Blood Center, New York City, the University of Edinburgh, Scotland, and the Tropical Medicine Research Station, Kumba, have used expressed sequence tag analysis and immunoscreening of *Onchocerca volvulus* larval cDNA (complementary DNA) libraries to identify potential vaccine and drug-target candidates. In FY 00, NIAID made a new award to New York Blood Center to expand this collaboration to explore protective immunity in humans against *O. volvulus* larvae.

Canada

AIDS. NIAID funds a foreign grant award to Simon Fraser University, Burnaby, British Columbia, to define the peptide mimics of neutralizing sites on HIV-1 envelope proteins, to gain insight into approaches for vaccine development.

The Laboratory of Infectious Diseases (NIAID), Walter Reed Army Institute of Research, Washington, D.C., Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland, Yerkes Regional Primate Center, Atlanta, Georgia, New England Regional Primate Center, Southborough, Massachusetts, and Health Canada, Ottawa, Ontario, showed that attenuated SIV effectively protected macaque monkeys against challenges with homologous viruses, but protection against heterologous strains was less effective.

Aaron Diamond AIDS Research Center, New York City, the International Center for Medical Research and Royal Victoria Hospital, Montreal, Quebec, and the British Columbia Center of Excellence, Vancouver, documented rapid reconstitution of the T-cell receptor repertoire after antiretroviral treatment during primary HIV infection.

The University of British Columbia, Vancouver, has a foreign award from NIAID to carry out integrated approaches to acute HIV infection, especially the reduction of viral load in lymphoid and nonlymphoid organs, as well as the peripheral circulation.

Bacterial Diseases. Investigators at Veterans Affairs Medical Center, Washington, D.C., the University of California, San Francisco, the University of Denver, Colorado, Emory University, Atlanta, Georgia, and the University of Edmonton, Alberta, conducting a placebo-controlled trial, found that adding rifabutin to a regimen of clarithromycin and ethambutol did not add to efficacy in the treatment of *Mycobacterium avium* complex bacteremia.

Mycotic Diseases. In FY 00, NIAID made a new foreign award to Victoria University, British Columbia, to carry out the genomic sequencing of *Aspergillus fumigatus*.

Researchers at Northwestern University Medical School, Chicago, Illinois, the University of Minnesota School of Public Health, Minneapolis, Harlem Hospital Medical Center, New York City, New York, Glaxo Wellcome, Inc., Research Triangle Park, North Carolina, and Toronto Hospital, Ontario, found that atovaquone suspension has a safety and efficacy similar to that of aerosolized pentamidine and may provide advantages over the use of dapsone in patients who are intolerant to co-trimoxazole in the prophylaxis of *Pneumocystis carinii* pneumonia.

Parasitic Diseases. NIAID supports a foreign grant to Montreal General Hospital. The scientists reported in vivo IL-12 production, and expression of IL-12 receptors $1 and $2 mRNA (messenger RNA) in the spleen was differentially increased in resistant B6 and susceptible A/J mice during early infection of the blood with *Plasmodium chabaudi.*

Immunology. A foreign award to McGill University, Montreal, showed that mutation of macrophage protein 1 (Nramp1), which is associated with natural resistance, impairs phagosomal acidification.

The University of Alberta, Edmonton, participates in the NIAID-funded Immune Tolerance Network. Investigators developed the Edmonton Protocol to transplant insulin-producing pancreas cells. This procedure has reversed dependence on insulin injection in seven patients with type 1 diabetes mellitus.

Chile

University of New Mexico/Albuquerque ICIDR. This new ICIDR and FIC's Actions for Building Capacity award supports collaboration among the University of New Mexico, the Ministry of Health, Catholic University and the University of Chile, Santiago, Coyhaique Regional Hospital, and Temuco Regional Hospital in research on Hantavirus ecology and disease in Chile.

University of Maryland/Baltimore Vaccine Evaluation Unit. This Vaccine Evaluation Unit has taken advantage of the University of Maryland ICIDR to perform surveillance for acute respiratory infections in Chile, in collaboration with the Center for Vaccine Development, Santiago.

The University of Maryland also had support from NIAID in FY 00 to perform oral immunization against enteric infections in Chile, in cooperation with the North Metropolitan Health Services, University of Chile, Roberto del Rio Children's Hospital, and the Ministry of Health, Santiago.

Salmonella. The Vaccine Evaluation Unit and the University of Valparaiso School of Medicine are attempting to define critical parameters for heterologous antigen expression that can rapidly be adapted to new antigens from emerging or reemerging infectious diseases, by incorporating them into an attenuated *Salmonella enterica serovar typhi* live vector vaccine.

Vibrio cholerae. The Vaccine Evaluation Unit is assessing the efficacy of a single dose of cholera vaccine strain CVD 103-HgR in infants and toddlers in an effort to identify the reasons for lower immunogenicity of enteric vaccines in low-income countries.

China

Johns Hopkins University/Baltimore HPTU. NIAID also made an HPTU award to Johns Hopkins University that involves collaboration with the National Center for AIDS Prevention and Control, Chinese Academy of Preventive Medicine, Beijing, and field sites in Guangxi and Xinjiang. The investigators are performing prevention studies primarily in populations in which intravenous drug abuse is the major risk factor for HIV and the epidemic is threatening heterosexual partners who are discordant for HIV positivity, primarily women. They will study specific protocols to evaluate the usefulness of topical microbicides, interventions to prevent perinatal HIV transmission, and antiretroviral treatment as prevention modalities.

Johns Hopkins University/Baltimore HVTU. The Johns Hopkins University HVTU is collaborating with Morgan State University, Baltimore, Maryland, Guangxi Health and Anti-Epidemic Center, and the National Center for AIDS Prevention and Control, Chinese Academy of Preventive Medicine, Beijing, with field sites in Guangxi and Xinjiang.

Institute of Parasitology/Shanghai TMRC. NIAID provides direct funding to the Institute of Parasitology, Chinese Academy of Preventive Medicine, to collaborate with Yale University, New Haven, Connecticut, on the impact of the Three Gorges Dam on human populations.

Hookworm infection. This project is concerned with the genetic diversity of hookworm infections and the development of recombinant vaccine candidates. The TMRC is studying the population genetics of human hookworms in two villages in Sichuan Province to anticipate the risk of development of resistance to antihelminthic drugs that might be used in community deworming campaigns and potential future vaccines. The TMRC has used molecular cloning to identify and characterize two potent hookworm vaccine antigens that are being evaluated in a mouse model system.

Paragonimiasis. The TMRC is using DNA sequencing to study the evolution and diversity of lung flukes collected from various parts of China.

Medical malacology. The project is studying the snail vectors of *Schistosoma* and *Paragonimus* species.

AIDS. Aaron Diamond AIDS Research Center, New York City, and the National Center for AIDS Prevention and Control, Beijing, are studying HIV variation and cross-clade recognition of CTLs in isolates collected in China. With collaboration from Aaron Diamond AIDS Research Center, Ditan Hospital and the National Center for AIDS Prevention and Control, Beijing, initiated the first efficacy trial of combivir, lamivudine, and indinavir in 24 HIV-positive patients with chronic infection, in May 1999.

Bacterial Diseases. Johns Hopkins University, Baltimore, and the Institute of Microbiology and Epidemiology, Beijing, have identified *granulocytic Ehrlichia* in Ixodes persulcatus ticks collected in northeastern China.

Parasitic Diseases. The University of California, Berkeley, is using remote sensing and global information systems (GIS) in support of programs to control schistosomiasis in Sichuan and Jiangxi Provinces.

LPD (NIAID) has a Cooperative Research and Development Agreement with the Hong Kong Institute of Biotechnology for the development, scale-up, and manufacturing of a vaccine to block transmission of malaria.

Viral Diseases. USDA, Ames, St. Jude Children's Research Hospital, Memphis, Tennessee, the National Veterinary Research Institute, Anyang, Korea, the Department of Agriculture and Fisheries and the University of Hong Kong, Hong Kong, and the Institute of Virology, Beijing, have characterized the pathogenicity of members of the recently established H9N2 influenza viruses in Asia.

NIAID provides St. Jude Children's Research Hospital, Memphis, with a research contract to assist with ensuring preparedness for an influenza pandemic in Asia. During FY 00, St. Jude Children's Research Hospital and the University of Tennessee, Memphis, and the University of Hong Kong conducted molecular characterization of H9N2 influenza viruses collected in Hong Kong, to determine whether they were the donors of the "internal" genes of H5N1 viruses in Hong Kong.

St. Jude Children's Research Hospital, the University of Wisconsin, Madison, Tottori University, Yonaga, and Hokkaido University, Sapporo, Japan, Jiangxi Medical College, Nanchang, and the University of Hong Kong documented the persistence of influenza viruses in poultry markets in Hong Kong and the transmission of these viruses to humans, emphasizing the importance of these markets to the epidemiology of influenza.

Colombia

University of Texas Medical Branch/Galveston EVC. The EVC and the National Institute of Health, Bogotá, have completed a preliminary identification of mosquito vectors and reservoir hosts of subtype ID of Venezuelan equine encephalitis in asylvatic focus in the Magdalena River Valley, Santander.

University of Notre Dame/South Bend TDRU. In FY 00, the TDRU received an NIAID institutional research-training award to complement its field activities in Colombia for study of the parasitology and ecology of vector-borne diseases.

Bacterial Diseases. The University of North Carolina, Chapel Hill, and the International Center of Medical Investigations Foundation TMRC, Cali, are collaborating in studies on the diagnosis and human disease associated with paucibacillary tuberculosis.

Parasitic Diseases. The University of Antioquia and Bolivarian Pontifical University, Medellín, have determined that, in humans, a T_H1 profile is associated with the absence of granuloma formation in neurocysticercosis brain lesions, whereas the combined T_H1–T_H2 response or a shift to a T_H2 profile may indicate a more chronic infection that involves granuloma formation.

Vector Biology. Yale University, New Haven, and the National Institute of Health, Bogotá, have used GIS technology to match Colombian species of sand fly by using Holdridge GIS life zones. This strategy provides maps delimiting ranges of each species and, by inference, risk maps for the diseases associated with each species.

Immunology. In association with the University of the West Indies, Bridgetown, Barbados, and Charity Hospital, Berlin, Germany, Johns Hopkins University School of Medicine, Baltimore, and the University of Cartagena developed evidence that atopic dermatitis is associated with a functional mutation in the promoter of the C-C RANTES chemokine.

Congo

Parasitic Diseases. LPD (NIAID) and Oxford University, England, are using *Plasmodium falciparum* strains from Congo and four other countries to study genetic structure inferred from microsatellite markers.

Cook Islands

Parasitic Diseases. LPD (NIAID) has maintained a long-term, population-based, prospective study of the natural history of lymphatic filariasis.

Côte D'Ivoire

AIDS. The University of Alabama, Birmingham, Indiana University, Indianapolis, and St. Thomas Hospital, London, England, found that Pneumocystis carinii specimens from patients in Côte D'Ivoire were morphologically different from specimens obtained from Australia, Europe, and the United States.

Croatia

Bacterial Diseases. The University of Kentucky Medical Center, Lexington, and the University of Rijeka determined that the pore-forming activity of *Legionella pneumophila* is not required for either phagosomal trafficking or intracellular replication.

Cuba

Bacterial Diseases. USDA and Washington State University, Pullman, the National Polytechnic Institute, Mexico City, Mexico, and CENSA, San Jose de las Lajas, Havana, are studying the expression of polymorphic msp1β genes during acute rickettsemia with *Anaplasma marginale*.

Czech Republic

Bacterial Diseases. Scientists at University of Texas Southwestern Medical Center, Dallas, and the Institute of Hematology and Blood Transfusion, Prague, detected phase variation in the expression of proteins involved in hemoglobin and hemoglobin–haptoglobin binding by nontypeable *Haemophilus influenzae*.

Viral Diseases. Genotypes of hepatitis C virus (HCV) differ in their responses to antiviral treatment and prognosis. The University of California, Berkeley, and Charles University, Prague, evaluated a nested restriction site–specific PCR test for the diagnosis of HCV subtype 1b. The investigators found the test to be rapid, sensitive, specific, and suitable for general laboratory use.

Democratic Republic of the Congo

Projet SIDA. The Laboratory of Immunoregulation and DAIDS (NIAID), CDC, the Armed Forces Institute of Pathology, Washington, D.C., the Institute of Tropical Medicine, Antwerp, Belgium, and the Ministry of Health, Kinshasa, partnered in Projet SIDA during 1984–1992. In FY 00, the Laboratory of Immunoregulation (NIAID) and Projet SIDA investigated the genetic diversity and potential mosaic genomes of HIV-1 isolates from female commercial sex workers during the early part of the AIDS pandemic in the Democratic Republic of Congo. Phylogenetic analyses of the gag protein 24, C2V3, and glycoprotein 41 (gp41) regions showed that all were group M.

Denmark

AIDS. Hvidore Hospital, Copenhagen, Aarhus University Hospital, and the University of Washington School of Medicine, Seattle, determined that genital β-chemokine secretion is associated with HIV-1 shedding from the human cervix. Researchers at the University of Washington, National University Hospital, Copenhagen, and Aarhus Hospital found that cervical HIV-1 DNA correlated with a viral load greater than 50,000 copies per milliliter, and RNA levels ranged from 10% to 100% of plasma levels, posing a continuous risk of transmission in HIV-positive women at all stages of disease.

Bacterial Diseases. Scientists at the Public Health Research Institute, New York City, New York, Charity Hospital, Berlin, and the Institute for Medical Microbiology, Cologne, Germany, and the State Serum Institute, Copenhagen, are developing new mycobacterial antigens for the specific detection of tuberculosis infection in children. In addition, investigators at Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, Mayo Clinic, Rochester, Minnesota, Grady Memorial Hospital, Atlanta, Georgia, and the State Serum Institute, Copenhagen, discovered that dual testing with *Mycobacterium avium* sensitin and purified protein derivative discriminates pulmonary disease due to *M. avium* complex from pulmonary disease due to *M. tuberculosis*.

Immunology. Scripps Research Institute, La Jolla, California, and Novo Nordisk, Bagsvaerd, discovered that a difference of one amino acid in position 30 of the insulin B chain abrogated the ability of insulin to confer protection in models for type 1 diabetes mellitus—both the nonobese diabetic mouse and the transgenic mouse with virus-induced diabetes.

Dominican Republic

AIDS. Researchers at the University of Washington, Seattle, the University of Miami, Florida, the University of Connecticut, Storrs, and AIDSCAP, Santo Domingo, found that risk of HIV for women living in sugar cane communities (bateyes) on large plantations was as high as that for commercial sex workers. Risk factors included younger age, being single with children, having more than one lifetime sexual partner, engaging in sex during menses, and self-description as a prostitute.

Ecuador

Parasitic Diseases. LPD (NIAID), the University of Maryland, Baltimore, St. George's Medical School, London, England, and Hospital Voz Andes and the Ministry of Public Health, Quito, showed that *Ascaris lumbricoides* infection may impair immunity to oral cholera vaccine in patients with non-O blood groups. This finding may be due to hypersecretion of mucus-containing A and B blood group antigens that prevent attachment of attenuated *Vibrio cholerae* during active helminthic infection. The scientists subsequently showed that albendazole therapy for children with ascariasis enhanced the vibriocidal antibody responses to the live, attenuated, oral cholera vaccine CVD 103-HgR.

Egypt

University of Maryland/Baltimore ICIDR. This new ICIDR supports collaboration with researchers at Minia University School of Medicine in studies on the high prevalence of HCV in Egypt.

Washington University/St. Louis ICIDR. In FY 99, NIAID renewed this ICIDR award to Washington University, St. Louis, Missouri, to collaborate with Ain Shams University, Cairo, in research on filariasis, for an additional 5 years. The new focus will be on research relevant to the elimination of human filariasis in Egypt. With Hebrew University, Jerusalem, Israel, the ICIDR has identified and characterized a long, dispersed, repetitive DNA sequence of *Wuchereria bancrofti* that may aid in survival of parasites after transmission to humans.

The ICIDR conducted a field evaluation of a rapid-format card test kit for detection of antigen (AMRAD-ICT), for the diagnosis of bancroftian filariasis in Egypt. With Smith College, Northampton, Massachusetts, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany, and Cairo University, the ICIDR also conducted a field evaluation of a quantitative PCR assay to determine the parasitic load in the mosquito vector of filariasis.

Parasitic Diseases. Michigan State University, East Lansing, Lowell University, Massachusetts, Zagazig University, and Teodor Bilharz Research Institute, Cairo, are characterizing the schistosomes isolated from Egyptian patients who do not respond to praziquantel. The aim is to determine whether drug resistance is involved and, if so, the nature of the drug resistance. Michigan State University, East Lansing, Al Azar University, Cairo, and Pharco Pharmaceuticals, Alexandria, tested the safety and therapeutic efficacy of a new schistosomicidal drug derived from myrrh, in patients with active intestinal schistosomiasis complicated by hepatosplenomegaly. The investigators found the compound to be safe and efficacious.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID), the University of Maryland Medical School, Baltimore, Georgetown University Medical Center, Washington, D.C., Minia University School of Medicine, and Assiut University Faculty of Medicine documented high levels of hepatitis E virus infection in a rural community in upper Egypt.

Ethiopia

Bacterial Diseases. Rockefeller University, New York City, New York, and the Armauer Hansen Research Center, Addis Ababa, are studying the pathobiology of leprosy.

Parasitic Diseases. Louisiana State University, Baton Rouge, is applying GIS to define the distribution of schistosomiasis in Ethiopia.

Finland

Bacterial Diseases. Scientists at Rocky Mountain Laboratories, Hamilton, Montana (NIAID), CDC, Baylor College of Medicine and University of Texas Health Science Center, Houston, Genomics, New York City, New York, the University of Toronto, Ontario, and the National Institute of Public Health, Helsinki, discovered that epidemic waves of group *A Streptococcus* are composed of strains expressing a remarkably heterogeneous array of variants of streptococcal inhibitor of complement. These variants arise very rapidly through natural selection on mucosal surfaces.

The University of Alabama, Birmingham, the University of Texas Southwestern Medical Center, Dallas, and the National Institute of Public Health, Helsinki, demonstrated the usefulness of pneumolysin-based PCR testing for the diagnosis of *Streptococcus pneumoniae* as the cause of lower respiratory infections in children.

France

AIDS. Allegheny University of the Health Sciences, Philadelphia, Pennsylvania, the Institute of Human Virology, Baltimore, Maryland, and Pierre and Marie Curie University and H^pital Necker, Paris, have established and are studying cohorts of "fast" and "slow" HIV "progressors" since 1995, to determine genetic and serological factors associated with the natural history of AIDS.

NCI (NIH), Frederick, Maryland, the University of Alabama, Birmingham, the Southwest Foundation for Biomedical Research, San Antonio, Texas, the University of Nottingham, England, and ORSTOM and CNRS Laboratory of Structural and Genetic Information, Montpellier, determined that all HIV-1 strains known to infect humans are closely related to only one of the recently sequenced chimpanzee *(Pan troglodytes troglodytes)* SIVcpz lineages. This finding, together with the geographic distribution of chimpanzees, points to the chimpanzee as the primary reservoir for HIV-1 that has been the source for at least three independent introductions of SIVcpz into human populations.

Pierre and Marie Curie University, Paris, Allegheny University of the Health Sciences, Philadelphia, and the University of Maryland, Baltimore, are working in a multicenter effort involving institutions in Argentina, Belgium, and Italy, to evaluate an HIV-1 Tat toxoid vaccine as a candidate for prevention and therapy in both HIV-positive and HIV-negative persons.

The University of Washington, Seattle, Johns Hopkins University, Baltimore, Duke University, Durham, North Carolina, St. Louis University, Missouri, Chiron Vaccines, Emeryville, California, and Pasteur-Merieux Connaught, Marnes-les-Coquette, reported that canarypox vaccine vectors encoding multiple HIV-1 gene products induced durable CTL responses in a majority of volunteers in phase I vaccine trials.

Viral Diseases. Scientists at the University of North Carolina, Chapel Hill, and the Jouy-en-Josas Research Center found that persistent infection promoted cross-species transmissibility of mouse hepatitis virus.

Immunology. Hôpital Necker, Paris, a member of the NIAID Immune Tolerance Network, is conducting a clinical trial of CAMPATH 3 and sirolimus in prevention of rejection of kidney transplants.

Gabon

AIDS. New York University, New York City, and the International Medical Research Center, Franceville, are studying SIVrcm and related primate lentiviruses in West Africa.

The International Medical Research Center, Franceville, in collaboration with CDC, the University of Alabama, Birmingham, the Institute of Tropical Medicine, Antwerp, Belgium, and Hôpital Bichat, Paris, France, used PCR diagnostic techniques to identify a variety of HIV-1 groups M, N, and O and SIVs from Central African chimpanzees.

Parasitic Diseases. The Veterans Affairs Medical Center and Duke University Medical Center, Durham, North Carolina, the University of Tübingen, Germany, and the Albert Schweitzer Hospital, Lambaréné, studied blood mononuclear cell nitric oxide (NO) production and plasma cytokine levels in healthy Gabonese children with previous mild or severe falciparum malaria. The scientists discovered differences in NO, NO production, and NO synthase activity in peripheral blood cells and differences in plasma tumor necrosis factor-α levels that suggest a role for these inflammatory mediators in resistance to disease or as markers for previous severity of disease.

The Gambia

Bacterial Diseases. NIAID is providing support to the Medical Research Council Laboratories, Banjul, to carry out an efficacy trial of pneumococcal polysaccharide–protein conjugate vaccine in the Upper River and Central River Divisions of the Gambia.

Collaborative studies by Dartmouth College, Hanover, New Hampshire, and the Medical Research Council Laboratories showed that administration of inactivated *Mycobacterium vaccae* in experimental animals was protective against challenge with *M. tuberculosis*. Early clinical studies have demonstrated that a five-dose series of *M. vaccae* vaccine is safe and induces a durable cellular immune response in healthy individuals with previous bacille Calmette-Guérin vaccination.

Parasitic Diseases. NIAID has given an exploratory grant to the Walter Reed Army Institute of Research, Rockville, Maryland, to collaborate with the Medical Research Council Laboratories in research on the immune responses of cord blood cells to malaria.

Georgia

University of Maryland/Baltimore ICIDR. The ICIDR is linked to FIC's Actions for Building Capacity Program and the International Training and Research Program in Emerging Infectious Diseases, which provides for international research training in emerging and reemerging bacterial infections for residents of Georgia.

University of Virginia/Charlottesville TDRU. The TDRU, CDC, and the Ministry of Health, Tbilisi, investigated an outbreak of amebic liver abscesses in urban Tbilisi. The investigators concluded that there was statistically significant evidence that drinking water was the source, either because of inadequate municipal water treatment or problems in the water distribution system.

AIDS. In FY 00, Johns Hopkins University, Baltimore, Emory University, Atlanta, Georgia, and the Georgian AIDS and Clinical Immunology Research Center, Tbilisi, received a new Civilian Research and Development Foundation (CRDF) award to expand collaborative research on the molecular epidemiology of HIV in Georgia to include hepatitis B virus (HBV) and HCV.

Germany

AIDS. NCI (NIH), University of Massachusetts Medical Center, Worcester, and the University of Erlangen-Nuremberg, Erlangen, are studying long-term, nonprogressive HIV-1 infection in a cohort of persons with hemophilia.

Rockefeller University and Bernhard Nocht Institute for Tropical Medicine, Eppendorf University, and Carl Zeiss Company, Hamburg, determined that HIV-1 replicates and accumulates in lymphoid tissue before damage to the immune system; that at this stage of disease, de novo production of T cells occurs in the lymphoid tissue; and that the infection is sensitive to triple-drug therapy in both plasma and lymph nodes.

Rockefeller University, Bernhard Nocht Institute for Tropical Medicine, Hamburg, and the German Primate Center, Göttingen, have shown that the mucosal-associated lymphoid tissue of the oral cavity is an efficient site for the atraumatic transmission of SIV.

Walter Reed Army Institute of Research, Rockville, Maryland, the Armed Forces Institute of Pathology, Washington, D.C., Rockefeller University, and Bernhard Nocht Institute for Tropical Medicine, Hamburg, treated 12 recently infected HIV-positive patients with highly active antiretroviral therapy (HAART). Although viral replication was eliminated for 24 months, there was persistent HIV-1 RNA expression in lymphoid tissue and peripheral blood mononuclear cells.

In a comparative German-U.S. study, Case Western Reserve University, Cleveland, Ohio, Rush Presbyterian-St. Luke's Hospital, Chicago, Illinois, and Boehringer Mannheim, Penzberg, the investigators found similar high prevalence of hepatitis G virus RNA and of antibody to probable viral envelope protein, but not both, in the plasma of HIV-positive patients.

Bacterial Diseases. Harvard School of Public Health, Boston, Humboldt University, Berlin, and George-August University, Göttingen, reported that the three main genospecies of Borrelia spirochetes that cause Lyme disease share common rodent hosts.

Immunology. Researchers at Johns Hopkins University, Baltimore, found evidence for linkage of chromosome 12q15–q24.1 markers and total serum IgE concentrations in children enrolled in the German Multicenter Allergy Study.

Justus-Liebig University, Giessen, participates in the NIAID Immune Tolerance Network.

Ghana

Noguchi Memorial Institute for Medical Research/Legon Malaria Clinical Research and Trials Contract. In FY 00, NIAID made a research contract award to Noguchi Memorial Institute for Medical Research, Legon, to collaborate with the Naval Medical Research Center, Silver Spring, Maryland, and the Navrongo Health Research Center to carry out vaccine-related clinical research in Ghana. Plans call for (a) defining the clinical epidemiology of malaria in the Kassena-Nankana area of northern Ghana, (b) orga-

nizing a phase I trial of the safety and efficacy of malaria vaccine, and (c) training of persons from endemic countries in the conduct of field trials of good clinical practice.

Bacterial Diseases. CDC, Rocky Mountain Laboratories, Hamilton, Montana, the University of Groningen, the Netherlands, and Noguchi Memorial Institute for Medical Research, Legon, are collaborating to document the epidemiology and the exotoxins involved in the emergence of Buruli ulcer in West Africa.

Parasitic Diseases. The University of Florida, Gainesville, St. George's Hospital, London, England, and Komofo-Anokye Teaching Hospital, Kumasi, are evaluating dichloroacetate in combination with standard antimalarial drugs, to determine whether this approach will reduce mortality in African children with *Plasmodium falciparum* malaria complicated by lactic acidosis.

Greece

Bacterial Diseases. The University of Alabama, Birmingham, and the Alexander Fleming Biomedical Sciences Research Center, Vari, reported that human C-reactive protein is protective against fatal *Salmonella enterica serovar Typhimurium* in transgenic mice.

Guatemala

Parasitic Diseases. Researchers at the University of Georgia, Athens, Epimmune Corporation, San Diego, California, and the University of the Valle, Guatemala City, determined that human infection with *Trypanosoma cruzi* induced parasite antigen–specific T-lymphocyte responses.

Haiti

University of Alabama/Birmingham HPTC. Although the HPTC is focused primarily on Zambia, it will have a component in Haiti.

Vanderbilt University/Nashville HVTC. The HVTC at Vanderbilt University, Nashville, Tennessee, will collaborate with GHESKIO, by using a field site in Port-au-Prince that was developed by the Cornell-Vanderbilt HIVNET in Haiti.

AIDS. For the past 14 years, NIAID has supported Cornell University Medical College, New York, City, New York, to collaborate with GHESKIO, Port-au-Prince, on prospective studies of the natural history of HIV infection in Haiti. In collaboration with the University of Miami, Florida, and Vanderbilt University, Nashville, the researchers reported that HIV transmission occurred in 27% of infants born to HIV-infected women in Haiti and that 60% of infected infants in Haiti died by 6 months of age, compared with 10% of infected Haitian infants in Miami.

Hungary

Bacterial Diseases. Scientists at Albert Einstein College of Medicine, Bronx, New York, Washington University, St. Louis, Missouri, Rockefeller University, New York City, Texas A&M University, College Station, and Albert Szent-Gyorgi Medical University, Szeged, reported that persistence of *Mycobacterium tuberculosis* in macrophages and mice requires the glycoxylate shunt enzyme isocitrate lysase.

Viral Diseases. Academic Hospital Medical Center, Cincinnati, Ohio, Wistar Institute, Philadelphia, Pennsylvania, Chiron Corporation, Emeryville, California, Aventis Pasteur, Marcy l'Etoile, France, and Albert Szent-Gyorgi Medical University, Szeged, evaluated a CMV vaccine candidate that used a canarypox vector expressing CMV g$ and CMV g$ subunit vaccine to prime and boost the immune response. The study showed that immune responses were similar.

Iceland

Immunology. The National Institute on Aging and the National Heart, Lung, and Blood Institute (NIH), Marshfield Medical Research Foundation, Wisconsin, and Queensland Institute for Medical Research, Brisbane, Australia, reported that genes on chromosome 6p21 (HLA-D region) may influence the expression of *Dermatophagoides pteronyssinus*–specific allergen IgE responsiveness in the white populations studied in Iceland.

India

Johns Hopkins University/Baltimore HIVNET. This HIVNET involved Johns Hopkins University, the Laboratory of Immunoregulation (NIAID), and the ICMRT National AIDS Research Institute, Pune. After the initial 5 years of funding during 1993–1997, some HIVNET activities continued under separate NIAID awards.

Viral characterization. With the California Department of Health, Berkeley, the HIVNET researchers have cloned full-length HIV-1 genomes from recent infections in residents of India, in an effort to identify antigens with potential for use in vaccine candidates. In examining full-length HIV-1 genomes from persons with seroconversion and subtype C in India, they found evidence of intersubtype recombination.

Testing and counseling. In a cohort of men attending STD clinics, the HIVNET determined that ongoing HIV testing and counseling were positively associated with risk-reduction behavior (e.g., condom use with commercial sex workers). Men who always reported using condoms had the lowest risk of seroconversion.

Sexually transmitted diseases. The HIVNET used PCR technology to determine the etiology of genital ulcer disease (GUD) in STD clinic patients and the relationship of GUD to HIV infection. The researchers found that herpesvirus infection and chancroid are the predominant causes of GUD in India. The study showed that the presence of chancroid, GUD symptoms for more than 10 days, and a concurrent diagnosis of cervicitis or urethritis were significantly associated risk factors for HIV-1 DNA shedding in the ulcers.

Brown University/Providence HPTC. NIAID made an HPTC award to Brown University, Providence, Rhode Island, to collaborate with the YRG Care Center in prevention research in Chennai.

Johns Hopkins University/Baltimore HPTC. NIAID also made an HPTC award to Johns Hopkins University, which involves collaboration with the ICMRT National AIDS Research Institute, Pune.

Johns Hopkins University/Baltimore HVTC. This new Johns Hopkins HVTC is also collaborating with the ICMRT National AIDS Research Institute, Pune.

AIDS. Harvard School of Public Health, Boston, Louisiana State University, Lafayette,

Grant Medical College and Specialty Ranbaxy Limited, Mumbai, and the National AIDS Research Institute and Mabastra Industrial Development Corporation, Pune, confirmed the high prevalence of HIV-1 clade C in several sites in India and found evidence of an increasingly complex phylogeny of HIV-1 clade C to a degree suggesting that the subclustering observed previously may no longer adequately reflect the diversity of isolates currently circulating within India.

NIAID provides grant support to an investigator at Johns Hopkins University to collaborate with the ICMRT National AIDS Research Institute, Pune, on the pathogenesis of acute primary HIV infection in India. Additional independent grants deal with HIV-specific CTL activity in concordant and discordant couples and with a clinical trial to compare the efficacy of combination therapy with zidovudine (AZT) and lamivudine compared with AZT monotherapy in the prevention of mother-to-infant HIV transmission in India.

In FY 00, NIAID made a new HIV Vaccine Innovation Grant award to a scientist at the Indian Institute of Sciences, Bangalore.

Bacterial Diseases. Scientists at University of Maryland School of Medicine and the Veterans Affairs Medical Center, Baltimore, and the National Institute of Cholera and Enteric Diseases, Calcutta, cloned and sequenced the genes downstream from the wbf gene cluster of the *Vibrio cholerae* serogroup 0139. Findings from analysis of the junction genes in other serogroups raised the possibility of the emergence of new pathogens by homologous recombination via the junction genes. New England Medical Center, Boston, Massachusetts, the Indian Institute of Microbiology and Technology, Chandigarh, and the National Institute of Cholera and Enteric Diseases, Calcutta, are studying the diversity of choleratoxin and its role in the evolution of new pathogenic *V. cholerae*.

Parasitic Diseases. Investigators at LPD (NIAID) and the ICMRT Tuberculosis Research Center and Government General Hospital, Chennai, determined that the alteration of cellular responsiveness after treatment of filarial infection is temporary and reflects the dynamics of IL-10 production.

Cornell University Medical College, New York City, Corixa Corporation, Seattle, Washington, and the Kala-Azar Medical Center, Banaras Hindu University, Varanasi, have assessed the ability of a rapid diagnostic finger-stick test using the K39 antigen to detect visceral leishmaniasis. The researchers concluded that the test is both sensitive and specific and is suitable for use in field conditions in the tropics. Scientists at Cornell University Medical College and Pfizer, Inc., New York City, New York, Glaxo Wellcome, Research Triangle Park, North Carolina, and Banaras Hindu University, Varanasi, reported that oral therapy with atovaquone alone or in combination with fluconazole is moderately effective for Indian kala-azar. LPD (NIAID), the U.S. Food and Drug Administration, and Banaras Hindu University, Varanasi, have evidence that the high incidence of treatment failures in Indian kala-azar is due to the emergence of antimony-resistant strains of *Leishmania donovani*.

CDC, the Naval Medical Research Institute, Rockville, Maryland, Case Western Reserve University, Cleveland, Ohio, Johns Hopkins University, Baltimore, and the National Institute of Immunology, New Delhi, have developed and tested the immunogenicity and in vitro protective efficacy of a prototype, recombinant, multistage candidate vaccine for *Plasmodium falciparum*.

Indonesia

Jackson Foundation/Bethesda Malaria Immunity Collaborative Agreement. NIAID also made a new collaborative agreement award to the Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, and for the Naval Medical Research Institute, Rockville, Maryland, to collaborate with the Naval Medical Research Unit No. 2 and the Ministry of Health, Jakarta, and Bethesda Hospital, Tomohon, Sulawesi, in a prospective study of the acquisition of immunity to malaria in nonimmune transmigrant populations.

University of Massachusetts/Worcester Dengue Program Project. The University of Massachusetts, Worcester, the National Institute of Child Health, Bangkok, Thailand, and the University of Indonesia, Jakarta, developed a quantitative PCR test for comparison of reverse transcription under various conditions. The scientists are using this test to analyze plasma levels of viral RNA during acute infection with dengue virus.

Ireland

Immunology. Investigators at Columbia University, New York City, New York, and St. Vincent's Hospital, Dublin, found that CD8-positive T cells in synovium in psoriatic arthritis seem to be antigen driven, with a non-antigen–specific infiltration of CD4-positive T cells.

Israel

Columbia University/New York City ICIDR. The ICIDR supported collaboration among Columbia University, New York City, and Ben Gurion University of the Negev and Soroka University Medical Center, Beersheva, to study the epidemiology, risk factors, clinical manifestations, and consequences of infection with intestinal parasites in Jewish and Bedouin children in Israel.

AIDS. The Laboratory of Immunology (NIAID) and Tel Aviv University School of Medicine have preliminary evidence to suggest that HAART may be more effective in reducing the spread of HIV by reduction in viral load than by blocking cellular infection by HIV-1. The findings suggest that virus detected during HAART is produced by cells infected after, not before, initiation of therapy.

Bacterial Diseases. CDC, Washington University, St. Louis, Missouri, and Shaare Zedek Medical Center, Jerusalem, evaluated PCR technology in the diagnosis of ehrlichiosis and Rocky Mountain spotted fever in the United States and in the diagnosis of boutonneuse fever caused by *Rickettsia conorii* in Israel. The investigators reported that PCR testing detected more *Ehrlichia* infections than serology did, but it was less sensitive than serology for detection of rickettsial infections.

Parasitic Diseases. In FY 00, NIAID renewed a foreign award to Hebrew University, Jerusalem, to evaluate reversed siderophores (iron-chelating compounds), which compete with the malaria parasite for iron within the red blood cell.

Vector Biology. A foreign grant to Hebrew University, Jerusalem, is exploring the effect

of the plant diets of sand flies on the transmission of leishmaniasis in Israel.

Immunology. Harvard University, Cambridge, Massachusetts, and the Weizmann Institute of Science, Rehovot, have identified and characterized binding motifs of copolymer 1 to HLA-DR molecules in patients with multiple sclerosis and rheumatoid arthritis.

Italy

AIDS. The Center for Blood Resources and Harvard Medical School, Boston, Johns Hopkins University, Baltimore, Georgetown University, Washington, D.C., Janssen Praxis, Berlin, Germany, and San Matteo Polyclinic, Pavia, observed that the combined administration of hydroxyurea, didanosine, and indinavir produced HIV suppression and improvement in immune function.

Investigators at Tulane Cancer Center, New Orleans, Louisiana, Advanced BioSciences Laboratories, Inc., Kensington, Maryland, and the Institute of Molecular Virology and Istituto Superiore di SanitB, Rome, discovered that the HIV-1 Tat protein promotes angiogenesis and the development of Kaposi's sarcoma by engaging arginine–glycine–aspartic acid–binding integrins.

Bacterial Diseases. University of Wisconsin Medical School and the Regional Primate Research Center, Madison, Spallanzani Institute, Rome, and the University of Palermo showed that infection with *Mycobacterium tuberculosis* increased reactivity of Vg9Vd2 T cells to phosphoantigens and that this increased reactivity appears to be dependent on constant antigenic exposure.

Vaccine Research. Researchers at the University of Alabama, Birmingham, the University of Cincinnati College of Medicine, Ohio, and the University of Bari have evidence that shifts in systemic immune responses with intact mucosal secretory IgA antibodies that occur after oral delivery of IL-12 liposomes are due to cytokine effects in the Peyers' patches. This finding suggests new strategies for the targeted manipulation of TH1- and TH2-type responses to mucosal vaccines.

Vector Biology. In FY 00, NIAID made a new award to Yale University, New Haven, Connecticut, and the University of Rome to investigate possible gene exchanges between *Anopheles gambiae* complex vectors of malaria in Africa.

Immunology. The Blood Center of Southeastern Wisconsin, Milwaukee, the University of Naples, the Medical Center of Pavia, Istituto Superiore di Sanitá, Rome, the National Research Council, Palermo, and the University of Genoa and San Martino Hospital, Genoa, have identified a specific peptide-mediated antagonism that may be useful in controlling the T-cell component of an allergic response to *Parietaria judaica*, a plant responsible for most allergic sensitization in the southern Mediterranean area.

The University of Milan participates in the NIAID Immune Tolerance Network.

Jamaica

University of Maryland/Baltimore HVTC. This newly awarded HVTC will initially build on the current HIVNET site in Trinidad and Tobago but will expand to Jamaica and other Caribbean sites.

Sexually Transmitted Diseases. The University of Alabama, Birmingham, is conducting a phase III trial of azithromycin for the treatment of primary syphilis at three sites in the United States and an overseas site in Kingston.

Japan

Bacterial Diseases. Scientists at Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, the University of Minnesota, Minneapolis, Marianna University School of Medicine, Kawasaki, and Tsukuba College of Technology discovered that serotypes VI and VIII predominate in group B streptococci isolated from pregnant women in Japan; serotypes 1a, 1b, II, III, and V predominate in group B streptococci from pregnant women in the United States.

Viral Diseases. Researchers at SUNY, Stony Brook, and the University of Tokyo determined that dual stem loops within the poliovirus internal ribosomal entry site control neurovirulence.

Immunology. The University of North Carolina, Chapel Hill, and Kanazawa University reported that IL-8 induced by the drug paclitaxel reduced the growth of human ovarian cancer in vivo through neutrophil infiltration.

Kazakhstan

Bacterial Diseases. An NIAID-supported investigator at the Veteran's Affairs Medical Center, Denver, Colorado, received a CRDF award to collaborate with the Institute of Chemical Sciences, Almaty, to develop new active and nontoxic drugs against tuberculosis that are based on novel midoximes of β-aminopropionic acids and acylformamidoximes.

Kenya

University of Washington/Seattle Center for AIDS and STD Research. The Center collaborates with the University of Manitoba, Winnipeg, the University of Nairobi, and the Ministry of Health, Mombasa, in studies of HIV and STD. The major research effort is the prospective follow-up of high-risk, female commercial sex workers in Nairobi and Mombasa.

Risk factors. A particularly interesting subgroup within the high-risk cohort of commercial sex workers are persons who remain HIV-1 negative despite risky behavior. The observation that 30% of the persistently HIV-1–negative prostitutes are first-degree relatives prompted a family study. In the study, it was more likely that both high-risk and lower-risk relatives would be HIV-negative prostitutes than that they would be HIV-positive prostitutes. This finding raises the possibility that inherited factors may mediate HIV resistance.

Prevention. Working with Coat Provincial General Hospital, Mombasa, the researchers documented that, after a behavioral risk–reduction program, a cohort of HIV-negative trucking company workers decreased sexual contact with high-risk partners and experienced significantly lower incidence of gonorrhea, nongonococcal urethritis, and GUD, even though use of condoms did not increase.

Haemophilus ducreyi. They also found that seroprevalence of *Haemophilus ducreyi* in HIV-negative Kenyan trucking company workers was 26.5% and yearly incidence was 3.6%.

Topical microbicides. The researchers found that low-dose nonoxynol 9 did not

confer significant protection against acquisition of HIV-1 in high-risk female prostitutes.

Tulane University/New Orleans ICIDR. This new ICIDR involves cooperation with SUNY, Buffalo, the International Center for Insect Physiology and Ecology, Nairobi, the Kenyan Institute for Medical Research, the Ministry of Health, and Jomo Kenyatta University, Nairobi, in research on African mosquito vectors of malaria. The focus will be on the relationships between the intensity of malaria parasite transmission by mosquitoes and the public health burden of malaria in communities.

Case Western Reserve University/Cleveland Program Project ICIDR. In FY 00, Case Western Reserve University competed successfully for a new ICIDR to replace a Program Project award and continues collaboration with the Kenyan Medical Research Institute (KEMRI) and the Ministry of Health, Nairobi, but focuses on one disease, schistosomiasis.

Filariasis. The Program Project studied the impact of maternal filarial infection on immune responsiveness and infection in children. The scientists showed that maternal infection is a risk factor for offspring and that this risk correlates with the development of a TH2-type immune response.

Leishmaniasis. The scientists carried out a historical review of visceral leishmaniasis in Kenya over the past century. Current data indicate a decrease in prevalence in the formerly epidemic areas of the east (1950–1980), a recent increase in the northwest, and growing evidence of HIV-driven changes in the epidemiology and transmission of the disease.

Malaria. The Program Project reported frequent infections with *Plasmodium falciparum, P. malariae,* and *P. ovale* in the low-density umbilical cord blood and in maternal blood in Kenyan women. These infections were apparently acquired before parturition in Kenya. Investigation of immune responses in the newborns of these women demonstrated that the fetus developed patterns of cytokine production similar to those observed in adults. The findings indicate that prenatal exposure to malaria may not lead to tolerance or altered fetal immunity but could stimulate partial protection against malaria in infancy.

Schistosomiasis. The ICIDR is investigating the influence of in utero exposure to parasite antigens on subsequent infection and disease due to *Schistosoma haematobium.* The researchers examined the emergence of drug resistance to praziquantel in the treatment of *S. haematobium* in Kenya during 1983–1993 in a highly endemic area. Despite substantial year-to-year variation, the pattern was not consistent with primary or progressive emergence of drug resistance in this control program.

University of Notre Dame/South Bend TDRU. The TDRU and KEMRI, Nairobi, are evaluating the Pegasus transposon PCR as a marker for population genetics studies of Anopheles gambiae in Africa.

Case Western Reserve University/Cleveland Immunology of Malaria Cooperative Agreement. The cooperative agreement for research on immunologic memory of preerythrocytic *Plasmodium falciparum* antigens involves collaboration with KEMRI, Nairobi, to compare the B- and T-cell immune responses in an area with intense malaria transmission (Siaya) with the responses in a highlands area that has sporadic transmission (Uasin Gishu).

AIDS. NIAID supports an investigator-initiated grant award to the University of Washington, Seattle, to collaborate with the Ministry of Health, Mombasa, to study the factors that influence viral shedding (HIV and human herpes simplex virus) in HIV-positive women. In FY 00, NIAID made a new grant to support a randomized, double-blind, placebo-controlled trial to investigate whether vitamin A supplementation will reduce vaginal shedding of virus in HIV-positive Kenyan women. A third award, to the Fred Hutchinson Cancer Research Center, Seattle, Washington, provides for cooperation with the Ministry of Health, Mombasa, to investigate early infection in women with mucosal exposure to HIV-1.

Parasitic Diseases. The University of Washington, Seattle, the University of Liverpool, England, the University of Nairobi, and the Center for Geographic Medicine Research, Kilifi, have documented a changing pattern of in vitro susceptibility to pyrimethamine–sulfadoxine in *P. falciparum* isolates from Kilifi.

Researchers at LPD (NIAID), CDC, and KEMRI, Kissian, have found that the 19-kilodalton IgG antibody response to merozoite surface protein 1 in mother–infant pairs naturally exposed to *P. falciparum* develops with age, not with multiple experiences with parasitemia. Thus, an antimalaria vaccine strategy for pregnant mothers could delay infants' first parasitemia until they are more capable of mounting a favorable 19-kilodalton IgG antibody response to merozoite surface protein 1.

Vector Biology. The University of New Mexico, Albuquerque, the University of California, Santa Barbara, and KEMRI, Nairobi, are examining the evolution of *Schistosoma mansoni* and its snail hosts.

Immunology. The University of Virginia, Charlottesville, and KEMRI, Nairobi, determined that the prevalence of atopy and asthma and measures of immediate hypersensitivity were similar in Kenyan children living in industrial and rural settings.

South Korea

Case Western Reserve University/Cleveland TBRU. In this TBRU network, Ewha Women's University, Seoul, participates in a multicountry study of the importance of general drug tolerance to the outcome of therapy for tuberculosis.

Lebanon

American University of Beirut MERC. During FY 00, this Middle Eastern Regional Contract (MERC) reported on the prevalence of cutaneous leishmaniasis in urban (0.18%) and rural (0.41%) subpopulations representing approximately 3.4% of Lebanon's population. Visceral leishmaniasis was practically nonexistent.

Madagascar

Vector Biology. The Laboratory of Human Bacterial Pathogens (NIAID), Institut Pasteur, Paris, France, and Institut Pasteur, Antananarivo, documented, for the first time, the transfer of genes for antimicrobial drug resistance from *E. coli* to the plague bacillus *Yersinia pestis* in the intestine of the flea vector.

Malawi

Johns Hopkins University/Baltimore HIVNET. The HIVNET supports collaboration between Johns Hopkins University School of Hygiene and the University of Malawi, Blantyre, to investigate HIV/AIDS in women of childbearing age, infants, and children in Malawi.

Vertical transmission. The HIVNET is conducting a phase III trial of antibiotics in women with a recent delivery, in an effort to reduce chorioamnionitis-related HIV transmission from mother to infant.

Breast-feeding. In the largest study of the role of breast-feeding to date, the HIVNET and NCI found that HIV-1 transmission was more common than human T-cell leukemia/lymphoma virus type I (HTLV-I) transmission in the early months of breast-feeding and that mothers who transmitted HIV to their infants were more likely than those who did not transmit HIV to have high viral loads and high levels of sodium in breast milk, suggesting subclinical mastitis.

Infant studies. Infants with HIV-positive cord blood showed a distinct rise in HIV positivity from the sample of cord blood to the first HIV-positive sample taken later. This finding suggests a recent infection.

Topical microbicides. The HIVNET is conducting a phase IIB clinical trial of new microbicide candidates in Blantyre and Lilongwe.

Johns Hopkins University/Baltimore HPTC. In FY 00, NIAID made a grant for a new HPTC at Johns Hopkins University, to continue the collaboration with the University of North Carolina, Chapel Hill, and the University of Malawi, Blantyre.

Michigan State University/East Lansing ICIDR. After sustained grant support to Michigan State University to collaborate with Queen Elizabeth Central Hospital and the Wellcome Trust Center, Blantyre, in research on severe malaria, NIAID made an ICIDR award in FY 99 to continue the work in Malawi.

Cofactors. Preliminary findings of an ICIDR study with the University of North Carolina, Chapel Hill, and Johns Hopkins University, Baltimore, suggest that either malaria infection increases HIV viral load or a high HIV viral load increases susceptibility to malaria. The investigators also determined that, at least in some patients, antimalarial drugs may reduce viral load.

Parasitic Diseases. A new grant to the University of Maryland, Baltimore, will involve collaboration with the Michigan State University ICIDR, East Lansing, to identify the genotypic basis for the malaria in Malawi and other African countries that is resistant to pyrimethamine–sulfadoxine.

Malaysia

AIDS. Johns Hopkins University School of Public Health, Baltimore, Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland, Walter Reed Army Institute of Research, Bethesda, Maryland, and the University of Malaysia and the National Transfusion Center, Kuala Lumpur, determined that the dominant HIV-1 serotypes in Malaysia are B, which is more prevalent in intravenous drug users, and E, which is more common in other risk groups.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID) collaborated on the isolation and characterization of Langat virus, a naturally attenuated tick-borne flavivirus in Malaysia that does not appear to cause human disease under natural conditions. An E5 Langat virus mutant is being evaluated as a potential vaccine candidate against other flaviviruses, such as tick-borne encephalitis virus.

Mali

Malaria Research and Training Center/Bamako TMRC. Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, and several other academic institutions collaborate with the TMRC, Bamako, at the Faculty of Medicine and Pharmacology, University of Mali. On September 20, 2000, the TMRC dedicated a new medical research facility that contains two large laboratories, a conference room, a library, and several classrooms.

Epidemiology. The TMRC completed a study of the incidence of *Plasmodium falciparum* infection in a cohort of children who were 9 years of age or younger, as an estimate of intensity of infection. By microscopic examination of blood smears, the scientists discovered evidence of significant transmission during the dry season (December–May), despite the difficulty of capturing sufficient numbers of infected mosquitoes for calculation of an entomological inoculation rate.

Clinical manifestations. With Gabriel Toure Hospital, Bamako, the TMRC carried out the first study of ocular complications of severe malaria in Africa. Severe anemia was frequently (40%) associated with ocular signs; ocular complications were statistically more significant among children with rosetting; and papillary edema and exudates were more frequent among the children who died.

Geographic information systems. The TMRC has used differential global positioning to test for clustering of severe cases of malaria and to examine the geographic distribution of severe cases of malaria relative to major mosquito breeding sites.

Research training. LPD (NIAID) and the University of Maryland, Baltimore, are responsible for an international research-training program at the TMRC for U.S. minority undergraduate and graduate students.

Vector biology. New York University, New York City, and the TMRC are investigating the genetics of the susceptibility of Anopheles gambiae mosquitoes as vectors of malaria. The TMRC and the University of Rome, Italy, have used mark–release–recapture techniques to study the dynamics and flight range of *Anopheles gambiae sensu lata* in Banambani.

Marshall Islands

University of Virginia/Charlottesville ICIDR. Columbia University, New York City, New York, the University of Hawaii, Honolulu, and the ICIDR validated the use of retinol-binding protein as a surrogate measure of vitamin A (retinol) in children in the Marshall Islands.

Mexico

University of Texas Medical Branch/Galveston EVC. The EVC collaborates with several Mexican institutions to study a variety of vector-borne viral and rickettsial pathogens. The EVC is also investigating *Rickettsia felis,* the etiologic agent of a potentially emerging disease in Mexico.

Stanford University/California ICIDR. The ICIDR was competitively renewed in FY 99 and provides support to Stanford University,

California, to collaborate with the National Institute of Public Health, Cuernavaca, and the National Institute of Diagnostics and References, Mexico City, on the molecular epidemiology of tuberculosis in Mexico.

Colorado State University/Fort Collins ICIDR. This new ICIDR links Colorado State University with the National Polytechnic Institute, Mexico City, Autonomous University of the Yucatán, Mérida, and Autonomous University of Nuevo León, Monterrey, in studies of the vector biology and virology of dengue and other mosquito-borne diseases in Mexico. In FY 00, NIAID also made a new grant award to Colorado State University to study the molecular determinants of dengue epidemic potential in Nuevo León.

Vector biology. The ICIDR conducted a population genetics analysis of gene flow among 10 *Aedes aegypti* mosquito collections from seven cities along the northeastern coast of Mexico. The collection from Nuevo Laredo had unique, randomly amplified polymorphic DNA and mRNA haplotype frequencies and reduced heterozygosity, suggesting that only a few mosquitoes established this mosquito population.

Virology. The ICIDR is examining the molecular determinants of dengue epidemic potential in North America and developing molecular strategies for the interruption of mosquito transmission against dengue virus field isolates from Mexico that were collected over a 17-year period.

AIDS. DAIDS (NIAID), CDC, Johns Hopkins University School of Medicine, Baltimore, the Veterans Affairs Medical Center, Washington, D.C., the University of Minnesota, Minneapolis, and the National Institute of Diagnostics and References, Mexico City, conducted a 2-month randomized trial of rifampin–pyrazinamide versus isoniazid for HIV-positive, tuberculin-positive adults. The investigators reported no significant differences in the development of tuberculosis.

Bacterial Diseases. In FY 00, NIAID made an award to University of Texas Health Science Center, Tyler, to study the molecular epidemiology and transmission dynamics of tuberculosis along the U.S.-Mexico border at sites in Tyler, Texas, and Matamoros, Mexico.

Parasitic Diseases. Harvard School of Public Health, Boston, and Hospital Infantil, Mexico City, documented a high rate of occult infection with *Entamoeba histolytica* in Mexican children who did not have dysentery.

Viral Diseases. CDC, Fort Collins and San Juan, Puerto Rico, Colorado State University, Fort Collins, and the National University of Yucatán, Mérida, documented that concurrent infections by multiple dengue virus serotypes are common in areas where all four serotypes are circulating.

Mozambique

South African Medical Research Council/Durban HVTN. The HVTN has a component in Mozambique for prevention trials.

Myanmar

Parasitic Diseases. In FY 00, NIAID made a new award to the Southwest Foundation for Biomedical Research, Dallas, Texas, to collaborate with LPD (NIAID) and Mahidol University, Bangkok, Thailand, to apply recently developed microsatellite technology developed at the NIH to measure the in vitro susceptibility of *Plasmodium falciparum* to chloroquine, artemisinin, mefloquine, and quinine. The isolates tested were collected from patients at the Thai-Myanmar border.

Nepal

Bacterial Diseases. Colorado State University, Fort Collins, and Anandaban Leprosy Hospital, Katmandu, reported that interferon g responses to candidate leprosy skin-test reagents detected exposure to the bacillus in a population in Nepal in which leprosy is endemic.

Rockefeller University, New York City, New York, and the Anandaban Leprosy Hospital, Katmandu, are studying the pathobiology of human leprosy, the effect of thalidomide in the treatment of erythema nodosum leprosum in patients with leprosy, and the genetic determinants of susceptibility to reactional episodes in leprosy.

Parasitic Diseases. In FY 00, NIAID awarded a new grant to the Southwest Foundation for Biomedical Research, San Antonio, Texas, to perform a genome scan in a single, large, well-studied pedigree population in eastern Nepal, to identify genetic traits associated with susceptibility to helminthic infections.

The Netherlands

AIDS. NIAID made a new foreign grant award to a scientist at Erasmus University, Rotterdam, to study the protective capacity of HIV protein–specific CTLs. A second NIAID foreign grant to the University of Amsterdam is exploring mini–HIV variants as strains for a live, attenuated vaccine candidate.

Investigators at Emory University School of Medicine, Atlanta, Georgia, Bayer AG, Wuppertal, and the University of Leipzig, Germany, the AIDS Research Center, Tokyo, Bayer Yahuhin, Osaka, and the University of Occupational Health, Kitakyushu, Japan, and the Biomedical Primate Research Center, Rijswijk, studied nonhuman primates infected with SIV. They concluded that post-exposure prophylaxis with non-nucleoside reverse transcriptase inhibitors is followed by the generation and maintenance of long-term, virus-specific, cellular immune responses likely to lead to long-term protection against disease.

New York Blood Center, New York City, the Department of Public Health, San Francisco, California, and the Department of Health, Amsterdam, examined long-term survival after HIV-1 infection among homosexual men who participated in a study of HBV vaccine in New York City and Amsterdam in 1978–1995. The researchers reported a mean survival time of 12.1 years after seroconversion, with a constant death rate for the 1st 8 years, followed by a decrease in the death rate. These findings indicate that this HBV vaccine may confer relatively effective resistance to progression of HIV-1.

Immunology. Scientists at the University of California, San Diego, and Leiden University Medical Center found that overexpression of the p53 tumor-suppressor gene in synovial tissue is specific for rheumatoid arthritis, compared with levels found in patients with reactive arthritis and osteoarthritis.

New Zealand

AIDS. The University of Washington School of Medicine, Seattle, Westmead Hospital and New South Wales Blood Bank, Sydney, Aus-

tralia, and Auckland Hospital have detected HIV-1 subtypes B and C in New Zealand.

Nicaragua

Parasitic Diseases. The University of California School of Public Health, Berkeley, the Ministry of Health, and the National Dermatological Hospital, Managua, have studied the epidemiologic and immunologic characteristics of atypical cutaneous leishmaniasis caused by *Leishmania chagasi* in Nicaragua.

Viral Diseases. The University of California, Berkeley, the Ministry of Health, Jesus Rivera Pediatric Hospital, Managua, and Oscar Danilo Rosales Arguello Hospital, León, investigated the clinical, epidemiologic, and virological features of the 1998 epidemic of dengue fever in Nicaragua.

Nigeria

Bacterial Diseases. University of Maryland School of Medicine and Johns Hopkins University School of Hygiene, Baltimore, and Obafemi Awolowo University, Ife-Ife, reported that enteroaggregative *E. coli* strains isolated from children in southwest Nigeria are of heterogeneous virulence and that genes encoding the AAF/II fimbriae are strongly associated with diarrhea in this population.

Harvard Medical School, Boston, the Veterans General Hospital, Kaohsiung, Taiwan, and the Nigerian Institute for Biomedical Research, Lagos, examined HLA-DRB1 alleles in three Nigerian ethnic groups with leprosy and identified several motifs associated more frequently with lepromatous leprosy.

Parasitic Diseases. The University of Alabama, Birmingham, and the University of Witwatersrand, Johannesburg, South Africa, have used PCR technology to map the distribution of blinding and nonblinding strains of *Onchocerca volvulus* in Nigeria.

Norway

Immunology. The University of California, Los Angeles, and the University of Bergen demonstrated antibodies to primary sequences of human neutrophil defensin in patients with connective tissue disorders, including Wegener's granulomatosis, rheumatoid arthritis, systemic lupus erythematosus (SLE), ankylosing spondylitis, and systemic sclerosis.

Panama

University of Texas Medical Branch/Galveston EVC. The Center reported that isolates of St. Louis encephalitis virus from Mexico and Panama are genetically similar to isolates from Florida.

Papua New Guinea

Case Western Reserve University/Cleveland ICIDR. The ICIDR supports collaboration between Case Western Reserve University and the Papua New Guinea Institute of Biomedical Research, Madang, in research on tropical diseases. In FY 99, the ICIDR recompeted successfully and will focus on comparisons of the heterogeneity of lymphatic filariasis in Kenya and Papua New Guinea.

Filariasis. During FY 00, the ICIDR completed a proof of principle project in a community of 3,000 in an area highly endemic for *Wuchereria bancrofti*. The hypothesis was that annual therapy with diethylcarbamazine alone or with ivermectin could eradicate infection. An unexpected benefit derived from this prospective study was the observation that preexisting lymphatic swelling of the legs and genital areas was significantly reduced in both the group receiving diethylcarbamazine (36%) and the group receiving diethylcarbamazine plus ivermectin (65%).

Malaria. The ICIDR used a ribosomal DNA-based PCR test to identify a random distribution of mixed-species malaria infections in Papua New Guinea. This finding suggests that *Plasmodium falciparum, P. vivax, P. malariae,* and *P. ovale* mixed infections are common and that each species establishes infection independently.

University of Notre Dame/South Bend TDRU. The TDRU has established an overseas field site in Papua New Guinea for studies in parasitology and vector biology.

Peru

University of Texas Medical Branch/Galveston EVC. The EVC collaborated with Cayetano Heredia Peruvian University, Lima, on the emergence and epidemiology of Oropouche virus in the Peruvian Amazon Basin. The EVC is also investigating the molecular epidemiology of *Rickettsia prowazekii,* the agent that causes epidemic typhus, and *R. felis,* a recently described agent, both of which are endemic to Peru.

Fred Hutchinson Cancer Research Center/Seattle HVTC. This new HVTC will collaborate with Cayetano Heredia Peruvian University, Lima, on the conduct of large, multicenter efficacy trials of one or more vaccine candidates in Seattle, Washington, and Lima.

Johns Hopkins University School of Public Health/Baltimore ICIDR. The ICIDR has supported collaboration between Johns Hopkins University School of Public Health and Cayetano Heredia Peruvian University, Lima, in research on emerging enteric infections and hydatidosis. ICIDR patient populations are accessed through the Projects in Information, Health, Medicine, and Agriculture (PRISMA) Beneficial Association, Lima. The ICIDR has competed successfully for renewal and, under the terms of the solicitation, will focus on tapeworm (cestode) infections and an integrated approach to the control of cysticercosis due to *Taenia solium.*

Taenia solium. CDC, the University of Salford, England, the University of San Marcos, Lima, and the ICIDR have developed a serological immunoblot assay using *T. solium* excretory–secretory antigens. The test is 95% sensitive in persons with known *T. solium* infections from pork tapeworm and does not cross-react in control subjects with known *T. saginata* beef tapeworm and other parasitic infections. The ICIDR has developed a simple, inexpensive, but highly sensitive PCR–restriction fragment length polymorphism test to differentiate between the eggs of *T. solium* and *T. saginata* in stool specimens.

Tuberculosis. The ICIDR and PRISMA Beneficial Association found that the microscopic observation broth–direct susceptibility assay is a highly appropriate technology for detection of tuberculosis and testing for susceptibility in the Peruvian setting. With the Ochsner Medical Center, New Orleans, Louisiana, the ICIDR found that yields of bacteria from nasopharyngeal and gastric aspirations were comparable to yields from culture, staining, and PCR tests for the diagnosis of *Mycobacterium tuberculosis* in children.

Bacterial Diseases. Stanford University, California, and Cayetano Heredia Peruvian University and the Naval Medical Research Center Detachment, Lima, determined

that acute *Helicobacter pylori* infection in Peruvian children is followed by growth retardation.

Mycotic Diseases. The University of Alabama, Birmingham, Cayetano Heredia Peruvian University, Lima, and Santa Teresa Medical Center, Abancay, described an area of hyperendemic sporotrichosis in the Peruvian highlands.

Parasitic Diseases. CDC, Walter Reed Army Institute of Research, Washington, D.C., the University of Maryland, Baltimore, and the Naval Medical Research Center Detachment and the National Institute of Health, Lima, investigated a dramatic increase in malaria cases and regional differences in drug resistance in the Peruvian Amazon. The researchers discovered that a very limited number of parasite genotypes (strains) accounted for the highly resistant *Plasmodium falciparum* found in the region.

Viral Diseases. The University of Alabama, Birmingham, and the International Potato Center, Lima, isolated the first alphanodavirus outside Australia.

In FY 00, NIAID made a new grant award to the University of Texas Medical Branch, Galveston, to collaborate with the Naval Medical Research Center Detachment, Lima, for research on the epidemiology of alphaviral diseases in the Amazon Basin, with emphasis on Venezuelan encephalitis and Mayaro virus.

Scientists at Johns Hopkins University School of Medicine, Baltimore, and Cayetano Heredia Peruvian University, Lima, discovered that infection in brain endothelial cells is frequent in children with acute fatal measles. They postulate that this site of infection may provide a portal of viral entry in patients who subsequently develop subacute sclerosing panencephalitis, encephalitis with measles inclusions visible by microscopy, or postmeasles immunoencephalitis.

Immunology. University of Texas Health Science Center, Houston, the University of Alabama, Birmingham, and Cayetano Heredia Peruvian University, Lima, conducted a controlled clinical, serological, and immunogenetic study of SLE in mestizo Peruvian women. The scientists concluded that different genetic factors are associated with SLE in indigenous Indian populations.

Philippines

Brown University/Providence Center for AIDS Research. The Center for AIDS Research at Brown University, Providence, Rhode Island, collaborated with the Research Institute of Tropical Medicine (RITM), the Department of Health, Manila Hospital, and the National HIV/STD Control Program, Manila, to study the molecular epidemiology of HIV-1 infection in the Philippines during 1985–1997, in an effort to understand the low-transmission pattern that has persisted despite initial projections of a major epidemic.

University of Washington/Seattle STD Center. The STD Center, San Francisco Department of Public Health, California, RITM, Manila, and Cebu Institute of Medicine, Cebu City, explored the factors responsible for the dramatic increase in resistance of *Neisseria gonorrheae* to ciprofloxacin in 1994–1997 in female commercial sex workers. The investigators reported that self-proscription of prophylactic antibiotic use and inconsistent use of condoms appeared to be the most important factors associated with drug resistance.

Research Institute of Tropical Medicine/Manila TMRC. The TMRC provided direct support to RITM, Manila, to collaborate with Brown University, Providence, and Case Western Reserve University, Cleveland, in studies of leprosy, malaria, and schistosomiasis in the Philippines during 1991–1996.

Filariasis. The TMRC, the Ministry of Health, Manila, and Michigan State University, East Lansing, documented the persistence of *Wuchereria bancrofti* in the Bicol Peninsula, a historically endemic area.

Malaria. In collaboration with New York University, New York City, the TMRC is studying the genetic diversity in the sporozoite surface antigens of *Plasmodium falciparum* strains in the Philippines.

Schistosomiasis. Researchers at Cambridge University, England, and the TMRC have data indicating that humans develop IgE responses to several muscle-associated, calcium-binding antibodies to *Schistosoma japonicum*. This finding suggests that these idiotypes may be responsible for the protective effect of anti-worm antibodies in humans.

AIDS. NIAID supports the University of California, Los Angeles, in behavioral research studies in support of HIV/AIDS prevention in high-risk populations in the Philippines.

Bacterial Diseases. In research at Rockefeller University, New York City, New York, and the Leonard Wood Memorial Leprosy Research Foundation, Cebu, scientists found that thalidomide was superior to pentoxifylline and prednisone in the management of erythema nodosum leprosum in patients with leprosy.

Poland

Immunology. The Laboratory of Allergic Diseases (NIAID) and the International Institute of Molecular and Cell Biology, Warsaw, determined that human mast cells express the hyaluronic acid–binding isoforms of CD44 and adhere to hyaluronic acid.

Portugal

Bacterial Diseases. Colorado State University, Fort Collins, and the University of Porto found that neutrophils play a protective nonphagocytic role in systemic infection with *Mycobacterium tuberculosis* in mice.

Rockefeller University, New York City, the National University Hospital, Reykjavik, Iceland, New University of Lisbon, Oeiras and Monte da Caparica, and the Ministry of Education, Lisbon, determined that the nasopharyngeal flora of children in day-care centers may be a global reservoir of worldwide prevalent strains of drug-resistant pneumococci.

Romania

Bacterial Diseases. Rockefeller University, New York City, Ben Gurion University of the Negev, Beersheva, Israel, and the Faculty of Medicine, Iasi, identified unique clones of *Streptococcus pneumoniae* isolated from children hospitalized for infections and from both healthy and HIV-positive children in the community.

Russia

University of North Carolina/Chapel Hill HPTC. Russia will host a new HPTC that will involve collaboration among the University of North Carolina, Chapel Hill, SUNY,

Downstate, Medical College of Wisconsin, Milwaukee, and St. Petersburg University.

Bacterial Diseases. The Laboratory of Host Defenses (NIAID) initiated a Biotechnology Engagement Program project with the State Research Institute for Applied Microbiology, Obolensk, on comparative mycobacterial genomics. Colorado State University, Fort Collins, was awarded a CRDF grant to collaborate with the Nesmeyanov Institute of Organoelement Compounds, Moscow, on study of the antituberculous and neurochemical activities of pyridasino[4,3-*b*] indoles and their analogues via facile synthesis of heterocyclic β-cyano-α-enaminoketones.

Mycotic Diseases. In FY 00, an NIAID-supported investigator at Medical College of Wisconsin, Milwaukee, received a new CRDF grant to work with colleagues at the Shemyakin Institute of Bioorganic Chemistry, Obolensk, on the induction of tolerance to Asp f2, a major allergen of *Aspergillus fumigatus*.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID) and the State Research Center of Virology and Biotechnology (VECTOR), Koltsovo, are developing a method for the genetic manipulation of flaviviruses. Specifically, mutants of Langat flavivirus, a tick-borne virus that apparently does not cause human disease, have protected mice from challenge against highly virulent Far Eastern strains of tick-borne encephalitis virus.

SUNY, Stony Brook, received a new CRDF grant to work with VECTOR, Koltsovo, to detect antibody from a combinatorial library against Hantavirus.

The University of Wisconsin, Madison, St. Jude Children's Research Hospital, Memphis, Tennessee, and M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, determined that influenza A viruses lacking sialidase activity can undergo multiple cycles of replication in cell culture, eggs, or mice. During FY 00, St. Jude Children's Research Hospital and M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides also received a renewal of their CRDF grant to investigate the molecular and antigenic basis for immune protection against influenza A H5 virus, a possible agent of a future pandemic.

The Laboratory of Infectious Diseases (NIAID) and VECTOR, Koltsovo, are sequencing and analyzing the genome of monkeypox virus.

The Laboratory of Infectious Diseases (NIAID) and M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, are evaluating a novel, live, attenuated strain of tick-borne encephalitis virus for the development of a human vaccine against the disease.

Rwanda

AIDS

The University of Alabama, Birmingham, the Municipal Health Service, Amsterdam, the Netherlands, and the National AIDS Control Program studied the HLA profiles of cohorts of HIV-positive Dutch male homosexuals and Rwandan heterosexual women. The investigators found that HLA class I homozygosity was associated with more rapid disease progression, whereas other haplotypes examined did not exert a deleterious effect.

In FY 00, NIAID made a "bridge" award to the University of Alabama, Birmingham, to finish analysis of host immune responses in a HIVNET cohort of Rwandan HIV-positive patients who have either rapidly progressing or nonprogressing disease.

Senegal

Harvard School of Public Health/Boston HIVNET. The HIVNET provided for collaboration between Harvard School of Public Health and Cheikh Anta Diop University, Dakar. Research focused on the interactions between HIV-1 and HIV-2. The HIVNET funding stopped in 1997, but collaborative work continues with regular NIAID funding.

Viral characterization. The HIVNET carried out genetic characterization of viral quasi-species in blood and cervical secretions of HIV-1–positive and HIV-2–positive women in Senegal.

Viral load. The HIVNET reported that low plasma HIV-2 viral load is independent of proviral load, suggesting that the low viral load in HIV-2 infection is due to decreased rates of viral production, rather than differences in target cell activity.

HIV-2. The HIVNET determined that HIV-2 proviral loads in persons infected with HIV-1 and HIV-2 were significantly lower than in those infected with HIV-2 only, despite comparable CD4-positive lymphocyte counts.

Natural history. During 1985–1997, HIV-1 seroincidence in Senegalese women rose from 0% to 3.9% per year, whereas HIV-2 seroincidence was stable at about 1%. HIV-1–positive women also had disease progression to clinical AIDS much more rapidly than HIV-2–positive women did. The HIVNET also generated data suggesting that different HIV-1 strains differed in progression to clinical AIDS. In a prospective cohort study started in 1985, women infected with a non-A clade (C, D, or G) were eight times more likely to develop clinical AIDS than women infected with clade A.

Risk factors. Study findings suggest that high levels of tumor necrosis factor-α and IL-1β in bacterial vaginosis may increase susceptibility to HIV-1 infection.

Cross-protection. With the University of Massachusetts, Worcester, the HIVNET has explored the mechanisms behind the observation that previous infection with HIV-2 provides relative protection against HIV-1 infection.

University of Washington/Seattle HVTU. The HVTU will build on other projects in Senegal to conduct studies of seronegative persons who had been exposed to HIV-1, those acutely infected with HIV, those with long-term HIV positivity and no disease progression, and those infected with HIV-1 and HIV-2. The goal is to gain insights about immune responses appropriate to elicit vaccine protection.

AIDS. In FY 00, NIAID awarded a new grant to Harvard University, Boston, Massachusetts, to investigate in vitro correlates of HIV-1 protection in Senegal with Cheikh Anta Diop University, Dakar, and Johns Hopkins University School of Public Health, Baltimore.

The University of Washington, Seattle, Oxford University, England, the University of Dakar, and the Institute of Social Hygiene, Dakar, used molecular genotyping to discover that, among Senegalese commercial sex workers, absence of the gene for epithelial nonsecretion (FUT2) was associated with reduced risk of HIV-1 infection. In FY 00, NIAID made a new award to the University of Washington to build on earlier observations in Senegal that patients infected with

both HIV-1 and HIV-2 had markedly lower mean plasma HIV-1 RNA levels, higher counts of CD4-positive T cells, and lower rates for decline of CD4-positive T-cell counts than those infected with HIV-1 only.

Parasitic Diseases. LPD (NIAID), Institut Pasteur, Paris, France, the National Institute for Medical Research, Mill Hill, England, and ORSTROM, Dakar, reported that *Plasmodium falciparum* recombinant MSP1-19 antigens differ in their capacities to stimulate in vitro peripheral blood T lymphocytes in persons from various areas where the parasite is endemic.

Sierra Leone

Parasitic Diseases. Morgan State University and Johns Hopkins University, Baltimore, Maryland, Papua New Guinea Institute of Medical Research, Madang, and the University of Sierra Leone and Curney Barnes Memorial Hospital, Freetown, Liberia, investigated infection with *Wuchereria bancrofti* in displacement camps in Freetown and documented, for the first time, that lymphatic filariasis is widespread in periurban areas.

Singapore

AIDS. Los Alamos National Laboratory, New Mexico, Singapore General Hospital, New Changi Hospital, Tan Tock Seng Hospital, and the Ministry of Health, Singapore, found a predominance of subtype E and then subtypes B, A, and C, in that order, in the heterosexual population, but a predominance of subtype B in the intravenous drug users in the population.

South Africa

South African Medical Research Council/Durban HIVNET. With the California Department of Health Services, Berkeley, the HIVNET found that enzyme-linked immunosorbent assay tests and age-specific prevalence correlated with each other as estimates of age-specific HIV incidence. The HIVNET is conducting viral and immunology studies in patients who recently acquired HIV infection. The HIVNET is also conducting a phase I vaginal microbicide study of PRO2000/5 gel.

In addition, the HIVNET is scheduled to begin phase I clinical trials of a Venezuelan equine encephalitis (VEE) virus vector vaccine against HIV-1 clade C. DAIDS (NIAID) and the South African AIDS Vaccine Initiative funded the development of the candidate vaccine, which is being produced in seed lots by Greer Laboratories on behalf of Alphavax, Chapel Hill, North Carolina. The HIVNET is also responsible for preparing to conduct the vaccine trial in the rural village of Hlabisa. Parallel trials will take place concurrently in the United States and South Africa.

University of Witwatersrand-Baragwanath HIVNET. The HIVNET is performing viral and immunologic studies of recently infected HIV-positive patients. With the University of Chicago, Illinois, the HIVNET completed a community study in Soweto that showed an initial willingness to participate in trials of HIV vaccine. The HIVNET is conducting a phase I study of the vaginal microbicide PRO2000/5 gel. Also, the HIVNET is performing a phase IIA study of escalating doses of chlorhexidine, a topical microbicide, for intrapartum vaginal cleansing and postpartum cleansing of the newborn, to prevent HIV transmission from mother to newborn. The HIVNET is also conducting a phase I–II study in breast-feeding infants from birth to 6 months of age, to assess the safety and plasma concentrations of nevirapine given daily, twice a week, or once a week as prophylaxis for HIV transmission from mother to infant. The HIVNET also conducted a study of the pharmacokinetics and safety of emivirine in HIV-positive pregnant women and their newborns. The investigators reported that administration of emivirine did not result in significant toxic effects.

South African Medical Research Council/Durban HPTC. In FY 00, NIAID made this HPTC award directly to the South African Medical Research Council, Durban, to perform prevention studies at three sites in South Africa and one site in Zimbabwe, in collaboration with the University of Natal, Durban, Oxford University, England, and Columbia University, New York City, New York.

Columbia University/New York City HVTU. The domestic HVTU at Columbia University, which was awarded in FY 00, will collaborate with the South African Medical Research Council.

South African Medical Research Council/Durban HVTC. NIAID also made a foreign HVTC award to the South African Medical Research Council, Durban, in collaboration with Columbia University, New York City, other New York institutions, and the University of Zimbabwe, Harare.

University of Washington/Seattle HVTU. The University of Washington HVTU will collaborate with South African investigators to perform focused studies on mucosal and clade-specific, T-cell responses in vaccine recipients.

Tufts-New England Medical Center/Boston ICIDR. Tufts-New England Medical Center, Boston, Massachusetts, received a new ICIDR award in FY 00 to study the interaction between micronutrients and infections, particularly diarrheal diseases in South Africa. Collaborating South African institutions are the South African Medical Research Council and University of Natal Medical School, Durban.

University of Minnesota/Minneapolis ICIDR. Over the past 10 years, NIAID has supported the University of Minnesota, Minneapolis, to collaborate with the South African Medical Research Council, Durban, in research on the epidemiology, risk factors, pathogenesis, and natural history of amebiasis in South Africa. NIAID will phase out the ICIDR in FY 00. NIAID support and collaboration are likely to continue through the regular competitive grants program.

AIDS. The University of Alabama, Birmingham, New York University, Tuxedo, Institut Pasteur, Paris, France, and the University of the Free State, Bloemfontein, conducted studies on the susceptibility of female chimpanzees to genital infection with HIV-1 and showed that (1) effective HIV-1 infection by the cervicovaginal route usually requires more than one exposure; (2) low levels of infection without seroconversion occurred; and (3) vaccine efficacy studies involving a single virus challenge of immunized chimpanzees will not be possible.

During FY 00, NIAID made a new award to Massachusetts General Hospital, Boston, to collaborate with the University of Natal, Durban, in comparative studies in Boston and Durban on what constitutes an effective

CTL response in patients infected with HIV-1 clade C.

The University of North Carolina, Chapel Hill, is collaborating with the South African Medical Research Council, Durban, in the development of a VEE virus vector as an HIV vaccine that will use antigens derived from prevalent, circulating HIV-1 strains in South Africa.

Rockefeller University, New York City, New York, and the University of Cape Town are studying and characterizing thalidomide-induced, antigen-specific immune stimulation in HIV-1–positive patients with tuberculosis.

In FY 00, NIAID made an award to Massachusetts General Hospital, Boston, to collaborate with two sites in Durban to study the CTL-mediated control of infection with HIV-1 clade C in children and adults, which is prevalent in South Africa but rare in the United States.

Bacterial Diseases. The University of Pennsylvania, Philadelphia, and the South African Institute for Medical Research, Johannesburg, have initiated collaboration on the regulation of dormancy in *Mycobacterium tuberculosis*.

Parasitic Diseases. Case Western Reserve University, Cleveland, Ohio, and the South African Medical Research Council, Durban, are collaborating on the role of secretory IgA in mucosal infection and immunity to amebiasis.

Spain

AIDS. The University of Colorado, Denver, Hampton Road Medical Specialists, Virginia, Pharmacia and Upjohn, Kalamazoo, Michigan, and Provincial Clinical Hospital, Barcelona, reported that twice-daily doses of delavirdine in combination with nelfinavir, didanosine, and stavudine resulted in significant reduction in plasma viral load.

Bacterial Diseases. Scientists at SUNY, Stony Brook, Children's Research Foundation, Cincinnati, Ohio, and Hospital de Galdacano, Vizcaya, determined that the plasminogen-activation system enhances brain and heart invasion in murine borreliosis (relapsing fever).

Sri Lanka

AIDS. Specimens from blood donors in Sri Lanka are being used in data analysis of a study by NCI (NIH), New York University, New York City, North Shore University Hospital, Manhasset, New York, George Washington University, Washington, D.C., the University of Maryland, Baltimore, the University of Southern California and Specialty Laboratories, Los Angeles, and the University of Malaysia, Kuala Lumpur, to explore the association between HHV-8 and a variety of cancers.

Sudan

Parasitic Diseases. The Infectious Disease Research Institute and Corixa Corporation, Seattle, Washington, Federal University of Bahia, Salvador, Brazil, and the University of Khartoum are characterizing secreted antigens of *Leishmania,* to develop recombinant, antigen-based, subunit vaccine candidates and diagnostic cocktails containing multiple antigens.

The University of Alabama, Birmingham, Auburn University, Alabama, the Ministry of Health, Yemen, and the University of Khartoum and Sudan Medical Parasitology Research Laboratory, Khartoum, studied the genetic diversity of *Onchocerca volvulus* isolates from the Sudan and Yemen and reconfirmed that there is little intrapopulation and interpopulation heterogeneity in these specimens, compared with that in the population of West Africa.

Vector Biology. The University of Alabama, Birmingham, and the University of Khartoum and Sudan Medical Parasitology Research Laboratory, Khartoum, identified a blackfly distinct from *Simulium damnosum* and *S. sirbanum* that they named *S. hamedense*.

Sweden

AIDS. University of Pennsylvania School of Medicine, Philadelphia, University of South Florida College of Medicine, Tampa, the University of California, San Francisco, and Karolinska Institute, Stockholm, have developed a human monoclonal antibody to the gp41 protein of HIV-1 that exhibits neutralizing activity against diverse laboratory isolates.

Bacterial Diseases. University of Texas Southwestern Medical Center, Dallas, Ohio State University, Columbus, and the University of Göteborg identified a diffusible cytotoxin of *Haemophilus ducreyi* that may play a role in the development or persistence of the ulcerative lesions characteristic of chancroid.

Public Health Research Institute, New York City, New York, and Pharmacia Biotech AB, Piscataway, New Jersey, and Stockholm, Sweden, have used *Mycobacterium avium* complex–specific antigen cocktails to develop a skin test specific for tuberculosis.

Parasitic Diseases. A foreign grant to the University of Uppsala is supporting a study of the *Trypanosoma cruzi* genome.

Switzerland

AIDS. The University of North Carolina, Chapel Hill, and St. Gallen Canton Hospital are investigating the factors associated with changes in the shedding of HIV-1 in semen. The scientists reported that levels of HIV-1 in semen were high in primary infection, and they postulated that heterosexual transmission may occur early in infection. Subsequently, they reported that potent antiretroviral treatment resulted in marked suppression of seminal shedding of HIV RNA and DNA and improved immune status.

Bacterial Diseases. Investigators at Harvard School of Public Health, Boston, Public Health Research Institute, New York City, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, New York, and Vaudois University Hospital Center, Lausanne, determined that the molecular beacon assay is a simple, rapid, and highly sensitive method for the detection of isolates of rifampin-resistant *Mycobacterium tuberculosis* and of resistance to isoniazid in multidrug-resistant isolates.

University of Maryland School of Medicine, Baltimore, the University of Cincinnati, Ohio, and the Swiss Serum and Vaccine Institute, Bern, conducted a randomized, double-blind, placebo-controlled, multicenter trial in U.S. volunteers. The participants received a single dose of live, oral cholera vaccine (CVD 103-HgR) to prevent cholera after challenge with *Vibrio cholerae* 01 El Tor Inaba at 3 months after vaccination. Compared with control subjects, vaccinated

volunteers had reduced excretion of *V. cholerae* and fewer episodes of moderate-to-severe diarrhea (4% versus 39%) or any diarrhea at all (18% versus 91%).

Parasitic Diseases. New York University, New York City, and the University of Geneva are determining the immunogenicity of synthetic polyoxime malaria vaccines.

Viral Diseases. Johns Hopkins University School of Hygiene, Baltimore, SyStemix, Palo Alto, California, and the University of Zhrich showed that recombinant measles viruses with mutations in the C, V, or F gene have altered growth phenotypes in vivo.

Immunology. The University of Geneva participates in the NIAID Immune Tolerance Network.

Tanzania

Harvard School of Public Health/Boston HPTC. In FY 00, Harvard School of Public Health, Boston, was the recipient of a new NIAID HPTC award to collaborate with Muhimbili Medical Center, Dar es Salaam.

Harvard University/Boston ICIDR. In FY 00, NIAID awarded a new ICIDR to Harvard University to collaborate with Muhimbili Medical Center on the epidemiology of the interaction between nutritional status and immunology of tuberculosis in HIV-positive and HIV-negative patients in Tanzania.

Bacterial Diseases. The Laboratory of Immunoregulation (NIAID) and Johns Hopkins University School of Medicine conducted a 6-year follow-up of children aged 1–2 years in Kongwa, to identify risk factors for trachoma.

Parasitic Diseases. Researchers at Duke University Medical Center, Durham, North Carolina, and Muhimbili Medical Center, Dar es Salaam, are examining the molecular mechanisms responsible (1) for the increased production of NO and expression of NO synthetase type 2 in Tanzanian children with asymptomatic malaria and (2) for the markedly decreased levels observed in children with severe malaria.

Thailand

Johns Hopkins University/Baltimore HIVNET. The HIVNET provides Johns Hopkins University with funding to collaborate with Chiang Mai University.

Viral variation. The HIVNET reported that the genetic diversity within HIV-1 subtype E, which is the predominant type in Thai heterosexuals, has increased significantly but is still less than has been seen in the more mature U.S. epidemic.

Risk behavior. The HIVNET determined that Thai men who have sex with men were more likely to be HIV-positive than men who report having sex only with women. Because most Thai men who have sex with men also have sex with women, they are a potential bridge population, as well as being a target for special prevention efforts. The HIVNET scientists determined that the prevalence of HIV positivity in male blood donors, who constitute 80% of donors, declined from 4.4%–5.9% to 2.4%–2.7% between 1991 and 1996, because of prevention programs made available through commercial sex facilities. However, prevalence of HIV positivity in female blood donors has remained in the range of 1%–2% as HIV transmission increases in married couples.

Discordant couples. The HIVNET examined factors influencing marital stability of couples who were discordant for HIV positivity. The investigators discovered that support by the extended family, the presence of children, and fear of stigmatization by the community were important in preserving the marital union.

Prevention programs. The HIVNET documented a dramatic decrease in incidence rates of HIV and STD infections among young men in military service in northern Thailand after the establishment and implementation of the 100% Condom Program.

Opportunistic infections. The HIVNET conducted an open-label, nonrandomized trial to evaluate the safety and effectiveness of a 2-week course of intravenous amphotericin B followed by 10 weeks of oral itraconazole to treat Penicillium infection. The study found that this regimen was safe and effective, with a 97.3% positive clinical response.

Johns Hopkins University School of Hygiene and Public Health/Baltimore HPTC. In FY 00, NIAID made an HPTC award to Johns Hopkins University School of Hygiene and Public Health to collaborate with Chiang Mai University in research on HIV prevention.

Johns Hopkins University School of Hygiene and Public Health/Baltimore HVTC. Also in FY 00, NIAID made an award of an HVTC to Johns Hopkins University School of Hygiene and Public Health, to work with Chiang Mai University and other Thai institutions in research on HIV vaccine.

Columbia University/New York City ICIDR. The ICIDR provided Columbia University College of Physicians and Surgeons with support to collaborate with Mahidol University, Bangkok, in clinical studies of malaria. Scientists at Howard University, Washington, D.C., and the ICIDR determined that the possession of the hemoglobin E trait, which is common in Thailand, did not significantly enhance clearance of the malaria parasite but that the trait might potentiate the antimalarial effects of artemisinin derivatives.

University of Massachusetts/Worcester Dengue Program Project. The Program Project provides for collaboration with Walter Reed Army Institute of Research, Washington, D.C., Kamphaeng Phet Provincial Hospital, and the Armed Forces Research Institute of Medical Sciences, Queen Sirikit National Institute of Child Health, and Siriraj Hospital, Bangkok, in multidisciplinary studies of dengue fever and dengue hemorrhagic fever.

Clinical manifestations. In a prospective study in northern Thailand, the investigators found that leptospirosis was a frequent cause of fever in children.

Pathogenesis. A multi-institute prospective clinical study of the pathogenesis of dengue fever and dengue hemorrhagic fever was started in 1994. The research showed that children with secondary dengue hemorrhagic fever had higher antibody titers relating to neutralization of dengue-specific plaque reduction than did control subjects with secondary dengue fever, as early as 3 days before defervescence. In addition, these titers were directly proportional to the severity of the dengue hemorrhagic fever.

Immunology. The Program Project and the National Institute of Infectious Diseases,

Toyama, Japan, documented that acute dengue infection is associated with impaired T-cell proliferation. Early immune activation in acute dengue fever is related to both development of plasma leakage and the severity of disease.

AIDS. Researchers at CDC, Indiana University School of Medicine, Indianapolis, and Khon Kaen University reported that HIV-positive patients with high levels of serum creatinine and low albumin levels were at increased risk of developing severe histoplasmosis, but previous treatment with AZT reduced the risk.

Parasitic Diseases. LPD (NIAID), the Southwest Foundation for Biomedical Research, San Antonio, Texas, and Shoklo Malaria Research Unit, Mae Sot, are measuring in vitro susceptibility of *Plasmodium falciparum* isolates collected along the Myanmar-Thailand border to mefloquine, quinine, artemisinin, and chloroquine. The investigators will then try to map genes for resistance.

Researchers at the University of Michigan, Ann Arbor, and Mahidol University, Bangkok, found that intravascular levels of artesunate in patients with α-thalassemia and control subjects peaked at 1 hour, but subsequently, patients had considerably higher plasma levels of the drug throughout the periods measured. These findings raise the possibility that different artesunate dosages may be necessary for patients with thalassemia who develop malaria. In the course of this work, the investigators documented emerging artemisinin-resistant malaria.

Vector Biology. Johns Hopkins University School of Public Health, Baltimore, and Chulalongkorn University and the Ministry of Health, Bangkok, used PCR-based testing to investigate the high infectivity rate of *Wuchereria bancrofti,* Myanmar strain, in Culex quinquefasciatus mosquitoes, in areas of Thailand where this strain of *W. bancrofti* is endemic.

Trinidad and Tobago

University of Maryland/Baltimore HVTC. In FY 00, NIAID made an award for this HVTC to collaborate with the University of the West Indies, Port of Spain, in a coalition for HIV vaccine development.

AIDS. NCI (NIH), Duke University Medical Center, Durham, University of Maryland Medical School, Baltimore, and University of the West Indies Medical Research Center, Port of Spain, are studying patterns of clinical, immunologic, and virological markers in acute HIV seroconversion.

Tunisia

Institut Pasteur/Tunis MERC. The MERC Program provided direct support to Institut Pasteur, Tunis, to collaborate with Ibn el Jazzar University, Sousse, and the Regional Public Health Department, Kairouan. With the National School of Veterinary Medicine, Sidi Thabet, the MERC compared classic parasitological and serological evaluation techniques with PCR tests for the diagnosis of leishmanial infection in dogs. The MERC investigated the spread of human visceral leishmaniasis in central Tunisia and found an association with higher-than-average rainfall the preceding 3 years. The highest rates of the disease were in areas with the most intensive agricultural projects.

Turkey

Hebrew University/Jerusalem MERC. Ege University, Izmir, and the Royal Tropical Institute, Amsterdam, the Netherlands, have collaborated with the MERC on the epidemiology of canine leishmaniasis in western Turkey. The investigators documented that both canine and human visceral leishmaniasis (kala-azar) are widespread and that both the indirect immunofluorescence assay and direct agglutination serodiagnostic tests are useful tools to monitor the infection.

Mycotic Diseases. University of Texas Health Science Center and South Texas Veterans Health Care System, San Antonio, and Gulhane School of Medicine, Ankara, found that SCH56592, itraconazole, and voriconazole were effective and promising antifungal agents.

Immunology. Harvard Medical School, Boston, the University of Vienna, Austria, and Marmara University Hospital, Istanbul, published the results of a randomized, double blind, placebo-controlled trial to evaluate the effect of intravenous immunoglobulins on steroid needs in patients with severe asthma.

Uganda

Case Western Reserve University/Cleveland HIVNET. The HIVNET provided funds to collaborate with Makerere University, Kampala.

Vaccine evaluation. Before initiation of HIV vaccine trials, the HIVNET did a study showing that fear of stigmatization associated with participation as a volunteer is not a significant barrier to participation in the HIVNET population cohort. The HIVNET is evaluating the safety and immunogenicity of live, recombinant, canarypox ALAC-HIV (vCP205) in HIV-negative volunteers in Uganda. Immunogenicity and CTL activity were detected in the study population. The investigators also demonstrated activity of this HIV clade B vaccine against HIV clade C and D antigens, suggesting cross-clade responses of CD8-negative T cells.

Subsequently, the HIVNET is carrying out a phase I trial to evaluate the safety and immunogenicity of ALVAC (vCP1452) and a vaccine containing subunit HIV-1 rgp120 in combination with antiretroviral therapy in infants born to HIV-1–positive women in Uganda.

Johns Hopkins University School of Medicine/Baltimore HIVNET

Perinatal transmission. DAIDS (NIAID), the National Institute of Child Health and Human Development (NIH), Johns Hopkins University School of Medicine, Boston University School of Medicine, Massachusetts, the University of Washington, Seattle, Case Western Reserve University, Cleveland, Ohio, Family Health International, Durham, North Carolina, Boehringer-Ingelheim, Ridgefield, Connecticut, and Makerere University, Kampala, performed a HIVNET phase I–II study of the safety and pharmacokinetics of nevirapine in HIV-1–positive pregnant Ugandan women and their neonates. The investigators also completed a phase III HIVNET study of oral AZT and nevirapine in prevention of vertical transmission. One group of women received a single dose of nevirapine during labor, and their infants received one dose within 72 hours of birth. A second group of women received AZT during labor, and their newborns received twice-daily doses for 7 days. After 6–8 weeks, both regimens were equally well tolerated, but infants receiving nevirapine had a 42% lower risk of acquiring HIV than

those receiving AZT. Follow-up studies of breast-fed infants who had received nevirapine or AZT continued to show a lower rate of transmission in the nevirapine group (39%) than in the AZT group (42%). Risk of HIV transmission in both groups was related to the HIV viral load in the mother's blood and counts for CD4-positive T cells.

Columbia University/New York City HPTC. Uganda is the recipient of an HPTC award to Columbia University to collaborate with Uganda Viral Research Institute, Entebbe, and Makerere University, Kampala, in research on protocols for HIV prevention.

Makerere University-Johns Hopkins University/Baltimore HPTC. In FY 00, NIAID made a new HPTC award to Johns Hopkins University to collaborate on the Johns Hopkins University-Makerere University HPTC, Kampala, in research on protocols for HIV prevention.

Case Western Reserve University/Cleveland TBRU. Makerere University and the Ministry of Health, Kampala, participate in the TBRU network.

Natural history. In a study of patients from a voluntary counseling and testing clinic in Kampala, the TBRU documented that, in HIV-positive patients, tuberculosis was independently associated with an increased risk of death, particularly when the count of CD4-positive T cells was greater than 200 cells/mL.

Epidemiology. The TBRU evaluated the impact of HIV infection on the household transmission of tuberculosis and found comparable levels in both HIV-positive and HIV-negative patients with tuberculosis.

Vaccine evaluation. Biomedical Research Consulting, Cabin John, Maryland, the TBRU, and Makerere University and the National Tuberculosis and Leprosy Control Program, Kampala, conducted a randomized, controlled trial of immunotherapy with *Mycobacterium vaccae* in HIV-positive Ugandan patients with newly diagnosed pulmonary tuberculosis. The investigators reported that patients receiving immunotherapy had an initial early clearing of sputum and greater improvement in chest x rays at 6 and 12 months than did placebo control subjects.

Columbia University/New York City Rakai Project. The Rakai Project involves collaboration among Columbia University, Johns Hopkins University School of Public Health, Uganda Viral Research Institute, Entebbe, and Makerere University, Kampala, to define a population-based cohort in rural and semirural villages and communities in Rakai Province. For 10 years, the Rakai Project involved prospective studies of epidemiology, risk factors, natural history, education, and prevention. NIAID support for the Rakai Project is being continued under a new investigator-initiated grant that will pursue research on STD control for AIDS prevention in Uganda.

Risk factors. The Project reported that prepubertal circumcision is associated with reduced HIV risk, whereas circumcision after age 20 years is not significantly protective against HIV.

In a historic, retrospective study of discordant couples who participated in the Rakai STD Study, the Rakai Project Study Group concluded that HIV-1 viral load is the chief predictor of the risk of heterosexual transmission and that transmission is rare among persons with levels less than 1,500 copies of HIV-1 RNA per milliliter.

STD treatment. The Project conducted a retrospective analysis of data from a study on HIV/AIDS transmission that was performed in 1994–1998 to compare the impact of syndromic versus community-based treatment of STDs on the reduction of HIV transmission. The original study showed no significant effect on HIV transmission in the Rakai setting. The retrospective analysis, however, showed that discordant couples with low HIV viral load in the HIV-positive partner had reduced transmission rates. These results have raised interest in the use of antiretroviral drugs in resource-poor settings, for prevention of transmission in addition to therapeutic effects.

AIDS. Scientists at the University of Massachusetts, Worcester, the University of Minnesota, Minneapolis, Liverpool School of Tropical Medicine, England, and Uganda Viral Research Institute, Entebbe, concluded that HIV-positive patients in Uganda who developed acute invasive bacterial infections showed evidence of more advanced HIV disease, as shown by clinical, immunologic, and virological markers. The same scientists reported that invasive bacterial infections, such as salmonellosis, are associated with a more rapid decline in counts of CD4-positive T cells over time, with increase of HIV-1 replication and an increased risk of death.

Parasitic Diseases. The University of California, San Francisco, and Makerere University investigated the epidemiologic risk factors for chloroquine-resistant malaria in children and adults in Kampala. The researchers found that age younger than 5 years was significantly associated with treatment failure after chloroquine administration.

Ukraine

AIDS. Harvard School of Public Health, Boston, conducted molecular epidemiology studies of an HIV-1 clade A subtype among injection drug users in southern Ukraine.

Vector Biology. An NIAID-supported investigator at Colorado State University, Fort Collins, received a CRDF grant to collaborate with Tars Shevchenko University, Kiev, on determinants of the host range of mosquito densinucleosis viruses.

United Kingdom

AIDS. Los Alamos National Laboratory, New Mexico, the University of Alabama, Birmingham, Northwestern University, Chicago, Illinois, and Manchester Institute of Technology, England, analyzed HIV-1 sequences to estimate the timing of the ancestral sequence of the main HIV-1 group and estimated the date of the last common ancestor to be 1931 (range, 1915–1941). This study is evidence against current hypotheses that HIV spread to human populations in Africa as a result of early poliomyelitis vaccine studies in the 1950s.

NIAID supports a foreign grant award to the Edward Jenner Institute for Vaccine Research, Newbury, Berkshire, England. The researchers are investigating the role of virus-specific CTLs in viral control of HIV-1 in infected persons.

The University of Alabama, Birmingham, the University of California, San Francisco, Harvard Medical School and School of Public Health, Boston, University of Miami School of Medicine, Florida, Boehringer-Ingelheim Pharmaceutical, Ridgefield, Connecticut, and the London School of Hygiene

and Tropical Medicine conducted an AIDS Clinical Trials Group (ACTG) protocol to examine the pharmacokinetics of nevirapine, AZT, and didanosine in HIV-positive patients.

Mycotic Diseases. In FY 00, NIAID made a large foreign grant award to the University of Manchester, England, to complete the genomic sequencing of *Aspergillus fumigatus*.

Viral Diseases. Investigators at Johns Hopkins University, Baltimore, SyStemix, Palo Alto, California, and the University of Belfast, Ireland, found that prolonged replication of measles virus vaccine strains in human tissue resulted in altered virulence.

Immunology. The University of Virginia Medical Center, Charlottesville, and North West Lung Center, Manchester, England, found that clinical activity and severity of asthma in mite-sensitive patients was related to exposure to mite allergens in the dust reservoir, with levels in bed being an important indicator that correlated with disease activity.

Venezuela

University of Texas Medical Branch/Galveston EVC. The EVC is collaborating with the National Institute of Health, Caracas, on mechanisms of the emergence of VEE and other zoonotic virus pathogens. With CDC, Fort Collins, the Regional Health Office of Portuguesa State, and the National Research University of the Llanos, Guanare, the Center examined Guanarito virus isolates from endemic and outlying areas of Venezuela.

With the Ezequiel Zamora National Experimental University of the Western Llanos, Guanare, the EVC experimentally infected the *Sigmodon alstoni* cotton rat with Cao Delgadito virus, a newly discovered South American Hantavirus.

University of Massachusetts/Worcester ICIDR. In FY 00, the University of Massachusetts, Worcester, received a new ICIDR award to continue the EVC collaboration with the National Institute of Health, Caracas, on the pathogenesis of severe dengue infections in Venezuela.

Parasitic Diseases. Corixa Corporation, Seattle, and Central University of Venezuela and the Ministry of Health and Social Assistance, Caracas, investigated an outbreak of canine *Leishmania donovani* visceral leishmaniasis on Margarita Island and instituted dog control measures based on the findings.

Harvard School of Public Health, Boston, and the Central Amazon Center for the Research and Control of Tropical Diseases, Puerto Ayacucho, used standard molecular epidemiologic methods to measure genetic diversity in an epidemic of *Plasmodium falciparum* malaria among Yanomami Amerindians.

Vietnam

Parasitic Diseases. The University of Michigan, Ann Arbor, received a bridge award to document and characterize the presence of artemisinin-resistant falciparum malaria in Vietnam and other areas of Southeast Asia.

Zambia

University of Alabama/Birmingham HIVNET. The HIVNET provides support for collaboration with University Hospital and the University of Zambia, Lusaka, in research on protocols for HIV prevention.

University of Alabama/Birmingham HPTC. NIAID made an award to the University of Alabama, Birmingham, to initiate a new University of Alabama-Zambia-Haiti HPTC, to conduct HIV/AIDS prevention studies in collaboration with University Teaching Hospital and the University of Zambia, Lusaka.

University of Alabama/Birmingham HVTC. The HVTC involves collaboration with University Teaching Hospital and the University of Zambia, Lusaka, to conduct HIV vaccine studies in Zambia and the United States.

AIDS. The University of Alabama, Birmingham, has an award to study the heterosexual transmission of HIV in Zambia.

Dartmouth College, Hanover, New Hampshire, is planning a 5-year study of *Mycobacterium vaccae* vaccine in HIV-positive patients at high risk for tuberculosis.

Parasitic Diseases. In FY 00, NIAID made a new award to continue the malaria research in Zambia with a focus on severe malarial anemia and altered immune function, in collaboration with Picower Institute for Medical Research, Northbrook, New York, Macha Malaria Research Institute, Dillsburg, Pennsylvania, the University of Innsbruck, Austria, and Livingstone General Hospital and Macha Mission Hospital, Choma.

Zimbabwe

Stanford University/California HIVNET. The HIVNET supports collaboration with the University of Zimbabwe, Harare.

Epidemiology. The HIVNET is studying the virological and immunologic parameters of persons with recent HIV-1 seroconversion.

Male factory cohort. Prospective studies of HIV acquisition and the clinical course of disease have resulted in preliminary evidence that male factory workers have a more rapid decline in counts of CD4-positive T cells and function of the immune system after HIV acquisition than has been observed in industrial, developed countries.

Despite a high rate of HIV acquisition (3% per year), the HIVNET researchers discovered that syphilis was rare. Men who tested positive for active syphilis were older, of lower socioeconomic status, and more likely to have sexual activity with prostitutes. In contrast, a study conducted with collaboration from Chiron Corporation, Emeryville, California, found that herpes simplex virus type 2 seroconversion was a strong marker of sexual risk and was the leading cause of genital ulcers in the cohort.

Topical microbicides. The HIVNET is the site of a phase IIB trial of new microbicide candidates.

Vertical transmission. The HIVNET is conducting a phase I–II study to assess the safety and plasma concentrations of nevirapine administered daily, twice a week, or weekly as prophylaxis in breast-feeding infants of HIV-positive mothers, from birth to 6 months of age.

Stanford University/California HPTC. In FY 00, NIAID made a new HPTC award to Stanford University for a Stanford-Zimbabwe HPTC to collaborate with the University of Zimbabwe, Harare, in research on protocols for HIV/AIDS prevention.

South African Medical Research Council/Durban HVTC. The HVTC has a component to collaborate with Stanford University and

the University of Zimbabwe on HIV vaccine and vaccine-related studies in Zimbabwe.

Taiwan

University of Notre Dame/South Bend TDRU. The TDRU, Michigan State University, East Lansing, the University of California, Irvine, and National Yang-Ming University, Taipei, are using a molecular genetic approach to genetically engineer transgenic mosquitoes with an element of systemic antibacterial immunity activated by a bloodmeal–triggered cascade, rather than infection with the pathogen.

Bacterial Diseases. The University of Washington, Seattle, and National Cheng Kung University, Tainan, showed that *Chlamydia trachomatis* induced inflammatory changes in the heart and aorta of C57BL/6J mice with healthy levels of cholesterol.

Activities With International and Multinational Organizations

World Health Organization

Parasitic Diseases. Researchers at Case Western Reserve University, Cleveland, Ohio, the University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program found that, after the topical administration of diethylcarbamazine to patients infected with *Onchocerca volvulus,* the cellular infiltrate in the dermis and abscesses in the epidermis that developed contained mononuclear cells, intact and degranulated eosinophils, and eotaxin. These observations are consistent with eotaxin having a role in recruitment of eosinophils to the skin in diethylcarbamazine-induced onchodermatitis.