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 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 in 1955, in recognition of the importance of the immune system to human health and disease. When the Office of International Research of the National Institutes of Health (NIH) was disbanded in 1968, NIAID assumed responsibility for the Office's International Centers for Medical Research 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 carry out and fund research. The Division of Intramural Research and the Vaccine Research Center are responsible for coordination of the research conducted in NIAID's laboratories. 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). The Division of Extramural Activities is responsible for groups that perform 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. Authority for the NIH to conduct international research was formally defined in the U.S. Public Health Service (PHS) Act of 1963, which limited it to "international research relevant to health and welfare of U.S. populations." The PHS Act of 1988 ("AIDS" Act) expanded this authority to training, technology, and institutional strengthening for research in HIV/AIDS and related areas. In 1994, NIAID was, for the first time, given a specific mandate for research on tropical disease. NIAID uses six mechanisms to conduct international research: (1) collaboration with the Division of Intramural Research; (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

The Division of Intramural Research consists of 17 laboratories supported by the Animal Care Branch, the Administrative Management Branch, and the Biological Resources Branch. The laboratories are concentrated on the NIH campus in Bethesda, Maryland, but some are located in Rockville and Frederick, Maryland, and at the Rocky Mountain Laboratories in Hamilton, Montana.

The 17 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 Molecular Structure; Laboratory of Parasitic Diseases; Laboratory of Persistent Viral Diseases; and Laboratory of Viral Diseases.

The Division of Intramural Research consists of tenured clinicians, tenure-track scientists, tenured scientists, nontenured scientists (one-third from foreign countries), and a support staff of nonscientists. During 1999, the largest national groups of foreign scientists receiving short-term research training at NIAID were from Japan (47), China (27), France (23), Italy (23), Canada (19), Germany (19), India (14), the United Kingdom (14), Korea (13), Australia (10), Brazil (10), Russia (9), and Spain (7). Other countries represented were Algeria, Argentina, Austria, Bangladesh, Belgium, Bolivia, Colombia, Croatia, Czech Republic, Denmark, Greece, Hungary, Iceland, Iran, Israel, Jordan, Mali, Mexico, Morocco, the Netherlands, New Zealand, Philippines, Poland, Portugal, Slovakia, Swaziland, Switzerland, Thailand, Turkey, Uzbekistan, and Taiwan. The personnel in this Division constitute the majority of NIAID staff but only about 10% of the NIAID budget.

The Vaccine Research Center opened in FY2000.

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 the development and evaluation of human vaccines. Extramural research accounts for about 90% of the NIAID funding but only 10% of staff positions. Historically, the Division of Microbiology and Infectious Diseases has been responsible for most NIAID collaborative research on endemic disease problems of tropical or developing countries. For the past decade, however, the Division of AIDS has funded major international studies in resource-poor settings overseas.

In contrast to many 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, is so competitive that direct application is not

practical for most overseas scientists. A more effective strategy for foreign scientists is to identify a U.S. collaborator with experience and success in writing applications for NIH grants. Collaborative proposals can then be submitted to the NIH by the U.S. partner. 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 pool of grants. 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 International Collaboration in Infectious Disease Research (ICIDR) Program provides funding to U.S. institutions to link with institutions in developing countries.

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

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

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

In 1997, NIAID initiated three domestic, multidisciplinary Emerging Viral Diseases Research Centers (EVCs) and four Viral Hepatitis Research Centers, as part of the Emerging and Reemerging Infectious Diseases Research Initiative.

To more closely coordinate and monitor international research activities, NIAID established the International Centers for Tropical Disease Research Network in 1992. This network has the following components:

1. NIAID Office of Tropical Medicine and International Research;

2. NIAID Laboratory of Parasitic Disease and Laboratory of Malaria Research and other intramural laboratories;

3. institutions that are participants in the EVC, ICIDR, TBRC, TDRU, and TMRC programs; and

4. other U.S. institutions receiving substantial NIAID support for research in tropical medicine.

The International Centers for Tropical Disease Research Network convenes each spring in an open scientific meeting in Bethesda, Maryland, for coordination, exchange, and identification of research needs and opportunities.

In 1987, the Division of AIDS 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, which supported U.S. institutions for an intensive 2-year effort to work with colleagues in developing countries in training, technology transfer, and strengthening of institutions. The Division of AIDS supports an International AIDS Vaccine Master Contract, through which awards are made to U.S. institutions to participate in the HIV Network (HIVNET). In this capacity, these institutions conduct specific HIV/AIDS prevention and intervention projects in the United States or developing countries.

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 17 countries and Taiwan: Brazil, China, Croatia, Finland, France, Georgia, Germany, India, Israel, Italy, Japan, Macedonia, Mongolia, Poland, Russia, Slovenia, and South Africa. 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 (P.L. [Public Law] 480) Program, but most are implemented with regular NIAID resources.

Interagency Agreements

In the current period of expanding opportunity and finite resources in the U.S. Government agencies, it is increasingly common for agencies to combine resources to carry out joint programs. For example, the Biotechnology Engagement Program is a joint effort of the U.S. Department of State and the U.S. Department of Health and Human Services in collaborative research with the Newly Independent States of the Former Soviet Union.

Multilateral Activities

Infectious diseases, including AIDS, are the major causes of preventable death and disease throughout the world, and new knowledge and advances made possible by NIAID research 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 on AIDS, infectious diseases, tropical diseases, and immunology. NIAID laboratories and programs also serve as WHO Collaborating Centers in Antiviral Agents (Division of Microbiology and Infectious Diseases); Epidemiology of Asthma and Allergic Diseases (Division of Allergy, Immunology, and Transplantation); Microbial Vector Research (Laboratory of Viral Diseases); and the AIDS Reagent Center (Division of AIDS).

NIAID also has a close working relationship with the Regional Office of WHO for the Americas and with 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 (PAHO), 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 Accelerated Vaccine Initiative. The role of NIAID's Division of Microbiology and Infectious Diseases is to invest in basic and applied research leading to the development and evaluation of new or improved pediatric vaccines.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

AIDS

NIAID funds the Atlantic Study, which is sponsored by the AIDS Clinical Trials Group (ACTG). Participants in this international, multicenter study include St. Pierre University, Brussels, Belgium; the University of British Columbia, Vancouver; Goethe Uni-

versity, Frankfurt, and Medizische Hochschule, Hanover, Germany; St. Lazlo Hospital, Gyali, Hungary; the University of Milan, Italy; the Netherlands AIDS Treatment and Education Center, Amsterdam; and the Warsaw AIDS Center, Poland. The study is a randomized, placebo-controlled, open-label trial comparing the effectiveness of two protease inhibitors with that of standard highly active antiretroviral therapy (HAART) regimens containing a single protease inhibitor.

The Esprit Project is a multinational study funded by the Laboratory of Immunoregulation (NIAID) and coordinated by the University of Minnesota, Minneapolis. In this 16-country study, which has 18 sites, investigators are evaluating the clinical response of HIV-positive patients treated either with interleukin 2 (IL-2), a cytokine immunostimulator, in addition to a standard HAART regimen, or with a conventional HAART regimen alone. The following countries are collaborating in this research: Australia, Belgium, Canada, England, France, Germany, Greece, Hungary, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Sweden, and Thailand.

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

Bacterial Diseases

NIAID funds the International *Klebsiella* Study Group, which is evaluating the in vitro susceptibility of *Klebsiella pneumoniae* and the clinical outcome of bacteremia due to *K. pneumoniae* that produces extended-spectrum β-lactamase, in different geographic and institutional settings. The study group consists of 11 hospitals in seven countries: Argentina, Australia, Belgium, Canada, South Africa, Turkey, and the United States.

The University of California, San Francisco, is working with the University of Alexandria, Egypt, in a clinical trial in the Gambia and Tanzania comparing mass treatment of communities where trachoma is endemic with a single oral dose of azithromycin versus the recommended WHO 2-week administration of topical tetracycline, with a 22-month follow-up. This clinical trial will be the basis for other research studies on the epidemiology of trachoma in the communities, molecular epidemiology of *Chlamydia trachomatis*, and measurement of tears in the eyes before and after treatment, to determine the response to antibody.

Immunology

The University of Maryland/Baltimore ICIDR hosted a study of immunogenicity to an outer-membrane protein of group B meningococcus used in vaccines developed by the Finlay Institute, Havana, from bacteria from patients in Cuba and Norway. The study subjects were Chilean infants, children, and adults at risk from a heterologous epidemic strain.

The University of Virginia, Charlottesville, Federal University of São Paulo, Brazil, the University of Manchester, England, and the National University of Singapore are engaged in a multicenter study of the biological activity of recombinant group 5 mite allergens.

Parasitic Diseases

The Research Institute of Tropical Medicine/Manila (Philippines) TMRC, Case Western Reserve University, Cleveland, Ohio, Brown University, Providence, Rhode Island, Nanjing Medical University and Sichuan Institute of Parasitic Diseases, China, Kenya Medical Research Institute, Nairobi, and WHO, Geneva, Switzerland, participated in a double-blind, placebo-controlled study of concurrent administration of albendazole and praziquantel in African and Asian rural school children infected with *Schistosoma mansoni, Schistosoma haematobium,* or *Schistosoma japonicum* and other intestinal helminths. The study concluded that the two drugs could be administered concurrently by teachers. The regimen had no effect on trichuriasis, and ascariasis rebounded to pretreatment levels in 6 months, but reductions in schistosomiasis and hookworm infection were sustained. A significant reduction in anemia and increase in hemoglobin were observed in children receiving praziquantel. The study provides the basis for safe and cost-effective deworming campaigns for school children in rural Africa and Asia with mixed helminth infections and should result in a significant increase in hemoglobin levels in this population.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Argentina

University of Georgia/Athens TDRU. This TDRU is assessing human immune responses to antigens that are candidates for vaccine against *Trypanosoma cruzi*, the causative agent of Chagas' disease.

Mycotic Diseases. Seven Argentinean sites are participating in an NIAID Mycoses Study Group comparing the efficacy of voriconazole with that of amphotericin B and fluconazole for candidemia in patients without neutropenia.

Viral Diseases. The University of Nevada, Reno, and the National Institute of Human Viral Diseases, Pergamino, are investigating the genetic diversity and epidemiology of Hantaviruses in Argentina.

Australia

Bacterial Diseases. Johns Hopkins School of Public Health and School of Medicine, Baltimore, Maryland, and CSL Ltd., Parkville, determined that the new assay of whole blood for release of interferon γ (IFN-γ) was more sensitive than tuberculin skin testing, for the detection of tuberculosis infection among patients at risk for tuberculosis exposure.

Parasitic Diseases. The Walter and Eliza Hall Institute for Medical Research, Sydney, received an NIAID grant to study the immunobiology of malaria glycosylphosphatidylinositol. In fiscal year 1999 (FY 99), NIAID made a new award to the Walter and Eliza Hall Institute for Medical Research, to study the mechanisms involved in the adherence of red blood cells infected with malaria parasites.

Viral Diseases. Scripps Research Institute, La Jolla, California, Westmead Hospital, Sydney, and the University of Sydney demonstrated that neutralizing antibodies inhibit

the in vitro spread of herpes simplex virus type 1 to epidermal cells.

Vaccine Development. NIAID made an award to the University of Queensland, Brisbane, to develop and evaluate novel hybrid mucosal vaccines.

Immunology. NIAID supports an award to the Walter and Eliza Hall Institute for Medical Research, which is using CD38 expression to reveal the kinetics of establishing the memory B-cell population.

A second NIAID award to the Walter and Eliza Hall Institute for Medical Research deals with the regulation of peripheral tolerance versus immunity.

The Australian National University, Canberra, is one of approximately 40 research institutions participating with the University of Chicago, Illinois, in the new NIAID contract for the Collaborative Network for Clinical Research on Immune Tolerance.

Austria

AIDS. Walter Reed Army Institute of Research, Rockville, and the Naval Medical Research Institute, Bethesda, Maryland, the Armed Forces Institute of Pathology, Washington, D.C., Rockefeller University, New York City, New York, Scripps Research Institute, La Jolla, and the University of Vienna reported that neutralizing monoclonal antibodies (MAbs) block human immunodeficiency virus type 1 (HIV-1) infection of dendritic cells and transmission of the virus to T cells. Subsequently, Stanford University Medical Center, California, Activated Cell Therapy, Inc., Mountain View, California, and ImmunoAG, Vienna, carried out a pilot clinical trial of therapy with HIV antigen plus pulsed administration of allogeneic and autologous dendritic cells in HIV-positive patients, but the investigators observed no reduction in viral load.

Parasitic Diseases. Washington University School of Medicine, St. Louis, Missouri, Institut Pasteur, Paris, France, and the Institute for Specific Prophylaxis and Tropical Medicine and the Institute of General and Experimental Pathology, Vienna, protected mice against invasive amebiasis with a single MAb directed against a lipophosphoglycan antigen localized on the surface of *Entamoeba histolytica*.

Bangladesh

Bacterial Diseases. Harvard Medical Center, Boston, Massachusetts, and the International Center for Diarrheal Diseases Research (ICDDR), Dhaka, documented the lysogenic conversion of environmental *Vibrio mimicus* strains by CTXϕ, a filamentous bacteriophage that encodes cholera toxin in *Vibrio cholerae*. This finding suggests that diverse CTXϕs may be important in the evolution of new, pathogenic strains of cholera.

NIAID supports Johns Hopkins School of Hygiene and the University of Maryland, Baltimore, and the ICDDR, Dhaka, for studies of the epidemiology and ecology of *V. cholerae* in Bangladesh. The researchers successfully used polymerase chain reaction (PCR) technology for the first time to detect noncultivatable *V. cholerae* 01 in association with *Anabaena* spp. of Cyanobacteria, a possible reservoir for the cholera organism in brackish water.

Enteric Diseases. New England Medical Center, Boston, Massachusetts, and the ICDDR are examining the role of micronutrients in enteric infections in Bangladeshi children.

Parasitic Diseases. The University of Virginia, Charlottesville, and the ICDDR showed that PCR, isoenzyme chain reaction, and the antigen-detection test for *Entamoeba histolytica* (TechLab, Inc., Blacksburg, Virginia) were all more sensitive than traditional microscopic examination of fresh stool for the detection of *E. histolytica*. In addition, the new tests could distinguish pathogenic *E. histolytica* from the commensal *Entamoeba dispar*.

Barbados

Immunology. Johns Hopkins University, Baltimore, and the University of the West Indies, Bridgetown, found a positive linkage between atopy and chromosomal 12q markers in the Afro-Caribbean population on Barbados.

Belgium

Case Western Reserve University/Cleveland TBRC. The Prince Leopold Institute of Tropical Medicine, Antwerp, is collaborating with the TBRC to study the relationship between apoptosis and T-cell hyporesponsiveness in pulmonary tuberculosis.

AIDS. New York University Medical Center, New York City, and the Institute of Tropical Medicine, Antwerp, mapped epitopes exposed on HIV-1 virions and are evaluating the usefulness of this approach in studying the immunologic relatedness of HIV-1 isolates.

Bacterial Diseases. New York Medical College, Valhalla, and the Pasteur Institut, Brussels, developed a dot immunobinding assay for antigen 85, a secretory product of actively growing *Mycobacterium tuberculosis*, and determined that serum levels of antigen 85 were significantly higher in patients with active tuberculosis, previously treated tuberculosis, or active *Mycobacterium avium* disease than in patients with nonmycobacterial lung disease.

Benin

Parasitic Diseases. The University of Iowa, Iowa City, and the University of Benin, Cotonou, conducted a 10-year follow-up of a patient population residing in an area previously identified as endemic for *Wuchereria bancrofti*. The researchers documented a significant decrease in microfilaremia (from 9.4% to 0.48%) for no obvious reason.

Botswana

AIDS. NIAID awarded a new grant to the Harvard School of Public Health, Boston, to perform a genomic analysis of HIV-1 transmission in Botswana.

Brazil

University of Texas Medical Branch/Galveston EVC. This EVC and the Evandro Chagas Institute, Belém, are studying the epidemiology and ecology of Oropouche virus in the Brazilian Amazon.

University of Pittsburgh HIVNET. This HIVNET has moved from Johns Hopkins University, Baltimore, to the University of Pittsburgh, Pennsylvania, but the Brazilian partnership continues with Federal University of Rio de Janeiro.

Retroviral co-infection. In examining Brazilian patients with HIV-1 and human T-cell leukemia/lymphoma virus type I (HTLV-I) infection, the HIVNET researchers found that cutoff values for levels of the CD4-positive T cells, which are used in making clinical decisions in HIV infection, may not

be appropriate and that HIV viral load may be a more reliable barometer for clinical decisions.

Vaccine evaluation. In FY 99, the HIVNET developed protocols for a phase II, multisite, phase I–II study to evaluate the immunogenicity and reactogenicity of a combined vaccine regimen using canarypox HIV vaccine as a primer and a gp120 (glycoprotein 120) HIV vaccine as a booster in HIV-negative adults in Brazil and the Caribbean.

Antiretroviral therapy and reduction of HIV transmission. This HIVNET evaluated the effect of antiretroviral therapy on HIV-1 viral load in semen and serum and found a substantial and equivalent reduction in both sites.

Colorado State University/Fort Collins ICIDR. This new ICIDR supports collaboration with the Evandro Chagas Institute, Belém, to identify the molecular determinants of dengue viruses that are associated with increased potential for epidemics.

Harvard University/Boston ICIDR. For the past 20 years, NIAID has supported Harvard School of Public Health to collaborate with the Oswaldo Cruz Foundation (FIOCRUZ) in studies of leishmaniasis, malaria, and schistosomiasis.

Leishmaniasis. The researchers have been exploring the hypothesis that humans may be an important reservoir for cutaneous or visceral leishmaniasis, or both, in northeastern Brazil. The ICIDR has also supported a clinical trial comparing the effectiveness of allopurinol and traditional therapy with glucantime for leishmaniasis caused by *Leishmania braziliensis viannia*.

Malaria. In collaboration with the U.S. Army Medical Research Unit and FIOCRUZ, in Rio de Janeiro, and a field site in Mato Grosso, the ICIDR is examining the biochemical and molecular basis of drug resistance, particularly resistance to quinine. In support of clinical trials of atovaquone and proquanil against drug-resistant *Plasmodium falciparum* in the Amazon Basin, the ICIDR carried out molecular characterization of parasite populations resistant to chloroquine.

Schistosomiasis. In schistosomiasis, the focus has been to extend human leukocyte antigen (HLA) typing at the field site in Bahia, to determine antibody and cellular responses to native, deglycosolated, and different types of recombinant schistosomes, in efforts to identify potential vaccine antigens and to understand how certain carbohydrates on antigens appear to direct the response of type 1 (T_H1) to type 2 (T_H2) helper T cells.

Johns Hopkins University/Baltimore Tuberculosis ICIDR. This new ICIDR award involves collaboration with Federal University of Rio de Janeiro to develop and evaluate rapid diagnostic tests for tuberculosis, carry out a randomized trial for tuberculosis control, and conduct a second randomized clinical trial of preventive therapy for tuberculosis.

State University of New York/Buffalo ICIDR. During FY 99, NIAID made this new ICIDR award to New York State to collaborate with Federal University of Minas Gerais, Belo Horizonte, on host genetic correlates with schistosomiasis infection and clinical disease.

University of Texas Medical Branch/Galveston ICIDR. This ICIDR has been working with Federal University of Minas Gerais in research on Chagas' disease and schistosomiasis.

Chagas' disease. The ICIDR is evaluating the long-term results of treatment for a cohort of patients with acute Chagas' disease.

Schistosomiasis. With Tufts University School of Medicine, Boston, Massachusetts, and the University of Rio Dulce Valley, Governador Valadares, the ICIDR is investigating the response of T-cell epitopes to the major egg antigen p40 in humans infected with *Schistosoma mansoni*.

University of Virginia/Charlottesville ICIDR

Early diarrhea. Intensive evaluation of a cohort of children in an urban slum in Fortaleza showed that early childhood diarrhea and cryptosporidial infection were associated with subsequent impaired physical fitness, and in pilot studies, with impaired cognitive function. Early helminthic infections were independently associated with later growth retardation. This is the first study to show a potentially substantial impact of early childhood diarrhea and cryptosporidiosis on subsequent functional status.

Chronic diarrhea. This ICIDR is conducting a prospective cohort study of persistent diarrhea in poor, urban children in Fortaleza, Ceará. Chronic diarrhea accounted for one-third of the cases of diarrhea, led to substantial growth retardation, and was substantially reduced in infants who were breast-fed during the 1st 6 months of life.

Diarrhea and malnutrition. The ICIDR demonstrated a marked correlation between diarrhea burden and nutritional status in urban slum children and a significant association between malnutrition and increased incidence of diarrhea. Glutamine-based oral rehydration and nutrition therapy holds promise for repairing the disrupted function of the intestinal barrier in young children with diarrhea.

Leishmaniasis. With the University of Rochester, New York, and Federal University of Rio Grande do Norte, the ICIDR completed a prospective 10-year study of the epidemiology and natural history of *Leishmania chagasi* infection in northeastern Brazil. The investigators found that patients who had experienced asymptomatic, self-resolving *L. chagasi* as children did not develop visceral leishmaniasis, suggesting that they were immune to visceral leishmaniasis.

Case Western Reserve University/Cleveland TBRC. This TBRC supports a subcontract with Federal University of Espirito Santo, Vitória, to carry out clinical studies in tuberculosis. During FY 99, Federal University participated in an international study of tolerance, as measured by in vitro delayed or reduced killing of *M. tuberculosis*, to determine treatment outcome in patients with drug-sensitive tuberculosis.

Federal University of Bahia TMRC. NIAID provides direct funding to Federal University of Bahia for research in Chagas' disease, leishmaniasis, and schistosomiasis.

Chagas' disease. This TMRC demonstrated that patients with either of two clinical forms of Chagas' disease (i.e., symptomatic or asymptomatic cardiomyopathy) had peripheral blood mononuclear cells that responded to *Trypanosoma cruzi* antigen with a cytotoxic response and that this response was increased by IL-2.

Leishmaniasis. The TMRC is investigat-

ing the initial responses of human macrophages and lymphocytes to *Leishmania* parasites.

New York University/New York City Malaria Program Project. This Program Project (P01) consists of several projects with Brazilian universities and research institutions for development of vaccines and drugs for prevention and treatment of malaria.

AIDS. NIAID made a new award to the University of Pittsburgh, Pennsylvania, to collaborate with Federal University of Rio de Janeiro on the origin and dynamics of HIV-1 in semen.

Johns Hopkins School of Public Health, Baltimore, and Federal University of Minas Gerais evaluated the usefulness of immune-complex–dissociated p24 antigen in the diagnosis of infants in Belo Horizonte who were vertically exposed to HIV by their HIV-positive mothers. The investigators concluded that the test for this antigen is sensitive, specific, rapid, and inexpensive and that the test may be an alternative to viral culture, PCR tests, or both, in resource-poor settings.

The University of North Carolina, Chapel Hill, Duke University, Durham, the Laboratory Corporation of America, Research Triangle Park, North Carolina, and Federal University of Espirito Santo found that monitoring of virological and immunologic parameters such as viral loads and levels of CD4-positive T cells was necessary for determining the effectiveness of HAART in Brazil.

The Laboratory of Parasitic Diseases (NIAID) and Federal University of Bahia studied IFN-α and IL-4 responses in relation to serum immunoglobulin E (IgE) levels in HTLV-I–positive Brazilians also infected with *Strongyloides stercoralis*. The investigators concluded that the impaired IgE responses and other effects of decreased IL-4 levels may contribute to the more severe manifestations of the parasite and to impaired response to treatment in some HTLV-I–positive patients.

Bacterial Diseases. Colorado State University, Fort Collins, and FIOCRUZ, Rio de Janeiro, used the definition of the genome of *Mycobacterium leprae* to define in vivo expression of *M. leprae* proteins.

Federal University and Corixa Corporation, Seattle, Washington, have preliminary results indicating that a combination of specific *M. tuberculosis* antigens will allow for the construction of an immunochromatographic strip test for rapid screening of *M. tuberculosis* infections in patients with suspected disease.

Rockefeller University, New York City, the University of Pennsylvania, Philadelphia, PAHO/WHO, Federal University of São Paulo, and the Ministry of Health of Brazil initiated a continuous surveillance of invasive *Streptococcus pneumoniae* isolates in Brazil for prevalent types, antimicrobial drug resistance, and the spread of penicillin-resistant strains of *S. pneumoniae*.

Mycotic Diseases. Seven hospitals in Brazil are members of the NIAID Mycoses Study Group, which is comparing treatment of candidemia with voriconazole or amphotericin B and fluconazole.

Parasitic Diseases. Corixa Corporation, Seattle, and Federal University of Bahia constructed a recombinant K39 antigen, a part of the *Leishmania chagasi* LcK gene, which reacts strongly to the serum of patients with early visceral leishmaniasis (kala-azar) but not to milder forms of the disease. The Laboratory of Parasitic Diseases (NIAID), Corixa Corporation, and Federal University selected four *Leishmania* antigens common to human pathogens that stimulate T-cell immune responses and found that they protect against infection when administered to mice in combination with IL-12. The investigators are moving ahead to incorporate these antigens into a recombinant therapeutic vaccine for use in the treatment of intractable mucocutaneous leishmaniasis in northern Brazil.

The Laboratory of Parasitic Diseases (NIAID) and FIOCRUZ, Rio de Janeiro, performed in vitro and in vivo studies showing that *Plasmodium* ookinetes preferentially invade a previously undescribed type of midgut epithelial cell that can be characterized by several histochemical, ultrastructural, and biochemical features. The preferential invasion of these cells suggests that they may contain invasion receptors that could be used as targets for blocking transmission of the parasite.

In addition, the Laboratory of Parasitic Diseases, the Naval Medical Research Institute, Bethesda, Maryland, Yale University School of Medicine, New Haven, Connecticut, and Federal University of Minas Gerais developed and are testing avirulent *Toxoplasma gondii* recombinants as vaccine carriers for immunization against the circumsporozoite protein of *Plasmodium yoeli*.

The Laboratory of Clinical Investigation (NIAID), FIOCRUZ, Belo Horizonte, Federal University of Minas Gerais, and Instituto Oswaldo Cruz, Rio de Janeiro, have evidence that macrophages may be a major source of chemokines during chronic chagasic cardiomyopathy.

Corixa Corporation, Seattle, the American Red Cross, Rockville, Maryland, and Federal University of Bahia developed a multiple-epitope synthetic peptide and recombinant protein that can detect antibodies to *Trypanosoma cruzi* more accurately than radioimmunoprecipitation and sera from Brazilian blood donors.

Vector Biology. University of Texas Medical Branch, Galveston, and Federal University of Minas Gerais conducted studies on the genetic variability of populations of *Lutzomyia longipalpis*, the sand fly vector of visceral leishmaniasis in Central and South America.

Bulgaria

Bacterial Diseases. The National Center for Infectious and Parasitic Diseases, Sofia, and Johns Hopkins School of Medicine, Baltimore, found serological evidence of human granulocytic ehrlichiosis infection in 9.7% of Bulgarians with a history of tick bite, clinical symptoms consistent with the disease, or both.

Burkina Faso

Parasitic Diseases. The University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program used O-150 PCR analysis of skin scratches, rather than the traditional skin snips, to detect *Onchocerca volvulus* infection. The investigators found the technique more sensitive than microscopic evaluation of skin snips, minimally invasive, more acceptable to patients, and without risk of transmitting bloodborne infections.

Cambodia

University of Washington/Seattle CASR.

This Center for AIDS and STD Research (CASR) is collaborating with Family Planning International Assistance, Institut Pasteur, and the Ministry of Health of Cambodia, Phnom Penh, on studies of the natural history of cervical neoplasia in HIV-positive Cambodian women.

Cameroon

Georgetown University/Washington, D.C., ICIDR. This ICIDR supported collaboration with the University of Yaoundé in research on (1) acquisition of immunity in children and adults; (2) immunization of neonates; (3) the influence of malaria on fetal development; and (4) the effect of an excess of T_H2 cells on malarial immunity.

AIDS. During FY 99, Aaron Diamond AIDS Research Center, New York City, New York, received a new grant to study simian immunodeficiency virus (SIV) and related lentiviruses in Cameroon and elsewhere in West Africa.

Family Health International, Research Triangle Park, North Carolina, completed a study evaluating the use of nonoxynol 9 film as a topical vaginal microbicide to reduce the risk of HIV-1 transmission. Nonoxynol 9 had an impact on STD transmission but did not reduce HIV transmission in Cameroon.

Parasitic Diseases. Independently from the ICIDR, Georgetown University, Washington, D.C., received a new grant to collaborate with the University of Yaoundé on cytoadherence in maternal malaria. A second award to Georgetown University will deal with immune resistance to malaria in pregnant women and toddlers. The research will investigate the effect of an excess of T_H2 cells on the development of immunity to malaria.

Canada

AIDS. The University of British Columbia, Vancouver, participates in the Tricontinental HIV/AIDS Project, which performs follow-up on defined populations of homosexual men with HIV in Australia, Canada, the Netherlands, and the United States.

The Institute of Clinical Research, Montreal, is the recipient of a grant to investigate factors controlling T-cell responses in primary HIV infection. The Laboratory of Immunoregulation (NIAID), the National Institute of Neurological Disorders and Stroke (NIH), and the Institute of Clinical Research, the University of Montreal, and McGill University, Montreal, found evidence that initially stimulated HIV-specific, CD8-positive T-cell clones rapidly disappear during primary HIV infection.

NIAID supports an award to Simon Fraser University, Burnaby, British Columbia, to study the peptides that mimic neutralizing sites on HIV envelope proteins. In FY 99, NIAID made a second foreign award to Simon Fraser University to use libraries of antigen-binding fragments to create innovative approaches for discovery of candidate vaccines against HIV/AIDS.

Aaron Diamond AIDS Research Center, New York City, the Institute of Clinical Research, Montreal, and the British Columbia Center of Excellence, Vancouver, have preliminary evidence that early treatment of HIV-positive patients with antiretroviral drugs helps to preserve an intact pool of T cells capable of reconstituting the damaged immune system.

NIAID is funding the Canadian Trials Network to carry out two clinical trials. The first study is a randomized trial of the safety and efficacy of nelfinavir versus ritonavir added to background antiretroviral therapy in HIV-positive patients with levels of CD4-positive T cells lower than 100/mm^3. The second study is a prospective evaluation of HIV-1 genotypic resistance to these two drugs in the same cohort of patients.

Bacterial Diseases. The Laboratory of Microbial Structure and Function (NIAID), the Centers for Disease Control and Prevention (CDC), Washington State Department of Health, Seattle, Sacred Heart Medical Center, Spokane, Washington, British Columbia Centers for Disease Control, and the University of British Columbia, Vancouver, identified 133 confirmed and 49 probable cases of tick-borne relapsing fever due to *Borrelia hermsii* in the western United States and southern British Columbia.

The National Center for *Streptococcus*, Edmonton, Alberta, participates in a NIAID-supported international study using sequencing of the variable region of the emm gene to validate provisional M types of group A *Streptococcus*.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID), Georgetown University Medical Center, Rockville, Maryland, and Ottawa Civic Hospital and the University of Ottawa, Ontario, have preliminary data suggesting that a recombinant DNA vaccine against hepatitis B virus (HBV) is immunogenic and comparable to other HBV vaccines.

Immunology. NIAID made a new grant award to the Institute of Clinical Research, Montreal, for development of a new assay for recently migrated thymic T cells.

NIAID is supporting a grant award to the British Columbia Cancer Research Center, Vancouver, to study the proliferation of purified hematopoietic stem cells.

The University of Alberta, Edmonton, participates in the new NIAID contract to the University of Chicago, Illinois, to manage the Collaborative Network for Clinical Research on Immune Tolerance.

Central African Republic

AIDS. The University of Washington, Seattle, the University of Pittsburgh, Pennsylvania, and the STD Reference Center, Bangui, found a high prevalence of bacterial vaginosis (54%) and HIV (34%) in nonpregnant women attending STD clinics.

Chile

University of Maryland/Baltimore ICIDR. This ICIDR partners the Center for Vaccine Development, University of Maryland, with the Center for Vaccine Development, University of Chile, and the National Institute of Public Health, Santiago, to develop and evaluate new or improved candidates for vaccines against childhood enteric and respiratory infections.

Shigella infection. The ICIDR assessed the burden of *Shigella* diarrhea and invasive pneumococcal infections in Santiago and explored the relative importance of individual serotypes in planning vaccine intervention strategies.

University of New Mexico/Albuquerque ICIDR. In FY 99, NIAID made this new multiple- project ICIDR award for collaboration with the Ministry of Health, Catholic University, and the University of Chile, Santiago, and regional hospitals in Coyhaique and Temuco on studies of Hantaviruses in Chile.

Expected activities include work on the ecological factors regulating outbreaks of Hantavirus in Chile, the epidemiology of Hantaviruses in Chile, and treatment of Hantavirus infections.

Bacterial Diseases. CDC, the University of Maryland, Baltimore, and North Metropolitan Health Service, Roberto del Rio Hospital, and the Ministry of Health of Chile, Santiago, showed that 91%–100% of infants immunized with one-half or one-third of a full dose of *Haemophilus influenzae* type b (Hib) conjugate vaccine developed protective antibody concentrations, an approach that might make these alternative regimens accessible to countries that cannot afford the vaccine.

Viral Diseases. Baylor College of Medicine, Houston, Texas, and the University of Chile, Catholic University, and the Group for the Development of Health Research, Santiago, determined that, of the human caliciviruses, Norwalk virus and Mexico virus were more prevalent in Santiago than in Punta Arenas and were associated with low economic status, consumption of seafood or vegetables, and child day-care attendance. The association of a factor with a particular virus depended on the city.

China

University of Texas Medical Branch/Galveston HCV Center. The U.S. Food and Drug Administration (FDA), the University of Texas Medical Branch, Galveston, and Third Military Medical University, Chongqing, have evidence that persistence of hepatitis C virus (HCV) after acute infection is associated with quasi-species complexes and host immune response to hypervariable region 1 of the virus.

Institute of Parasitology/Shanghai TMRC. This direct award to the Institute of Parasitology, Chinese Academy of Preventive Medicine, Shanghai, involves collaboration with several U.S. universities, in an effort to anticipate and document the impact of the Three Gorges Dam Project on the Yangtze River on the health of human populations.

Hookworm. The ASP proteins derived from hookworm in the L-3 stages are being evaluated as potential vaccine antigens. During FY 99, the TMRC studied protective immunity elicited by living, infective, stage L-3 *Ancyclostoma caninum* hookworm larvae in mice.

Medical malacology. This TMRC subproject involves collaboration with the Academy of Natural Sciences, Philadelphia, Pennsylvania, and the Institute of Parasitic Diseases, Shanghai.

AIDS. The University of California, Los Angeles, Yingshang County Anti-Epidemic Station, and Anjua Provincial Anti-Epidemic Station, Hefei, conducted studies in rural populations, which showed that sexual norms in rural China are changing rapidly and that high-risk sexual behavior among young rural residents is increasing.

Bacterial Diseases. Washington University School of Medicine, St. Louis, Missouri, the University of Amsterdam, the Netherlands, and Shanghai Second Medical University found no association between any vacA allele and peptic ulcer disease, suggesting that, although the composition of *Helicobacter pylori* gene pools varies geographically, unknown polymorphic genes are important to peptic ulcer disease.

The University of Texas Health Sciences Center, Tyler, Hoffmann-La Roche, Nutley, New Jersey, and Nanjing Medical University found that IL-12R expression correlates well with IFN-γ production in human tuberculosis and that IL-12Rβ_1 and IL-12Rβ_2 may have a central role in mediating a protective helper T-cell response.

Parasitic Diseases. Seattle Institute of Infectious Diseases, Washington, Chicago Medical School, North Chicago, Illinois, the University of Tokyo, Japan, the Institute of Parasitic Diseases, Shanghai, the Institute of Endemic Diseases, Xinjiang, and the Institute of Endemic Diseases, Lanzhou, evaluated a dipstick test for *Leishmania chagasi* that uses a recombinant antigen product of the 39 amino acid repeats from a gene similar to that for kinesin (rk39), for the diagnosis of visceral leishmaniasis in a region of low endemicity in northwestern China. The investigators concluded that the rk39 dipstick test is more rapid, specific, and sensitive, yet less invasive, than the splenic and bone marrow aspirates usually required to diagnose this condition in areas of low prevalence.

The Laboratory of Parasitic Diseases (NIAID), Ehime University School of Medicine, Matsuyama, Japan, and China Medical University, Shenyang, identified and are characterizing two novel ookinete surface protein genes (Pvs28 and Pvs25) from *Plasmodium vivax* that are candidates for inclusion in a transmission-blocking malaria vaccine against vivax malaria.

Harvard School of Public Health, Boston, and Hong Kong Polytechnic University used a yeast complementation system to identify novel genes for drug resistance and to assay transport function in *Plasmodium falciparum*.

Viral Diseases. St. Jude Children's Research Hospital and Le Bonheur Children's Hospital, Memphis, Tennessee, the State University of New York Medical Center, Brooklyn, and Jiangxi Medical College, Nanchang, discovered that reassortment, insertions, and hemagglutinin deletions are strategies used by influenza viruses for evolution in nature. St. Jude Children's Research Hospital and Jiangxi Medical College have also collaborated with the U.S. Department of Agriculture (USDA) Midwest National Animal Disease Center, Ames, Iowa, the North Carolina Department of Agriculture and Consumer Services, Raleigh, and the University of Minnesota, St. Paul, in documenting the genetic reassortment of avian, swine, and human influenza A viruses in pigs in the United States. St. Jude Children's Research Hospital and the University of Tennessee, Memphis, the University of Wisconsin, Madison, Chumakov Institute of Poliomyelitis and Viral Encephalitis, Moscow, Russia, and Jiangxi Medical College reported that surface proteins of H5 influenza viruses isolated from humans, chickens, and wild aquatic birds have distinguishable differences. St. Jude Children's Research Hospital, Leiden University Medical Center, the Netherlands, Queen Mary Hospital, Hong Kong, the University of Hong Kong, and Jiangxi Medical College studied strains of H5N1 influenza strains from Hong Kong that had spread directly from poultry to humans. The scientists found that the strains comprised two distinguishable phylogenic lineages in all genes that were in very rapid evolution. Furthermore, the consensus amino acid sequences of "internal" virion proteins showed amino acids, previously found in human strains, that may be important in zoonotic transmission.

California Pacifica Medical Center, San Francisco, the University of Colorado, Denver, Triangle Pharmaceuticals, Durham, North Carolina, and Prince of Wales Hospital, Hong Kong, conducted phase I–II clinical studies evaluating emtricitabine activity against HBV and found that the drug had considerable activity against chronic HBV infection.

Colombia

University of Texas Medical Branch/Galveston EVC. This EVC is collaborating with the National Institute of Health, Bogotá, in studies on the mechanisms behind the emergence of Venezuelan equine encephalitis.

AIDS. Johns Hopkins School of Hygiene, Baltimore, and the National Faculty of Public Health, Medellín, evaluated the efficacy of bacille Calmette-Guérin vaccine in protecting against tuberculosis in HIV-positive and HIV-negative populations in Colombia.

Bacterial Diseases. The University of North Carolina, Chapel Hill, and the CIDEIM TMRC are evaluating current and new diagnostic tests to improve the diagnosis of paucibacillary tuberculosis and to evaluate the morbidity caused by this disease.

Parasitic Diseases. University of Texas Health Sciences Center, San Antonio, and the Corporation for Biomedical Research, Medellín, also developed a BALB/c mouse–*Mesocestoides corti* animal model for neurocysticercosis.

The University of Notre Dame, South Bend, Indiana, and the University of the Valle at San Fernando, Cali, administered recombinant *Plasmodium vivax* Duffy binding protein to Colombian villagers to confirm that populations exposed to this parasite for vivax malaria react to this protein and that it boosts immunity.

Vector Biology. Yale University, New Haven, and the National Institute of Health, Bogotá, are collaborating in an effort to determine the genetics and biogeography of sand fly–transmitted diseases in Central and South America.

Cook Islands

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID) has monitored the population of the Cook Islands for more than 20 years, in an effort to study the natural history of bancroftian filariasis. Because of the recent recognition that filariasis may be widespread in children. The investigators were able to document cryptic infection beginning around ages 3–4 years.

Costa Rica

Immunology. The University of California, Los Angeles, School of Medicine, Virginia Mason Research Center, Seattle, Washington, and the National Children's Hospital, San José, developed simple genomic assays for the ataxia-telangiectasia mutated (ATM) gene that is associated with the disease in 65% of Costa Ricans who have the disease or are at risk for development of the disease.

Côte D'Ivoire

AIDS. CDC, St. Luke's-Roosevelt Hospital, New York City, New York, the University of Alabama, Birmingham, the Center for Military Services Research, La Tronche, France, and Project Retro-CIDA (AIDS), Abidjan, showed that human immunodeficiency virus type 2 (HIV-2) use of co-receptors may correlate with disease progression.

Parasitic Diseases. Case Western Reserve University, Cleveland, Ohio, the University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program, Bouaké, examined eotaxin expression in the skin of patients infected with *Onchocerca volvulus*, after topical application of diethylcarbamazine. The researchers found excess eosinophils in the skin, raising the possibility that this recruitment of eosinophils to the skin may be the mechanism for onchodermatitis induced by diethylcarbamazine.

Vector Biology. The University of Alabama, Birmingham, and the WHO Onchocerciasis Control Program, Bouaké, determined that the six groups of *Simulium damnosum senso lato* sand flies do not preferentially transmit the "forest" and "sylvatic" strains of *O. volvulus*.

Czech Republic

Bacterial Diseases. The University of Virginia, Charlottesville, and the Institute of Microbiology, Czech Academy of Sciences, Prague, are carrying out epitope mapping of MAbs against *Bordetella pertussis* adenylate cyclase toxin, in an effort to determine the regions necessary for the activation of this neurovirulence factor.

Democratic Republic of Congo

AIDS. During FY 99, NIAID made a small grant award to Johns Hopkins Medical Center, Baltimore, to determine HIV-specific, cytotoxic T-lymphocyte (CTL) activity in specimens from Project SIDA (AIDS) that were obtained from HIV-concordant and HIV-discordant heterosexual partners in the Democratic Republic of Congo.

Denmark

AIDS. The State Serum Institute, Copenhagen, is collaborating with Dartmouth Medical School, Lebanon, New Hampshire, on immunization to prevent *Mycobacterium avium-intracellulare* infection and disease in HIV-positive patients.

Dominican Republic

University of Washington/Seattle CASR. This CASR is supporting studies in the Dominican Republic on the transmission and acquisition of HIV and other STDs.

Ecuador

Parasitic Diseases. The Laboratory of Parasitic Diseases (NIAID), Medical University of South Carolina, Charleston, and Hospital Voz Andes, Quito, found that, in Afro-Ecuadorians, KM-3 protein allotype is associated with a lower relative risk and the KM-1,3 allotype is associated with increased risk for onchocerciasis.

Egypt

Washington University/St. Louis ICIDR. This ICIDR funds cooperation with Ain-Shams University, Heliopolis, on studies related to the elimination of human filariasis in Egypt, including the development of improved diagnostic tests and preventive agents. Field studies in FY 99 provided evidence that humans develop a degree of immunity to filariasis after years of exposure, but relatively little is known about targets of protective immunity in humans. Using human sera collected from longitudinal field studies in Egypt, the investigators are exploring the premise that human antibody responses to L-3 antigens may provide clues to targets of protective immunity.

The ICIDR is carrying out a prospective study of bancroftian filariasis in defined populations in the Nile Delta, for a better understanding of the dynamics and risk factors for infection. Researchers at the ICIDR examined the role of parental infection as a risk factor for bancroftian filariasis and observed familial clustering. Also, the ICIDR successfully used ultrasonography of the scrotum to visualize adult worms, document subclinical lymphatic pathology, and evaluate the effect of diethylcarbamazine in men with bancroftian filariasis.

In addition, the researchers evaluated the ICT filariasis card test, which uses whole blood and provides immediate results in the diagnosis of bancroftian filariasis. This test performs as well as the earlier serum ICT test and has great potential as a tool for filariasis surveillance and control programs.

Bacterial Diseases. Case Western Reserve University, Cleveland, and Al Azar University, Cairo, are investigating the role of macrophages in the pathogenesis of *Mycobacterium tuberculosis*.

Parasitic Diseases. Case Western Reserve University, Cleveland, is conducting comparative studies of the genetics of hepatic fibrosis due to schistosomiasis in Egypt, where the condition is common and severe, with the genetics in Kenya, where hepatic fibrosis is less common and milder.

Case Western Reserve University and Assiut University showed that IL-4 and IL-5 production that is driven by schistosome adult worm antigen correlates with immunity to reinfection in Egyptian adolescents exposed to urinary schistosomiasis.

The University of California, San Francisco, developed species-specific protease antigens to detect infective cercariae of *Schistosoma haematobium* and *Schistosoma mansoni* and is cooperating with Ain-Shams University, Heliopolis, to evaluate the tests in the Nile Delta, where both forms of schistosomiasis are endemic.

The University of Massachusetts, Lowell, Michigan State University, East Lansing, and the University of Zagazig identified villagers infected with schistosomiasis that cannot be cured with three doses of praziquantel. The scientists characterized the biological properties of parasites that are less responsive to drug. They found direct evidence of resistance to praziquantel in vivo and in vitro in *S. mansoni* isolated from Egyptian villagers and are now working to identify the gene(s) responsible for this drug resistance. They also expect to develop an assay to detect resistant isolates in miracidia obtained from eggs shed by infected individuals.

Ethiopia

Bacterial Diseases. Rockefeller University, New York City, is collaborating with the Armauer Hansen Research Institute, Addis Ababa, to study the pathobiology of leprosy in Ethiopia.

Parasitic Diseases. Louisiana State University, Baton Rouge, the Food and Agricultural Organization, Rome, Italy, and Addis Ababa University, Debre Zeit, developed a geographic information system to measure the environmental factors associated with the overlapping distribution and abundance of the temperate zone species *Fasciola hepatica* and the tropical *Fasciola gigantica* liver flukes in East Africa. They also have NIAID support to work with the Ministry of Health of Ethiopia to develop a geographic information system to measure the distribution of schistosomiasis.

Finland

Bacterial Diseases. NIAID is funding a trial by Tampere University Central Hospital to evaluate two pneumococcal conjugate vaccines (PncCRM and PncOMPC) for the prevention of acute otitis media due to pneumococcal serotypes contained in the vaccines.

France

AIDS. The University of Pennsylvania, Philadelphia, NERPC, Scarborough, Massachusetts, and Institut Pasteur and Hôpital Cochin, Paris, developed and are evaluating the effectiveness of an experimental DNA vaccine in protecting macaque monkeys against HIV/SIV infections.

Several institutions in France will participate in the Pediatric AIDS Clinical Trials Group (PACTG) phase III protocol, a randomized, double-blind study in which a single dose of nevirapine is administered to the mother at delivery and to the neonate at 48–72 hours after birth.

Bacterial Diseases. Texas A & M Medical Center, College Station, and Institut Pasteur, Paris, are testing the persistence and protective efficacy of mutant, auxotrophic, attenuated agents that are candidate *Mycobacterium tuberculosis* vaccines in mouse and guinea pig models.

Parasitic Diseases. The Laboratory of Clinical Investigation and the Laboratory of Parasitic Diseases (NIAID), the University of Chicago, Illinois, and the CNRS Institute of Cellular and Molecular Pharmacology, Valbonne, showed that a DNA vaccine that encodes the cloned *Leishmania* LACK protein confers protective immunity to mice challenged with *Leishmania major*.

The Laboratory of Parasitic Diseases (NIAID) and Institut Pasteur, Paris, determined that transformation with human dihydrofolate reductase renders malaria parasites insensitive to WR99210, an experimental antimalarial drug, but does not affect the intrinsic activity of proguanil.

Researchers at Dartmouth Medical School, Hanover, New Hampshire, and Institut Pasteur and Institut National de la Santé et de la Recherche Médicale, Marseilles, reported that the defect in T-cell expression that occurs during acute murine toxoplasmosis is related to reduced activity of nuclear factor AT, a calcium-dependent transcription factor required for T-cell proliferation.

Vector Biology. CDC, the University of Notre Dame, South Bend, Indiana, the French Institute for Development, Marseilles, and the University Henri Poincare, Nancy, are collaborating to study the genetic differentiation among populations of *Anopheles arabiensis*, a malaria vector, from mainland West Africa and East African outer islands.

Viral Diseases. Medical College of Virginia, Richmond, the University of Pennsylvania, Philadelphia, the University of Washington, Seattle, and Pasteur-Merieux Connaught, Marnes-les-Coquette, reported that the Towne strain of cytomegalovirus (CMV) should be further evaluated for vaccine efficacy in women at risk for acquiring CMV infection during pregnancy and in children who may transmit CMV to pregnant women.

Gabon

Michigan State University/East Lansing ICIDR. This new ICIDR supports studies to evaluate the importance of intraleukocyte pigment as a prognostic feature of severity of malaria and of survival.

AIDS. Aaron Diamond AIDS Research Center, New York City, and the International Center for Medical Research, Franceville, are conducting studies of SIV rcm and related lentiviruses isolated from red-capped mangabey monkeys in Cameroon and Gabon.

Parasitic Diseases. Duke University Medical Center, Durham, North Carolina, the University of Tübingen, Germany, and Albert Schweitzer Hospital, Lambaréné, showed that healthy children with a history of mild malaria had higher levels of nitric oxidase enzyme activity and a greater capacity to produce nitric oxide than did children with a history of severe malaria.

The Gambia

Michigan State University/East Lansing ICIDR. This new ICIDR includes a component with the Medical Research Council (MRC), Fajara, to examine fluid resuscitation in pediatric falciparum malaria.

Bacterial Diseases. The University of California, San Francisco, and MRC, Fajara, are carrying out a clinical trial to compare the efficacy of mass treatment with a single oral dose of azithromycin versus traditional 14-day daily treatment with topical erythromycin ointment in the community control of trachoma in endemic areas of Egypt, the Gambia, and Tanzania.

With USAID, the Gates Foundation, and MRC, London, England, NIAID is cosponsoring an infant immunization efficacy trial in the Gambia with PRP-T, a Hib conjugate vaccine with diphtheria–pertussis–tetanus vaccine. The study demonstrated that the vaccine was efficacious in preventing invasive disease in infants and pneumonia caused by Hib.

In FY 99, NIAID awarded a research contract to MRC, London, England, to perform a phase II study of 9-valent pneumococcal conjugate vaccine designed for use in Africa, in Gambian children. The study compares the efficacy of pneumococcal conjugate vaccine administered with another childhood vaccine versus the other vaccine alone.

Parasitic Diseases. NIAID supports a project at Walter Reed Army Institute of Research, Washington, D.C., to study the effect of maternal infection with malaria on umbilical cord red blood cells in infants from the Gambia.

Viral Diseases. In an NIAID-supported study at the MRC Laboratories, Banjul, measles vaccine boosted CTL responses at a low level. This finding suggests that the fusion and hemagglutinin proteins are important targets for the CTL response to measles.

Georgia

Parasitic Diseases. CDC, the University of Virginia Medical Center, Charlottesville, and the Ministry of Health of Georgia investigated an epidemic of amebic liver abscesses in Tbilisi that was epidemiologically associated with contamination of the municipal water supply.

Germany

University of California/San Francisco TDRU. This TDRU and the University of Heidelberg are exploring the potential of using synthetic cysteine proteinase inhibitors to treat *Trypanosoma brucei*.

AIDS. Harvard Medical School, Boston, Duke University Medical Center, Durham, Beckman-Coulter, Miami, Florida, Bernard Nocht Institute for Tropical Medicine, Hamburg, and the Technical University of Dresden controlled viremia in rhesus monkeys infected with SIV by restoration of SIV-specific, CD8-positive lymphocytes. Bernard Nocht Institute for Tropical Medicine and Rockefeller University, New York City, reported that tonsils and other mucosal-associated lymphoid tissues are rapidly infected after oral inoculation with SIV.

Bacterial Diseases. The Laboratory of Clinical Investigation (NIAID) and the National Institute of Neurological Disorders and Stroke and the National Cancer Institute (NCI) (NIH), Torrey Pines Institute for Molecular Studies, San Diego, California, and the University of Marburg identified candidate T-cell epitopes and molecular mimics in chronic Lyme disease.

Parasitic Diseases. Washington University, St. Louis, Missouri, and Bernard Nocht Institute for Tropical Medicine, Hamburg, identified an epitope on the 170-kilodalton lectin of *Entamoeba histolytica* that conferred antibody-mediated protection against invasive amebiasis.

Vector Biology. Humboldt University, Berlin, and Harvard School of Public Health, Boston, used DNA techniques to detect Lyme disease spirochetes in archived *Ixodes ricinus* ticks collected in 1882, thus documenting the earliest presence of the spirochete in Europe.

Ghana

Michigan State University/East Lansing ICIDR. The Noguchi Institute for Medical Research will participate in this new ICIDR in studies of severe malaria in children.

AIDS. The University of Alabama, Birmingham, is collaborating with the Noguchi Institute for Medical Research to study the molecular structure and function of HIV-1 and HIV-2 isolates from nonhuman primates.

Parasitic Diseases. The University of Florida, Gainesville, and the Noguchi Institute for Medical Research are evaluating dichloroacetate as adjunctive therapy in the treatment of malaria. During FY 99, NIAID made a new contract award to the Naval Medical Research Institute, Rockville, Maryland, to work with the Noguchi Institute for Medical Research to develop field sites for clinical research and trials of vaccine against malaria.

Viral Diseases. The University of North Carolina, Chapel Hill, and the Ministry of Health of Ghana, Accra, found that the risk factors for horizontal transmission of HBV in a rural district in Ghana were sharing of bath towels, chewing gum, partially eaten materials, or dental-cleaning materials or biting fingernails in conjunction with scratching the backs of HBV carriers.

Greece

Immunology. The Laboratory of Clinical Investigation (NIAID), the University of Mainz, Germany, and the Hellenic Pasteur Institute reported that tumor necrosis factor-α (TNF-α) was the predominant pathogenic factor associated with experimental murine chronic colitis.

Guatemala

Parasitic Diseases. The University of Georgia, Athens, Epimmune Corporation, San Diego, California, and Universidad del Valle, Guatemala City, determined that human infection with *Trypanosoma cruzi* induces CTL responses specific to the parasite antigen.

Vector Biology. A new NIAID grant supports Loyola University, New Orleans, Louisiana, to work with Universidad del Valle in using RAPDS analysis to determine the genetic structure of the reduviid vectors of Chagas' disease in Guatemala.

Haiti

Cornell Medical College/New York City HIVNET. The HIVNET cooperates with Vanderbilt University, Nashville, Tennessee, in a multisite, phase I–II clinical trial in Brazil and the Caribbean to evaluate the immunogenicity and reactogenicity of a two-phase HIV immunization scheme involving an initial injection of recombinant canarypox vaccine followed by a booster of gp20 vaccine.

Johns Hopkins University/Baltimore HIVNET. This HIVNET provided for collaboration with the Center for Health and Development, Port-au-Prince, and participated in pediatric studies to evaluate the efficacy of zidovudine (AZT) in preventing transmission of HIV from infected mothers to their newborns.

AIDS. In addition to the Cornell Medical College HIVNET, NIAID continues to provide significant grant support to study the natural history of HIV in Haiti in a cohort of HIV-discordant couples, to identify the infecting strain, the source of infection, immune status, viral load levels over time, and correlation of viral load with clinical status.

Johns Hopkins University is working with the Center for Health and Development, Cité Soleil, to study the efficacy of chemoprophylaxis against tuberculosis in HIV-positive persons who are negative for purified protein derivative.

Parasitic Diseases. CDC and the University of Georgia, Athens, are involved in a longitudinal analysis of the development of filarial infection and antifilarial immunity in a cohort of Haitian children. The investigators found that children acquire infection early in life and that antifilarial antibody responses may peak early in childhood. In collaboration with investigators at Maimonides Hospital, Brooklyn, New York, and Hospital Sainte Croix, Léogane, Haiti, they determined that, for children with *Wuchereria bancrofti* microfilaremia, combined treatment with ivermectin and albendazole was more effective than treatment with ivermectin alone and was not associated with more adverse reactions.

Honduras

AIDS. The University of Miami, Florida, Harvard University, Boston, and the Ministry of Health of Honduras, Tegucigalpa, determined that, in Honduras, there is a strong relationship between HIV infection and STD and that the predominant HIV-1 subtype circulating in Honduras is clade B.

Hungary

Viral Diseases. Virginia Commonwealth University, Richmond, Wistar Institute, Philadelphia, Pennsylvania, Virogenetics, Troy, New York, Pasteur-Merieux Connaught, Swiftwater, Pennsylvania, and Marcy-l'Etoile, France, and Albert Szent-Gyorgyi University, Szeged, found that a canarypox vector expressing CMV glycoprotein B primes for antibody responses to a live, attenuated CMV vaccine.

Iceland

Bacterial Diseases. Indiana University Medical Center, Indianapolis, the University of Texas Medical Branch, Galveston, Quidel Corporation, San Diego, California, and the University of Iceland, Reykjavik, evaluated the Quidel Quick Vue and the Kodak Sure Cell rapid immunoassay tests to diagnose *Chlamydia trachomatis* in endocervical specimens.

Immunology. The Icelandic Cancer Society, Reykjavik, is working with the National Heart, Lung, and Blood Institute and the National Institute on Aging (NIH), Johns Hopkins School of Hygiene, Baltimore, and the Queensland Institute of Medical Research, Brisbane, Australia, on the linkage analysis of dust mite–specific IgE responsiveness in white families.

India

NIAID collaboration with India goes back more than 40 years. In addition to normal scientific channels, NIAID has engaged in collaboration under the terms of the Indo-U.S. Science and Technology Agreement; the Indo-U.S. Science and Technology (Reagan-Gandhi) Initiative; the USAID/New Delhi–funded Contraceptive Development and Research in Immunology Program; and the Indo-U.S. Vaccine Action Program (VAP). Supplementary funding has been available until recently, from the Special Foreign Currency Program (P.L. 480) and more recently from the U.S.-India Fund. The majority of current activities and all future activities will be carried out with regular appropriated funds, but VAP resources have been extended through a grant from the Starr Foundation.

Johns Hopkins School of Medicine/Baltimore HIVNET. This HIVNET award, which supported collaboration with the Indian Council for Medical Research (ICMR) National AIDS Research Center, Pune, the Ministry of Health, and Sassoon Hospital, Pune, ended in 1997.

HIV variation. With the California Department of Health, Berkeley, the HIVNET characterized full-length HIV-1 genomes from persons with subtype C seroconversion in India and found evidence of intersubtype recombination. The HIVNET reported the first isolation and characterization of two Indian syncytium-inducing HIV-2 isolates, which appear to be related to the Senegal HIV-2 strain.

Epidemiology. HIVNET investigators discovered that HIV infection is increasing in women who are not commercial sex workers. Because history of sexual contact with one male sex partner was the only risk factor significantly associated with HIV infection, it is likely that their spouses are infecting these monogamous women.

Prevention. The HIVNET was approved to conduct a phase I evaluation of BufferGel,

a vaginal microbicide. The HIVNET also is planning a phase I trial of a protocol to increase condom use by HIV-discordant couples.

Sexually transmitted diseases. The HIVNET showed that HIV-positive patients who also have genital ulcer diseases are efficient transmitters of HIV-1 subtypes A and C.

Case Western Reserve University/Cleveland TBRU. This Tuberculosis Research Unit (TBRU) and the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, are participating in the multicountry study on the importance of the drug tolerance of *Mycobacterium tuberculosis* in bacterial persistence and poor response to drug therapy.

AIDS. The University of Hawaii, Manoa, is working with the Christian Medical College, Vellore, to determine the molecular epidemiology of HIV-1 and HIV-2 isolates in Tamil Nadu State.

The Laboratory of Immunoregulation (NIAID), Johns Hopkins University, Baltimore, and the ICMR National AIDS Research Center, Pune, are studying the pathogenesis of acute HIV-1 infection in India. In FY 99, NIAID made a new award to Johns Hopkins University to initiate research on the prevention of mother-to-infant transmission in India.

Bacterial Diseases. University of Texas Health Center, Tyler, and the ICMR Tuberculosis Research Center, Madras, found that during the initial immune response of Indian children to *M. tuberculosis*, development of tuberculosis was associated with diminished IFN-γ production, rather than reduced production of IL-2 or enhanced production of IL-4 or IL-10.

Parasitic Diseases. Ana University, Madras, and the Laboratory of Parasitic Diseases (NIAID), have a long-standing Special Foreign Currency Program (P.L. 480) project under the Indo-U.S. VAP, to develop improved diagnostic tests and vaccine candidates for human lymphatic filariasis.

The Laboratory of Parasitic Diseases (NIAID), FDA, Cornell Medical College, New York City, New York, and Banaras Hindu University, Varanasi, are studying splenic cytokine responses in Indian kala-azar before and after treatment. In addition, the Laboratory of Parasitic Diseases, FDA, and Banaras Hindu University found evidence of resistance to treatment with antimony in *Leishmania donovani* strains from India. An NIAID-supported investigator at the University of Washington, Seattle, and an Indian colleague at Jawaharlal Nehru University, New Delhi, received support from an Indo-U.S. VAP grant, to develop a rapid test using a recombinant antigen to diagnose *Leishmania donovani infantum*, the causative agent of infantile kala-azar. Cornell Medical College, New York City, Liposome Company, Princeton, New Jersey, and Banaras Hindu University showed that short-course therapy with low-dose amphotericin B lipid complex is effective alternative treatment for visceral leishmaniasis. In cooperation with ASTA Medica, Frankfurt, Germany, the researchers evaluated miltefosine, an oral drug, in the treatment of visceral leishmaniasis and found that 100–150 mg/day for 4 weeks was effective against Indian kala-azar, including antimony-resistant infection.

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, constructed a multistage, multivalent, recombinant, synthetic *Plasmodium falciparum* vaccine, which encodes for 12 B-cell epitopes, 6 T-cell proliferative epitopes, and 3 CTL epitopes derived from nine stage-specific *P. falciparum* antigens corresponding to the parasite's sporozoite, liver, erythrocytic asexual, and sexual stages.

Indonesia

Bacterial Diseases. The University of Maryland Medical Center, Baltimore, Stanford University School of Medicine, California, and U.S. Naval Medical Research Unit No. 2, Jakarta, the National Institute of Health Research and Development, Directorate of General Communicable Disease Control, and Sulianti Soroso Infectious Disease Hospital, Jakarta, conducted a large-scale, randomized, double-blind, placebo-controlled field trial that showed a low protective efficacy of a single dose of live oral CVD 103-HgR cholera vaccine.

Parasitic Diseases. NIAID made a new award to Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, to collaborate with the Ministry of Health, Jakarta, to study the onset of acquired immunity to malaria in populations migrating from nonendemic Java to an endemic area of Irian Jaya. The Naval Medical Research Institute, Bethesda, Baylor College of Medicine, Houston, Texas, U.S. Naval Medical Research Unit No. 2, Jakarta, and the Ministry of Health found that the peripheral levels of TNF-α, IL-1, and IL-6 are not associated with reduced levels of consciousness per se in patients with *P. falciparum* cerebral malaria.

Duke University Medical Center and the Veteran's Affairs Medical Center, Durham, North Carolina, are working with the Ministry of Health on the relationship between nitric oxide levels and severe malaria in children.

Iran

AIDS. NCI (NIH), New Jersey Medical School, Newark, Niigata University School of Medicine, Japan, and Institut Pasteur, Tehran, linked HTLV-I infection with changes of cellular cyclin gene expression, providing clues to the development of T-cell leukemia.

Ireland

Immunology. Columbia University, New York City, New York, and St. Vincent's Hospital, Dublin, reported that the repertoire of CD8-positive T cells in the synovial fluid of patients with psoriasis appears to be antigen driven.

Israel

Columbia University/New York City ICIDR. This ICIDR provides funds to Columbia University to collaborate with Hebrew University of Jerusalem to study childhood *Giardia lamblia*, *Cryptosporidium*, and *Escherichia coli* infections in Arab and Jewish children.

Natural history. The ICIDR has studied the natural history of diarrheal disease in the Bedouin population in the southern Negev over a 10-year period during its transition from nomadic to settled lifestyle. Successive pediatric cohorts showed a dramatic reduction in the number of children with diarrhea (from 94.3% to 52.1%) and the number of episodes per child (from 1–12 to 1–3).

The investigators attribute the decline to improved environmental conditions and reduced exposure to grazing animals.

Chronic diarrhea. This ICIDR is conducting a prospective study of persistent diarrhea in Bedouin children to determine the importance of different pathogens, family factors, and the environment. Contrary to expectations, pathogens such as *Cryptosporidium* and enterotoxic *E. coli* associated with chronic diarrhea were no more prevalent than other pathogens. Independent and significantly associated risk factors for persistent diarrhea were age at first diarrheal illness, maternal age, and maternal education. These findings suggest that chronic diarrhea may be related more to the health experience of children and their home environment than to infectious pathogens.

Pathogen characterization. The ICIDR is trying to identify and assess factors related to the *Giardia lamblia* parasite and to host–parasite interaction that may account for the variability in duration and clinical manifestations of this infection in Bedouin and Jewish Israeli children. The researchers also are examining in vitro models to identify isolates with properties that suggest virulence and measuring the humoral and cell-mediated immune response to homologous and heterologous *G. lamblia* strains. They intend to develop PCR tests to detect *G. lamblia* in stools and water supplies.

Diagnosis. This ICIDR evaluated the comparative advantages of detecting *Cryptosporidium parvum* oocysts by serology and surveillance based on stool examination in Bedouin infants in southern Israel.

AIDS. The Laboratory of Immunoregulation (NIAID), CDC, Northwestern University Medical School, Chicago, Illinois, Aaron Diamond AIDS Research Center, New York City, Bar-Ilan University, Ramat Gan, and Hadassah Hospital, Jerusalem, have data suggesting that TNF-α genotypes do not play a direct role in HIV-1 disease progression but could be part of a multigenic linkage that may be involved in delaying progression to clinical AIDS.

Scientists at Rockefeller University, New York City, Northwestern University Medical Center, and Bar-Ilan University concluded that, of the many chemokine receptors implicated in HIV-1 entry into cells, CCR5 and CXCR4 are the physiologically important chemokine receptors used as entry cofactors in vivo by diverse strains of primary viruses isolated from blood. They also developed evidence that HIV viral load is a good predictor of disease progression, even if the time of infection is not known and even in the presence of gene mutations (CCR5, CCR2) that slow disease progression.

Mycotic Diseases. Albert Einstein College of Medicine, Bronx, New York, and Technion, Haifa, determined that isotype switching increases the efficacy of antibody production against *Cryptococcus neoformans* infection in mice.

Parasitic Diseases. NIAID supported a grant award to an investigator at Hebrew University of Jerusalem, for evaluation of reversed siderophores as antimalarial agents.

Vector Biology. NIAID supports a grant to Hebrew University of Jerusalem to study the effect of plant diets of sand fly vectors on the transmission of *Leishmania* infection in Israel. Hebrew University of Jerusalem and the University of Texas Medical Branch, Galveston, reported that *Phlebotomus papatasi* saliva inhibits protein phosphatase activity and nitric oxide production by murine macrophages. This finding may explain why sand fly saliva exacerbates cutaneous leishmaniasis.

Italy

The Division of Microbiology and Infectious Diseases (NIAID), Istituto Superiore di Sanità (ISS), Rome, and the University of Rome signed a Memorandum of Understanding, under the U.S.-Italy Bilateral Agreement on Science and Technology, to cooperate on malaria projects in Burkina Faso and Mali. A second new agreement between NIAID and ISS will pursue joint research on the Immunology and Molecular Biology of Cancer.

AIDS. The Laboratory of Immunoregulation (NIAID) and San Raffaele Scientific Institute, Milan, demonstrated that modulation of endogenous IL-1 and IL-1β receptor antagonist results in opposing effects on HIV expression in chronically infected monocytes. The Laboratory, San Raffaele Scientific Institute, Federico II University, Naples, and the University of Trieste showed that host factors impose selective constraints on the evolution of the HIV-1 structures involved in viral entry and that, in long-term, nonprogressive disease, these factors are likely to force the virus into attenuated variants.

ISS, Rome, is coordinating a multicenter Italian study of a PACTG protocol that will be used to evaluate the effect of a single dose of nevirapine administered to mothers at delivery and to neonates at 48–72 hours after birth.

The Laboratory of Immunoregulation (NIAID), Johns Hopkins School of Hygiene, Baltimore, Albert Einstein College of Medicine, Bronx, New York, and Catholic University, Rome, found that *Mycobacterium tuberculosis* increased HIV replication in vivo and in an in vitro model. The investigators concluded that this viral production, mediated by *M. tuberculosis*, occurs through the antigen-specific activation and infection of responding T cells.

Bacterial Diseases. ISS, Rome, is continuing postimmunization surveillance of adverse events and the duration of efficacy in an NIAID-supported trial of acellular pertussis vaccines.

Mycotic Diseases. Georgetown University, Washington, D.C., NOVA (Northern Virginia) Health System, Falls Church, and ISS, Rome, reported that the *Candida albicans* CaHK1 gene is required for the virulence of *C. albicans* in a murine model of hematogenously disseminated candidiasis but not for the virulence in a rat model of vaginal candidiasis.

Viral Diseases. The University of Arkansas, Little Rock, and the University of Brescia induced CD4- and CD8-positive lymphocytes specific to human papillomavirus (HPV), by using oncoprotein E7–pulsed autologous dendritic cells in patients with cervical cancer positive for HPV type 16 and type 18. Future efforts will evaluate the potential of this approach in the immunotherapy of patients with cervical cancer.

Immunology. The Laboratory of Allergic Diseases (NIAID), the University of North Carolina, Chapel Hill, Harvard Medical School and Beth Israel Hospital, Boston, and the University of Milan developed a "hu-

manized" mouse model for anaphylaxis that may be useful in studying human immune responses and in testing potential therapeutic reagents that can interfere with responses mediated through the human Fc_RI receptor.

The College of Physicians and Surgeons, Columbia University, New York City, and the National Research Council's International Institute of Genetics and Biophysics, Naples, documented differential expression of insulin-dependent diabetes mellitus–associated HLA-DQA1 in vivo. This finding may account for the discordance in the outcome of autoimmune disease in monozygotic twins and HLA-identical siblings.

Investigators at the College of Physicians and Surgeons, Columbia University, and La Sapienza University, Rome, concluded that diversification of the immune response against a graft contributes to chronic rejection of heart transplants. They are developing (1) a strategy to identify patients at risk of developing coronary artery vasculopathy and (2) a rationale for therapeutic intervention.

Jamaica

PAHO/Washington, D.C., Contract for HIV Studies. The Jamaican Ministry of Health, Kingston, participates in PAHO-coordinated efforts to study HIV in Latin America and the Caribbean. During FY 99, the research group reported that, in patients in the STD clinic, the incidence rates of HIV-1 per 100 years were 0.7% in men and 0.2% in women. HTLV-I rates per 100 years were 0.9% and 0.8%, respectively. HIV infection in men was associated with multiple risk factors, including drinking alcohol before sexual relations, using cocaine, and accepting money for sexual relations, as well as the total number of sexual partners.

Japan

AIDS. The University of Alabama, Birmingham, the University of California, Davis, the National Institute of Public Health and the National Institute of Infectious Diseases, Tokyo, and Osaka University found that nasal immunization of nonhuman primates with SIV p55 Gag protein and adjuvant cholera toxin induces virus-specific immune responses by T_H1 and T_H2 cells in reproductive tissue.

Bacterial Diseases. The University of Alabama, Birmingham, Kagoshima University, Oita University, and Osaka University found that nasal administration of a mucosal vaccine against nontypeable *Haemophilus influenzae* to mice induced responses of T_H1 and T_H2 cells that were specific to the bacteria.

Osaka University and the University of Alabama, Birmingham, demonstrated that pneumococcal surface protein A, nasally administered along with a nontoxic A subunit mutant of cholera toxin (S61F), elicited a protective immune response against *Streptococcus pneumoniae*.

Mycotic Diseases. NIAID signed a clinical trials agreement with Fujisawa Phamaceutical Company, Ibaraki, to compare the efficacy of intravenous AmBisome (lipsomal amphotericin B) versus amphotericin B in the treatment of life-threatening fungal infection.

Parasitic Diseases. The University of Illinois, Rockford, and Tokyo Medical College developed and evaluated improved formulations of *N,N*-diethyl-*m*-toluamide (Deet) that prolong activity on the skin and are effective in reducing penetration of *Schistosoma mansoni* cercaria and ticks for 24 hours or more.

Viral Diseases. St. Jude Children's Research Hospital and the University of Tennessee, Memphis, and Hokkaido University, Sapporo, determined that residues of the M2 protein are not required for influenza A virus replication.

Jordan

Irbid University MERC. In this Middle Eastern Regional Contract (MERC), the Laboratory of Parasitic Diseases (NIAID), Walter Reed Army Institute of Research, Washington, D.C., and Irbid University are developing novel approaches to improve the transmission of *Leishmania* by sand fly bites in animal models in the laboratory.

Kenya

University of Washington/Seattle CASR. The CASR has maintained active collaboration with the University of Manitoba, Winnipeg, and the University of Nairobi in research on STDs in Kenya for the past 9 years. During FY 99, NIAID competitively renewed the CASR for an additional 5 years to continue work on *Chlamydia* and gonorrhea and to begin research on human herpesvirus type 8 (HHV-8), including the epidemiology and natural history of HHV-8.

University of Washington/Seattle HIVNET

Viral characterization. In cooperation with Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland, and Gen-Probe, Inc., San Diego, California, the HIVNET determined that clade C represented the most prevalent HIV-1 subtype in Kenya, but intersubtype recombinant viral genomes were detected in 2.2% of isolates.

Commercial sex worker cohort. The majority of women in a cohort of commercial sex workers developed symptomatic infection in association with HIV-1 primary infection. STDs, particularly vulvitis, ulcerative lesions, vaginal discharge, and *Candida* vaginitis, were associated with higher rates of HIV-1 transmission. One component of the cohort is a group of commercial sex workers who have remained HIV-1 negative despite repeated exposure. To test the hypothesis that this refractoriness to HIV infection is genetic, the HIVNET contacted family members and determined that the relatives of HIV-1–resistant commercial sex workers are less likely to become HIV-positive than are relatives of susceptible commercial sex workers, despite similar risk-taking behaviors. The investigators also showed that women who used depot medroxyprogesterone acetate—an injectable, long-term contraceptive—had significantly higher HIV-1 conversion rates.

This HIVNET completed a phase I–II study evaluating the effectiveness of nonoxynol 9, a topical microbicide, in reducing HIV infection among female prostitutes in Mombasa. The researchers found no genital epithelial toxicity of nonoxynol 9 vaginal gel and concluded that this product is appropriate for evaluation of HIV-1 prevention in a phase III efficacy trial.

Male truck driver cohort. Trucking company employees had a high HIV-1 seroprevalence (7%–8%) at enrollment in the study and a high HIV-1 seroincidence (3.1%) during follow-up, despite counseling on risk factors for HIV transmission and the availability of free condoms. Risk factors for

HIV-1 transmission included being uncircumcised and having unprotected sexual encounters with high-risk partners.

Pregnant women cohort. In a prospective study of HIV-1–positive pregnant women and their sexual partners in Nairobi, 58% of couples were HIV concordant. Concordant women were more likely to be primiparous, have vaginal discharge, be infected with *Trichomonas vaginalis*, and have higher rates of HIV-1 cervical shedding. The fact that 38% of male partners were HIV negative identifies a high-risk group for focused prevention efforts.

The HIVNET conducted studies of HIV-1 mucosal viral shedding and heterosexual transmission in Kenya. The findings suggest that the virus transmitted may be different in male and female sexual partners.

STD clinic patients. The STD Center and University College, Dublin, Ireland, studied the HIV-1 shedding in cervical and vaginal secretions throughout the menstrual cycle in HIV-1–positive women. The investigators found considerable variation in the frequency of cervical (4%–100%) and vaginal (0%–71%) HIV-1 shedding, which was correlated with the log of plasma HIV load.

The HIVNET reported that cervicovaginal shedding of HIV-1 was increased with the use of hormonal contraception and low levels of vitamin A, as were gonococcal cervicitis and vaginal candidiasis.

Case Western Reserve University/Cleveland Filariasis ICIDR. In FY 99, NIAID competitively renewed this ICIDR as a single project for an additional 5 years, with a focus on the heterogeneity of lymphatic filariasis in Kenya.

Case Western Reserve University/Cleveland Schistosomiasis ICIDR. NIAID also awarded a second single-project ICIDR on *Schistosoma haematobium* to investigate the disease manifestations of urinary schistosomiasis.

Michigan State University/East Lansing ICIDR. One project of this ICIDR will involve collaboration with Kenya Medical Research Institute (KEMRI), Nairobi, to evaluate pentoxifylline, an iron-chelating agent, as adjunct therapy in the management of malaria in children.

Tulane University/New Orleans ICIDR. This new ICIDR award supports Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, to work with KEMRI, Nairobi, in research on malaria. Individual projects will address the vector ecology of African mosquitoes that transmit malaria, the behavior of African malaria mosquito vectors, vector competence, larval ecology of malaria vectors, and vector molecular biology.

Case Western Reserve University/Cleveland Program Project. This Program Project involves the cooperation of Case Western Reserve University with the Ministry of Health of Kenya and KEMRI, Nairobi, in research on echinococcosis, filariasis, helminthiasis, leishmaniasis, malaria, and schistosomiasis.

Echinococcosis. With CDC, the African Medical Research Foundation, Nairobi University School of Veterinary Medicine, and Jomo Kenyatta University of Agriculture and Technology, Nairobi, are evaluating oxfendazole as treatment for cystic hydatidosis in naturally infected Kenyan livestock.

Filariasis. The Program Project is comparing the heterogeneity of disease due to lymphatic filariasis in Kenya and Papua New Guinea and is investigating prenatal sensitization of newborns and infants to *Wuchereria bancrofti*.

Helminthiasis. The researchers found that the human fetus can be sensitized in utero to produce helminth-specific B cells and that these neonatal cells are intrinsically capable of IgE and immunoglobulin G (IgG) production.

Leishmaniasis. Review of leishmaniasis in Kenya over the past century revealed a decline of visceral leishmaniasis in the eastern portion of the country, where the disease had been prevalent in 1950–1980, and an increase in incidence in the northeastern portion, which may represent co-infection with HIV.

Malaria. In FY 99, NIAID made a new award to this Program Project to collaborate with KEMRI, Nairobi, on studies of human immune resistance to malaria, including immunologic memory for preerythrocytic *Plasmodium falciparum* antigens and T-cell immunity to preerythrocytic *P. falciparum* in two areas of western Kenya where malaria is endemic.

Schistosomiasis. The researchers found that repeated, selective chemotherapy of school-age children for *Schistosoma haematobium* infection results in long-term suppression of adult bladder morbidity and hydronephrosis, despite re-infection. This finding suggests that the cumulative intensity and duration of infection are risk factors for these chronic complications.

With the Institute of Primate Research, Karen, researchers in the Program Project determined that, in baboons but not in mice, *Schistosoma mansoni*–specific IgE in adults is uniquely associated with acquired immunity. These results suggest that baboons may be an excellent animal model in which to investigate innate and acquired immunity to schistosomiasis in humans.

AIDS. A grant to the University of Washington, Seattle, will support study of HIV shedding in women and the factors influencing infectivity.

Parasitic Diseases. Tulane University School of Public Health and Tropical Medicine, New Orleans, and KEMRI, Nairobi, are studying the spatial and temporal distribution patterns of anopheline mosquito populations and *Plasmodium falciparum* transmission along the Kenyan coast.

CDC, the University of Michigan, Ann Arbor, and KEMRI, Kisumu, determined that elevation in mosquito inoculation rates is significantly associated with anemia in children in western Kenya.

Vector Biology. Johns Hopkins School of Public Health, Baltimore, the University of Colorado, Denver, and Tulane University School of Public Health and Tropical Medicine used a soil moisture model to predict entomological factors of malaria transmission in Kenya.

Korea

Case Western Reserve University/ClevelandTBRU. Ewha Hospital, Seoul, is a member of the international consortium studying the role of drug tolerance in infection and disease due to *Mycobacterium tuberculosis*.

Immunology. Scripps Research Institute, La Jolla, California, and Seoul National University discovered that thymic selection by a single major histocompatibility complex

(MHC)–peptide ligand is controlled by low-affinity autoreactive T cells.

Laos

Immunology. University of Texas Health Sciences Center, Houston, Washington University School of Medicine, St. Louis, Missouri, and Oregon University Health Sciences University, Portland, are studying an inherited disorder involving reduced complement C3 and protein levels in a Laotian kindred.

Lebanon

American University of Beirut MERC. The MERC studied the prevalence of seropositivity to leishmaniasis in normal Lebanese and in patients with uremia and chemotherapy. The researchers found that, overall, citizens of Beirut had higher rates of seropositivity than rural populations and that patients with uremia had the highest rates, possibly because patients undergoing chemotherapy have reduced immune responses.

Viral Diseases. The University of Rochester School of Medicine and Rochester General Hospital, New York, IDEC Pharmaceuticals Corporation, San Diego, California, and the American University of Beirut cloned, expressed, and characterized two neutralizing human antibodies against respiratory syncytial virus that will be evaluated as potential agents for immunotherapy.

Liberia

Parasitic Diseases. The New York Blood Center, New York City, maintains a facility for chimpanzee-based research on *Onchocerca volvulus* in Liberia.

Viral Diseases. The New York Blood Center was awarded a new grant in FY 99 that will use the chimpanzee facility to support the development and evaluation of prophylactic and therapeutic DNA-based immunization products against HCV.

Madagascar

Virginia Polytechnic Institute/Blacksburg Biodiversity Project. The Virginia Polytechnic Institute Biodiversity Project involves collaboration with Missouri Botanical Garden, St. Louis, the National Center for Pharmaceutical Research and Applications, Antananarivo, and Dow-Elanco (United States) to identify biologically active compounds from plants indigenous to Madagascar.

Vector Biology. The French Institute of Research for Development, Antananarivo, participates in an intercountry study on the differentiation of *Anopheles arabiensis* mosquitoes collected in West Africa and East African islands.

Malawi

Johns Hopkins University/Baltimore HIVNET. This HIVNET provides funding for collaboration with Family Health International, Arlington, Virginia, and the University of Malawi, Blantyre, in research on HIV infection and transmission in Malawian women, infants, and children.

Virology and immunology. The HIVNET is developing a protocol to participate in a HIVNET multicountry study of virological and immunologic parameters in recently infected patients in southern Africa.

Mother-to-infant HIV transmission. This HIVNET determined in prospective cohort studies that rural residence and a low level of parental education were predictors of loss of follow-up. Furthermore, infant birth weight, twin birth, and maternal education were predictors of HIV transmission.

The HIVNET is participating in a phase III trial of antibiotics to reduce chorioamnionitis-related HIV infection. Prospective studies of serum HIV-1 viral load and sodium levels in HIV-1–positive women showed that both mastitis and higher HIV-1 levels in breast milk were associated with higher levels of mother-to-infant vertical HIV transmission. (A high sodium level is an indicator of mastitis.)

This HIVNET performed follow-up on a cohort of HIV-negative infants born to HIV-positive mothers, to determine the importance of breast-feeding in mother-to-infant HIV transmission. The scientists calculated that the overall risk of HIV transmission through breast- feeding in this setting was at least 9.2%. The acquisition of HIV was higher during the first 6 months of breast-feeding, which should be a consideration in formulating breast-feeding policy recommendations in the African setting.

The HIVNET participated in a comparative study of obstetric risk factors for vertical HIV transmission in Brazil and Malawi. The conclusions were that duration of ruptured membranes, gestational age, and stage of maternal HIV infection were similar in both countries.

Vaginal infection. During FY 99, the HIVNET studied the impact of HIV infection on bacterial vaginosis during pregnancy. The data also suggested that this condition may be associated with greater susceptibility to HIV infection. The HIVNET is conducting a phase I clinical trial of BufferGel, a vaginal microbicide. The HIVNET will also participate in a study to evaluate the impact of combined oral contraceptives versus injectable progestin on susceptibility to HIV infection.

Nutrition, growth, and development. Children born to HIV-positive mothers who were deficient in vitamin A during pregnancy were more likely to have slower growth than offspring of mothers with adequate levels of vitamin A.

Topical microbicides. In preparation for a phase I study of a topical microbicide, the HIVNET carried out a survey of the acceptability of such a product to men and women in India, Malawi, Trinidad and Tobago, and Zimbabwe. Because several vaginal products and tightening agents are widely used in Africa, a vaginal product was acceptable there but was much less acceptable in India and Trinidad and Tobago.

Michigan State University/East Lansing ICIDR. In FY 99, the ICIDR competed successfully for a multicountry, multiproject collaborative effort dealing with severe malaria in African children.

AIDS. The University of North Carolina, Chapel Hill, the JSI Project, Lilongwe, and Lilongwe Central Hospital found that herpes zoster, seborrhea, and psoriasis are highly predictive dermatologic manifestations of HIV infection, whereas pityriasis rosea is negatively associated with HIV infection.

Parasitic Diseases. Michigan State University, East Lansing, is cooperating with the Liverpool School of Tropical Medicine, England, the University of Edinburgh, Scotland, and Queen Elizabeth Hospital, Blantyre, to determine the pathological and clinical correlates of cerebral malaria. In FY 99, the investigators conducted an autopsy study that

showed macroscopic evidence of moderate brain swelling in pediatric cerebral malaria.

The project conducted a population kinetics study of a new rectal formulation of artesunate in repositories compared with parenteral quinine, in the treatment of moderately severe malaria in Malawian children. Rectal artesunate was well tolerated and superior to quinine in reduction of mean density of parasites and duration of fever.

NIAID made a new grant award in FY 99 to the University of Maryland, Baltimore, to study drug-resistant malaria in Malawi.

Malaysia

The University of Malaysia, Kuala Lumpur, worked with NCI (NIH), Immune Response Corporation, Carlsbad, California, the University of Southern California, Los Angeles, and Advanced Biotechnology, Inc., Columbia, Maryland, in a multicountry effort to detect IgG antibodies to HHV-8 in HIV-positive persons and HIV-negative blood donors in India, Jamaica, Malaysia, Thailand, and the United States.

Mali

University of Mali/Bamako TMRC. This TMRC is a direct award to the Malaria Research and Training Center, University of Mali, to conduct multidisciplinary research on malaria in an endemic setting. Collaborating U.S. institutions include the Laboratory of Parasitic Diseases (NIAID), Tulane University, New Orleans, Louisiana, the University of Maryland School of Medicine, Baltimore, New York University, New York City, and the University of Texas Medical Branch, Galveston.

Epidemiology. The TMRC is using data from a geographic information system and a global positioning system to test for clustering of severe malaria in time and space in the village study site of Bancoumana. The results indicate that significant transmission of malaria continues to occur during the dry season, even though it is difficult to capture sufficient numbers of infected mosquitoes to determine the inoculation rate. Furthermore, the *Plasmodium falciparum* infection occurs at random among children aged 0–9 years in Mali, but the magnitude of the parasitemia is affected by hemoglobin A, C, and M traits.

Parasite variation. Field-based epidemiologic studies identified parasites with hybrid (MAD20/RO33) sequences for the polymorphic block 2 region of merozoite surface protein 1 (MSP-1) in 8% of children with asymptomatic *P. falciparum* infections. Mosquito-feeding studies subsequently showed that the production of this hybrid occurs in the oocyst and is localized to the meiotic reduction division in the mosquito. Furthermore, the frequency of these hybrids was significantly higher (60%) among children hospitalized with symptomatic malaria than among malaria-infected children hospitalized for other conditions. This finding indicates that parasites with such hybrid sequences are associated with virulence.

Parasite infectivity. Field studies in Bancoumana showed significant monthly variations in mean prevalence of parasites and gametocytes, with a higher peak toward the end of the rainy season, followed by a smaller peak in the dry season. There was also a significant positive correlation between the oocyst load and the gametocyte load. Most mosquitoes had 0–12 cysts, but a few mosquitoes (1%) had very high oocyst infection rates (93%), and oocyst loads (up to 350 per mosquito) were associated with high gametocyte loads (up to 6,350 per mosquito).

Parasite drug resistance. The TMRC conducted a prospective study of the relationship between putative chloroquine-resistant genotypes and chloroquine efficacy, in Bandiagara. The K76T pftcr gene had an overall prevalence of 38.7% in randomly selected patients but was present in 100% of patients with chloroquine resistance. However, the finding that this gene was more prevalent than chloroquine resistance (14.5%) suggests that other host factors, parasite factors, or both contribute to parasite clearance after chloroquine administration.

This TMRC and Tulane University, New Orleans, are monitoring block 2 polymorphisms in MSP-1 antigen, to measure changes in chloroquine and pyrimethamine–sulfadoxine drug resistance after community-based management of malaria in Bancoumana over two transmission seasons.

The TMRC and the University of Maryland, Baltimore, found that the new WHO Protocol for the Assessment of Therapeutic Efficacy of Antimalarial Drugs for Uncomplicated Malaria in Areas With Intense Transmission was more labor intensive and conferred no advantages over traditional methods.

Vector biology. The University of California, Davis, the University of Texas Medical Branch, Galveston, and the TMRC are using microsatellite DNA allele distribution of *Anopheles gambiae sensu lata* collected near Bamako in alternative models of mutation.

Minority training initiative. In 1997, the Division of Intramural Research (NIAID), the University of Maryland School of Medicine, Baltimore, and the University of Mali Medical School entered into an agreement to provide for training of U.S. scientists at the TMRC and to train Malian researchers at NIAID. The TMRC can offer training for advanced undergraduates, graduate students, postdoctoral fellows, and junior-to-midcareer faculty interested in research training in tropical medicine.

University of Maryland/Baltimore Contract for Clinical Research and Vaccine Trials. In late FY 99, NIAID made a contract award to the University of Maryland to work with the TMRC to develop populations in which clinical trials, including malaria vaccine trials, could be conducted.

Parasitic Diseases. The University of Texas Medical Center, Houston, and the TMRC are studying complement receptor 1 (CR1) polymorphism in West Africa and found that the Sl(a-) phenotype may have evolved as a protection mechanism against malaria.

Vector Biology. The University of Texas Medical Branch, Galveston, is working with the TMRC to study the genetic structure of *Anopheles gambiae* mosquito populations in Mali. New York University, New York City, is also collaborating with the TMRC on the genetic susceptibility of *A. gambiae* to infection with *Plasmodium falciparum* parasites.

The University of California, Los Angeles, the University of Rome, Italy, and the TMRC used mark-release and recapture techniques to study *A. gambiae sensu latu* mosquito populations in Banambani, Mali.

Mauritius

Vector Biology. The Medical Entomology Division, Candos, is involved in an intercountry study comparing the genetic differentiation of vectors of anopheline mosquito malaria in West Africa and East African islands.

Mexico

NIAID-USAID Agreement on International AIDS Technical Assistance. The Armed Forces Institute of Pathology, Washington, D.C., and the Institute of Nutrition, Mexico City, conducted a survey of drug resistance to *Mycobacterium tuberculosis* in central Mexico. The investigators found 7% primary resistance to isoniazid in patients compared with 1.8% in 1980; 4% to rifampicin; 0.8% to ethionamide; 0.8% to streptomycin; and 3% resistance to more than one drug.

University of Texas Medical Branch/Galveston EVC. This EVC, the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, the U.S.-Mexico Exotic Animal Disease Commission, Mexico City and Tuxtla Gutiérrez, and the Institute of Health and Tropical Diseases, Mexico City, associated Venezuelan equine encephalitis subtype IE virus with two equine epizootic diseases on the Pacific Coast of Mexico in 1993. The EVC and Autonomous University of the Yucatán, Mérida, discovered that clinical cases consistent with dengue fever were actually due to a rickettsial agent similar to *Rickettsia akari*, which is prevalent and widely distributed in the Yucatán. The researchers named the new species *Rickettsia felis*.

Colorado State University/Fort Collins ICIDR. NIAID made this new ICIDR award to support work with National Polytechnical Institute, Mexico City, Autonomous University of Monterrey, Nuevo Laredo, and Autonomous University of Yucatán, Mérida, on studies of the mosquito vectors and molecular determinants of dengue fever and dengue hemorrhagic fever in Mexico.

Stanford University ICIDR. The Stanford University (California) ICIDR has been collaborating with the Salvador Zubiran National Institute of Nutrition and the National Institute of Epidemiological Diagnosis and Reference, Mexico City, on the molecular epidemiology of tuberculosis in Mexico.

With the National Institute of Public Health, Cuernavaca, the General Directorate of Public Health, Mexico City, and Sanitary Jurisdiction No. 7, Vera Cruz, the ICIDR published an analysis of tuberculosis epidemiology and control in Vera Cruz, where tuberculosis rates have remained high despite 77% compliance with the WHO-recommended program, which is based on direct observation of treatment.

During FY 99, the ICIDR examined the consequences of drug-resistant tuberculosis in Mexico, a country using direct observation of therapy. Resistance to a single drug was common (28.2%), and multidrug resistance to isoniazid and rifampin occurred in 10.8% of patients. The majority of patients (75%) were cured, 9% had treatment failure, and 4% died. An additional 2% relapsed, and 9% died after a 24.4-month median follow-up. The researchers concluded that drug resistance was a strong independent risk factor for treatment failure and that, although multidrug-resistant tuberculosis may be less likely to spread if treatment is directly observed, drug resistance has a profoundly negative effect on control of tuberculosis.

University of Georgia/Athens Biodiversity Project. This Project is a multidisciplinary effort to discover, isolate, and preclinically evaluate pharmacologically important plants from the Mayan areas of Mexico.

AIDS. The University of California, Los Angeles, Chiron Corporation, Emeryville, California, and Autonomous University of San Luis Potosí documented that increased immune activation precedes the infection point of CD4-positive T cells and the increased serum virus load in HIV-1 infection.

Bacterial Diseases. The University of Maryland, Baltimore, and the National University of Mexico and the National Polytechnic Institute, Mexico City, produced evidence that some strains of enteroaggregative *E. coli* produce a 108-kilodalton enterotoxin, which is encoded on the large plasmid for virulence.

Parasitic Diseases. The University of California, San Diego, and the Institute of Biotechnology, Cuernavaca, accomplished stable integration of foreign DNA into the genome of *Entamoeba histolytica* by using pantropic retroviral vectors.

Vector Biology. Texas A & M University, College Station, and the Autonomous University of Neuvo León are studying the competitive population dynamics of *Aedes aegypti* and *Culex pipiens* mosquitoes in the laboratory setting.

Viral Diseases. Stanford University School of Medicine, California, the National Institute of Epidemiological Diagnosis and Reference, Mexico City, and the Department of Public Health, San Cristóbal de las Casas, reported that astrovirus was the most common enteric pathogen isolated in this population of rural Mayan infants throughout the year, with peaks in March and May.

Colorado State University, Fort Collins, and Autonomous University of Yucatán, Mérida, are evaluating the efficacy of molecular strategies for interruption of mosquito transmission against dengue fever isolates from Mexico.

Johns Hopkins University, Baltimore, is isolating and characterizing HPV from Mexican women attending clinics for cervical cancer screening.

Mongolia

AIDS. The University of Alabama, Birmingham, and the Ministry of Health of Mongolia are collaborating in an HIV/STD research and research training project in high-risk, low-prevalence populations in Mongolia.

Morocco

Ibn Rochd University Hospital Center/Casablanca MERC. During FY 99, the MERC reported on the completion of isoenzyme characterization of *Leishmania tropica* responsible for an emerging epidemic of human cutaneous leishmaniasis in Taza, in north Morocco.

Myanmar

AIDS. The University of Hawaii, Manoa, is conducting studies on the molecular epidemiology of HIV-1 in Myanmar.

Nepal

Bacterial Diseases. The University of California, San Francisco, and Birendranager Eye Care Center, Bardia Eye Care Center, and the Swiss Red Cross, Nepalguni, examined, photographed, and used DNA tests of the conjunctiva for *Chlamydia trachomatis* infection and clinical trachoma, in the Surkhet District of midwestern Nepal.

Parasitic Diseases. The Southwest Foundation for Biomedical Research, San Antonio, Tribhuvan University, Kathmandu, and the Jiri Helminth Project conducted a genetic analysis of susceptibility to *Ascaris lumbricoides* infection in 1,261 Nepalese with a single pedigree, before and after albendazole therapy. They documented a strong genetic component, which accounted for 30%–50% variation in roundworm burden, compared with 3%–13% variation attributable to shared environmental (common household) effects.

The Netherlands

AIDS. The Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas, Greenville Hospital System, North Carolina, and the Netherlands Cancer Institute, Amsterdam, found high levels of circulating immune complexes mostly in later stages of HIV infection. The researchers speculated that immune complexes are instrumental in reducing the monocyte capacity to maintain surveillance against infection.

Bacterial Diseases. St. Radboud University Hospital, Nijmegen, is one of seven hospitals in as many countries participating in the international surveillance of antimicrobial resistance of hospital-acquired infections.

Viral Diseases. Eastern Virginia Medical School, Norfolk, Washington University School of Medicine, St. Louis, Missouri, Brown University, Providence, Rhode Island, and the Free University of Amsterdam have evidence that replication of murine CMV in differentiated macrophages may be a determinant of viral pathogenesis.

New Zealand

AIDS. The University of Washington School of Medicine, Seattle, Westmead Institutes of Health Research and New South Wales Blood Bank, Sydney, Australia, and Auckland Hospital documented that HIV-1 B clade predominates in New Zealand in male homosexuals but that clade C is found in some heterosexual women.

Bacterial Diseases. Albert Einstein College of Medicine, Bronx, New York, and the Wallaceville Animal Research Center demonstrated that mutation of the principal σ factor causes loss of virulence in a strain of the *Mycobacterium tuberculosis* complex.

Immunology. Johns Hopkins University, Baltimore, Children's Hospital of Philadelphia, Pennsylvania, the University of Washington and Immunex Corporation, Seattle, and the University of Auckland showed that children with X-linked hyperimmunoglobulin M syndrome, in addition to their severely depressed antibody responses, also have a measurable T-cell defect that may explain their susceptibility to pathogens such as *Pneumocystis carinii* and *Cryptosporidium*.

Nicaragua

Viral Diseases. The University of California, Berkeley, School of Public Health and the Ministry of Health, Managua, successfully used restriction site-specific PCR techniques to conduct rapid subtyping of dengue viruses.

Nigeria

AIDS. The University of New Mexico, Albuquerque, the University of Maryland, Baltimore, and the University of Maiduguri Teaching Hospital studied the seroprevalence of HIV infection in street children in Maiduguri.

The Laboratory of Immunoregulation (NIAID), NCI (NIH), Johns Hopkins School of Medicine and the University of Maryland, Baltimore, and the Federal Ministry of Health of Nigeria determined the prevalence rates of serological reactivity to several STDs in female sex workers in Lagos. The researchers reported the highest overall seroprevalence rates (86%) for *Haemophilus ducreyi* ever recorded.

Parasitic Diseases. Washington University, St. Louis, the University of Witwatersrand, Johannesburg, South Africa, and the University of Ibadan are conducting longitudinal studies in an endemic area of onchocerciasis in Nigeria. The University of Alabama, Birmingham, and the University of Ibadan are investigating the molecular epidemiology of onchocerciasis in Nigeria, to determine the impact of community-based ivermectin chemotherapy on levels of infection in the blackfly vectors of the disease. The researchers are using a PCR test directed toward O-150 antigen, which differentiates between blinding and nonblinding strains of *Onchocerca volvulus*, to determine the distribution of the strains in Nigeria.

Norway

Bacterial Diseases. Boston University, Massachusetts, and the National Institute of Public Health, Oslo, mapped T-cell epitopes from the meningococcal class 3 outer-membrane protein recognized after vaccination with the Norwegian outer-membrane vesical vaccine.

Pakistan

AIDS. The University of Alabama, Birmingham, and the AIDS Control Program, Karachi, are working together to provide HIV/STD training and research experience to health workers in Pakistan, where prevalence remains low.

Panama

Smithsonian Institute International Cooperative Biodiversity Group. NIAID cofunds the Smithsonian Tropical Research Institute, Panama City, to work with Monsanto-Searle, St. Louis, Missouri, Conservation International (United States), and the University of Panama and Gorgas Memorial Hospital, Panama City, to work with indigenous communities on the identification and evaluation of native plants in the treatment of tropical diseases.

AIDS. Tulane University, New Orleans, Louisiana, the University of South Florida All Children's Hospital, St. Petersburg, Bronx-Lebanon Hospital, New York City, New York, Glaxo Wellcome, Inc., Research Triangle Park, North Carolina, and Children's Hospital, Panama City, found that the antiretroviral drug abacavir is well tolerated in U.S. and Panamanian children. The dropout rate due to hypersensitivity to the drug was less than 1%.

Parasitic Diseases. Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, Maryland, is working with the Gorgas Memorial Laboratory, Panama City, to determine the onset of acquired immunity to malaria in nonimmune subjects.

Vector Biology. Yale University, New Haven, Connecticut, and the National Institute of Health, Bogotá, Colombia, are

collaborating with Panamanian medical entomologists to collect specimens to determine the genetics and biogeography of sand fly disease in Central America and Panama.

Papua New Guinea

Parasitic Diseases. Case Western Reserve University, Cleveland, Ohio, Cambridge University, England, and the Papua New Guinea Institute of Medical Research, Goroka, found that annual single-dose, community-wide treatment with diethylcarbamazine or ivermectin was effective for control of bancroftian filariasis in highly endemic areas (75.6%–79.4%), but combination therapy brought about greater decreases in infection rates (75.7%–98.8%) and intensity of microfilaremia.

Case Western Reserve University and the Papua New Guinea Institute of Medical Research, Goroka, have been studying T-cell immunity to preerythrocytic *Plasmodium falciparum* parasites. Case Western Reserve University, the University of Notre Dame, South Bend, Indiana, and the Papua New Guinea Institute of Medical Research, Madang, conducted a seroepidemiologic and immunologic study of *Plasmodium vivax* Duffy binding protein in an area of Papua New Guinea endemic for both falciparum and vivax malaria. Case Western Reserve University, the WHO Onchocerciasis Control Program, Burkina Faso, and the Papua New Guinea Institute of Medical Research, Goroka, determined that the Duffy-negative promoter mutation found in a region of Papua New Guinea where *P. vivax* is endemic is independent from Duffy-negative promoters found in Africa.

Paraguay

University of New Mexico/Albuquerque EVC. In an EVC study with New Mexico State University, Las Cruces, the University of Pennsylvania, Kennett Square, and the National University of Central Buenos Aires Province, Tandil, and the National University of Salta, Argentina, 40.4% of Indians living in western Paraguay and 17.1% of Indians in Salta Province had serological evidence of exposure to Sin Nombre-like Hantaviruses.

Peru

University of Washington/Seattle CASR. With Cayetano Heredia Peruvian University, the Ministry of Health of Peru, and the National AIDS and STD Program, Lima, the CASR determined that STDs in female commercial sex workers were reduced by condom use but not by the traditional periodic health examination program. The CASR is also studying the natural history of cervical neoplasia in HIV-positive Peruvian women.

University of Texas Medical Branch/Galveston EVC. This EVC and the U.S. Naval Medical Research Institute Detachment, Lima, isolated and carried out the genetic characterization of a Hantavirus isolated from a rodent (*Oligorhyzomys microtis*) in an urban area of Iquitos. The isolate appears to be Rio Mamore virus, which has been associated with human disease elsewhere in South America. The investigators also are collaborating on the epidemiology and ecology of Oropouche virus in the Peruvian Amazon. The EVC, CDC, Fort Collins, Colorado, the U.S. Naval Medical Research Institute, Bethesda, and the U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, Parma Community Hospital, Ohio, and the U.S. Naval Medical Research Institute Detachment, Lima, reported on the clinical, laboratory, and epidemiologic manifestations in 27 patients, including two U.S. visitors, who contracted Mayaro virus, an emerging mosquito-borne zoonosis in Peru.

Johns Hopkins University/Baltimore ICIDR. This ICIDR involves joint research with the National Institute of Child Health, PRISMA Beneficial Association, and Cayetano Heredia Peruvian University, Lima, on emerging diarrheal diseases and cysticercosis.

Emerging enteric diseases. During the 1997–1998 El Niño episode, the ambient temperature in Lima increased more than 5°C above normal. The ICIDR demonstrated that the number of daily admissions for pediatric diarrhea more than doubled. The number of hospital admissions for diarrhea increased about 8% for each degree of mean ambient temperature.

The ICIDR, the University of Cincinnati, Ohio, the University of Alabama, Birmingham, and Walter Reed Army Institute of Research, Washington, D.C., used the lactulose–mannitol assay for intestinal permeability to study infants with rotavirus and *Cryptosporidium* diarrhea. With CDC and McGill University, Montreal, the ICIDR is evaluating the usefulness of wheat germ agglutinin as a novel treatment for human cryptosporidiosis.

Cysticercosis. In collaboration with CDC, the National Institute of Neurological Sciences and the National University of San Marcos, Lima, and the National University of San Antonio, Cuzco, the ICIDR documented increased prevalence and risk of cysticercosis and *Taenia solium* infection among professional fried-pork vendors and the general population of a village in the Peruvian highlands. Future projects will include elucidation of the dynamics of *T. solium* transmission and development of field tests for diagnosis of cysticercosis in humans.

Echinococcosis. The ICIDR determined that, in remote areas where echinococcosis is endemic, both the coproantigen enzyme-linked immunosorbent assay (ELISA) and arecoline purging may be used for the study of canine echinococcosis. The enzyme-linked immunoelectrotransfer blot is useful in establishing the diagnosis of echinococcosis in sheep before slaughter. The ICIDR developed evidence that a staggered dosing regimen of oxendazole and possibly other benzimidazoles in sheep may be as effective as daily dosing regimens for hydatidosis and that it would decrease both the cost and adverse effects of daily dosing.

Bacterial Diseases. Stanford University, California, Johns Hopkins University, Baltimore, and the U.S. Naval Medical Research Institute Detachment and PRISMA Beneficial Association, Lima, documented that acute *Helicobacter pylori* infection in Peruvian children is followed by an increase in diarrheal disease for at least the following year.

Johns Hopkins University and Cayetano Heredia Peruvian University and PRISMA Beneficial Association have preliminary evidence that the inability to produce IFN-γ or to mount a positive response to the skin test for tuberculosis may, in most patients, be a consequence of diminished cellular immunity that accompanies other manifestations of the disease.

University of Maryland Health Sciences Center, Baltimore, and Cayetano Heredia Peruvian University are investigating factors that contributed to the emergence of *Vibrio cholerae* 0139 in Peru.

The University of Texas Medical Branch, Galveston, the U.S. Naval Medical Research Institute Detachment, Lima, and the Ministry of Health, Lima and Cuzco, investigated three outbreaks of *Rickettsia prowazekii* typhus fever in the Peruvian highlands in 1996–1998.

Mycotic Diseases. The University of Alabama, Birmingham, and Cayetano Heredia Peruvian University, Lima, characterized the epidemiology and clinical manifestations of a hyperendemic area of sporotrichosis in the highlands of Peru.

Viral Diseases. The University of Texas Medical Branch, Galveston, Evandro Chagas Institute, Belém, Brazil, and the U.S. Naval Medical Research Institute Detachment, Lima, are examining the epidemiology and ecology of Oropouche virus obtained from various geographic regions and time periods in the Amazon Basin. With the National Institute of Health, Lima, the investigators also used molecular epidemiology to identify six genotypes of the yellow fever virus in the Amazon.

Philippines

University of Washington/Seattle CASR. The CASR, Osaka University, Japan, and the Research Institute of Tropical Medicine, Manila, investigated the genetic subtypes of HIV-1 in the Philippines and identified multiple genetic subgroups. The CASR is working with the Research Institute of Tropical Medicine, Manila, in a prospective study of the natural history of cervical neoplasia in HIV-positive Philippine women.

Brown University/Providence (Rhode Island) CFAR. The Center for AIDS Research (CFAR), the Research Institute for Tropical Medicine, Muntinlupa City, San Lazaro Hospital, Santa Cruz, Philippines, and the University of the Philippines and the National AIDS/STD Control Program, Manila, conducted molecular epidemiology analysis of HIV-1 infection in the Philippines in 1985–1997. Initially, the prevalent subtypes were B and E in female commercial sex workers and homosexual men, but recently, subtypes C and F have become more common.

Research Institute of Tropical Medicine/Manila TMRC. This TMRC focused on epidemiologic and clinical studies of leprosy, malaria, and schistosomiasis.

Leprosy. The TMRC is collaborating with Yonsei University, Seoul, Korea, and Colorado State University, Fort Collins, in a WHO pilot project to evaluate the use of serological and PCR tests to monitor the effects of preventive treatment of leprosy.

Malaria. New York University, New York City, and the TMRC are investigating genetic diversity in surface antigens of *Plasmodium falciparum* in the Philippines.

Schistosomiasis. The researchers determined that *Schistosoma japonicum* myosin is a major target of the human immunoglobulin A (IgA) immune antibody isotype response, strengthening the potential of paramyosin as a vaccine candidate, which could be administered through mucosal routes.

AIDS. NIAID has supported the University of California, Los Angeles, and the University of the Philippines, Manila, for the past several years in studies to evaluate the impact of peer educational counseling alone, managerial training alone, and peer educational counseling and managerial training together, to effect behavioral change and risk reduction in female commercial sex workers and their managers. Brown University, Providence, Rhode Island, and the University of Manila found that female college students in an education program for prevention of HIV, AIDS, and STD are potentially effective peer educators and that this program provides a low-cost, sustainable effort in both the academic and community settings.

Poland

Immunology. Harvard Medical School, Boston, Massachusetts, Jagiellonian University, Kraków, and Southampton General Hospital, England, reported that the bronchial biopsy specimens of patients with aspirin-intolerant asthma showed overexpression of leukotriene C4.

Thomas Jefferson University, Philadelphia, and the Philadelphia Biomedical Research Institute, King of Prussia, Pennsylvania, Kumamoto University School of Medicine, Japan, and the Institute of Oncology, Gliwice, prevented experimental allergic encephalomyelitis by blocking nitric oxide and peroxnitrite production and increasing scavenging of these compounds in the brains of experimental animals.

Portugal

Bacterial Diseases. Johns Hopkins University, Baltimore, CDC, Los Angeles County Department of Health Services, California, and the National Institute of Health, Aquas de Moura, isolated *Bartonella* spp. from the blood of 5.1% of *Rattus norvegicus* tested in Portugal and 8.4% of *Rattus rattus* tested in the United States. The study suggested that rats are a reservoir host for pathogenic *Bartonella* spp. and that the isolates from the United States are consistent with infection originating in the Old World.

Rockefeller University, New York City, and the University of Porto compared the survival of *Mycobacterium tuberculosis* and *Mycobacterium avium* in acidified vacuoles of murine macrophages. The investigators found that, although both mycobacteria inhibit phagosome–lysosome fusion, they may be differentially susceptible to the toxic effects of the acidic environment in the mature phagolysosome. Colorado State University, Fort Collins, and the University of Porto are investigating the immunopathogenesis of clinical disease due to *M. avium* in persons with immunosuppression.

Réunion Island

Vector Biology. The Anti-Malarial Service, St. Denis, is a member of the international group comparing the genetic differentiation of East African and West African island strains of *Anopheles arabiensis*.

Romania

AIDS. Baylor College of Medicine, Houston, Texas, received a new program project award that will include collaboration in research on pediatric HIV/AIDS in Romania.

Bacterial Diseases. Rockefeller University, New York City, Soroka University, Beersheva, Israel, and the Faculty of Medicine, Iasi University, performed molecular typing of *Streptococcus pneumoniae* recovered from children in a recent surveillance study in Romania and found a close epidemiologic connection between the flora of *S. pneumoniae* colonizing children in a day-care center and infection in hospitalized children.

Russia

Historically, NIAID participated in the Union of Soviet Socialist Republics (USSR)-U.S. Science and Technology Joint Health Protocol in Infectious Diseases, with a focus on influenza and hepatitis viruses and antiviral compounds. Since the breakup of the USSR, NIAID has participated in the Russia-U.S. (Gore-Putkin) Binational Commission. During FY 99, NIAID also became a participant in the new Biotechnology Engagement Program (BTEP) of the U.S. Department of State and the U.S. Department of Health and Human Services with Russian Biological Warfare and laboratories with work relevant to biological warfare, to redirect their research effort toward civilian areas. The NIH component of BTEP will provide support for site-visit teams, workshops, research training for Russians in the United States, reentry awards, revisitation support, and grant and contract supplements.

In November 1998, NIAID participated in discussions on future mutual interests and prospects for scientific exchange with two representatives of the Civilian Research and Development Foundation from the State Research Center of Virology and Biotechnology, Novosibirsk.

NIAID organized a BTEP-funded team of the NIH, CDC, FDA, and university tuberculosis researchers to visit leading Russian institutions to identify scientific exchange, research, and training opportunities to incorporate into a BTEP research work plan.

Bacterial Diseases. The Institute of Experimental Medicine, St. Petersburg, is a part of the international consortium to determine the relationship of emm typing to traditional M typing of group A *Streptococcus*.

Washington University School of Medicine, St. Louis, Missouri, Clontech Laboratories, Inc., Palo Alto, California, and the Shemyakin-Ovchinikov Institute of Bioorganic Chemistry, Moscow, developed a PCR-based subtractive hybridization technique that identifies differences in gene content among strains of *Helicobacter pylori*.

Viral Diseases. St. Jude Children's Research Hospital, Memphis, Tennessee, the University of Wisconsin, Madison, Jiangxi Medical College, Nanchang, China, and the Chumakov Institute of Poliomyelitis and Viral Encephalitis (Chumakov Institute), Moscow, determined that the surface glycoproteins of H5 influenza virus isolated from humans, chickens, and wild aquatic birds have distinguishable properties.

St. Jude Children's Research Hospital, the National Institute for Biological Standards and Control, Potter's Bar, England, and the Chumakov Institute are studying the effects of egg adaptation on the receptor-binding properties of human influenza A and B viruses. St. Jude Children's Research Hospital and the University of Tennessee, Memphis, the University of Wisconsin, Madison, and the Chumakov Institute are investigating the molecular mechanisms of serum resistance of human influenza H3N2 virus and their involvement in virus adaptation in a new host. St. Jude Children's Research Hospital and the University of Tennessee, Memphis, and the Chumakov Institute are performing studies of mice to determine the immunogenicity and protective efficacy of influenza B virus vaccines grown in mammalian cells or embryonated chicken eggs.

Rwanda

University of Alabama/Birmingham HIVNET. Suspended in 1994–1998 because of political strife and genocide in Rwanda, the HIVNET is becoming operational again. The renewed focus will be on clinical and laboratory prognostic indicators in a cohort of long-term, HIV-positive female survivors and on the development and evaluation of an algorithm for the early detection and treatment of tuberculosis in HIV-positive adults.

Natural history. The HIVNET worked with WHO, Geneva, the Ministry of Health of Rwanda, Kigali, and Abbott Laboratories, Chicago, Illinois, to determine the levels of vitamin A in HIV-positive patients in early and advanced disease. The investigators showed an association of high HIV load, rapid progression, and low serum levels of vitamin A late, but not early, in disease progression. These results reduce the likelihood that vitamin A supplementation in HIV-1–positive individuals early in the disease would have a significant impact on disease progression.

With the Municipal Health Services, Amsterdam, the Netherlands, the HIVNET reported that HLA class I homozygosity accelerated the progression of HIV infection in both Dutch and Rwandan patients.

Senegal

University of Washington/Seattle CASR. This CASR is collaborating with the University of Dakar to study the natural history of cervical neoplasia in women in Senegal who are infected with HIV-1, HIV-2, or both.

Harvard School of Public Health/Boston HIVNET. This HIVNET provided support to Harvard University to work with the University of Dakar and the Ministry of Health of Senegal in studies on HIV-1 and HIV-2 infection in Senegal.

HIV-2 versus HIV-1 infection. The HIVNET documented that HIV-positive Senegalese women carry lower HIV-2 viral loads than those infected with HIV-1. The findings suggest that this difference in viral load may reflect the difference in pathogenicity of HIV-1 and HIV-2.

Infection with HIV-1 and HIV-2. This HIVNET produced data suggesting that infection with HIV-1 and HIV-2 may not be a static condition. Levels of HIV-2 may decrease with disease progression or may sequester in tissue reservoirs. In general, however, HIV-1 effectively overgrows HIV-2.

Viral shedding. The HIVNET found that viral genital shedding is more common in HIV-1 infection than in HIV-2 infection, which may account for the lower HIV-2 transmission rates.

Clinical progression. The HIVNET identified antibodies to HIV-2 core protein p26 and Vpx associated with disease progression. These are the first virus-specific serological markers for HIV-2–related disease progression.

Condom promotion. With the University of Texas, Houston, the HIVNET documented that female commercial sex workers were actively involved in promoting condom use and in ensuring the proper use of condoms by their male partners.

AIDS. The University of Washington, Seattle, completed a study with the University of Dakar on the epidemiology of HIV-1 and HIV-2 in the cervix and vagina of Senegalese women.

NIAID made new grants to Harvard University, Boston, to work with the University of Dakar on in vivo HIV-2 protection and the evaluation of a model for HIV primary infection. A second new grant to Harvard University will provide for evaluation of

cross-reactive cellular immunity with HIV-1 and HIV-2.

Vector Biology. In FY 99, NIAID awarded a new grant to the University of Notre Dame, Indiana, to collaborate with Institut Pasteur, Dakar, on species boundaries in the *Anopheles gambiae* species complex.

Sierra Leone

Viral Diseases. Using Lassa fever virus isolates collected from Sierra Leone and working in CDC's biosafety level 4 facility, scientists from the University of Wisconsin, Madison, are trying to identify determinants of virulence and correlates of immunity.

Singapore

Immunology. The University of Virginia, Charlottesville, and the National University of Singapore determined that *Blomia tropicalis* allergens exist at high levels and constitute one of the major dust allergens in Singapore. They also determined that rBlot5 is highly allergenic in U.S. and Singapore populations and has little cross-reactivity with other allergenic skin antigens.

Slovakia

AIDS. Picower Institute for Medical Research, Manhasset, New York, and the Institute of Virology, Bratislava, showed that bacterial lipopolysaccharide is a potent inhibitor of HIV-1 replication in T lymphocytes and macrophages.

Slovenia

AIDS. The University of California, San Francisco, Pierre and Marie Curie University, Paris, France, and the Institute of Biochemistry, Ljubljana, showed that the Nef protein activates a homologue of p21-activated kinase derived from HIV-1.

Bacterial Diseases. New York Medical College, Valhalla, Rush-Presbyterian Medical Center, Chicago, Illinois, and the University of Ljubljana compared European cases of erythema migrans caused by *Borrelia afzelii* and U.S. cases caused by *Borrelia burgdorferi*. The diseases have different symptoms, clinical manifestations, and laboratory findings, suggesting that the two spirochetes may be separate species.

South Africa

Baragwanath Hospital/Soweto HIVNET. This HIVNET is a direct award to the University of Witwatersrand, Johannesburg, to work with the Ministry of Health of South Africa, Pretoria, in the Ministry of Health's Baragwanath Hospital, Soweto.

The HIVNET infrastructure supported the completion of the PETRA Trial, which evaluated the mode of delivery and other variables related to the early efficacy of three short combination regimens of AZT and lamivudine, to prevent mother-to-child transmission of HIV-1. The PETRA study showed that this short-course antiretroviral therapy is effective in reducing intrapartum HIV transmission in the developing world and that cesarean section has an independent protective effect.

MRC/KwaZulu HIVNET. This HIVNET will participate in a phase I study of Pro2000/5 gel, an antiretroviral vaginal microbicide, which may block the vaginal transmission of HIV. The HIVNET will also collaborate in a multicenter, phase III trial of a high-dose nonoxynol 9 topical microbicide. The investigators found that the microbicide was culturally acceptable to commercial sex workers in KwaZulu.

University of Minnesota/Minneapolis ICIDR. This ICIDR collaborates with MRC, Durban, in studies on amebiasis. The ICIDR is investigating predictive factors for the acquisition of *Entamoeba histolytica* and the commensal *Entamoeba dispar*. During FY 99, the ICIDR neared completion of a prospective follow-up study of 100 patients with amebic liver abscess and more than 1,000 control subjects in KwaZulu. The goals are identification of determinants of amebic infection; evaluation of the reliability of new diagnostic tests; characterization of mucosal and humoral immune responses to the galactose-inhibitable adherence lectin and a recombinant cysteine-rich section of the lectin 170-kilodalton LC3 subunit; and development of mucosal immunity to intestinal infection by new *Entamoeba* spp. Epidemiologic risk factors for amebic liver abscesses are male gender, age, and increased prevalence of asthma. There were no differences between patients and control subjects in the source of drinking or wash water, the site of defecation, or the site for food preparation.

New England Medical Center/Boston ICIDR. Under the NIAID ICIDR Program, the National Institute of Child Health and Human Development (NIH) made a new ICIDR award for joint research with New England Medical Center on micronutrients and enteric infections in African children.

AIDS. NIAID awarded a contract to Public Health Foundation Enterprises, City of Industries, California, to conduct virological and immunologic studies of HIV-1 infection in newly infected persons in South Africa. There is a subcontract with the National Institute of Virology, Pretoria, to coordinate a regional effort to isolate and characterize clade C HIV-1 isolates from Malawi, South Africa, Zimbabwe, and elsewhere in southern Africa. The National Institute of Virology has studied more than 200 isolates; confirmed that the majority are indeed clade C; and determined that intersubtype recombination, primarily with clade A, is low (3%) and that clade C isolates from South Africa do not group separately from subtype C isolates from elsewhere in Africa. These findings suggest that a single subtype C vaccine may be suitable for the region.

The University of Alabama, Birmingham, Institut Pasteur, Paris, France, New York University, Tuxedo Park, and University of the Free State, Bloemfontein, carried out genital infection of female chimpanzees with HIV-1. The investigators found that productive infection requires more than one exposure; that low-level infection without seroconversion can be established after mucosal exposure; and that studies of vaccine efficacy involving a single virus challenge of immunized chimpanzees by the cervicovaginal route probably will not be possible.

The Laboratory of Immunoregulation (NIAID) and Johns Hopkins School of Medicine, Baltimore, received supplemental funding from the Office of the Director, NIH, to collaborate with MRC, Pretoria, to investigate the relationship between HIV and tuberculosis and the importance of breast-feeding in HIV transmission from mothers to infants in South Africa.

In FY 99, NIAID made a new collaborative agreement award to New York University, New York City, and a separate grant to the

Population Council, New York City, to work with the University of Cape Town to begin a trial of a carageenan-based topical microbicide that blocks the adherence of HIV to host cells.

Bacterial Diseases. Creighton University, Omaha, Nebraska, and University of the Free State, Bloemfontein, recovered the β-lactamases responsible for resistance to extended-spectrum cephalosporins in *Klebsiella pneumoniae*, *E. coli*, and *Proteus mirabilis* isolates obtained from South Africa.

The University of Arkansas Medical Center, Little Rock, and the University of Stellenbosch, Cape Town, are working on the genetics of *Mycobacterium tuberculosis*. Rockefeller University, New York City, is working with the University of Cape Town to study the regulation of TNF in host immune response to tuberculosis and the effectiveness of IL-2 as an adjunct to combination drug therapy for tuberculosis. The researchers investigated the immunologic basis for the clinical evidence of deterioration in patients with tuberculosis, after initiation of chemotherapy. They discovered that a significant, transient weight loss, lowered Karnofsky score, and increased serum lactate levels were associated with a concomitant rise in TNF-α. Rockefeller University, the National Institute for Medical Research, London, England, and the University of Cape Town are studying differential gene expression in response to adjunctive immunotherapy with recombinant IL-2 in patients with multidrug-resistant tuberculosis.

Parasitic Diseases. Washington University School of Medicine, St. Louis, Missouri, and MRC, Durban, are conducting a longitudinal study of the antibody response to recombinant *Entamoeba histolytica* antigens in patients with amebic liver abscess. The study showed that treated patients lost their seropositivity to recombinant SRHEP or 170-kilodalton, antigen-based tests more rapidly than with conventional serological tests, thus providing a useful tool for differentiating patients with amebic abscess in a setting where infection with intestinal *E. histolytica* is frequent.

The University of Virginia, Charlottesville, TechLab, Inc., Blacksburg, Virginia, and MRC, Durban, reported that, in an animal model of invasive *E. histolytica*, immunization with the carbohydrate recognition domain of *E. histolytica* inhibited liver abscess formation. In humans, however, a naturally acquired immune response against the carbohydrate recognition domain did not persist. Case Western Reserve University, Cleveland, Ohio, and MRC initiated a joint project to investigate mucosal immunity and infection with *E. histolytica*.

Viral Diseases. The Laboratory of Infectious Diseases (NIAID), Georgetown University Medical Center, Rockville, Maryland, Rancho Los Amigos Medical Center, Downey, California, and the University of Witwatersrand, Johannesburg, experimentally infected chimpanzees with genotype HCV, carried out the genetic analysis, and generated a standardized pool of chimpanzees to be used for immunologic challenge. The findings showed that the South African HCV is genetically distinct.

CDC, Johns Hopkins University, Baltimore, and the University of Cape Town studied changes within T-cell receptor V-beta subsets in infants after measles vaccination and generated data suggesting that measles virus may affect immune responses in part by altering the T-cell receptor repertoire.

The Laboratory of Infectious Diseases (NIAID) and MRC, Pretoria, are investigating the molecular epidemiology of rotaviruses in South Africa.

Spain

AIDS. The Laboratory of Immunoregulation (NIAID), Frederick Cancer Research and Development Center, Maryland, the National University of Madrid, and Gregorio Maranon Hospital, Madrid, determined that progression of HIV disease is associated with increasing disruptions within the CD4-positive T-cell repertoire.

CDC and Emory University, Atlanta, Georgia, and Carlos III Institute of Health, Madrid, developed a rapid, non–culture-based assay for the clinical monitoring of phenotypic antiviral resistance of HIV-1 type B to lamivudine.

Harvard Medical School, Boston, and Foundation irsiCaixa, Barcelona, are studying the replicative fitness of HIV-1 mutants that are resistant to protease inhibitors.

The University of Colorado, Denver, Hampton Roads Medical Specialists, Virginia, Daly Institute of Medicine, Dallas, Texas, and Provincial Clinical Hospital, Barcelona, demonstrated that administration of delavirdine twice a day in combination with nelfinavir plus d4T, plus dideoxynucleoside, or plus both agents resulted in significant decreases in viral RNA through 24 weeks of therapy.

The Laboratory of Immunoregulation (NIAID) and the German Trias I Pujol University Hospital, Barcelona, conducted a clinical trial in which 25 Spanish patients with advanced HIV-1 infection randomly received HAART alone or HAART plus low-dose recombinant IL-2 subcutaneously once a day. This subcutaneous administration of recombinant IL-2 was well tolerated and improved immunologic surface markers.

Massachusetts General Hospital, Brigham and Women's Hospital, and Harvard Medical School, Boston, and Foundation irsiCaixa, Barcelona, discovered that effective antiretroviral therapy resulted in improved response of CD4-positive T cells.

Bacterial Diseases. University Hospital Clinic, Salamanca, participates in an NIAID-supported surveillance system designed to evaluate the current status of antimicrobial resistance to hospital-acquired bacterial pathogens. Hospital Ramon y Cajal, Madrid, participates with the University of Iowa College of Medicine, Iowa City, in an international consortium to study the mechanisms for induction of β-lactamase–mediated antibiotic resistance to third-generation cephalosporins.

Parasitic Diseases. Yale University School of Medicine, New Haven, Connecticut, and the Center of Biological Investigations, Madrid, determined that *Leishmania*-infected macrophages sequester endogenously synthesized parasite antigens from presentation to CD4-positive T cells.

New York University, New York City, and the National Center of Biotechnology, Madrid, reported that recombinant viruses expressing a human malaria antigen can elicit potentially protective immune CD8-positive responses in mice. The scientists are working together on the development and evaluation of an attenuated influenza virus as a vector for the delivery of antigens in a malaria vaccine.

Viral Diseases. New York University and Mt. Sinai School of Medicine, New York City, and the National Center of Biotechnology, Madrid, characterized in vivo primary and secondary CD8-positive T-cell responses induced by recombinant influenza and vaccinia viruses.

The University of Pennsylvania, Philadelphia, and the Center for Research on Animal Health, Madrid, found that the B5R protein of vaccinia virus is a key viral protein with multiple functions in the process of virus envelopment and release and may be involved in viral evasion from host immune response.

Immunology. The University of Madrid participates in the international research on the roles of HLA genes, asthma, and atopy in the development of mite-induced asthma.

Sri Lanka

Viral Diseases. Yale University School of Medicine, New Haven, CDC, and the Ministry of Health, Colombo, determined that dengue virus type 3 is responsible for the recent outbreaks of dengue hemorrhagic fever in Sri Lanka.

Sudan

Parasitic Diseases. The University of Alabama, Birmingham, Auburn University, Alabama, the University of Khartoum, and the National Center for Research, Khartoum, found little intraspecies or interspecies DNA heterogeneity in the mitochondrial genomes of *Onchocerca volvulus* isolates from Sudan.

Suriname

Virginia Polytechnic Institute/Blacksburg Biodiversity Project. In FY 99, in its 7th year, the Biodiversity Project provided for collaboration with Conservation International (United States), Missouri Botanical Garden, St. Louis, BSVS, Paramaribo, and Bristol-Myers Squibb (United States) to extract biologically active products from plants collected in Suriname.

Sweden

AIDS. Rush-Presbyterian Medical Center, Chicago, Illinois, and Karolinska Institute, Stockholm, reported that chemokine receptor CCR5, the predominant HIV-1 co-receptor, is selectively upgraded in women with STDs and genital ulcer disease.

Walter Reed Army Institute of Research and Henry M. Jackson Foundation for the Advancement of Military Medicine, Rockville, Maryland, the California State Department of Health, Berkeley, and Karolinska Institute reported that patients with rapid- or slow-progressing HIV-1 disease exhibit different immune responses against HIV envelope proteins and peptides in early infection.

Vector Biology. The Laboratory of Microbial Structure and Function (NIAID) and the National Defense Establishment, Umeå, discovered that *Yersinia pestis* murine toxin, a phospholipase D homologue, is required for stable bacterial colonization of the flea midgut.

Switzerland

AIDS. Rockefeller University and New York University, New York City, British Biotech Pharmaceuticals, Oxford, England, and Serono Pharmaceutical Research Institute, Geneva, showed that RANTES, a CC cytokine, increases the attachment of HIV-1 to target cells via glycosaminogylcans and also activates a signal transduction pathway that enhances viral infectivity.

The University of North Carolina, Chapel Hill, Laboratory Corporation of America, Research Triangle Park, North Carolina, and the Institute for Clinical Microbiology and Immunology, St. Gallen, discovered that HIV-1 variants with genotypic resistance markers are present in the male genital tract and evolve over time when the patient receives antiretroviral therapy resulting in incomplete immunosuppression. The discrepancy between genomes for drug resistance in the serum and semen suggests the possibility of limited penetration of these agents into the male genital tract and may influence sexual transmission and drug resistance in newly infected individuals.

Bacterial Diseases. The University of California, Irvine, and the University of Basel Dental Center found a family of cross-reactive proteins in *Borrelia* that are expressed both in vitro and in the course of Lyme disease.

Parasitic Diseases. New York University School of Medicine, New York City, and the University of Geneva conducted a small-scale, phase I trial to test the safety and immunogenicity of a synthetic peptide malaria vaccine containing repeated B-cell epitopes combined with a universal T-cell epitope.

Syria

Parasitic Diseases. In FY 99, the American University of Beirut, Lebanon, and Tachrine University, Lattakiyeh, investigated recently recognized foci of cutaneous leishmaniasis in cases that displayed a clinical picture and response to therapy different from those observed in well-known foci elsewhere in Syria.

Tajikistan

Bacterial Diseases. The Laboratory of Immunoregulation (NIAID), Harvard Medical School, Boston, the Institute of Immunology, Moscow, Russia, and Clinical Research Consultants, Basel, and WHO, Geneva, Switzerland, reported on the ongoing epidemic of multidrug-resistant typhoid fever in Tajikistan. More than 90% of *Salmonella typhi* isolates are multidrug resistant. Furthermore, 82% of recent isolates are also resistant to ciprofloxacin. This finding is the first documentation of quinolone-resistant typhoid fever.

Tanzania

Harvard University/Boston ICIDR. NIAID made this new ICIDR award to support joint research with Harvard School of Public Health on the interaction of nutritional and immune status with the epidemiology of tuberculosis in Tanzania.

AIDS. Harvard School of Public Health and Muhimbili Medical Center, Dar es Salaam, conducted a randomized, double-blind, placebo-controlled trial in which vitamin A supplements reduced mortality rates in HIV-positive children in Tanzania.

Parasitic Diseases. Duke University Medical Center, Durham, North Carolina, and Muhimbili Medical Center, Dar es Salaam, reported that Tanzanian children with cerebral malaria demonstrated decreased nitric oxide production, whereas children with subclinical infection had increased production that correlated inversely with plasma levels of IL-10.

Thailand

Johns Hopkins Schools of Hygiene and Public Health/Baltimore HIVNET

Epidemiology. This HIVNET found that, in populations with high rates of HIV transmission and incomplete follow-up, estimates of incidence using p24 antigen prevalence among HIV-negative subjects could give useful and economical estimates of HIV incidence. This approach permitted estimates of whether the incidence rates are similar in subjects with successful follow-up and those lost to follow-up.

Risk factors. The HIVNET determined that Thai men who have sexual activity with men are at greater risk of HIV infection than heterosexual men. In addition, because most Thai men who have sexual activity with men also have sexual activity with women, they represent a potential "bridge" population.

Cofactors. In HIVNET prospective studies of Thai military recruits, infection with *Haemophilus ducreyi*, herpes simplex virus type 2, or both organisms at entry to the study were markers for high-risk sexual behavior and risk factors for HIV infection in young men.

Heterosexual transmission. With CDC, the HIVNET showed a direct correlation of viral load levels to transmission of HIV from HIV-positive men to HIV-negative women. The investigators concluded that strategies to reduce the viral load and prevent STDs could reduce the rates of HIV transmission in northern Thailand.

In Thailand, men constitute 85% of all blood donors, and they have higher HIV rates than women do. HIV prevalence in male donors peaked in 1991–1993 and has decreased since then. The prevalence of HIV in female donors, however, has steadily increased as a result of heterosexual HIV transmission.

Prevention. The HIVNET evaluated the acceptability of topical microbicides in Thailand and found less acceptance than in Africa. The researchers attributed this finding to the less frequent use of vaginal tightening agents in Thailand. The HIVNET is working with the Research Institute for Health Sciences, Bangkok, to implement a phase I study of BufferGel, a vaginal microbicide.

Vaccine studies. In collaboration with Walter Reed Army Institute of Research, Rockville, Maryland, and the Thai Ministry of Public Health, the HIVNET determined the feasibility of organizing community cohorts for HIV-1 vaccine trials in northern Thailand. The researchers concluded (1) that these cohorts could be organized but would have to include large numbers of patients and offer tangible benefits to participants and (2) that the effort would require considerable community support and involvement and active collaboration among a number of Thai and U.S. institutions.

Hepatitis viruses. With CONRAD, Atlanta, Georgia, the HIVNET found that HIV-1 prevalence among regular female partners of HIV-1–positive blood donors in northern Thailand was high (50%) and, furthermore, was associated with active HBV infection.

Reduction of HIV/AIDS and STDs. Although studies have shown a decreasing prevalence of HIV and STDs in Thailand for several years, the HIVNET data show a dramatic decrease in STD incidence rates, including HIV infection (from 2.48 to 0.55 per 100 person-years) in young men entering military service in northern Thailand in 1993–1995 compared with 1991–1993. The greatest risk for this group was inconsistent use of condoms. Earlier risk factors, such as intravenous substance abuse, frequent brothel visits, and low socioeconomic status, were no longer significant risks.

Columbia University/New York City ICIDR. This ICIDR supports joint research with George Washington University, Washington, D.C., Pennsylvania State University Medical Center, Hershey, and Mahidol University, Bangkok, on the management of severe malaria in Thailand.

Management of severe malaria. In FY 99, the ICIDR examined the stage of the parasite and ultrastructural sites of action of two new desferrithiocin derivatives—(β,β)-dimethyl-(*S*)-dmDFG and *N*-methylhydroxamate of (*S*)-dmDFG. The first derivative is active on the late trophozoite to early schizont stages of *Plasmodium falciparum*; the second derivative is active on the early trophozoite stages. The ICIDR studies demonstrate that desferrithiocin-based iron chelators have potent antiplasmodial effects and deserve further evaluation as antimalarial drugs.

Malaria pathogenesis. The ICIDR, Case Western Reserve University, Cleveland, and Tokai University, Isehara, Japan, examined the role of the hemoglobin E trait, which is common in Thailand, in the severity of falciparum malaria in patients treated in Bangkok. The scientists found evidence that hemoglobin E may ameliorate the clinical course of acute malarial infection.

Johns Hopkins Schools of Hygiene and Public Health/Baltimore ICIDR. In FY 99, NIAID made this new ICIDR award to support collaboration with Chiang Mai University on the epidemiology of HCV in Thailand.

University of Massachusetts/Worcester Dengue Program Project. This Program Project is studying the mechanisms of immunopathology in dengue hemorrhagic fever and dengue shock syndrome. The University of Massachusetts is working with Queen Sirkit National Institute for Child Health, the Armed Forces Institute of Medical Sciences, and Siriraj Hospital, Bangkok, and Kamphaeng Phet Provincial Hospital.

Immunology. The Program Project documented decreased T-cell proliferative responses in children with acute dengue fever.

AIDS. With independent grants from NIAID and the National Institute on Drug Abuse (NIH), the HIVNET showed that the genetic diversity of subtype E of HIV-1 envelope sequences in Thailand appears to be increasing in study subjects. This finding suggests that vaccine candidates eliciting immune responses to the conserved regions of the HIV-1 envelope protein may have greater potential for success.

In coordination with the HIVNET, Johns Hopkins School of Hygiene, Baltimore, manages a research contract to study the use of hormonal contraception and the risk of acquiring HIV infection in northern Thailand.

Trinidad and Tobago

University of Maryland/Baltimore HIVNET. In collaboration with Vanderbilt University, Nashville, Tennessee, the HIVNET is developing a protocol to perform a phase I–II evaluation of the safety, immunogenicity, and reactogenicity of a two-step HIV immunization. This procedure consists of a recombinant canarypox primer, followed by a gp120 booster shot.

University of Notre Dame/South Bend TDRU. This TDRU and the Ministry of Health of Trinidad and Tobago used restriction fragment length polymorphism markers to establish families in *Aedes aegypti* mosquitoes collected in Trinidad and Tobago.

University of Wisconsin/Madison TDRU. This TDRU, the University of Notre Dame, South Bend, Indiana, and the Ministry of Health of Trinidad and Tobago are studying the molecular and population genetics of resistance to insecticide in *A. aegypti*, the mosquito vector of yellow fever.

AIDS. Taking advantage of the HIVNET, the University of Maryland, Baltimore, and the University of the West Indies, Port of Spain, established a cohort of high-risk patients, in an effort to study host–virus interactions during acute HIV infection and to identify correlates of the immune response. NCI (NIH), Duke University Medical Center, Durham, the University of Maryland Medical Center, Baltimore, and the University of the West Indies documented the primary cellular immune response during acute HIV infection and are monitoring the relationship between helper T-cell responses and viral load. NCI, Duke University, and the University of the West Indies are also monitoring patterns of clinical, virological, and immunologic markers of acute HIV-1 seroconversion.

Vector Biology. The University of Illinois, Urbana, and the Ministry of Health of Trinidad and Tobago reviewed more than 200 cases of malaria reported in Trinidad and Tobago in 1968–1997. The researchers identified a cluster of *Plasmodium vivax* associated with *Anopheles aquasalis* in 1990–1991 and an outbreak of *Plasmodium malariae* transmitted by *Anopheles bellator* and *Anopheles homunculus* in 1994–1995. They then used a global positioning system and a global information system to map the precise location of these and other cases of cryptic infection and to associate them with breeding habitats of potential anopheline mosquito vectors. Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana, and the Ministry of Health investigated the *P. malariae* cluster. The scientists found that a significant number of infected persons had been born after Trinidad had been certified free of malaria 30 years earlier. Examination of nearby residents showed that 12.9% had *P. malariae* titers higher than 1:256.

Immunology. Brigham and Women's Hospital, Boston, and the University of the West Indies, Port of Spain, are collaborating in studies on the cellular basis of hypersensitivity of U.S. and Trinidadian inner-city populations.

Tunisia

Institut Pasteur/Tunis MERC. The MERC and University of Texas Health Sciences Center, San Antonio, examined the immunologic determinants of localized cutaneous leishmaniasis due to *Leishmania major* in Tunisia. The investigators concluded that an unfavorable outcome was not due to an inadequate helper T-cell response but most likely to the inhibition of the macrophage-activating effect of IFN-γ by concomitant expression of IL-10.

Turkey

Hebrew University of Jerusalem MERC. This MERC, the Royal Institute of Tropical Medicine, Amsterdam, the Netherlands, and Ege University, Izmir, conducted a comparative analysis of serological, molecular biological, and parasitologic procedures to study the epidemiology of canine visceral leishmaniasis in western Turkey, where human visceral leishmaniasis is endemic. Anti-*Leishmania* antibodies were found in 5.3% of dogs and confirmed by parasitologic (65%) or PCR detection (77%) in lymph node aspirates of seropositive dogs. The researchers concluded that canine visceral leishmaniasis is widespread and that the available serodiagnostic tests are valuable for monitoring infection in dogs.

Bacterial Diseases. The University of California, San Francisco, and Hacettepe University, Ankara, are evaluating a β-lactam antibiotic (amoxicillin–clavulanate) in patients with tuberculosis. The researchers found activity comparable to that of other antituberculosis agents.

Parasitic Diseases. Chicago Medical School, Illinois, used the *Leishmania*-specific ELISA test for recombinant K39 antigen to identify cases of visceral leishmaniasis in dogs and found an association in villages with human cases of kala-azar but no cutaneous leishmaniasis. Chicago Medical School, Cukorova University, Adana, and Ege University, Izmir, have identified considerable *Leishmania* heterogeneity in different geographic areas of Turkey and have predicted multiple clinical and epidemiologic patterns of disease in human and animal populations.

Immunology. The University of Virginia, Charlottesville, and Ankara University also identified a fungal allergen–specific IgE antibody in patients with atopic dermatitis.

Uganda

Case Western Reserve University/Cleveland CFAR. This CFAR is supporting a study of HIV-positive women in Uganda, to determine the influences of STDs, hormonal contraceptives, and other factors on HIV infectivity.

Case Western Reserve University received a separate award to work with Makere University, Kampala, to conduct a phase II–III randomized, double-blind, three-arm study to evaluate the safety of, tolerance to, and optimal dosage of HIV immunoglobulin in pregnant women and its effect on HIV transmission from mother to infant.

Case Western Reserve University/Cleveland HIVNET. This HIVNET supports collaboration with the Ugandan Ministry of Health and Makere University, Kampala.

Host immune response. With Massachusetts General Hospital, Boston, the HIVNET has documented that non–B clade HIV-1 infection can induce virus-specific CTL and proliferative responses that are cross-reactive with clade B.

Sexually transmitted diseases. The HIVNET determined that risk assessment involving score-based clinical decision models that incorporate socioeconomic and other factors predictive of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection may represent affordable alternative methods for diagnosis and screening for these conditions among women in resource-poor settings.

Mother-to-infant transmission. This HIVNET has completed a phase I–II study of nevirapine to determine the safety, tolerance, bioavailability, and pharmacokinetics of a single dose, in three cohorts of HIV-1–positive pregnant women during labor.

Vaccine evaluation. With evidence of cross-clade immune responses, the HIVNET moved forward with phase I evaluation of clade B–based canarypox vaccine in HIV-negative, uninfected adult volunteers in Uganda. The HIVNET explored the feasibility of recruiting Ugandan adults to participate in a randomized, placebo-controlled trial of HIV-1 vaccine. The researchers found that, after initial motivation of the adults to participate, enthusiasm waned during the approval process.

Johns Hopkins School of Medicine/ Baltimore HIVNET. This HIVNET provides support for cooperation with the Mulago General Hospital, Kampala, to reduce HIV transmission from mother to infant and in HIV-discordant couples.

Reduction of mother-to-infant HIV transmission. This HIVNET has completed a phase I–II trial of HIV immunoglobulin for prevention of HIV-1 vertical transmission in Uganda. HIV immunoglobulin was safe and well tolerated and had a long half-life at all three doses evaluated, but few virological or immunologic effects were observed immediately after infusion. The sample size was too small to support any conclusions about efficacy.

The HIVNET had previously performed a study to assess the efficacy of a short course of AZT from 37 weeks' gestation to delivery, in preventing mother-to-infant HIV transmission. The investigators then evaluated changes in viral load after discontinuation of AZT and found that there were variable changes in plasma HIV-1 RNA levels from initiation to termination of therapy, but that, overall, the postpartum viral load increased and there was no significant overshoot response in the viral load on termination of AZT monotherapy.

This HIVNET was a lead institution in the historic trials of administration of a single dose of nevirapine to reduce mother-to-infant HIV transmission. Interim results suggest that a single oral dose of nevirapine given to an HIV-positive woman in labor and another to her newborn within 3 days of delivery reduced the transmission rate (13.1%) more than a more elaborate, much more expensive short course of AZT (25.1%). Application of this finding on a large scale could be a major breakthrough, with the potential to prevent 300–400,000 HIV infections in newborns worldwide each year.

Studies of HIV-discordant couples. The HIVNET is developing a protocol for a phase I study of interventions to increase the use of condoms by HIV-discordant couples. The researchers also are working on a protocol to evaluate the impact of oral contraceptives alone versus oral contraceptives plus parenteral progestin as risk factors for HIV acquisition.

Columbia University/Johns Hopkins University Rakai STD/HIV Project. NIAID has provided funding through Columbia University, New York City, for the Laboratory of Immunoregulation (NIAID) to collaborate with Makere University, Kampala, and the Uganda Virus Research Institute, Entebbe, in the Rakai STD/HIV Project. The Rakai Project is a randomized, controlled, single-blinded, community-based trial to examine the hypothesis that control of STDs would result in lower incidence of HIV-1 infection than in control communities. Ten communities in the Rakai District were assigned randomly to intervention or control groups. The baseline prevalence of HIV was 15.9%. Study participants were villagers aged 15–59 years. The treatment groups received azithromycin, ciprofloxacin, and metronidazole, and the control groups received vitamins and antihelminthic drugs. As expected, STDs were reduced in the treatment villages. However, the incidence rate of HIV-1 was 1.5 per 100 person-years in both treatment and control communities. The investigators concluded that, in Rakai, where HIV infection was extremely common, a substantial proportion of HIV-1 acquisition occurred independently of treatable STD cofactors.

In Rakai, adolescents and young women remain vulnerable to HIV infection despite educational programs and subsequent behavioral change in the general population, indicating a need for more innovative educational and prevention approaches.

The Project determined that sexual coercion occurs frequently in Rakai and that resistance to coercion is often falsely perceived as an indicator of HIV seropositivity in both the woman and her partner.

A randomized trial of STD control during pregnancy, involving one-time single oral doses of azithromycin, cefiximine, and metronidazole, showed that the regimen was feasible and well tolerated and resulted in significant reductions in bacterial vaginosis, gonorrhea, chlamydia, urinary tract infection, neonatal gonorrhea and chlamydia infections, and low-birth-weight infants. With Walter Reed Army Institute of Research, Washington, D.C., the Rakai Project documented that, although single-dose treatment with antibiotics (azithromycin, ciprofloxacin, and metronidazole) at any time during pregnancy did not reduce incidence of maternal HIV, it did reduce maternal and infant STDs and improve pregnancy outcome.

In collaboration with Digene Corporation, Silver Spring, Maryland, the Project used a hybrid capture assay of self-collected vaginal swabs to detect HPV, in the Rakai District. The researchers concluded that this approach could be used to identify women with high risk of cervical neoplasia in this rural African setting.

Case Western Reserve University/Cleveland TBRU. This TBRU supports collaboration with Mulago General Hospital and Makere University, Kampala, in studies on the epidemiology, pathogenesis, risk factors, treatment, and prevention of tuberculosis in Uganda.

The TBRU is conducting a household contact study of patients with tuberculosis in Uganda, to further understanding of disease transmission and to attempt to identify correlates of the protective human immune response.

In addition, the TBRU conducted a prospective study of community-acquired bloodstream infections among febrile patients admitted to Mulago General Hospital. The investigators reported that, although the bulk of cases were due to pneumococci and gram-negative enteric bacilli, especially nontyphi *Salmonella*, the rate of mycobacteremia was 13.0%.

With Duke University, Durham, North Carolina, and Federal University of Espirito Santo, Vitória, Brazil, the TBRU determined that the induction of the antigen 85 complex of *Mycobacterium tuberculosis* in sputum is a determinant of outcome in treatment of pulmonary tuberculosis, independently of compliance. The TBRU reported that persistence of the antigen 85 complex of *M. tuberculosis* in sputum after 14 days of therapy was associated with poor outcome of therapy in studies in both Brazil and Uganda.

In HIV-positive persons in Uganda, tu-

berculosis was associated with an increased risk for death, especially when the CD4-positive T-cell count was higher than 200/mL. This finding suggests that presumptive tuberculosis chemoprophylaxis may be beneficial in areas with high prevalence of both diseases.

Makere University, Kampala, has collaborated with the TBRU in evaluating the importance of innate drug tolerance as a determinant of the outcome of tuberculosis therapy.

The TBRU showed that the addition of ethambutol in the continuation phase of direct observation of therapy for tuberculosis in HIV-positive patients is comparable to a standard regimen containing thiacetazone or a regimen containing rifampacin.

AIDS. Case Western Reserve University, Cleveland, Johns Hopkins School of Medicine, Baltimore, and Makere University Medical School, Kampala, found that the HIV-1 gp120 V3 region sequences from Ugandan infants remained similar to those in HIV-positive adults.

The University of Minnesota, Minneapolis, is collaborating with the Uganda Virus Research Institute, Entebbe, and Liverpool School of Tropical Medicine, England, to examine the efficacy of pneumococcal vaccine in HIV-positive Ugandan patients, to determine whether HIV infection is promoted by pneumococcal infection or vaccination and to determine why HIV-positive patients are at increased risk for pneumococcal disease.

Parasitic Diseases. During FY 99, NIAID made a new exploratory grant award to the University of California, San Francisco, to collaborate with Mulago General Hospital, Kampala, on molecular approaches to drug-resistant malaria. Michigan State University, Ann Arbor, and the Ugandan Ministry of Health carried out a prospective study documenting that comparatively low vector densities are capable of sustaining severe falciparum malaria epidemics in the southwestern highlands of Uganda.

Ukraine

Bacterial Diseases. The University of Washington, Seattle, and Bogomoletz Institute of Physiology, Kiev, identified predominant configurations of genes that regulate the human antibody response to capsule polysaccharide of *Haemophilus influenzae*.

United Kingdom

University of Washington/Seattle CASR. In cooperation with CDC, Washington University, St. Louis, Missouri, and Oxford University, England, the CASR reported that mixing patterns of sexual partners influence the risk of specific STD infections and should be considered in risk assessments for individuals and in the design of screening, health education, and notification strategies for populations.

University of California/San Francisco TDRU. The Babraham Institute, Cambridge, England, is cooperating with this TDRU in research to identify and characterize the primitive protease associated with excystation in *Giardia* eukaryocytic parasites.

Tufts University/Boston TDRU. This TDRU is working with Bath University, England, in research on the structure and function of protozoan sialidases.

AIDS. Aaron Diamond AIDS Research Center, New York City, New York, Los Alamos National Laboratory, New Mexico, and the University of Nottingham, England, sequenced various strains of HIV-1 and dated the origin of HIV-1 subtypes B, D, and F to around 1959.

NIAID supports an award to the Edward Jenner Institute for Vaccine Research, Newberry Berkshire, United Kingdom, to investigate the role of virus-specific CTLs in the control of human HIV-1 infections.

The University of North Carolina, Chapel Hill, Duke University Medical Center, Durham, University of Colorado Health Sciences Center, Denver, the University of Alabama, Birmingham, Royal Free Hospital School of Medicine, London, England, and Glaxo Wellcome, Greenford, England, found that the effects of AZT plus lamivudine in reducing plasma HIV RNA and raising peripheral blood CD4-positive T-cell counts were associated with concurrent clinical benefits.

NIAID made an award to Royal Free and University College Hospital, London, England, to perform an observational study to assess the virological and immunologic markers of imminent CMV disease in HIV-positive individuals.

Bacterial Diseases. Albert Einstein College of Medicine, Bronx, New York, the University of Pittsburgh, Pennsylvania, and Central Veterinary Laboratory, Surrey, England, developed a system using conditionally replicating mycobacteriophages to deliver transposons to *M. tuberculosis* and to generate libraries containing thousands of independent mutants.

Mycotic Diseases. The Laboratory of Infectious Diseases (NIAID), the University of Wales, Aberystwyth, and Sheffield Children's Hospital, England, purified and reconstituted antifungal drugs and showed that such drugs inhibit cytochrome P-450 sterol delta-22 desaturase from the pathogenic fungus *Candida glabrata*. The findings raise the possibility of developing new drugs targeted to inhibit this cytochrome.

Parasitic Diseases. The University of Michigan, Ann Arbor, the University of Cincinnati College of Medicine, Ohio, Indiana University Medical Center, Indianapolis, and Oxford University and the London School of Hygiene and Tropical Medicine, England, identified variations in the sequence of the gene for cytochrome *b* in *Pneumocystis carinii*.

Pace University, New York City, and Roswell Park Cancer Institute, Buffalo, New York, and the University of Wales, Cardiff, identified a unique transporter of *S*-adenosylmethionine, a metabolite used in transmethylation reactions and polyamine synthesis in African trypanosomes that is not blocked by existing antitrypanosome drugs.

Viral Diseases. St. Jude Children's Research Hospital, Memphis, Tennessee, and Glaxo Wellcome Research and Development, Stevenage, England, characterized the H5N1 influenza virus isolated in Hong Kong in a mouse model and determined that zanimivir, an antiviral drug, was effective in reducing lung titers of the virus, with resultant lowering of morbidity and mortality. The Laboratory of Clinical Investigation (NIAID) participated in a multicenter study cosponsored by Hoffmann-La Roche and Company, Welwyn Garden City. The findings indicated that prophylaxis and early

treatment with oseltamivir, an oral neuraminidase inhibitor, were both associated with significant antiviral and clinical effects in experimental human influenza.

Uruguay

Bacterial Diseases. The University of Washington, Seattle, and the University of Montevideo described, for the first time, a complete conjugative transposon carrying an antibiotic resistance gene for the genus *Neisseria*. The University of Montevideo, Emory University School of Medicine, Atlanta, Georgia, and the Veterans Affairs Medical Center, Decatur, Illinois, discovered decreased azithromycin susceptibility of *N. gonorrhoeae* due to mtrR gene mutations.

Venezuela

University of Texas Medical Branch/Galveston EVC. This EVC is working with CDC and Rafael Rangel National Institutes of Health and University City, Caracas, on the molecular mechanisms behind the emergence of zoonotic viral pathogens such as dengue fever and Venezuelan equine encephalitis (VEE). The EVC, the USDA Center for Animal Disease Information, Fort Collins, Colorado, the National Institute of Health, Bogotá, Colombia, and Central University of Venezuela, Caracas, are investigating the genetic and phenotypic changes accompanying the emergence of epizootic subtype IC VEE viruses from an enzootic subtype ID progenitor.

The EVC and the National Research University of the Western Llanos and the Ministry of Health and Social Assistance, Guanare, documented that *Sigmodon alstoni* and *Zygodontomys brevi-cauda* are rodent reservoirs of Guanarito and Pirita viruses, two closely related arenaviruses endemic to the central plains of Venezuela.

AIDS. The University of California, Davis, and the University of the Andes, Mérida, Venezuela, have evidence that HIV-1 can produce direct functional neutrophil damage through binding of envelope components to the cell membrane.

Parasitic Diseases. The University of Maryland School of Medicine, Baltimore, CDC, and the Dr. Arnoldo Galbadon School of Malariology and Environmental Health, Maracay, found multiple point mutations in dihydrofolate reductase and dihydropteroate synthase genes of *Plasmodium falciparum* parasites in Venezuela. These findings suggest that the cumulative effect of mutations could account for the observed high levels of drug resistance to sulfadoxine–pyrimethamine.

Harvard School of Public Health, Boston, Massachusetts, and the Civil Association for the Investigation and Control of Endemic Diseases in the Amazon, San Antonio, Venezuela, reported that vivax malaria was prevalent but caused clinical disease primarily in Yanomami Amerindian children, whereas falciparum malaria was infrequent but caused epidemics in all ages. The investigators discovered that even partially effective chemotherapeutic interventions interrupted serial transmission of *P. falciparum* in these isolated populations.

Vector Biology. The University of Texas Medical Branch, Galveston, Central University of Venezuela, Caracas, and the University of Carabobo, Aragua, conducted morphogenetic studies of *Lutzomyia longipalpis* sand flies in Venezuela and have evidence for at least two distinct species.

Viral Diseases. The Southwest Foundation for Biomedical Research, San Antonio, Texas, Walter Reed Army Institute of Research, Washington, D.C., the National Institute of Public Health, Cuernavaca, Mexico, the Ministry of Health and Social Welfare, Caracas, and Central Hospital of Maracay used molecular biology to identify structural differences in the dengue virus type 2 that correlate with the pathogenesis of dengue fever and dengue hemorrhagic fever.

The University of Texas Medical Branch, Galveston, and Central University of Venezuela and the Ministry of Health and Social Assistance, Caracas, used satellite imaging to identify actual and potential sites of enzootic VEE.

Yugoslavia

Vaccine Development. Rockefeller University, New York City, the Basel Institute of Immunology, Switzerland, and the Institute for Molecular Genetics and Genetic Engineering, Belgrade, found that in the late stages of B-cell development there is continued expression of the recombination-activating gene (RAG) but no apparent reinduction of expression after immunization.

Zambia

University of Alabama/Birmingham HIVNET. The HIVNET collaborates with University Teaching Hospital and the Ministry of Health, Lusaka, and the Tropical Disease Research Center, Ndola. The core focus of the HIVNET is research on heterosexual HIV transmission and natural history in 650 couples who are discordant for HIV. In FY 99, the HIVNET became a participant in the NIAID Acute Infection and Early Disease Research Network.

During FY 99, the HIVNET and the Tropical Disease Research Center, Ndola, conducted a comparative analysis of commercial PCR assays for the quantification of plasma HIV-1 RNA in patients infected with HIV-1 subtype C. The scientists concluded that the assays were capable of detecting this clade and that the results of the various assays were strongly correlated with each other.

This HIVNET is supporting a phase IIA study of escalating doses of chlorhexidine, a topical microbicide, for intrapartum vaginal cleansing and postpartum cleansing of the newborn to prevent transmission of HIV infection from mother to infant. The HIVNET is developing a phase I clinical trial to study the safety of nevirapine and the plasma concentrations when the drug is given to breast-feeding infants daily, twice a day, or weekly as prophylaxis for HIV.

AIDS. The University of Alabama, Birmingham, has a collaborative agreement, separate from the HIVNET, to support participation in a network for research on acute HIV infection and early detection in Zambia.

The University of Texas Schools of Medicine and Public Health, Houston, Royal Free and University College Hospital, London, U.S. Naval Medical Research Unit No. 3, Cairo, Egypt, and University Teaching Hospital, Lusaka, conducted community-based studies that showed a close association between acute diarrheal disease and HIV seropositivity in Zambian adults. The University of Texas Schools of Medicine and Public Health and the University of Zambia Medical School, Lusaka, documented a similar association between weight loss in HIV-1–positive children and adults and chronic diarrhea.

Parasitic Diseases. The Macha Mission Hospital, Choma, was the field site of studies conducted by George Washington University, Washington, D.C., Pennsylvania State University, Hershey, Case Western Reserve University, Cleveland, Moorhead State University, Minnesota, Utrecht University, the Netherlands, the University of Witwatersrand, Johannesburg, South Africa, and the University of Zimbabwe, Harare, to evaluate the effect of a loading dose of parenteral quinine in children with cerebral falciparum malaria. Children who received a loading dose on hospital admission recovered faster, experienced enhanced parasite clearance, and became afebrile more rapidly than control children treated with the conventional dosage regimen. The Macha Mission Hospital also was the site of studies by Allegheny University of the Health Sciences, Philadelphia, Pennsylvania, George Washington University, the University of Witwatersrand, and Ajinomoto Company, Inc., Tokyo, Japan, to compare the efficacy of curdian sulfate, a sulfanated glucan, with that of chloroquine in the treatment of asymptomatic moderate malaria. The treatment groups received curdian sulfate or chloroquine alone or in combination.

Viral Diseases. The University of Nebraska, Lincoln, the University of Miami School of Medicine, Florida, and University Teaching Hospital, Lusaka, found high levels of HHV-8 in both HIV-positive and HIV-negative Zambian women and speculated whether the high prevalence of HHV-8 might be a contributing factor to the increased frequency of Kaposi's sarcoma in this population.

Zimbabwe

Stanford University HIVNET. This HIVNET collaborates with Rockefeller University, New York City, the University of Washington, Seattle, and the University of Zimbabwe, Harare, on studies of HIV/AIDS in adult heterosexual populations in Zimbabwe.

Viral characterization. HIVNET assays of HIV gene sequences demonstrated that subtype C predominates in Zimbabwe. The majority of men recently infected with HIV-1 clade C had a history of a recent episode of an STD and fever before seroconversion. RNA levels of HIV isolates correlated with in vitro infectivity in peripheral blood mononuclear cells. Recent subtype C conversion in Zimbabwe, therefore, demonstrated clinical and virological features similar to those in seroconversion to subtype B in North America.

Studies of factory workers. The independent risk factors for acquisition of HIV infection in a cohort of low-risk urban factory workers were age (25–44 years), marriage, STDs, urethral discharge, multiple sexual partners, cash payment for sex, and inconsistent use of condoms. The HIVNET documented a high incidence and prevalence of HIV infection among monogamous wives of male factory workers; although each husband had at least one of these risk factors, the men considered themselves to be at low risk of HIV infection. The paradox of marriage being a risk factor could be attributed to separation from spouses who reside in rural areas, and the inconsistent use of condoms is associated with multiple sexual partners. The researchers reported that workplace-based peer education provided an effective and affordable HIV prevention program for industrial workers in Zimbabwe. Furthermore, employers were willing to bear much of the cost of sustaining the peer education because they recognized the benefits of decreased worker absences, illnesses, turnover, and death benefits.

With the San Matteo Polyclinic, Pavia, Italy, the HIVNET compared the frequency of gb genotypes 1–4 of human CMV in HIV-positive heterosexuals in Zimbabwe, intravenous drug users and homosexual men in Italy, and homosexual men in California. The gb2 genotype was increased in Italian homosexual men, as was the gb3 genotype in Italian intravenous drug users.

Preliminary information on recent HIV-1 seroconversion is that men in this population of factory workers that is at low risk for HIV have more rapid decline in CD4-positive T cells and consequent immunosuppression than men in developed countries. This observation may be due to a subset of HIV-1 that progresses more rapidly or a shorter natural history of HIV-1 infection in this population.

Mother-to-infant HIV transmission. During FY 99, the HIVNET reported that maternal level of HIV is an important determinant of vertical transmission and infant mortality in subtype C infection in Zimbabwe.

HIV prevention. This HIVNET participated in a multicenter study to determine the acceptability of a phase I safety and efficacy study of one or more topical microbicides in various African and Asian settings. Male and female participants had definite opinions about the characteristics of a topical microbicide that they would or would not like, but they expressed an overall willingness to try different products under consideration for future efficacy trials. The HIVNET is carrying out a phase III study of nonoxynol 9, a topical microbicide, as a means of preventing HIV transmission. In addition, the HIVNET is participating in a study to evaluate BufferGel, a topical microbicide.

The HIVNET is also a participant in a phase I study to assess the safety and plasma concentrations of nevirapine administered daily, twice a week, or weekly as prophylaxis against HIV in infants from birth to 6 months of age.

Taiwan

Vector Biology. Michigan State University, East Lansing, and the National Yang-Ming University, Taipei, reported that molecular characterization of the mosquito vitellogenin receptor reveals an unexpected high homology to the *Drosophila* yolk protein receptor.

Immunology. Scientists at the University of California, San Diego, Scripps Research Institute, La Jolla, California, Vanderbilt University, Nashville, Tennessee, and Veterans General Hospital, Taipei, concluded that C4A null alleles predispose strongly to the development of systemic lupus erythematosus, whereas the contributions of genes for weak susceptibility (e.g., hv3005) may be obscured by the stronger factor.

Picower Institute for Medical Research, Manhasset, New York, Monash Medical Center, Victoria, Australia, Sun Yat-Sen University of Medical Sciences, Ghongzhou, China, and the National Yang-Ming University, Taipei, reversed established crescentic glomerulonephritis in rats by blockading macrophage migration-inhibitory factor and are exploring the potential role of this factor in regulation of glucocorticoid production.

Activities With International and Multinational Organizations

Pan American Health Organization and World Health Organization

University of Maryland/Baltimore ICIDR. PAHO/WHO worked with this ICIDR in clinical studies of the immunogenicity of Cuban and Norwegian vaccines containing outer-membrane protein of *Neisseria meningitidis* type B. The vaccines are being used against a heterologous epidemic in Chile.

AIDS. PAHO is a partner in NIAID-funded clinical studies of HIV/AIDS in Brazil and the Caribbean.

PAHO/WHO is cooperating with the Ministry of Health, Kingston, Jamaica, the London School of Hygiene and Tropical Medicine, England, and the University of Alabama, Birmingham, on studies of HIV and HTLV-I incidence in STD clinic patients in Jamaica.

Bacterial Diseases. PAHO/WHO is also collaborating with Adolfo Lutz Institute, São Paulo, Brazil, Rockefeller University, New York City, and the University of Pennsylvania, Philadelphia, in the project on Surveillance of Invasive *Streptococcus pneumoniae* in Brazil, which identifies and characterizes penicillin-resistant strains of the bacteria.

World Health Organization

Parasitic Diseases. Prototek, Dublin, California, is receiving NIAID support to evaluate the effectiveness of protease inhibitors in the treatment of parasitic diseases, such as Chagas' disease and malaria. If promising protease inhibitors are identified, Prototek will submit them to WHO for approval of further clinical trials, which would be conducted in collaboration with another pharmaceutical firm.