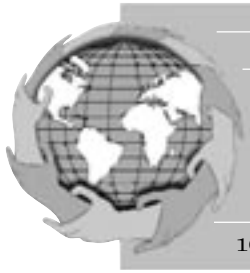

TROPICAL DISEASES

OVERVIEW

Diseases, like poverty, are not distributed uniformly among people and countries. Infectious diseases impose a particularly heavy burden on the people of developing countries, where the risk of death from infectious causes is 10 times greater than in industrialized nations. These diseases account for approximately one-half of all deaths in the tropical areas of the world, with most of them occurring among children younger than 5 years of age. Infectious diseases that are primarily found in the developing world or predominantly affect the health of people living in the tropics are frequently referred to as *tropical diseases*.

Infectious diseases are the second leading cause of death worldwide and the third leading cause of death in the United States. In addition to their impact on health, these diseases reduce economic productivity, consume valuable and scarce resources for health care, and impair the quality of life for individuals, communities, and nations. In developing countries, death and disability caused by infectious diseases can have a profound negative effect on issues such as economic development and political stability that are of worldwide concern. The impact of infectious diseases endemic to the tropics extends beyond developing countries in other ways. As a result of increased international travel for pleasure and commerce, tropical diseases pose a threat to increasing numbers of individuals from the United States and other industrialized countries. Diseases such as tuberculosis and certain arboviral and enteric infections have reemerged in this country, and there is the potential that other tropical diseases may emerge or reemerge in developed areas.

CAUSES OF TROPICAL DISEASES

What are the organisms that cause tropical diseases? Many are *bacteria* and *viruses*, infectious agents that may be familiar to most people because they cause illnesses common in the United States. Less well known are organisms that cause diseases that are more common in developing countries. These less familiar organisms include *parasites*, which live within or on another organism, or host, at whose expense they obtain some advantage such as nourishment or a protected environment. Parasites can range from microscopic single-celled organisms called *protozoa* to 3-foot-long multicellular organisms called *helminths* (commonly referred to as worms).

In the tropics, as in temperate zones, many diseases are spread directly from person to person, by airborne routes of transmission, or by sexual contact. However, in tropical

areas, diseases also are often spread by contaminated water and food sources because clean water and sanitary conditions are often a luxury in developing countries. Some tropical disease agents are transmitted by an intermediate carrier or *vector*, such as a mosquito. The insect or other vector picks up the infectious organism from an infected person or animal and transmits it to others in the process of feeding.

At one time, many of today's tropical diseases also occurred in temperate regions, since many of the same risk factors were found there. Today, however, industrial development and technological advances, including medical ones, have lessened the impact of these diseases in industrialized countries. For example, malaria (a parasitic disease causing fever, anemia, coma, and death) was once widespread in the United States. Due to improvements in land management and mosquito control, the disease is no longer prominent in this country. Similarly, improvements in sanitation have reduced contact between humans and infectious agents that are transmitted through contaminated food or water. Unfortunately, these improvements have not yet been successfully implemented in large segments of the developing world.

MAJOR TROPICAL DISEASES

Most Americans have probably never heard of many tropical diseases, even though a staggering half billion people, or 1 in 10 of the world's inhabitants today, suffer from these afflictions. Some of the most common and serious tropical diseases are described in the following pages.

Parasitic Diseases

Malaria

The sheer numbers of people affected by malaria make it one of the most intimidating tropical diseases facing humanity. Approximately 300 to 500 million people are infected with malaria parasites annually. More than 40 percent of the world's population lives in an area where there is risk of contracting the disease. Every year, approximately 1.5 to 3 million people die from malaria. Many of these deaths are among children living in sub-Saharan Africa.

Malaria is caused by protozoa from the genus *Plasmodium*. Each of the four species of malaria parasite that infect man causes a somewhat different form of the disease. Malaria caused by *P. falciparum* is the most dangerous form and accounts for the overwhelming majority of deaths. Unless appropriately treated, it can produce several life-threatening complications, including profound anemia, respiratory distress, and coma.

The parasites are transmitted to humans by female mosquitoes, which require nutrients from blood to make eggs. When the mosquito takes a blood meal on the host, she injects the parasites along with her saliva. The parasites migrate first to liver cells, where they undergo further development and multiplication. Upon release from liver cells, they infect red blood cells (erythrocytes), where they consume hemoglobin, the oxygen-carrying

component of the blood. The parasites divide in the red cell, and at the completion of development, the red cell ruptures, releasing parasites that can infect many other erythrocytes. Thus, the typical symptoms of malaria are cycles of chills, fever, and sweating caused by the host response to periodic red cell rupture and exposure to parasite materials.

In 1955, the World Health Organization (WHO) began an extensive campaign, using insecticides and drugs, to eradicate malaria. Despite a number of dramatic successes, the objective proved elusive. Mosquitoes not only modified their behavior to avoid coming into contact with insecticides, but actually developed resistance to these chemicals. Parasites also became resistant to the widely used drug chloroquine and other antimalarials. Mounting evidence shows that malaria is once again gaining the upper hand. Areas that have been free of malaria have been experiencing outbreaks, and the number of cases has been rising alarmingly in the Amazon and parts of Asia, especially Southeast Asia.

At one time, malaria was a serious health problem in the United States; in 1914, more than 600,000 cases of malaria occurred here. Although improved public health led to a substantial decline in the following decades, minor resurgences occurred as troops returned from both the Korean and Vietnam wars. In 1997, more than 1,500 cases of malaria were reported to the U.S. Centers for Disease Control and Prevention, six of which were fatal. Not all of these cases were "imported" (acquired outside the United States); some were recent infections acquired within the United States following the bite of indigenous mosquitoes. Recently, cases of locally transmitted malaria have appeared in regions as diverse as California, Florida, New Jersey, New York, Texas, and Michigan.

Schistosomiasis

Egyptian hieroglyphics and evidence of parasites in 3,000-year-old mummies document the lengthy association between humans and the organism that causes schistosomiasis. The disease is caused by several species of flatworms of the genus *Schistosoma*. Approximately 200 million people are infected with the parasite worldwide, with three times as many individuals at risk for infection. An estimated 200,000 people die every year from schistosomiasis; many more suffer chronic damage to vital organs, including the liver and bladder.

Although this parasite's life cycle also involves an invertebrate host, the parasite is not transmitted through the bite of an insect, but rather develops within freshwater snails. After exiting from the snail vector, schistosome larvae swim along until they contact a human host bathing or working in the water. They penetrate the skin and subsequently migrate through the blood vessels until finally establishing residence in veins of the intestines or urinary bladder, depending on the parasite species. The adult male and female worms pair, mate, and produce large numbers of eggs, some of which are excreted in either feces or urine and end up in the water supply, where they hatch and complete the cycle by infecting new snail hosts.

The adult worms do not cause the most common manifestations of schistosomiasis. That role belongs to eggs that are not excreted but instead become lodged in the body's tissues. In a process known as granuloma formation, masses of cells form around the eggs in an effort to destroy them. In so doing, however, these cells initiate a process of tissue scarring (fibrosis). In forms of the disease involving the liver and intestines, this scarring impedes blood circulation and can cause death due to rupture of distended blood vessels. In the form involving the bladder, the extensive scarring can result in obstruction of urinary outflow.

Schistosomiasis control, through either snail elimination or improved sanitation, has been difficult to achieve. Treatment of schistosomiasis has in recent years been greatly improved through use of the drug praziquantel, but reinfection remains a problem, and there is some evidence suggesting that resistance may eventually become an issue.

Leishmaniasis

Leishmaniasis is actually a group of diseases that are caused by infection with protozoa belonging to the genus *Leishmania*. Approximately 20 different species are transmitted to humans by the bite of infected female sandflies. In the mammalian host, the parasite is found within macrophages (immune system cells that destroy invading microorganisms). The remarkable ability of leishmanial parasites to evade the antimicrobial mechanisms of macrophages has attracted considerable scientific interest.

Like malaria, leishmaniasis is widely distributed over large portions of the tropical and subtropical areas of the world, including portions of southern Europe. WHO reports that 12 million individuals are infected and 300 million people are at risk in some 80 countries. Sandfly vectors are present in the United States, and human cases have been anecdotally reported in the Southwest. Reservoir hosts, such as dogs and rodents, play an important role in the distribution of the infection. Indeed, a recent outbreak of leishmaniasis has been reported in hounds within the United States. People contract leishmaniasis when their activities bring them into close association with sandflies. For example, workers in the forests of South America are frequently exposed.

Leishmaniasis takes many forms, depending on both host and parasite factors. Symptoms may range from self-healing skin ulcers to severe life-threatening disease. Cutaneous leishmaniasis, known locally by names such as Chiclero ulcer, Baghdad boil, Delhi boil, or Oriental sore, is manifested by skin lesions that usually resolve but may leave ugly scars. In some individuals, the disease spreads to the mucous membranes of the nose and mouth, resulting in hideous destruction of facial features. The most dangerous form is visceral leishmaniasis, where parasites invade the internal organs. This disease is commonly referred to as *kala-azar*, a Hindi term for black sickness, which describes the increased pigmentation of the skin. Symptoms include fever and weight loss. If left untreated, kala-azar invariably leads to death. Recent leishmaniasis epidemics in Sudan and India have highlighted the problem. Vector control is woefully inadequate, and

prophylaxis is nonexistent. The first-line drug for treatment contains antimony, a heavy metal that has harmful side effects and is not always effective.

Trypanosomiasis

The protozoa causing trypanosomiasis are closely related to leishmania parasites. In humans, different species of the genus *Trypanosoma* are responsible for diseases that are quite distinct in clinical outcome and in geographic distribution.

The New World form, Chagas' disease or American trypanosomiasis, caused by *T. cruzi*, affects approximately 18 million people living mostly in Latin America. The parasite is transmitted to humans by blood-sucking reduviid bugs, also known as kissing bugs, because of their predilection for feeding on the faces of their victims. Unlike malaria and leishmaniasis, the parasites are not injected during feeding; instead, they are deposited by defecating bugs. The parasite enters the host through the eyes, nose, or mouth or through breaks in the skin. Symptoms may appear as acute disease shortly after infection or as chronic disease years later. Acute disease involves fever, swelling of the lymph nodes, and sometimes inflammation of the heart muscle and the brain. Although the acute stage may be fatal, especially in children, most infected individuals survive and enter a long symptomless stage. One-quarter or more of these individuals will develop cardiac damage that may result in heart failure and sudden death; others may develop digestive disorders. *T. cruzi* infection is not limited to humans, and the presence of other infected mammals is sufficient to sustain the infection in nature. Control measures rely on limiting contact with infected bugs because prophylaxis and drug treatment are not effective. Vector-control methods involve insecticide spraying and eliminating the breeding grounds of the bugs. There is a major campaign in Latin America to eliminate Chagas' disease through vector control and improvements in housing construction. In areas where there are multiple vector species, however, these methods have proven difficult.

Unlike the parasites that cause Chagas' disease, the trypanosomes responsible for human disease in Africa, African trypanosomiasis or sleeping sickness, are transmitted to humans by the bite of tsetse flies. The parasites are closely related to trypanosomes that produce veterinary disease and prevent development of ranch lands in Africa, thereby depriving people of an important source of food. African trypanosomiasis affects some 25,000 people per year; however, epidemics involving many times that number are well known. Initial symptoms of sleeping sickness include fever, headache, dizziness, and weakness. Later, parasites invade the central nervous system, causing neurological and psychological problems such as loss of ability to concentrate, increased somnolence or other changes in sleeping patterns, speech and movement disorders, and seizures. Untreated patients may become comatose and die. A feature of parasite biology that has long intrigued scientists is the ability of these organisms to evade the immune response by a process known as antigenic variation. By means of a complex genetic mechanism that is being unraveled through basic research, the parasite is able to repeatedly change the protein that covers its entire surface, thereby staying one step ahead of the ability of the host immune system to recognize and react to it. The inability of the host to recognize

these new variants allows the parasite to survive for long periods of time. Only one new drug has been developed against sleeping sickness in 40 years, and this drug, eflornithine, is effective against only one form. The remaining drugs have limited effectiveness and significant toxicity.

Filariasis

Filarial diseases are rarely life threatening or acute. They are, however, extremely debilitating and disfiguring, and affected individuals become dependent on other people or limited health care resources. The roundworms that cause filariasis are related to the dog heartworm, which is well known to pet lovers in the temperate zones. Transmitted to humans by the bite of infected mosquitoes, filarial worms of the genera *Wuchereria* and *Brugia* cause lymphatic filariasis. One billion people live in areas where filariasis is found, and approximately 90 million people are estimated to have the disease. When the infected female mosquito feeds on humans, she injects larval stages of the parasite. These larvae migrate through the tissues and develop into adults that take up residence in the lymphatic system. Disease results from extensive obstruction and damage to the lymphatic system. The end result is frequently a buildup of lymph fluid in the limbs and sometimes the scrotal sac, which may cause the grotesque swelling known as elephantiasis, hanging groin, and hydrocele. Male and female worms mate to produce millions of progeny called microfilariae, which end up in the blood and serve to transmit the parasite back to the insect vector. Elimination of mosquito-breeding sites in urban areas of transmission helps to reduce the risk of infection. WHO recently initiated a Global Programme to Eliminate Lymphatic Filariasis based on annual community-wide treatment with two drugs (albendazole plus either diethylcarbamazine [DEC] or ivermectin) over the course of several years.

The form of filariasis known as onchocerciasis or river blindness, caused by *Onchocerca volvulus*, is transmitted by a group of insects known as blackflies, which breed in fast-moving rivers and streams. Some 90 million people are at risk for onchocerciasis in 36 countries, mostly in Africa and South America, and 18 million people are already infected. The adult forms of *O. volvulus* live under the skin, forming visible nodules. Most of the symptoms of the disease result from the migration of the larval stages (microfilariae) into the skin and eyes. Reaction to these stages leads to intense itching, disfiguring dermatitis, and damage to the eyes, including corneal scarring. Onchocerciasis is a frequent cause of blindness in the tropics, affecting well over 300,000 people. The Onchocerciasis Control Program has helped disease control in West Africa. The program is designed to eliminate the larval stages of the blackfly vector and coordinates the regular release of insecticides into the rivers and streams of 11 countries in the region. Ivermectin, a drug originally developed for veterinary use, has proven to be an effective treatment.

Intestinal worms

Hookworms infect approximately 900 million people and kill an estimated 60,000 each year. These bloodsucking intestinal roundworms can cause profound anemia and nutritional deficiencies, resulting in growth and developmental retardation in children. *Ascaris* worms are found in temperate as well as tropical regions. Indeed, they are probably the most common parasite in the world, infecting approximately 1 billion people. Although the mortality rate is relatively low (estimated at 20,000 per year), ascariasis can be debilitating, causing abdominal pain, malnutrition, and lack of weight gain in children and sometimes resulting in intestinal obstruction. Other intestinal roundworms are also prevalent in the developing world. *Trichuris* worms afflict approximately 750 million people and can cause anemia, abdominal discomfort, nausea, diarrhea, and weight loss. *Strongyloides* worms infect an estimated 80 million people and cause abdominal pain, nausea, and diarrhea. Given that many people living in tropical regions are infected with more than one of these parasites, it is easy to understand how they can affect the physical and mental development of children and the ability of adults to work.

Diarrheal Diseases

Cholera

Cholera is caused by infection with *Vibrio cholerae*, a bacterium most often found in contaminated water and shellfish. The bacterium produces a toxin that upsets the biochemical balance of cells lining the intestine, making them secrete copious amounts of water and electrolytes. Cholera is endemic in a number of tropical countries, and major epidemics break out periodically, such as the one that affected some 900,000 persons in South America between 1991 and 1993. Cholera is characterized by severe watery diarrhea that, left untreated, can result in serious dehydration and death. Treatment consists of replacement of lost water and salts.

E. coli and other bacteria

Many types of bacteria other than *Vibrio cholerae* can cause attacks of acute diarrhea, with symptoms lasting less than 2 weeks. These bacteria, including *Shigella, Campylobacter,* and *Salmonella,* are usually transmitted by the fecal-oral route. The seemingly ubiquitous *Escherichia coli*, which is present in soil, water, and vegetation and comprises a major component of the normal intestinal flora, can also cause serious illness. Strains of *E. coli* that cause gastroenteritis produce toxins, some of which function like the cholera toxin, that produce cramps, nausea, vomiting, and watery diarrhea. Enterotoxigenic *E. coli* (ETEC) is associated with the classic traveler's diarrhea. Far more serious disease is caused by the enterohemorrhagic strain of *E. coli* (EHEC), which produces different toxins as well as a factor that allows the bacteria to adhere tightly to the intestinal wall. This type of *E. coli* can cause not only bloody diarrhea but also kidney failure, especially in children and the elderly. EHEC has been found in unpasteurized milk and fruit juices, fresh vegetables or fruits, and undercooked ground beef and other meat products. The presence of this type of bacteria in undercooked

hamburgers resulted in widespread illness, leading to the deaths of four children, in the United States in 1993. It was more recently associated with an outbreak of diarrhea traced to unpasteurized apple juice.

Viruses

Rotaviruses cause watery diarrhea and vomiting, primarily in young children. These viruses are distributed worldwide, and transmission is usually due to contact with infected individuals or fecally contaminated objects. The majority of infections are self-limiting, but infant mortality is higher in developing countries and is generally associated with severe dehydration. As with cholera, treatment consists of replacing lost fluids and electrolytes. Other viruses causing acute gastroenteritis include astroviruses and caliciviruses. Disease caused by these agents usually resolves after a few days without serious consequences.

Parasites

Two parasitic infections that have recently come to widespread public attention in the United States are *Cryptosporidium parvum* and *Cyclospora cayetanensis*. These protozoan causes of enteritis with persistent diarrhea are usually acquired by ingestion of contaminated water or food. The first outbreak of cryptosporidiosis in a child care center was observed in 1983. In 1993, an outbreak associated with contaminated drinking water occurred in Milwaukee, Wisconsin, and affected some 403,000 people. Cryptosporidiosis causes especially severe diarrhea in AIDS patients. It has been estimated that 10 to 15 percent of the chronic diarrhea and wasting observed in AIDS patients in the United States is due to this infection, and it may account for as much as 30 to 50 percent of severe diarrhea in AIDS patients in developing countries. There is still no adequate treatment of cryptosporidiosis. Although probably discovered around the turn of the century, *C. cayetanensis* was actually characterized and named in the course of ongoing studies in Peru. Like cryptosporidiosis, our understanding of *Cyclospora* infection has been influenced by the AIDS epidemic and subsequent improvements in diagnosis. It appears that globally, *Cyclospora* affects approximately equivalent numbers of immunocompetent (with healthy immune systems) and immunosuppressed individuals. The emergence of this parasite as a problem in developed countries became widely recognized in the summer of 1996, when more than 1,500 cases were reported in Canada and in 14 U.S. States. Another waterborne protozoan, *Giardia lamblia*, which causes diarrheal disease, is also endemic in the United States.

The protozoan *Entamoeba histolytica*, which causes severe dysentery and liver abscesses, is estimated to cause severe disease in 48 million people and to kill 70,000 people annually. This parasite is found throughout the world, although it is especially problematic in underdeveloped tropical and subtropical regions. The main source of transmission are people who carry a chronic infection; feces infected with the cyst form of the parasite may contaminate fresh food or water.

Mycobacterial Diseases

Tuberculosis

Caused primarily by *Mycobacterium tuberculosis*, this infection can last a lifetime, resulting in disease to virtually every organ in the body but primarily affecting the lungs. Tuberculosis occurs all over the world. Eight million new cases of active tuberculosis occur every year, and one-third of the world's population is already infected. Until recently, the disease was thought to be well controlled in the more developed countries. Unfortunately, it is again on the increase due to its association as an opportunistic infection of AIDS and its prevalence in drug abusers. Tuberculosis remains a major problem in the developing world. More than 1.5 million new cases of the disease occur every year in sub-Saharan Africa, and nearly 3 million cases occur annually in Southeast Asia.

It has been estimated that 5 to 15 percent of infected individuals develop disease. Pulmonary tuberculosis is the most common manifestation worldwide and is associated with fatigue, weight loss, coughing, and difficulty in breathing. Several drugs are available, but drawbacks include the need for lengthy treatment and increasing development of drug resistance by the bacteria.

Hansen's disease

Myths and misperceptions surrounding Hansen's disease (leprosy) are numerous. It is caused by the bacterium *Mycobacterium leprae*, which is related to the agent that causes tuberculosis. Some 3.7 million cases are officially registered, but the actual number of infected individuals is at least two to three times higher. The exact mechanism of transmission from person to person remains unknown but likely involves contact with infected skin or nasal secretions. The bacteria grow primarily in macrophages in the skin and in Schwann cells surrounding nerves. As in the case of some of the parasitic diseases, the body's reaction to the leprosy bacillus is responsible for disease. The clinical course of leprosy is extremely variable. Some infected individuals may remain without symptoms. In its worst form, bacterial growth is uncontrolled, leading to loss of sensation in the affected area, which may predispose to trauma and consequent deformity. Presently, no methods for prevention exist. Treatment relies on long-term administration of antibiotics. Difficulties are encountered because of the development of drug resistance and the failure of patients to comply with treatment regimens.

Arboviruses

Arboviruses, which are transmitted by insect vectors, are of special relevance as tropical diseases. Dengue fever, caused by a mosquito-borne flavivirus, is found in tropical and subtropical regions of the Americas, Africa, Asia, and Australia. In its acute form, dengue is characterized by flu-like symptoms. Some patients develop dengue hemorrhagic fever, a severe and sometimes fatal variation involving circulatory failure and shock. The incidence of both forms of dengue infection has recently been increasing, as expanding urbanization enlarges the regions inhabited by the *Aedes* mosquito vector. Mosquitoes

capable of transmitting this disease are also found within the United States. Yellow fever is another arboviral disease, characterized by fever, hemorrhage, and liver complications, and is found in tropical South America and Africa, where it is sometimes epidemic in spite of the existence of a safe and effective vaccine.

Emerging Viruses

West Nile virus

West Nile virus belongs to a group of disease-causing viruses known as flaviviruses, which are spread by insects, usually mosquitoes and ticks. The first step in the transmission cycle of West Nile virus occurs when a mosquito bites an infected bird. Although the virus cycles are primarily between mosquitoes and birds, infected female mosquitoes can transmit West Nile virus to incidental hosts, including humans, when taking a blood meal. Most human infections are mild, causing fever, headache, and body aches, often accompanied by a skin rash and swollen lymph glands. If the virus crosses the blood-brain barrier, however, it can cause life-threatening encephalitis, an inflammation of the brain.

West Nile virus was first isolated in Uganda in 1937. Today it is most commonly found in Africa, West Asia, and the Middle East. In 1999, the disease emerged in the Western Hemisphere for the first time in the New York City area, with seven deaths and 62 other cases reported. Upon investigation, researchers initially found crows to be the most commonly infected bird, but at least 25 other infected bird species have now been identified. Currently, no specific medicines exist to treat the illness, and no vaccine is available to prevent it. Because West Nile virus has the potential to periodically cycle through the bird and human populations, it has the potential to become a larger public health problem and possibly cause a serious epidemic. Consequently, public health officials are intensifying research efforts to develop antiviral drugs and vaccines for West Nile virus.

Hantavirus

Hantavirus has drawn attention since 1993, when an outbreak of a mysterious, often fatal, illness occurred in the southwestern United States. Scientists quickly determined that the illness, characterized by fever, chills, and muscle pain followed by difficulty in breathing, was caused by a previously unrecognized strain of hantavirus, a family of disease-causing viruses that is common in both North and South America. Hantavirus is transmitted to humans by mice and other rodents through contact with the rodents' feces and urine. Hantavirus cardiopulmonary syndrome (HCPS), a severe manifestation of the disease, has been diagnosed in more than 500 people, approximately half of whom have died. Very little is known about HCPS and the virus that causes it. Research is focused on learning how hantavirus infection develops and how the body's immune system responds to it, with the goal of developing new treatment strategies. Researchers also are

examining the natural history of hantavirus infection in rodents and the ecological conditions that encourage the virus to spread among these animals.

AIDS

The human immunodeficiency virus (HIV) associated with acquired immunodeficiency syndrome (AIDS) has become widespread in developing nations. Currently, about 95 percent of worldwide HIV/AIDS cases occur in developing countries. An estimated 25 to 35 percent of the adult population in some African countries is infected, and the number of infected individuals in Asia is rising rapidly. The epidemic is exacerbated by crises such as natural disasters, armed conflict, and mass population movements. The progressive erosion of the immune system in HIV-infected individuals renders them more susceptible to other infections, which may appear atypical or more severe than in an immunocompetent person. Since different diseases are prominent in tropical regions, patterns of the HIV-associated infections may diverge significantly from those seen in the developed nations. Knowledge of the tropical disease agents likely to infect AIDS patients is the basis for effective disease control in this important subgroup of afflicted individuals.

NIAID Research on Tropical Diseases

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) has a long tradition of supporting research on infectious diseases that affect populations living in developing countries but are also of global importance. NIAID research in this area is predicated on the view that we live in a global community and the health problems of the United States cannot be separated from those of the rest of the world. Investigators in NIAID's intramural laboratories, as well as extramural scientists, are conducting basic, clinical, and field research that seeks to discover and develop vaccines, drugs, and vector-control methods to prevent and treat tropical diseases.

In 1991, NIAID established the **International Centers for Tropical Disease Research (ICTDR)** to confront the current challenges in international health. The ICTDR program unites NIAID-supported intramural and extramural centers of tropical disease research into a focused interactive network. The ICTDR fosters the development of partnerships between

- Domestic and foreign scientists to enhance transfer of modern technology to institutions in endemic areas and to increase opportunities for U.S. scientists to work in endemic areas;
- NIAID and other U.S. Government, private, and international agencies with interests in tropical disease research for optimal utilization of available resources; and
- Individual investigators, funding organizations, and biomedical industry to encourage relevant applications of recent scientific advances toward critical issues of international health.

Four major programs make up the core of the ICTDR network. The **International Collaboration in Infectious Disease Research (ICIDR)** is an international program designed to encourage collaboration between U.S. investigators and scientists working in countries where tropical diseases are endemic. The **Tropical Disease Research Units (TDRU)** program awards grants to domestic institutions in the United States for the application of modern biomedical technology to the discovery of new control measures for parasitic infections. The **Tropical Medicine Research Centers (TMRC)** grants are large awards made to outstanding foreign institutions to provide opportunities for the study of tropical diseases in endemic regions. The **Intramural Center for International Disease Research (INCIDR)** is focused on field and laboratory research projects related to tropical diseases. These projects are conducted by scientists at NIAID's intramural laboratories in Bethesda, Maryland, and in Hamilton, Montana. Over the years, other NIAID extramural programs have formally or informally joined the ICTDR network. Among these are several new malaria research projects with components in endemic countries, including two Malaria Clinical Research and Trial Preparation Sites. When the network was initiated, to encourage linkage between laboratory and field-based researchers, several U.S. academic institutions with a focus on tropical disease research through individual NIAID research grants were designated as ICTDR Cooperating Groups; the Institute still makes an effort to integrate scientists performing tropical disease research under individual awards into the annual meeting.

In addition to its support of specific research projects and programs, NIAID has developed other resources that are available to the tropical diseases research community. These resources include the following:

International Clinical Trials Support Contract—NIAID's Division of Microbiology and Infectious Diseases (DMID) administers this project, which is designed to meet the specific challenges involved in conducting clinical research in developing countries. The contract will support all aspects of clinical studies, including trial design, epidemiology, statistical analysis, regulatory issues, ethics, and database and computer systems management.

Vaccine and Treatment Evaluation Units—The Vaccine and Treatment Evaluation Units (VTEUs), under contract to DMID, consist of six research units affiliated with medical universities throughout the United States. The VTEUs are equipped to conduct surveillance for infectious diseases, and they provide access to human challenge models for cholera, malaria, influenza, and other infectious agents targeted for accelerated vaccine development. Parasitic disease candidate vaccines are tested in the United States before they undergo clinical trials in endemic areas, creating new opportunities for international collaboration.

NIAID Resource Repositories—DMID supports research repositories that supply the parasitic helminth worms, schistosoma, and filaria. It is very costly and often too difficult for investigators to maintain the life cycles of these parasites in their own laboratories.

In 1999, NIAID funded a new Malaria Research and Reference Reagent Resource Center (MR4) that will improve worldwide access to malaria research reagents.

Resources for Additional Information

NIAID Office of Communications and Public Liaison
Building 31, Room 7A-50
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Bethesda, MD 20892-2520
Telephone: (301) 496-5717
Web site: http://www.niaid.nih.gov/

Office of Health Communication
National Center for Infectious Diseases
Centers for Disease Control and Prevention
1600 Clifton Road, Mailstop C-14
Atlanta, GA 30333
E-mail: ncid@cdc.gov
Web site: http://www.cdc.gov/ncidod/

American Society of Tropical Medicine and Hygiene
60 Revere Drive, Suite 500
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Web site: http://www.astmh.org/

World Health Organization
E-mail: info@who.int
Web site: http://www.who.int/home/map_ht.html#Tropical Diseases/

GLOSSARY

acquired immunity: Specific immunity that develops after exposure to a particular antigen or after antibodies are transferred from one individual to another.

adjuvant: A substance sometimes included in a vaccine formulation to enhance the immune-stimulating properties of a vaccine.

airborne transmission: Transmission of an infectious organism in which the organism is truly suspended in the air and travels from the source to the host.

ameba: A minute, one-celled protozoan.

antibiotic: A microbial product, or its derivative, that kills or inhibits the growth of susceptible microorganisms.

antibodies: The soluble immune molecules found in the blood and other tissues that are produced by B lymphocytes. Antibodies specifically react with particular microbes, causing the microbes to become inactivated or to be more rapidly cleared from the body.

antigenic variation: The process of changing surface molecules, which a parasite uses to avoid recognition by the immune system of the mammalian host.

antigens: Components or byproducts of a pathogen that are recognized by the host's immune system and might serve as components of a vaccine against the pathogen.

arthropod vectors: Bugs that transmit pathogens to man or other animals; "arthropod" is a broad term referring either to insects such as mosquitoes and flies or to arachnids such as ticks or mites.

assay: A test to determine the presence and the amount of a particular substance. For example, an assay may be done to determine the level of antigens in the blood of a person suspected of being infected with a particular organism.

bacteria: Small organisms containing genetic information and the equipment necessary to produce energy and replicate independently.

bioinformatics: The field of science in which biology, computer science, and information technology merge into a single discipline with the goal of revealing new insights and principles in biology.

carrier: An infected individual who is a potential source of infection for other people.

chemokine: One of a major family of small cytokines that function to attract and activate inflammatory cells, such as neutrophils or monocytes.

clone: (n.) A group of genetically identical cells or organisms descended from a single common ancestor; (v.) to reproduce multiple identical copies.

contact transmission: Transmission of an infectious agent by direct contact of the source or its reservoir with the host.

cytoadherence: The process by which cells stick to one another, as when malaria-infected red blood cells adhere to the cells of blood vessel walls.

cytokine: A soluble molecule that signals cells to participate in the immune response.

diagnosis: The identification of individuals who harbor infectious agents, and the relationship of those agents to the presence and transmission of disease.

diagnostic: A tool that is used to determine the cause of an illness or disorder.

DNA: Deoxyribonucleic acid; the molecule within a cell that carries genetic information.

DNA fingerprinting: A lab technique that compares the patterns of bands on analogous DNA fragments from two or more separate individuals. The test is done to find out how closely related they are to each another.

DNA sequencing: Determining the exact order of the base pairs in a segment of DNA.

drug resistance: The ability of bacteria and other microorganisms to withstand a drug to which they were once sensitive (controlled or killed outright).

endemic: A disease that is commonly or constantly present in a community.

endothelial cells: The cells that line blood vessels.

enzyme: A protein produced by living cells to accelerate, or "catalyze," a biological reaction without itself being altered.

enzyme-linked immunosorbent assay (ELISA): A highly sensitive blood test for detecting antigens or antibodies on the basis of a detectable color change in the test tube.

epidemiology: Study of the factors determining and influencing the frequency and distribution of disease, injury, and disability in a population.

gene: A discreet region of DNA that codes for a protein and constitutes a functional unit of heredity.

genetic engineering: The laboratory technique of recombining genes to produce proteins used for drugs and vaccines.

genome: All the genetic material in the chromosomes of a particular organism.

genomics: The study of genomes, which includes genome mapping, gene sequencing, and gene function.

glycoprotein: A protein linked to a sugar or polysaccharide that is a component of receptor molecules on the outer surface of cells.

helminths: Multicellular parasitic organisms commonly referred to as worms.

helper T cells: Abbreviated as Th; T lymphocytes that assist in the immune response. Two subsets, called Th-1 and Th-2, are currently known and defined according to their patterns of cytokine production.

hemoglobin: The protein in red blood cells that carries oxygen.

host: The body of an organism that harbors another organism. The host provides a microenvironment in which a parasite undergoes growth, development, and reproduction. This microenvironment is necessary for the parasite to complete its life cycle.

immune: Protected against a particular disease by either nonspecific or specific immune defenses.

immune response: The reactions of the immune system against foreign substances, including the formation of antibodies. Designed to render harmless the antigen and the pathogen producing the response.

immune system: A complex network of specialized cells and organs that is responsible for distinguishing the body from everything foreign to itself and defending the body against infection by agents such as bacteria, viruses, fungus, and parasites.

immunity: The ability of an organism to recognize a pathogen and resist or overcome an infection by the pathogen.

immunoassay: A test using antibodies to identify and quantify substances. Often the antibody is linked to a marker such as a fluorescent molecule, a radioactive molecule, or an enzyme.

immunoblot assay: A technique that uses antibodies and protein blotting to detect a specific protein.

immunogen: A substance that is capable of provoking (inducing) an immune response.

immunotherapy: A treatment that stimulates or modifies the body's immune response.

incidence: The number of newly diagnosed cases of a disease occurring in a specific population during a specific time period.

infection: Invasion of a host by an agent, with subsequent establishment and multiplication of the agent. An infection may or may not lead to disease.

infectious agent: Living or quasi-living organism or particle that causes an infectious disease. Bacteria, viruses, fungi, protozoa, helminths, and prions are infectious agents.

infectious disease: Change from a state of health to a state in which part or all of a host's body cannot function normally because of the presence of an infectious agent or its products.

inhibitor: A molecule that represses or prevents another molecule from engaging in a reaction.

interferon: A cytokine produced by Th-1 lymphocytes, which plays a role in several cell-mediated antiparasitic immune responses; abbreviated IFN.

interleukin: One of a large number of cytokines, identified by numbers, that communicates between the cell which produces it and the cell(s) it affects; abbreviated IL. For example, IL-1 is a major inflammatory mediator with effects on multiple other cells.

intermediate host: The species (or group of species) that a parasite infects during its immature, juvenile stages and that serves as a temporary but essential environment for the completion of the parasite's life cycle.

in vitro: In an artificial environment; generally referring to experiments conducted in culture outside an intact animal.

in vivo: In the living body; referring to experiments conducted in intact hosts.

lymphocytes: Immune cells that can either kill other cells infected with a microbe directly or produce substances that participate in the immune response. B lymphocytes are involved in antibody production; T lymphocytes either kill other cells directly or produce cytokines that assist in the immune response.

macrophage: Literally "big eater," a tissue-dwelling inflammatory cell that ingests microbes and debris, but in which some unicellular pathogens live.

merozoite: A blood-stage form of the malaria parasite.

microbes: Minute living organisms, including viruses, bacteria, fungi, and protozoa.

microfilariae: Minute larvae.

microorganisms: Microscopic plants or animals.

microscopy: Examination with a microscope.

molecule: The smallest amount of a specific chemical substance that can exist alone. (To break down a molecule into its constituent atoms is to change its character. A molecule of water, for instance, reverts to oxygen and hydrogen.)

molecular markers: Genetic markers (usually proteins or DNA sequences) that can be detected by biochemical methods.

mutation: A heritable change in DNA sequence involving either a physical change in chromosome relations or a biochemical change in the codons (basic unit of the genetic code) that make up genes.

mycobacteria: A family of gram-positive, rod-shaped bacteria that normally live in acidic conditions (soil, water, and dairy products); they include the bacteria that cause leprosy *(Mycobacterium leprae)* and tuberculosis *(Mycobacterium tuberculosis).*

nucleotide: The building blocks that make up DNA or RNA.

parasite: An organism that lives within or upon another organism, at whose expense it obtains some advantage (e.g., nourishment).

pathogen: A disease-causing organism.

pathogenesis: The origin and development of a disease. More specifically, the way a microbe (e.g., bacteria or virus) causes disease in its host.

phagocytes: Large white blood cells that contribute to the immune defenses by ingesting microbes or other cells and foreign particles.

phagocytize: To engulf and possibly destroy a microbe or other particle.

phenotype: The physical appearance or observable characteristics of an organism.

polymerase: An enzyme that creates genetic material, either RNA or DNA, from building blocks.

polymerase chain reaction: Abbreviated as PCR; a method of amplifying specific DNA sequences that constitutes the basis for extremely sensitive diagnostic procedures.

prevalence: The number of cases of a particular disease or condition in a given population. Often further distinguished as point prevalence (single point in time) or period prevalence (over a period of time).

protease: An enzyme that breaks down proteins.

protective immunity: Complete resistance to disease, whether long lasting or temporary.

protein: An organic compound made up of one or more chains of amino acids. Proteins are required for the structure, function, and regulation of plant and animal cells, tissues, and organs, and each protein has unique functions. Examples are hormones, enzymes, and antibodies.

protozoa: Single-celled parasitic organisms that are more complex than bacteria.

reagent: Any chemical used in a laboratory test or experiment.

receptor: A molecule on the surface of a cell that serves as a recognition or binding site for antigens, antibodies, or other cellular or immunologic components.

recombinant DNA technology: The technique by which genetic material from one organism is inserted into a foreign cell to mass produce the protein encoded by the inserted genes.

reservoir: An animal host for a parasite that serves as a source from which humans or other animals can be infected.

RNA: Ribonucleic acid; the genetic material that is transcribed from DNA and may carry the message for a protein or serve other functions in the cell.

source: Location or object from which a pathogen is immediately transmitted to a host.

sporozoite: The stage of the malaria parasite that is injected into the mammalian host by the mosquito vector and infects liver cells.

transformation: Insertion of a piece of foreign DNA into a cell, causing that cell to manufacture a product that it would not ordinarily express.

transposable element: A genetic element that is able to move from one genomic site to another, providing a potent force for genetic change.

tropical diseases: Infectious diseases that disproportionately affect people living in the developing countries of the tropics.

tumor necrosis factor: A cytokine involved in inflammation, which has both beneficial (e.g., antimicrobial and tumor inhibitory) and toxic (e.g., fever induction, hypotension) effects on the host, depending on concentration and other factors; abbreviated TNF.

vaccine: A substance that contains antigenic components from an infectious organism. By stimulating an immune response (but not disease), it protects against subsequent infection by that organism.

vector: An invertebrate host that transmits a parasite and is necessary for the parasite to complete its life cycle.

vector-borne transmission: Transmission of an infectious pathogen between hosts by way of a vector.

viruses: Minute infectious agents that generally consist only of genetic material covered by a protein shell. They replicate only within host cells, which provide the synthetic machinery necessary to produce new virus particles.