4
Description of Selected Tropical Diseases

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INTRODUCTION

This chapter describes the major tropical diseases that are discussed in this report. The diseases considered are a rather diverse group.

Representing the diseases traditionally considered "tropical" in this report are malaria, schistosomiasis, trypanosomiasis, leishmaniasis, filariasis, and leprosy. These are the six diseases singled out for attention by the Special Program for Research and Training in Tropical Diseases (TDR), which is sponsored jointly by the U.N. Development Program, the World Bank, and the World Health Organization (WHO). The six TDR diseases together affect between 700 million and 800 million people worldwide. Malaria, schistosomiasis, and filariasis each affects more than 200 million people.

Other diseases discussed in this report—tuberculosis, diarrheal diseases, acute respiratory infections (ARIs), and arboviral infections—occur in nontropical countries as well as tropical ones. The toll these diseases take in developing countries is much greater than the toll they take in the developed world because of developing countries' higher incidence rates and poorer diagnostic and therapeutic methods.

Tuberculosis was once a public health problem worldwide. It now persists mainly in developing countries, where it infects large numbers of people.

Diarrheal diseases and ARIs are the leading causes of death among infants and children in developing countries. In countries where the infant mortality rate is more than 100 per 1,000 live births, at least one-third of infant deaths are from diarrheal diseases.

Arboviral infections have a worldwide distribution, but are concentrated in the tropics. With no specific treatments available and a vaccine against only two (yellow fever and Japanese encephalitis), arboviral infections are a potential threat to the U.S. population.

These are far from the only health problems in tropical developing countries. In addition to being affected by the often debilitating infectious diseases discussed here, people in the developing world are increasingly affected by the chronic diseases that cause so much sickness and death in the developed world: heart disease, cancer, stroke, and diabetes, for instance. Ironically, these chronic diseases increase in incidence as life expectancy increases and as the probability of dying from infectious diseases decreases.

This chapter provides basic information about each of the diseases considered in the later chapters of this report. Chapter 5 discusses strategies for controlling tropical diseases, and chapters 6 through 9 examine the status of disease control measures: vector control technologies, immunization technologies, diagnostic technologies, and therapeutic technologies. Table 4-1 summarizes some basic information about each disease and guides the reader to the relevant sections, for each disease, in the remainder of the report.

MALARIA

Aspects of Natural History

In 1940, the Nobel Laureate Sir Macfarlane Burnet wrote (37):

> If we take as our standard of importance the greatest harm to the greatest number, then there is no question that malaria is the most important of all infectious diseases.

His statement still holds true. Malaria is one of the most studied of all tropical diseases. The disease is caused by various species of the protozoan genus Plasmodium . Malaria parasites have a com-

Table 4-1.—Location in This Report of Information About Selected Tropical Diseases

Disease/ type of infection	Causative agent	Vector or mode of transmission	Map (or distribution)	Disease description	Status of: Vaccines	Diagnostics	Therapeutics
Malaria			63	59	134,225	163	182
Protozoal	*Plasmodium* spp.	*Anopheles* spp.					
Schistosomiasis			68	65	137	164	185
Helminthic	*Schistosoma* spp.	Various snails					
Trypanosomiasis			71,74	67	138	165	186
Protozoal							
African sleeping sickness							
(West)	*Trypanosoma brucei gambiense*	*Glossina* spp. (tsetse flies)					
(East)	*T. b. rhodesiense*						
Chagas' disease	*T. cruzi*	Reduviid bugs ("kissing bugs")					
Leishmaniasis			77	74	140	167	187
Protozoal	*Leishmania* spp.	*Phlebotomus* spp. (sandflies)					
Filariasis			81	78	140	168	188
Helminthic	*Wuchereria bancrofti*	*Anopheles*, and others (mosquitoes)					
	Brugia malayi						
Onchocerciasis	*Onchocerca volvulus*	*Simulium* spp. (blackflies)					
Leprosy			83	80	140	169	188
Bacterial	*Mycobacterium leprae*	Suspect airborne					
Tuberculosis			Worldwide	84	142	170	189
Bacterial	*Mycobacterium tuberculosis*	Airborne droplets					
Diarrheal and enteric diseases			Worldwide	85	142	172	190,201
Viral	Various viruses	All by fecal contamination of food and/or water					
Bacterial	Various bacteria, e.g., *Vibrio-cholerae, Escherichia coli*						
Protozoal	*Entameba histolytica, Giardia lamblia*						
Helminthic	Various helminths, e.g., *Ascaris, Necator*						
Acute respiratory infections (ARIs)			Worldwide	88	144	173	193
Viral	Various viruses	All by airborne droplets					
Bacterial	Various bacteria						
Chlamydial	*Chlamydia* spp.						
Mycoplasmal	*Mycoplasma* spp.						
Arboviral infections			Worldwide (e.g., yellow fever [p. 94]; dengue fever [p. 95])	91	148	76	196
Viral	Various viruses	Various arthropods					

SOURCE: Office of Technology Assessment, 1985.

plex life cycle, alternating between vertebrate hosts and mosquito vectors of the genus *Anopheles.*

Four species of *Plasmodium* cause malaria in humans: *Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae.* Other species of *Plasmodium* infect a wide variety of other vertebrates.

The four species that infect humans have somewhat different clinical effects. *P. falciparum* can cause severe anemia, kidney failure, and brain damage and is often fatal, especially in children. *P. vivax* and P. *ovale* infections are seldom fatal, but relapses of the symptoms (chills, high fever, nausea, headache, etc.) can occur periodically for up to 3 years. *P. malariae* infections can persist in the blood for years without causing any symptoms.

Life Cycle

All species of *Plasmodium* progress through a similar life cycle, though each species differs in some of the details. All human malaria infection begins with the bite of an infected female Anopheles mosquito (see fig. 4-l). As the mosquito ingests a blood meal to nourish her eggs, she incidentally injects saliva containing plasmodial sporozoites (which have been clustered in the mosquito's salivary glands) into the human bloodstream.

Within about an hour, the threadlike sporozoites leave the bloodstream and move to the human liver. Over the next week or two, depending on the species of *Plasmodium,* each sporozoite that has invaded a liver cell becomes a schizont, a developmental stage that contains thousands of merozoites, the next stage in the life cycle of the parasite. When the schizont matures, it ruptures out of the infected liver cell and discharges merozoites into the human host's bloodstream. In *P. vivax* and *P. ovale* malaria, some sporozoites, instead of developing into shizonts, become hypnozoites, forms that can remain dormant in the liver for months or years before they start to proliferate.

Merozoites invade red blood cells (erythrocytes) and there undergo a second round of asexual reproduction, similar to that in the liver. In 2 or 3 days, the merozoites develop into trophozoites, then into a second dividing schizont form. When the schizonts mature, they rupture and release another round of merozoites, perpetuating the cycle of infection. It is at the time of this rupture that clinical symptoms of malaria appear. The cycle repeats every 2 or 3 days, depending on the species of *Plasmodium*.

Some merozoites, instead of developing into schizonts, differentiate into sexual forms, gametocytes. Mature gametocytes remain in the host's red blood cells, and can be ingested by female *Anopheles* when they bite. Gametocytes develop further into male and female gametes, which undergo sexual reproduction in the mosquito's gut. Eventually a new generation of sporozoites develops in the mosquito and migrates to the mosquito's salivary glands, ready to infect another human.

Incidence and Prevalence

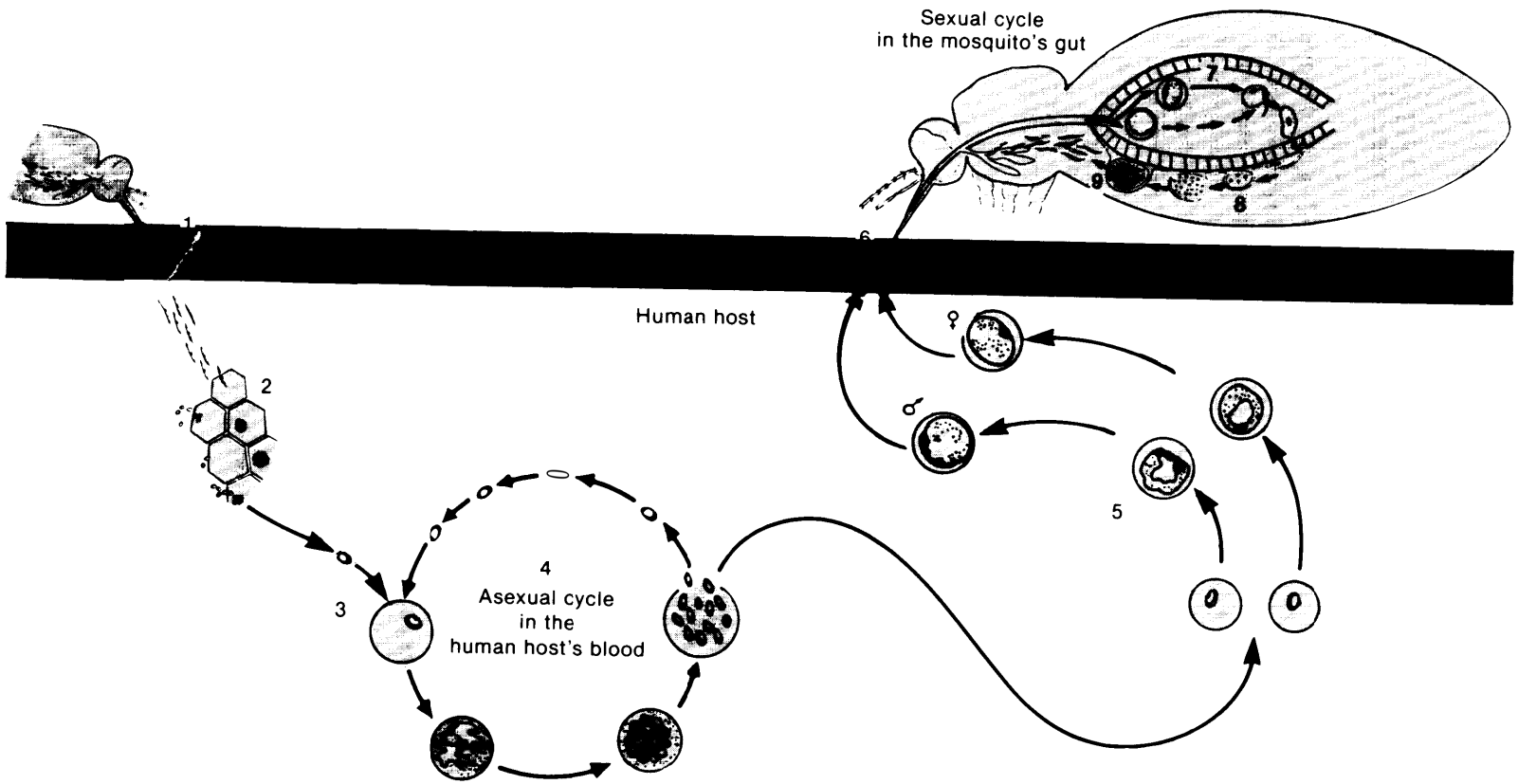
Malaria is one of the most widespread and destructive of diseases, having doubled in world prevalence in the last decade (430). Worldwide, an estimated 250 million to 300 million cases of malaria occur each year. In tropical Africa alone, an estimated 160 million to 200 million people are infected every year, and 1 million people die, mostly infants and small children (193).

About 1.5 billion people live in areas of the world where the risk of malaria ranges from moderate to high (see fig. **4-2).** The countries of highest malaria incidence are Haiti, Guatemala, Honduras, El Salvador, Colombia, Bolivia, Brazil, India, Sri Lanka, Pakistan, and many parts of Africa and Asia. In Europe, the Caribbean, North America, and parts of South America, and Australia, the gains against malaria brought about by the WHO eradication program (see discussion below) have been maintained. However, developed nations such as England and the United States have experienced an increase in the number of imported malaria cases.

Malaria Control

Before World War II, approximately two-thirds of the worlds population was at risk for malaria. DDT (dichloro-diphenyl-trichloro-ethane) was initially highly successful at controlling the *Anopheles*

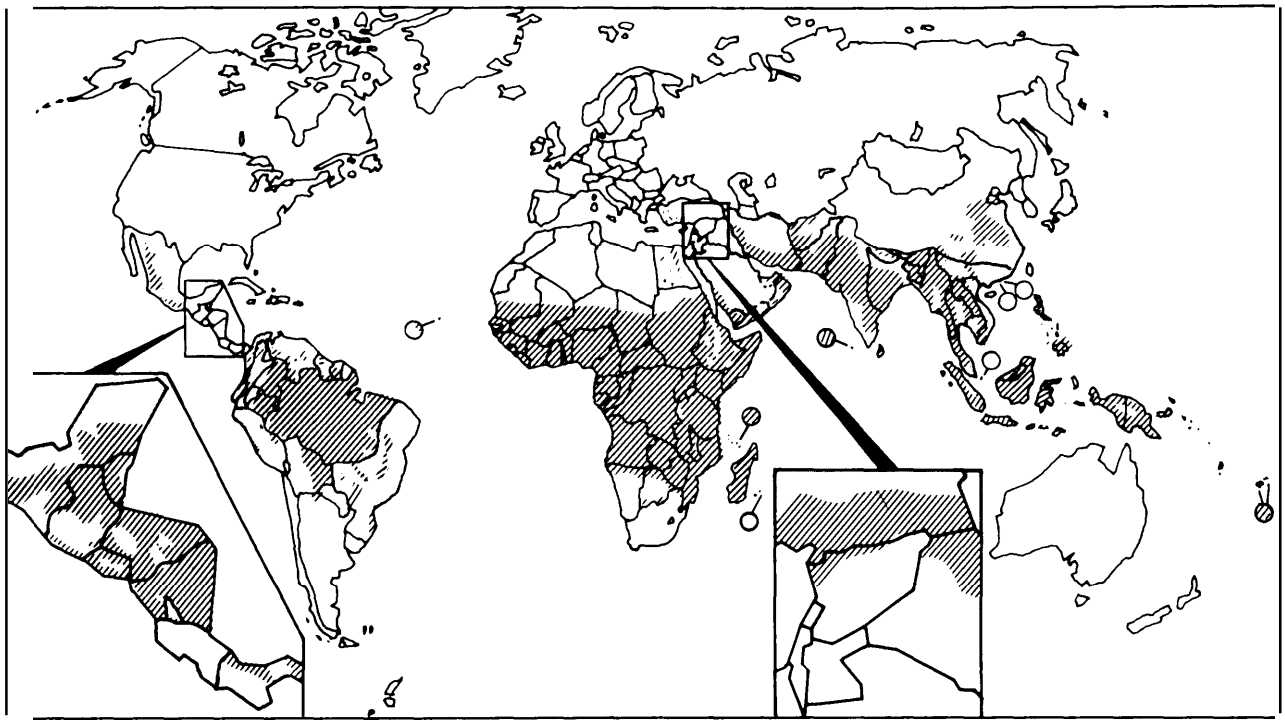
Figure 4-1.—Generalized Life Cycle of *Plasmodium*, the Cause of Malaria



1. Female *Anopheles* mosquito bites a human, injecting malaria sporozoites.
2. Sporozoites quickly move to the human host's liver cells, where they undergo asexual reproduction.
3. Merozoites released from liver cells enter the human host's bloodstream and invade red blood cells.
4. Merozoites undergo asexual reproduction in the human host's red blood cells, releasing more merozoites to infect more red blood cells. This cycle may be repeated many times in chronic infections.
5. Some merozoites differentiate to become gametocytes.
6. Gametocytes are picked up by a female *Anopheles* mosquito, in which the life cycle of the malaria parasite is completed.
7. Gametocytes develop further into male and female gametes, then fuse to form zygotes within the mosquito's gut.
8. The developing zygote burrows into cell lining of mosquito gut and develops into a cyst containing thousands of sporozoites.
9. Sporozoites are released into the mosquito's body cavity and migrate to the salivary glands, where hey are o position o enter a human when the mosquito bites.

SOURCE: Adapted from H. W. Brown and F. A. Neva, *Basic Clinical Parasitology* (East Norwalk, CT: Appleton-Century-Crofts, 1983).

Figure 4-2.—Geographic Distribution of Malaria as of 1982



SOURCE U S Department of Health and Human Services, Centers for Disease Control, *Health Information for /n ternational Travel.* HHS Publication No (CDC)840-8280 (Washington, DC U S Government Printing office, 1984)

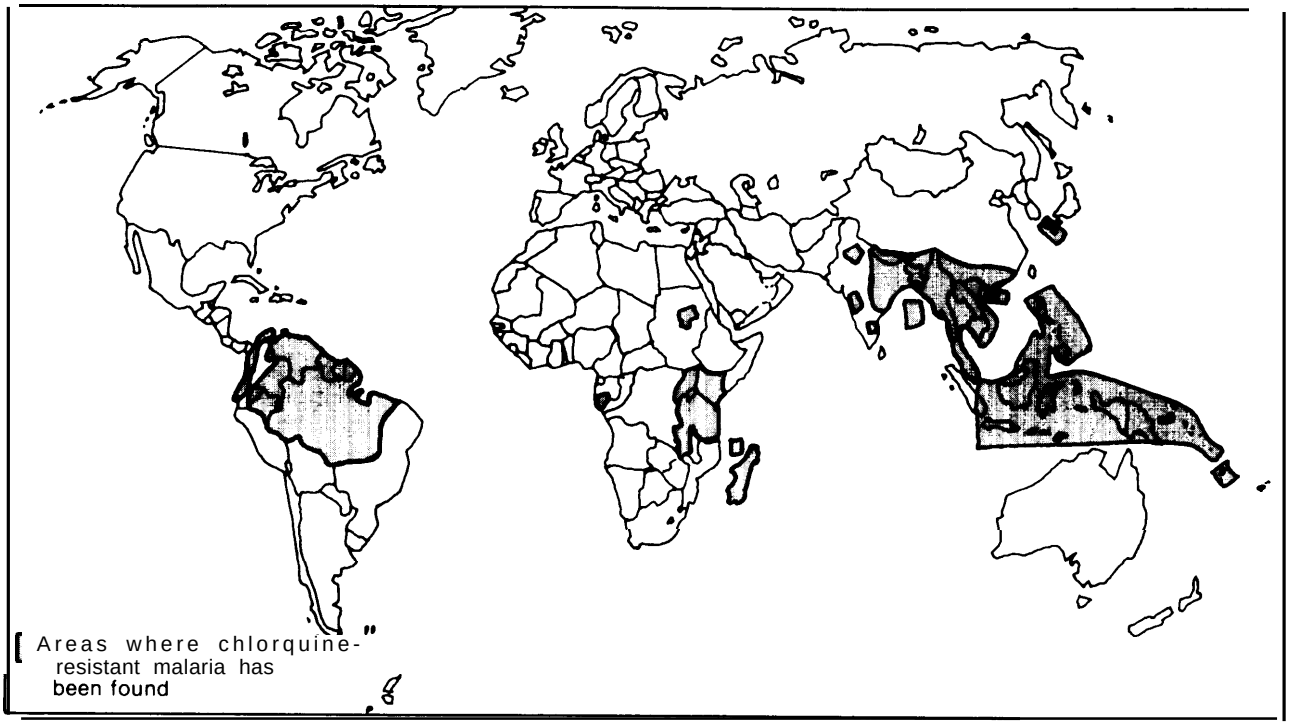
mosquito vector of malaria, however, and because of this, WHO began a worldwide malaria eradication program in the late 1950s. Large-scale spraying efforts kept the mosquito population down, eliminating the risk of disease for some 400 million people, mostly in temperate regions.

By the mid-1960s, malaria had been eliminated from nearly all of Europe, most of the Asian part of the U. S. S. R., several countries of the Near East, most of North America including all of the United States, most of the Caribbean, large areas of the northern and southern parts of South America, Australia, Japan, Singapore, Korea, and Taiwan. Eighty percent of the originally malarious area was almost free of malaria.

By 1969, however, there had been little additional progress. The worldwide eradication campaign failed for several reasons. Increasing mosquito resistance to DDT and *P. falciparum* resistance to chloroquine, the most widely used malaria drug, were two of the most important (33). Other factors in the increased incidence of malaria were behavioral changes in the mosquito vector species and the migration of workers who unintentionally brought the vectors with them to new areas.

While efforts to keep the *Anopheles* vector under control have been successful in some areas, the cost of applying traditional malaria interventions has greatly restricted the ability of developing countries to protect the populations at risk. Furthermore, few efforts to slow the spread of drug-resistant malaria have worked. Resistance of *P. falciparum* to chloroquine has been present in Panama, parts of some South American countries, India, Southeast Asia, Indonesia, China, the Republic of the Philippines, and other Pacific Islands for several years (see fig. 4-3). In Latin

Figure 4-3.—Geographic Distribution of Chloroquine-Resistant Malaria as of 1983



SOURCES: U.N. Development Program/World Bank/WHO. Special Program for Research and Training in Tropical Diseases. *Sixth Programme Report. 1 July 1981-31 December 1982* (Geneva: WHO, 1983).
U.S. Department of Health and Human Services, Centers for Disease Control. *Health Information for International Travel*, HHS Publication No. (CDC)840-8280 (Washington, DC: U.S. Government Printing Office, 1984).

America, resistant strains of the organism are appearing in most parts of Bolivia, Venezuela, French Guyana, and northern Peru, but serious drug-resistance has still not moved north of the Panama Canal. There is growing evidence of resistance in east Africa, which includes Kenya, Tanzania, eastern Zaire, Burundi, Uganda, Rwanda, Malawi, Zambia, northern Sudan, Madagascar, and the Comoro Islands (376).

Resistance to chloroquine is not the only problem. Some malaria parasites have also developed resistance to newer drugs. Regular monitoring of local parasite strains is necessary as an indicator of therapeutic changes that may be needed, both in type of drug and dose. Renewed efforts to develop new drugs are producing results, but moving new drugs from laboratory screening through animal testing to human trials takes years.

Recent Progress

Since 1976, with the development of methods allowing for the continuous cultivation of malaria parasites in the laboratory, research on the immunology of malaria has moved ahead considerably. All life cycle stages of the malaria parasite can now be grown in culture. An important recent discovery is that the proteins on the surface of the parasite (surface antigens) vary not only among the species of *Plasmodium* but also among strains of a single species. Perhaps of even greater interest is the finding that malaria parasites can change their surface antigens during the course of an infection. The human (or animal) host, in turn, must play "catch-up" in order to destroy the new forms of the parasite. This finding has direct implications for the development of vaccines and diagnostic tests (231).

Basic malaria research has advanced considerably. Metabolic studies have identified parasite-specific enzyme pathways that can be exploited to kill the malaria parasite without harming the human host. Membrane research has revealed how the parasite finds, attaches to, and invades the human host's red blood cells, yielding important clues for drug therapy and vaccine research. Recent clinical studies have suggested better ways of preventing and treating cerebral malaria, an often fatal complication of severe malaria infection.

A vaccine against the sporozoite stage of malaria may be available for testing by 1986. Vaccines against the merozoite and the gamete stages are behind this in development. If animal testing in humans confirms the feasibility of immunization against the malaria parasite, extensive human and field trials will be required before the vaccine can be widely used. Furthermore, given the difficulties that have plagued other disease immunization campaigns there is some debate about the usefulness of a malaria vaccine (see Case *Study B: The Development of a Malaria Vaccine* for a more comp ete discussion).

Research Needs

Field- and community-based studies are needed to assess the impact of antimalarial interventions. The emergence of insecticide-resistant mosquito vectors of malaria has seriously handicapped current malaria control efforts, making studies of the ecological impact of future interventions critically important. The effect of antimalarial activities on the actual immunity levels of populations needs clarification. Studies in the past have clearly documented the immediate impact of antimalarial projects on morbidity and mortality, but not the long-term consequences when projects cease or fail. Other studies are needed to evaluate the importance of sociological and human behavioral factors and the usefulness of health education, community self-help, and volunteer collaborators.

SCHISTOSOMIASIS

Aspects of Natural History

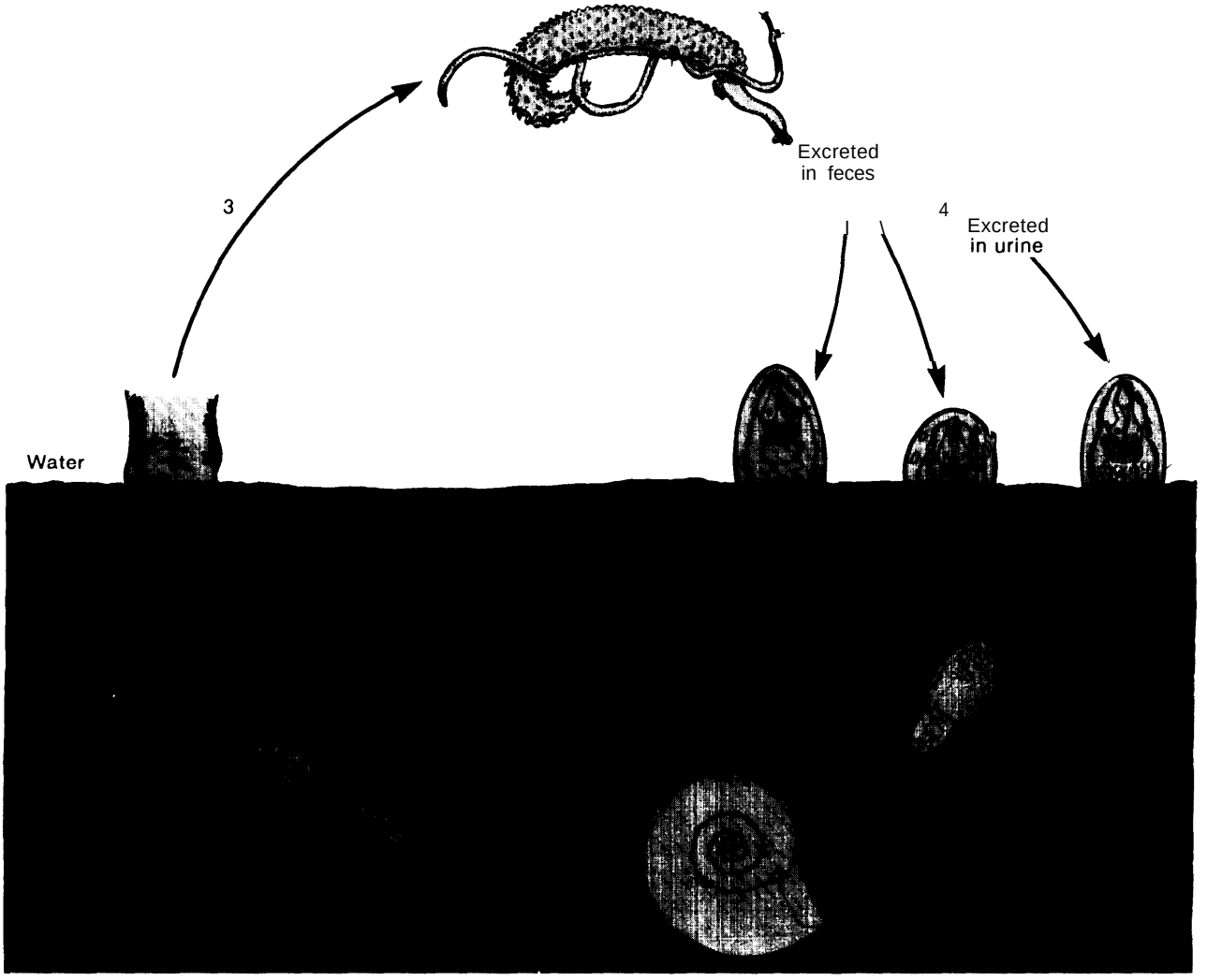
Schistosomiasis is a debilitating disease caused by trematode worms of the genus Schistosorna. There are three major species affecting humans, *Schistosoma mansoni, S. haematobium,* and S. *japonicum,* all of which originated in the Old World but now occur worldwide. S. *mansoni* originated in Africa, but now has become established in the Americas. A fourth species, S. *mekongi,* was discovered in the late 1960s and is endemic in areas of Southeast Asia.

Life Cycle

The adult parasitic worms that cause schistosomiasis live in pairs in the human host's bloodstream, sometimes for many years. Eggs (from a few hundred to several thousand per day) are produced by the female schistosome and are deposited in the host's blood vessels. The eggs escape into the host',s bowel (S. *mansoni, S. japonicum)* or bladder (S. *haematobium),* and then are excreted in feces or urine. If the eggs become trapped in the human host's bladder or liver, however, granulomas (masses of small blood vessels and connective tissue) form around them, and the eggs eventually die and calcify, producing inflammation and scars. The damage done by schistosomiasis is primarily due to the human body's reaction to accumulated eggs and their associated granulomas.

The schistosome eggs that are excreted by the host into freshwater lakes or streams hatch into ciliated larval worms (miracidia). Miracidia then enter an intermediate snail host, in which they proliferate. Immature worms (cercariae) are released from the snail and can rapidly penetrate the unbroken skin of persons who enter infected water (see fig. **4-4). The** tailless immature worms (now called shistosomules) enter the human circulatory system and proceed to the liver, where they mature. As they mature, they coat their surfaces with proteins acquired from their human hosts, which enable them to fool the hosts' immune system into tolerating their presence (130). After emerging from the liver, mature worms

Figure 4-4.—Generalized Life Cycle of Schistosoma, the Cause of Schistosomiasis



1. Microscopic cercariae are released from snail intermediate host.
2. Cercariae penetrate skin of human host.
3. Tailless cercariae, now called schistosomules, migrate to the human host's small blood vessels, are carried to lungs, then through the heart into the liver to mature; paired (male and female) mature schistosomes lodge in the human host's veins (S. *mansoni* shown).
4. Female schistosomes continually produce eggs (up to thousands each day), which penetrate the human host's intestine (S. *mansoni* and S. *japonicum)* or the urinary bladder (S. *haernatobium),* from which they are excreted in feces or urine, respectively.
5. Eggs hatch in fresh water into ciliated miracidia.
6. Miracidia penetrate intermediate snail host, lose cilia, and become sporocysts. Sporocysts reproduce asexually in the snail, proliferating greatly, eventually giving rise to cercariae.

SOURCES Adapted from T C Cheng. Symbiosis (New York Pegasus, 1970), and E R Noble and G A Noble Parasitology. 3d ed (philadelphia Lea & Febiger. 1973)

mate for life within small veins around either the bowel or bladder area, thus completing the parasite's life cycle.

Incidence

A worldwide survey in 1972 (including 71 countries) estimated that **500** million people were exposed to infection by schistosomiasis and 125 million were infected (169). The various forms of this disease occur in parts of Africa, the Caribbean, South America, and the Orient (see fig. 4-5). In Latin America, recorded schistosomiasis incidence is highest in Surinam, where 385 of every 100,000 inhabitants were infected in 1980 (265). S. *mansoni* is also established in suitable snail hosts in more than half of Brazil, where 10 million people are believed infected, and in parts of Venezuela, where 10,000 more people are thought to have the disease. Foci in the Caribbean occur in the Dominican Republic, Guadaloupe, Martinique, and St. Martin. A few cases have been detected in Montserrat.

Interventions

Over the last 10 years, the incidence and prevalence of schistosomiasis have dropped considerably in several countries. In Japan, the prevalence dropped from **25** percent in 1950 to less than 1 percent in 1973 (169). This formidable decrease was brought about by the concrete lining of irrigation ditches, snail control, land reclamation, environmental sanitation, chemotherapy, and health education. Similar decreases reported for some parts of Egypt, Iran, Puerto Rico, Tunisia, and Venezuela were brought about by more or less the same combination of control methods *and* improved socioeconomic conditions (169). On the minus side, schistosomiasis has spread to new areas as a result of water impoundment and irrigation projects which create and expand suitable environmental conditions for snail hosts and increase human-snail contact. Areas where large hydroelectric dams are being built, especially in South America, may require special surveillance and assessment.

Chemotherapy against schistosomiasis with the newest generation of chemotherapeutic agents is effective and relatively safe. However, total and complete control in endemic areas is difficult to achieve, since it requires attention to other measures, particularly water supply and sanitation, and treatment of snail breeding sites (molluscicide).

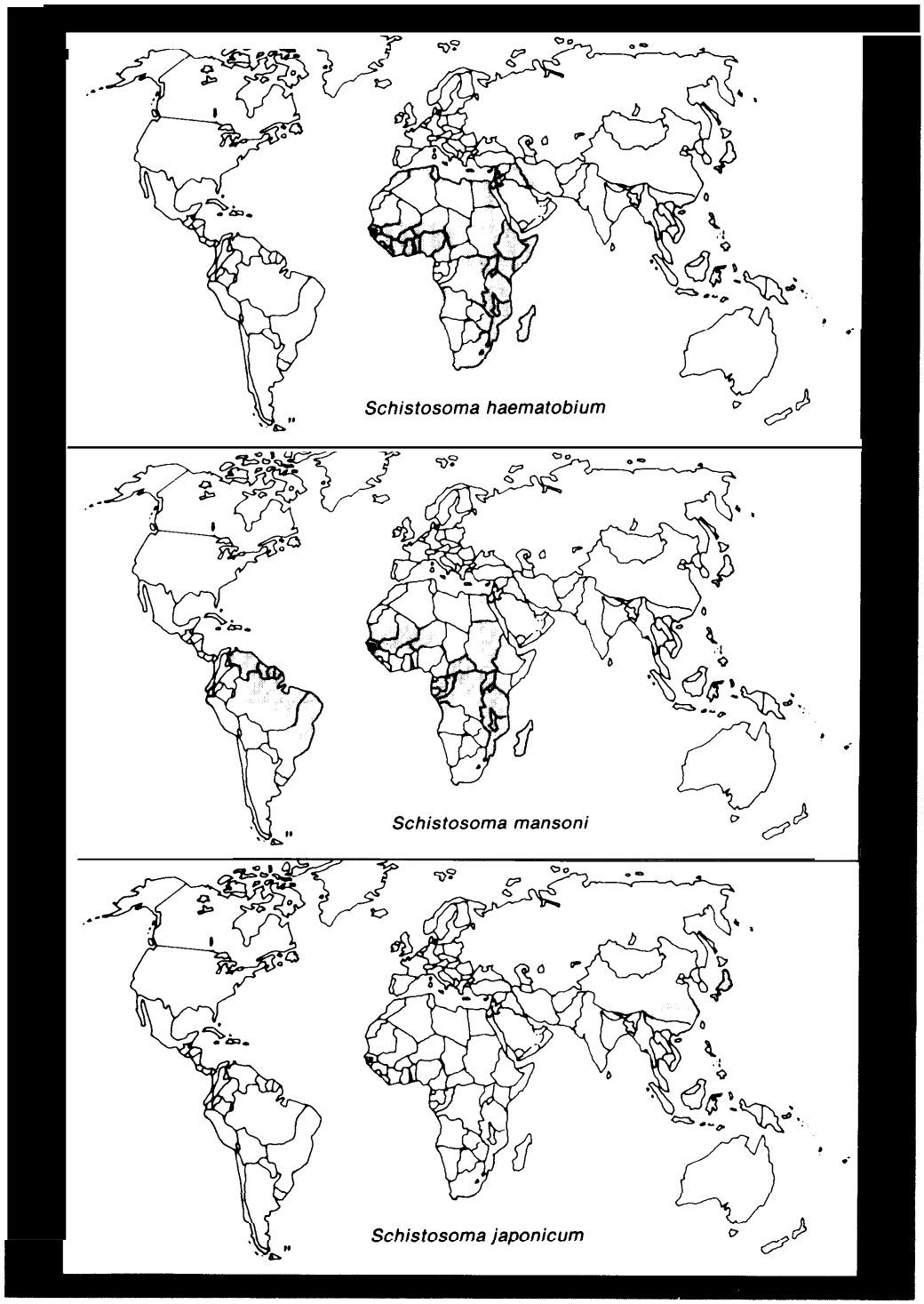
Recent Progress

A fairly large corps of American researchers studies schistosomiasis, and about a dozen laboratories use the techniques of biotechnology. The life cycle of the schistosomiasis parasite is readily adaptable to the laboratory, and small rodents are easily infected. The immunology of schistosomiasis has been studied extensively (39). Most workers are attempting to identify and isolate relevant protective antigens, and many are actively engaged in gene cloning experiments. A live irradiated larval vaccine has been used in cattle in the Sudan with encouraging results (338), but its use in humans is not feasible, because the larvae are alive (though unable to continue their life cycle) when injected.

TRYPANOSOMIASIS

Trypanosomiasis is a general term for two separate diseases caused by protozoan parasites of the genus *Trypanosoma. Trypanosoma brucei* infections cause African sleeping sickness (also called African trypanosomiasis), and T. *cruzi* infections cause Chagas' disease (also called American trypanosomiasis). The two diseases have completely different transmission cycles, different vectors, and cause a different pathology. Chagas' disease begins as a blood infection but ultimately attacks various body organs, principally the heart, African sleeping sickness also begins as a blood infection but progresses to central nervous system disease and death,

Figure 4-5.—Geographic Distribution of Schistosomiasis: *Schistosoma haematobium*, *S. mansoni*, and *S. japonicum*



SOURCES: V Zaman and L Keong, Handbook *of* Medical Parasitology (Australia: ADIS Health Science Press, 1982); and H. W. Brown and F A. Neva, *Basic Clincal Parasitology* (East Norwalk, CT: Appleton-Century-Crofts, 1983), used by permission

African Sleeping Sickness (African Trypanosomiasis)

Aspects of Natural History

T. *brucei,* the agent of African sleeping sickness in humans and nagana in livestock, is endemic to large areas of the African continent but does not occur naturally outside of Africa. In the United States, there have been six published reports of imported cases of African sleeping sickness since 1967. All the infected travelers had been on vacation in game parks in eastern or southern Africa, where they were exposed to the tsetse fly vector. The tsetse fly vector of African sleeping sickness is not found in the United States, so there is little danger that the disease will become established in this country (368).

Life Cycle.—There are actually two kinds of African sleeping sickness, each caused by a different variety of T. *brucei* and occurring in its own environmental niche. Both forms of the disease have an early stage involving the blood and lymphatic system and a late stage involving the brain.

In west Africa, sleeping sickness is caused by the parasite T. *brucei gambiense,* which is transmitted by tsetse flies *(Glossina palpalis)* that feed only on humans. The disease is transmitted near streams where tsetse flies breed. T. *b. gambiense* infection usually results in a chronic condition that slowly leads to death.

In east Africa, sleeping sickness is actually a zoonosis (a disease of animals that can be transmitted to humans) caused by T. *b. rhodesiense* and transmitted by a different species of tsetse fly (G. *morsitans).* Humans acquire the disease when they venture into areas, such as hunting grounds and grazing lands, where animals are infected. The disease is fatal to humans within weeks or months and very destructive to livestock. Large expanses of land have become totally unusable because of the disease risk to humans entering them.

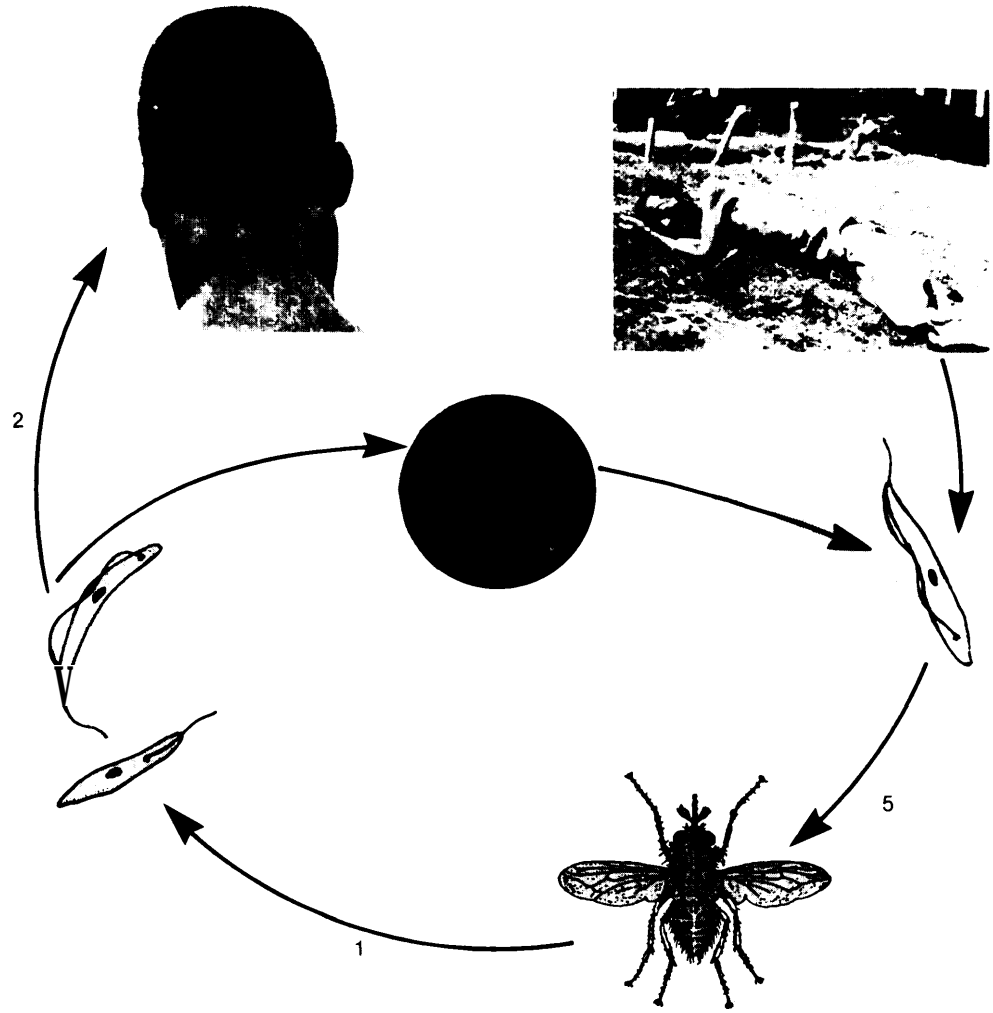
Either form of African sleeping sickness begins when an infected tsetse fly feeds on a human or animal host, depositing trypanosomes in the wound (see fig. **4-6).** The trypanosomes invade the host's blood, lymph, and tissue fluids. In cyclical waves, the trypanosomes wane, then reappear, as the body's immune system and the parasites interact. These parasites can undergo frequent changes in a specific surface protein, known as variant surface glycoprotein (VSG) or variant surface antigen. Located on the blood form of the trypanosome, VSGS stimulate the production by the host of a particular responsive and protective antibody.

Within any individual human or animal host, the VSGS of the trypanosome population shift over time through a repertoire of changes numbering potentially over 100, each having no exposed determinants in common with other past or future populations. Two distinct mechanisms appear to be responsible for the VSG changes, which are called antigenic switching. Each mechanism generates cohorts of parasites to which the mammalian host has not yet made antibody. Since antibodies raised against one variant are generally not effective against other variants, the trypanosome is able to evade the host's immune response.

Until the host can mount another antibody response, symptoms of fever, headache, and joint pain occur. As the infection progresses, lesions develop in the brain, heart, and small blood vessels. Ultimately, nervous system involvement develops, first with signs of insomnia and excitability, then coma and death. Symptoms and outcome are similar in both the acute and chronic forms, but the duration differs.

Incidence.—Recent estimates put 45 million people at risk of sleeping sickness infection in Africa. Until 1979, about 10,000 new cases were recorded annually, but since then, serious outbreaks have resulted in more than 20,000 new cases recorded per year (353). Because of the difficulties of diagnosing chronic cases and the usual occurrence of the disease in rural areas, these figures are probably underestimates. Although widespread across Africa (see fig. 4-7), sleeping sicknesss occurs in well-defined endemic foci because the tsetse fly vectors breed in rivers and streams. Unfortunately, those same water sources are essential to humans and grazing animals.

Figure 4-6.—Generalized Life Cycle of Trypanosoma *brucei* gambiense and T. b. *rhodesiense,* the Causes of African Sleeping Sickness (African Trypanosomiasis)



1. Trypanosomes develop in tsetse fly vector to a form infective to humans and other mammals.
2. Humans and animals are infected through bite of tsetse fly. Enlarged lymph nodes are an early sign of trypanosome infection.
3. Trypanosomes eventually invade the human host's central nervous system, causing classical symptoms of sleeping sickness, leading to coma and death.
4. Forms of trypanosome infective to tsetse fly vector are released into blood circulation.
5. Tsetse fly picks up infective form of trypanosome while biting infected human or other infected mammal.

SOURCE" Office of Technology Assessment, 1985. photos from H. W. Brown and F A Neva, Basic Clinical Parasitology (East Norwalk CT Appleton-Century-Crofts, 1983), used by permission

Interventions

Treatment for African sleeping sickness requires hospitalization because of the dangerous side effects and toxicity of the drugs, as well as the need for their intravenous administration. Although the infection is uniformly fatal without treatment, there is a risk (2 to 5 percent) of succumbing to the treatment itself.

Control of the tsetse fly vectors of sleeping sickness is currently the only feasible means of intervention. Because of the focal nature of transmission, insecticiding is feasible (no insecticide

Figure 4-7.—Geographic Distribution of African Sleeping Sickness (African Trypanosomiasis)

SOURCE: V. Zaman and L. Keong, *Handbook of Medical Parasitology* (Australia: ADIS Health Science Press, 1982), used by permission.

resistance exists, as yet, in the vectors) and has been used successfully, though it is expensive, contaminates the environment, and is labor-intensive. In some cases, clearing vegetation near river breeding sites has worked. Overall, vector control has met with only limited, sporadic success. Recent efforts have focused on the use of insecticide-impregnated traps that attract the vector flies.

Recent Progress

Since about 1979, trypanosomes have become increasingly popular for studies in molecular biology, The organisms of the T. *brucei* complex are becoming the *Drosophila* (fruit flies) of modern molecular biologists. The purpose of most of the studies using these trypanosomes has been to work out the intricacies of gene coding, transcription, translation, and expression, rather than to control African sleeping sickness. These studies have made many contributions to the fundamental understanding of gene function, however, and there is hope that useful spinoffs can be applied to controlling sleeping sickness.

More disease-focused work by American investigators is centered largely on the molecular biology of antigen switching of VSGS. Monoclinal antibodies (MAbs) to different VSGS have been produced in several laboratories (43). One laboratory deals exclusively with the nonvariant antigens and regulatory proteins, studying the stage-specific expression of membrane and internal proteins and host reactions to them. In this laboratory, an attempt is being made to find proteins that could be used in immunodiagnosis and metabolic targets for chemotherapy (16).

Chagas' Disease (American Trypanosomiasis)

Aspects of Natural History

Chagas' disease is caused by the protozoan parasite T. *cruzi*. Though sometimes congenital and occasionally transmitted through blood transfusion (308), Chagas' disease is primarily transmitted to humans (and other mammals) by reduviid bugs, blood-sucking insects found throughout Central and South America. Thus, it is primarily a disease of poor rural areas, where adobe brick houses and thatch roofs provide harboring sites for reduviid bugs to live and breed.

Several strains of T. *cruzi* exist in different parts of Latin America. The strains vary considerably in the pathology they produce in humans because of the range of immune system reactions they can evoke. About 150 species of mammals, including dogs, cats, guinea pigs, opossums, rats, and other rodents, are thought to be reservoir hosts of T. *cruzi*.

There is no effective cure for Chagas' disease. In the acute phase of the disease, when the parasites are invading internal organs, headaches, fever, anemia, and exhaustion may occur. The severity of this phase varies with the age of the patient. The younger the patient, the more severe the disease. Thus, children under the age of 2 may die, while adults may exhibit no symptoms. The

Photo credit: H. W. Brown and F. A. Neva, "Basic Clinical Parasitology, "Appleton-Century-Crofts, 1983. Reprinted by permission,

Megacolon, one effect of Chagas' disease.

acute stage of Chagas' disease may resolve completely in a few weeks or months or instead may pass into a subacute or chronic stage.

Long-term sequelae of Chagas' disease include grotesque enlargement of the digestive tract (megaesophagus and megacolon), circulatory problems, and central nervous system damages and most seriously, damage to the heart muscle, sometimes leading to death from heart failure.

Life Cycle. -T. cruzi infection in humans results when an infected reduviid bug bites a person, usually around the eye while the person is sleeping, and deposits feces containing 7'. *cruzi* parasites into the bite wound (see fig. 4-8). T. *cruzi* has two life stages in the mammalian host, one that circulates in blood and another that proliferates intracellularly within the tissues. Forms of the parasites infective to reduviid bugs are released into the mammalian host's circulation, ready to be picked up by reduviid bugs in the course of another insect bite.

Incidence.—Chagas' disease occurs in almost every country of Latin America: Brazil, Peru, Venezuela, Chile, Bolivia, Paraguay, Uruguay, Argentina, Colombia, Mexico, Costa Rica, and Panama (see fig. 4-9) (265). Although the vectors and reservoir hosts are also present across the Southern United States, only three indigenous cases of Chagas' disease have been reported. Two were infants reported to have contracted the disease in Texas in 1955, and the third was a woman from the Sacramento Valley area in California in 1982. None of the three had previously had contact with pets carrying the disease or had recent blood transfusions or had been outside the country (309).

It has been estimated that about 12 million of the 50 million exposed people living in endemic areas are infected with T. *cruzi* (229). Since notification of authorities regarding the presence of Chagas' disease is not compulsory, there are no reliable morbidity data. Studies in Brazil have shown Chagas' disease to be a significant cause of mortality in people under 45 years of age (287) and a heavy burden to society because of the need for hospitalization and disability assistance (268).

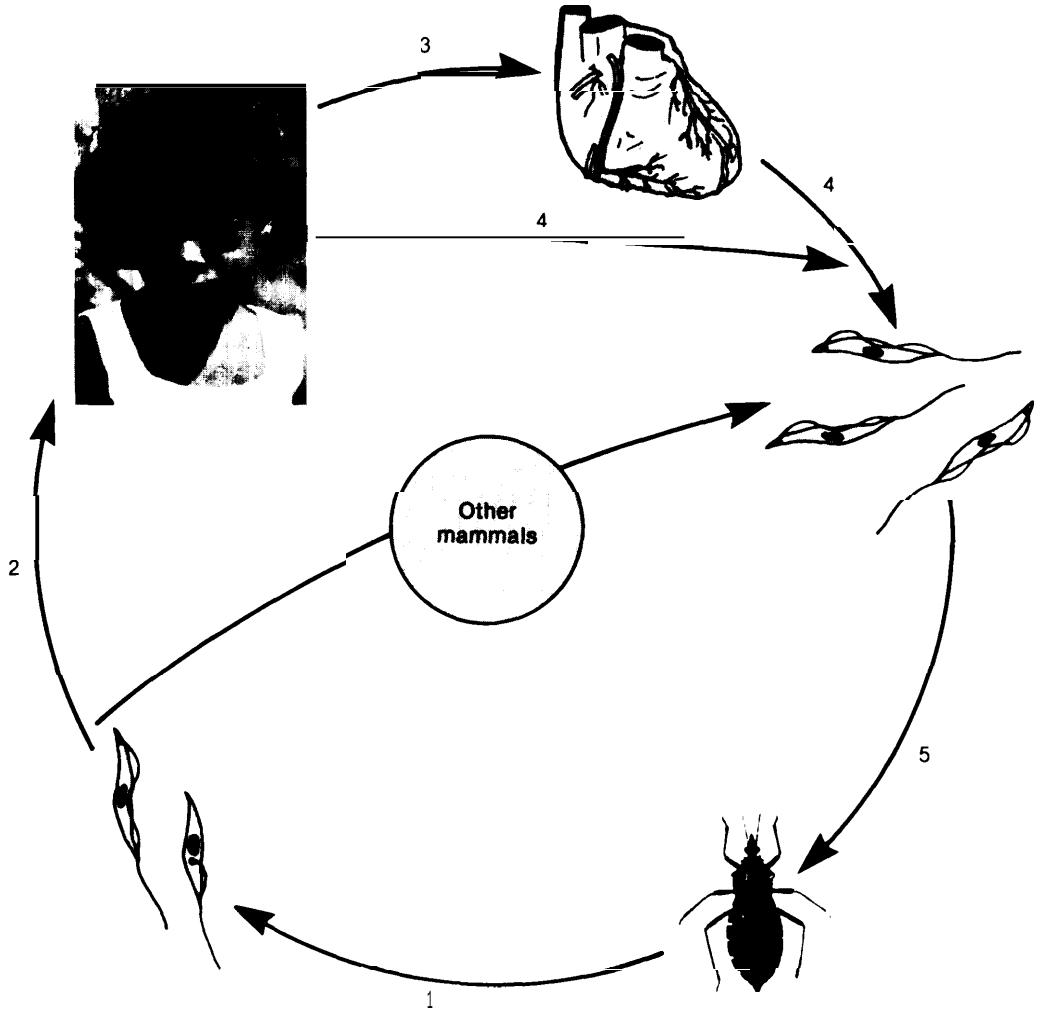
Interventions

Control measures for Chagas' disease concentrate on insecticide spraying of houses and upgrading of housing construction. In one area of Venezuela, the use of insecticides was believed to account for a significant decline in the percentage of the population infected with T. *cruzi* during the 1970s (29). Vector bionomics remains an important research topic for defining transmission areas, vector behavioral characteristics, and improved control measures.

Recent Progress

In an attempt to understand why the human host's immune system is not effective in controlling Chagas' disease, some investigators have examined the proteins produced by T. *cruzi.* There is no evidence for VSGS in T. *cruzi* (322), although a large number of local genetic strains do exist. Some other mechanism must be responsible for T. *cruzi's* ability to evade the human immune system.

Figure 4-8.— Life Cycle of Trypanosoma *cruzi*, the Cause of Chagas' Disease



1. Trypanosomes develop in the reduviid bug vector to a form infective to humans and other mammals.
2. Parasites deposited on human skin in insect feces at time of insect bite invade human through the bite wound. "Romana's sign," the swelling of one eye, is a sign of a reduviid bite.
3. Trypanosomes enter and multiply in muscle tissue, including the heart.
4. Forms of trypanosomes infective to reduviid bug vector are released into blood circulation.
5. Reduviid bug picks up infective form of trypanosome while biting infected human or other infected mammal.

SOURCE Office of Technology Assessment, 1985

Major surface proteins isolated from T. *cruzi* organisms resembling the insect stages of the parasite (grown in culture) and from mammalian blood stages were recognized by immune sera from naturally infected humans and experimentally infected mice **(259).** This means the immune system raises antibodies against both insect and blood stages of the parasite. MAbs to culture and intracellular stages of T. *cruzi* have been made by several workers, and Snary and colleagues (323) have demonstrated that the antigenic determinants are strain-specific. The ideal vaccine must

Figure 4-9.—Geographic Distribution of Chagas' Disease (American Trypanosomiasis)

SOURCES: World Health Organization, Geneva, Switzerland, and London School of Hygiene and Tropical Medicine.

produce antibodies that do not cross-react with heart and nerve tissue and that are effective against all strains and stages of T. *cruzi.*

The development of an effective therapeutic drug for Chagas' disease is a critical research need. With a therapeutic drug in hand, a simple effective test for early diagnosis of the disease would be essential, for once the long-term effects appear they are irreversible. Vaccine research is under way, but because the long-term pathology seems to result from the body's immune response against the parasite and cross-reacting with its own heart and nerve tissue, prospects for an effective vaccine are uncertain.

Fewer than 10 laboratories in the United States focus on T. *cruzi.* Most are in academic institutions, with one or two each in government and in industry. Significant research is taking place in South America, as well as in a few European laboratories. In part because of this dearth of effort, work on Chagas' disease has not advanced as much as that on some other diseases (16).

LEISHMANIASIS

Aspects of Natural History

Leishmaniasis is the collective term for the diseases caused by several species of the protozoal genus ***Leishmania.*** Among the protozoan diseases, leishmaniasis is commonly considered second in importance, following malaria.

Depending on the infecting species, leishmaniasis may appear in different forms. Cutaneous leishmaniasis, which appears as self-limiting and usually self-resolving sores located at the point of infection, is caused by *L. mexicana, L. braziliensis,* or *L. tropica.* Mucocutaneous leishmaniasis, which also begins as a sore, is caused by certain geographic strains of *L. brazdiensis* that commonly metastasize and proliferate in the nasal and pharyngeal mucous membranes. Gross destructive disfigurement of the face, nose, and throat results.

A third type of this leishmaniasis is a visceral form, caused by *L. donovani.* In this form, called "kala azar, " the spleen, liver, bone marrow, and lymph glands are the sites of parasite proliferation. Fatal outcome in children is common. Kala azar occurs sporadically in many tropical areas, but it has also appeared in epidemics, killing many thousands of people at a time in southern Asia. Recent epidemics of kala azar have resulted from the reemergence of the sandfly vector after spray programs were discontinued.

Photo credit *Dr Roberf Edelrnan,* **National** *Institutes of Health*

A lesion of cutaneous leishmaniasis.

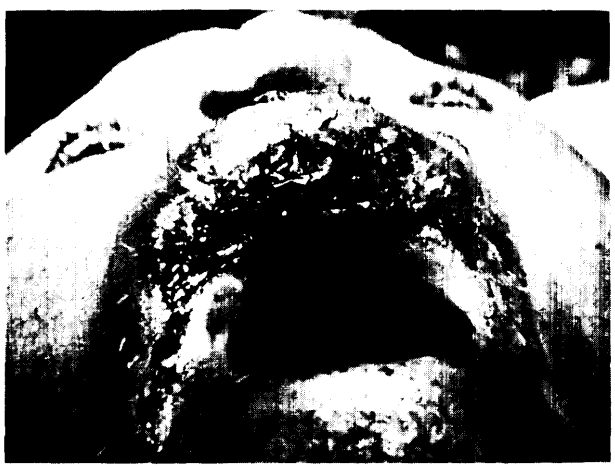


Photo credit" Office of Technology Assessment

Destruction of tissue resulting from mucocutaneous leishmaniasis.

Life Cycle

All types of leishmanial parasites are transmitted by blood-sucking phlebotomine sandflies, in which the parasitic organism undergoes part of its complex life cycle (see fig. 4-10).

Leishmania invade and multiply within the host's macrophages, cells that are part of the immune system. Since macrophages are specialized for ingestion and destruction of most foreign organisms, the ability of leishmanial organisms to live in them is paradoxical. A key to controlling leishmaniasis may be to identify a mechanism that will activate macrophages to kill *Leishrnania* and then to attempt to activate this mechanism with a vaccine or drug.

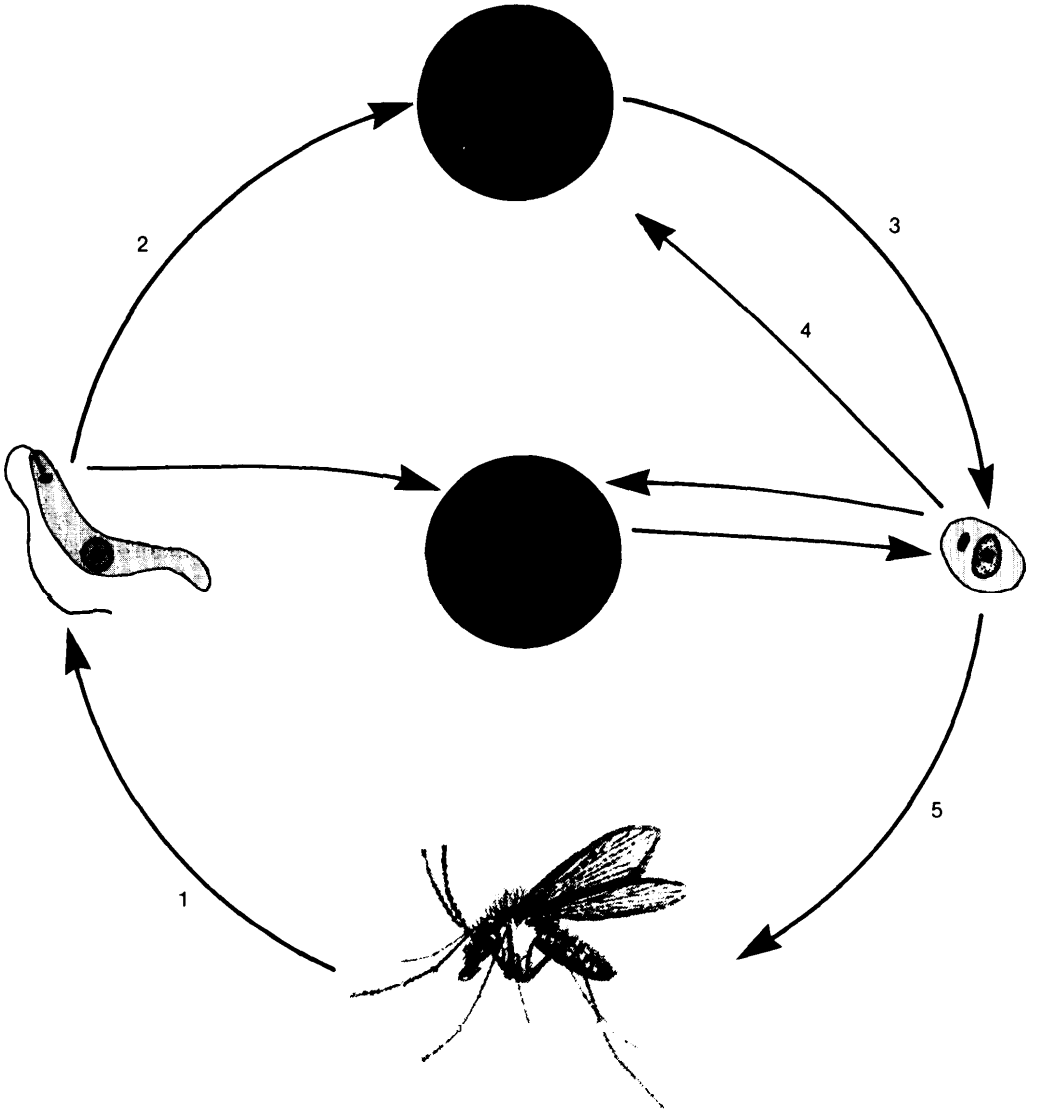
Incidence

The various forms of leishmaniasis are distributed widely, along the U.S. Texas / Mexico border, in Latin America, in the Mediterranean, and in Africa, India, and China (see fig. 4-11). Incidence rates range from a low in Guatemala of 1.2 per 100,000 in 1980, to a high of 60.5 per 100,000 in Costa Rica for the same year. A total of about 400,000 new cases *were* reported worldwide *in 1977,* 100,000 of which were in Bihar, a province of India where a severe epidemic of kala azar was occurring (341).

In some countries, the number of cases of leishmaniasis is increasing because of agricultural colonization of jungle areas. Most forms of the disease are transmitted to humans (via sandflies) from animals native to the jungle where the disease occurs. This makes living or working in areas in or near jungles a major health hazard. In the late 1970s, cutaneous leishmaniasis seriousl, impeded a Bolivian scheme to relocate people outside the overcrowded *altiplano.* Many of the colonists abandoned their land. More than 60 percent of the people who did said that leishmanial disease was their reason for returning to the mountains. Oil exploration and roadbuilding in several Andean countries have also been significantly hampered (265).

A seroepidemiologic survey in Panama revealed an apparent focus of leishmanial transmission, without detecting the presence of clinical infec-

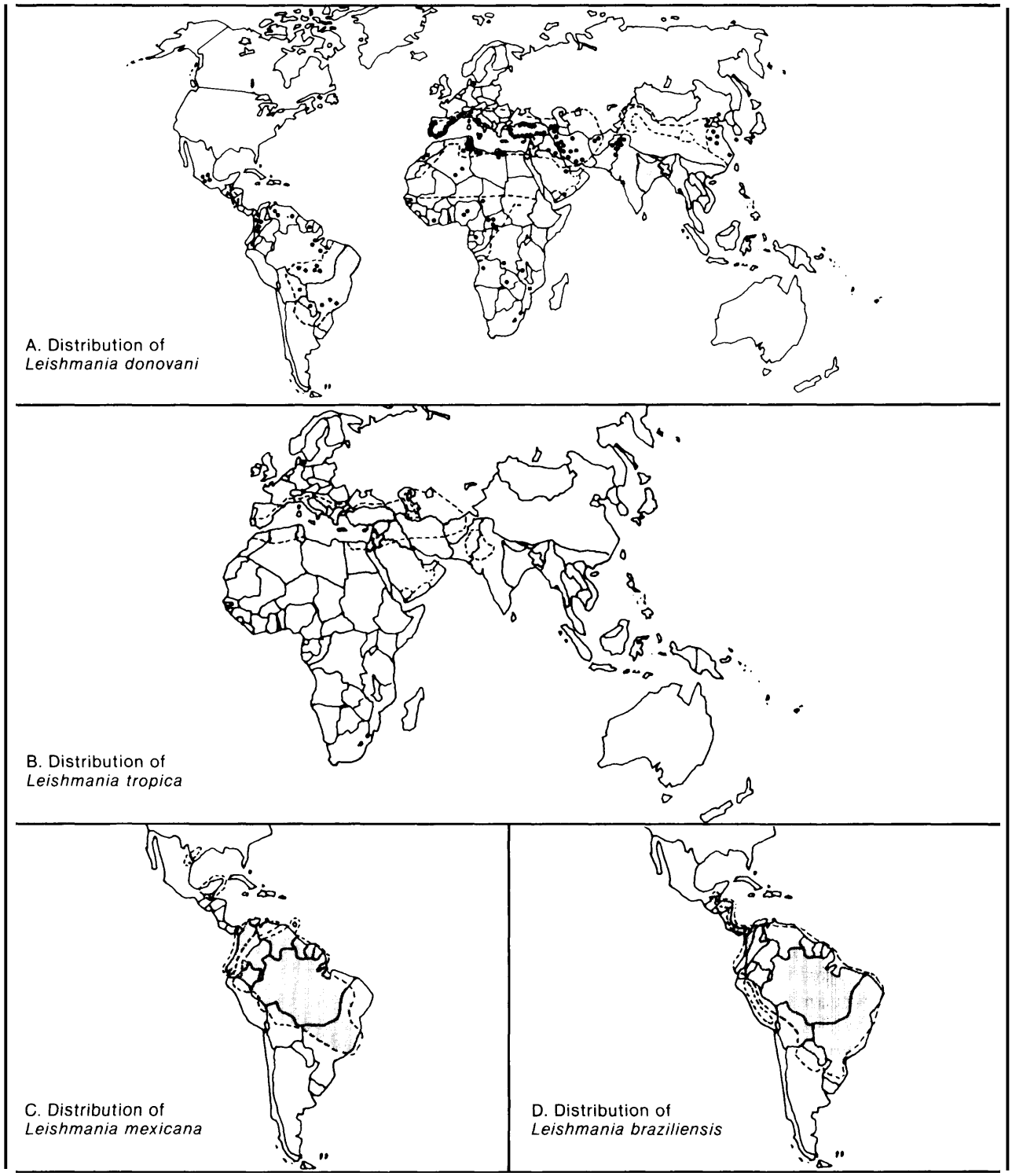
Figure 4.10.—Generalized Life Cycle of Leishmania, the Cause of Leishmaniasis



1. Parasites develop to "promastigote" stage infective to humans and other mammals in sandfly vector.
2. Parasites are transmitted to humans and other mammals through bite of sandfly.
3. Parasites transform to "amastigote" stage in mammalian host, multiplying within certain cells of the host's immune system.
4. Some amastigotes infect new cells in the mammalian host.
5. Some amastigotes are picked up by sandflies during bite of infected mammalian host.

SOURCE: Off Ice of Technology Assessment, 1985. Photo from H. W. Brown and F. A. Neva, *Basic Clinical Parasitology* **(East Norwalk, CT: Appleton-Century-Crofts, 1983), used by permission.**

Figure 4-11 .—Geographic Distribution of Leishmaniasis Caused by Four Species of Leishmania



SOURCE. U.N Development Program/World Bank/WHO, Special Program for Research and Training in Tropical Diseases, Slxth *Programme Report 7 Ju/y* **1981—31 December 1982 (Geneva: WHO, 1983).**

tion. Completely subclinical leishmaniasis **was** previously unknown and may be an important clue to vaccine development.

Interventions

For disease caused by most species of Lekh***mania,*** no effective prevention is known. However, immunity to Old World cutaneous leishmaniasis (also called Oriental sore) arising from *L. tropica* infection can be induced by inoculation of **a** susceptible person with organisms from an active lesion, **a** procedure apparently known from ancient times in endemic regions.

Specific treatment for leishmaniasis is now limited to antimony compounds. These compounds are not always effective and often have adverse toxic side effects. Another disadvantage of these compounds is that they require daily injections for 10 to 20 days, making them impractical for patients living in remote and inaccessible areas. Hospitalization for such **a** period is not only expensive but also a major inconvenience to patients who cannot afford to leave work or their farms for an extended period. For these reasons, improved treatment of the tens of thousands of existing **cases is a** priority research goal. The Pan American Health Organization/WHO is attempting to foster development of new therapeutic drugs. One, allopurinol, in combination with other drugs, is a promising new treatment (393).

Recent Progress

Fewer than 10 laboratories **in the United States study leishmanial organisms. The difficulty in distinguishing between** *Leishmania* **species (necessary to properly predict clinical outcomes and select treatment) has been a persistent problem.** The solution, however, may be aided by biotechnology. In recent years, MAbs have been prepared against a variety of antigenic determinants in *Leishmania* **spp. (16) and used to probe morphologic and taxonomic differences. Rapid identification of** *Leishmania* spp. may soon be possible with a recently published technique of DNA hybridization (40s).

A variation of the enzyme-linked immunosorbent assay (ELISA), called the "DOT-ELISA" method **(267),** is also a major advance, allowing for rapid easy field diagnosis. These and other methods would permit early treatment of the destructive mucocutaneous form of the disease and would also facilitate precise epidemiologic field studies.

The possibility of developing a vaccine against the promastigote form of the leishmaniasis parasite (the stage transferred through the bite of the sandfly) remains. Such a vaccine would have limited usefulness because it would be ineffective against the amastigote form of the parasite (the stage which lives within the microphage). The transformation from promastigote to amastigote occurs rapidly within the host, before a vaccine-initiated antibody response could be effective.

FILARIASIS

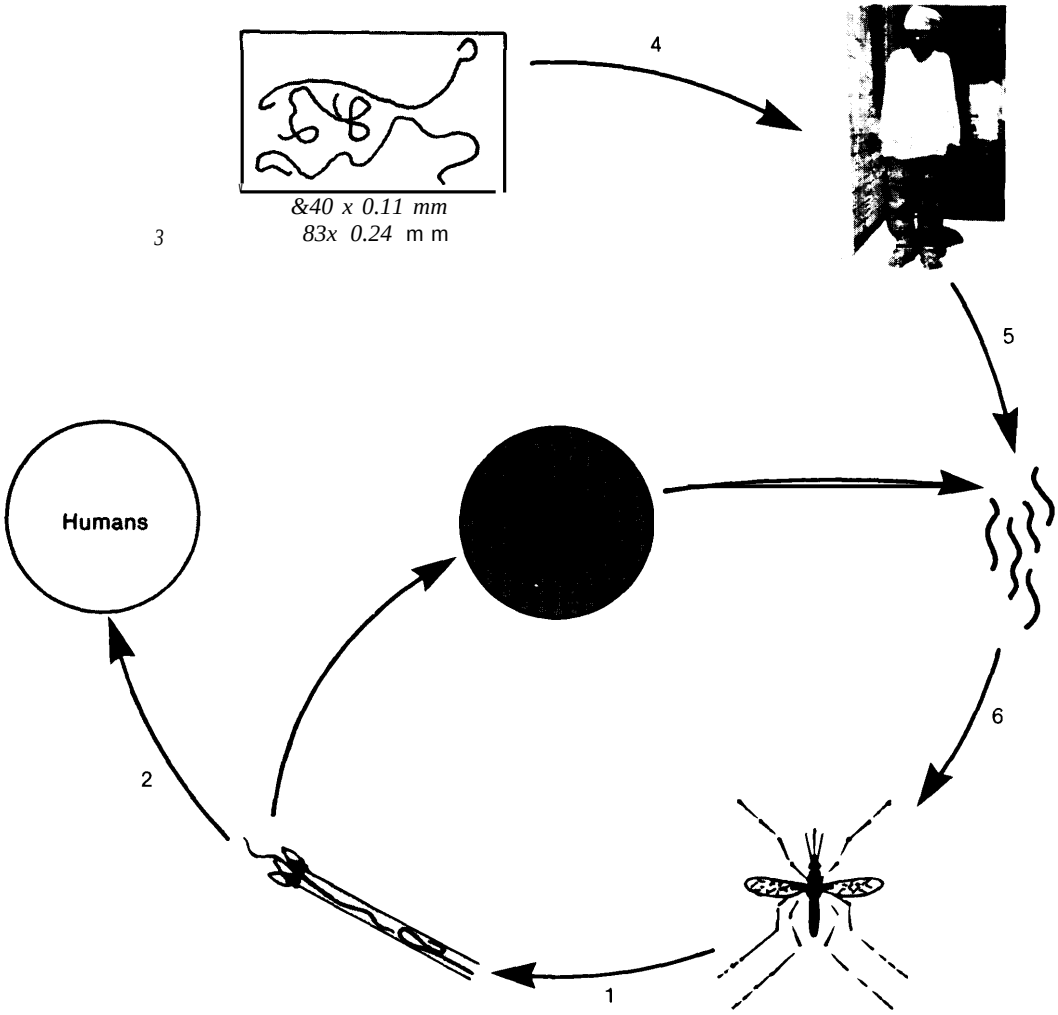
Aspects of Natural History

Filariasis is a collective term for several distinct parasitic infections of tissue-dwelling, threadlike nematodes, which **are** transmitted by mosquitoes and other insects. There are at least eight different types of human filarial infections, among them infection by the infamous guinea worm, which before modern chemotherapy evolved **was re**moved by gradually winding the protruding worm around **a** stick. Probably the most impor-. tant of the filarial parasites, in terms of worldwide prevalence and severity of disease, are *Wuchereria bancrofti* and *Brugia malayi,* which cause lymphatic forms of filariasis; and *Onchocerca volvulus,* the agent of onchocerciasis (river blindness).

Life Cycles and Interventions

The life cycles of *W. bancrofti* and *B. malayi* are fairly similar (see fig. 4-12). These organisms are transmitted to humans by several species of mosquitoes, including common household pest species. The adult filarial worms live in the human host's lymphatic system and cause pathol-

Figure 4-12.-Generalized Life Cycle of Two Important Filarial Worms: Wuchereria bancrofti and *Brugk* malayi



1. Infective larvae develop, but do not multiply, in mosquito vector.
2. Larvae deposited on skin of human or other mammalian host (B. *malayi* only) through mosquito proboscis at time of bite.
3. Larvae penetrate skin, migrate to host's lymphatic system, and mature.
4. Masses of adult worms can block lymph vessels, causing accumulation of lymph fluid and growth of lymph tissue, in a manifestation called elephantiasis.
5. Adult worms release immature microfilariae into blood circulation, usually in a circadian rhythm.
6. Mosquitoes ingest microfilariae during bite of infected human or other mammal.

SOURCE: Office of Technology Assessment, 1985. Photo from F. W. Brown and F. A. Neva, Basic Clinical Parasitology (East Norwalk, CT: Appleton-Century-Crofts, 1983), used by permission.

ogy that differs with the host's immune response. Inflammation and gross obstruction results in varying degrees of swelling of the lymph glands, which may result grotesque enlargement (elephantiasis) of the legs, breasts, or scrotum. Adult worms release immature forms (microfilariae) that circulate in the human blood and then infect feeding mosquitoes to complete the transmission cycle. Drugs are available to kill the microfilariae, but the means to kill mature worms are poor.

0. volvulus parasites are transmitted to humans by blackflies of the genus *Simulium.* These blackflies require running water to complete their life cycles, limiting their habitat mainly to areas around rivers (hence the name river blindness for onchocerciasis). The adult parasitic worms live in the tissues of the human body and often form large nodules where an intertwined clump of worms localizes. Microfilariae released by the adult worms migrate through the human host's body in subcutaneous tissues where they can be picked up by feeding blackflies. When microfilariae reach the human eye, blindness can result. The prevention of blindness is imperfectly achieved by chemotherapy and surgical removal of the nodules. Few preventive measures are available, and larvicides used to control the blackfly vector of onchocerciasis are subject to resistance and have only transient effects.

Incidence and Prevalence

Filariasis due to W. *bancrofti* has a wide but focal urban distribution throughout the Pacific region, Asia, Africa, and Latin America (see fig. 4-13) (406). Lymphatic filariasis caused by B. *malayi* is primarily found in rural foci in Sri Lanka, Thailand, Malaysia, Vietnam, China, South Korea, Borneo, and Indonesia. Onchocerciasis is found in central and western Africa, North Yemen, Saudi Arabia, Mexico, Venezuela, Colombia, Brazil, Ecuador, and Central America.

It is estimated that bancroftian filariasis and onchocerciasis are more prevalent today than they were more than 100 years ago (256). More than 300 million people are exposed to mosquito-transmitted lymphatic filariasis, and more than 30 million are infected. The main endemic areas in India remain, and there is little control of the disease in Africa, where in Savannah areas it is estimated **that more than 15 percent of the adults are infected.**

Obstacles to Research

Considering the great number of people affected or at risk, their widespread geographical distribution, and the severity of their pathology, the filarial diseases are relatively neglected by American researchers. A major obstacle to research on filariasis is the difficulty in maintaining filarial organisms for laboratory study. Their complicated life cycles and the unavailability of suitable animal models make these parasites among the most frustrating to work with.

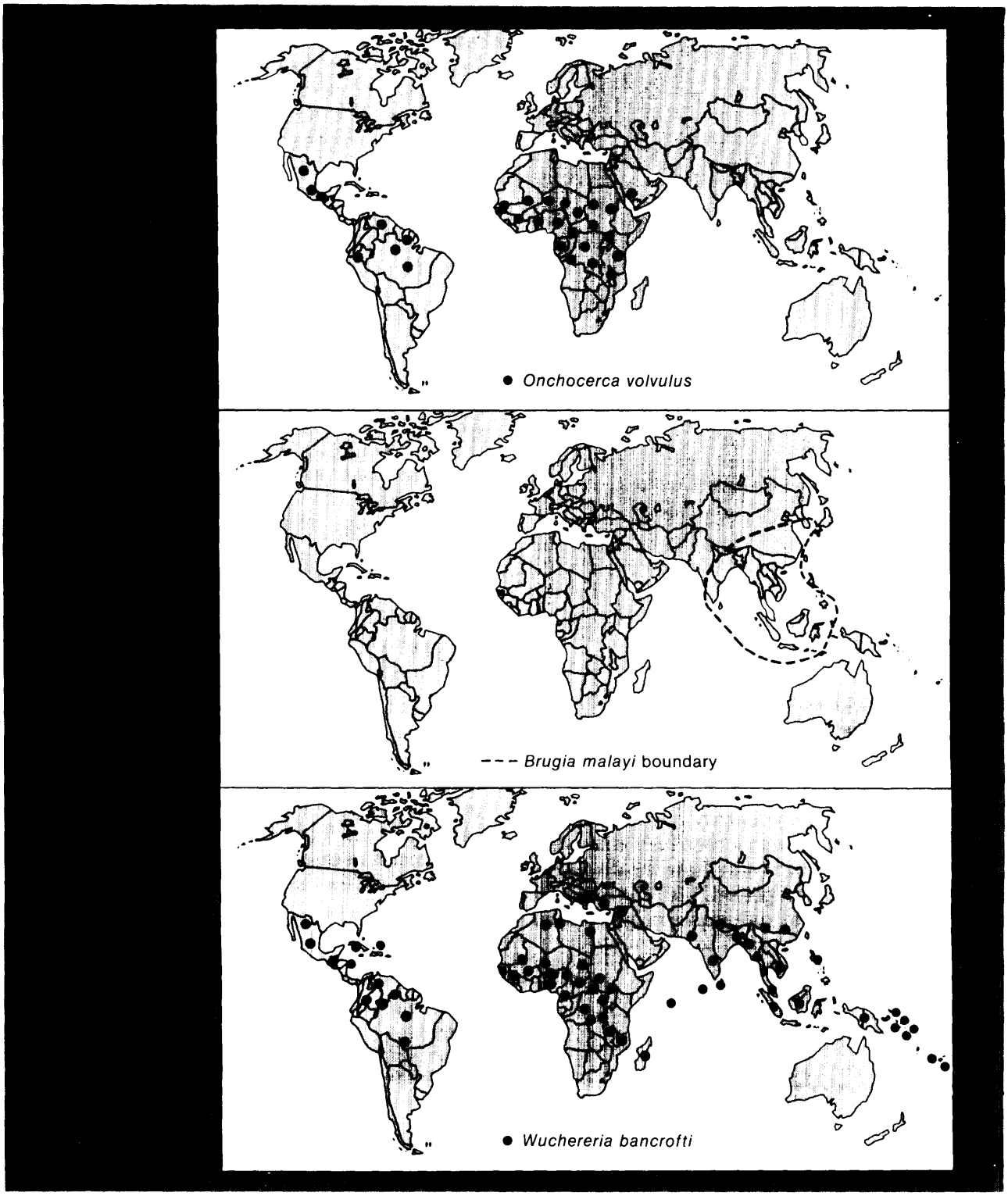
LEPROSY (HANSEN'S DISEASE)

Aspects of Natural History

Leprosy is a chronic bacterial infection that continues to be an important public health problem in many countries. The disease is caused by *Mycobacterium leprae,* a bacterium similar to the one that causes tuberculosis. Leprosy is mainly a disease of the skin and peripheral nerves, but it is characterized by a wide array of clinical presentations.

Much of the pathology of leprosy is associated with a defective cell-mediated immune response in certain individuals. Depending on the host's immunologic response, leprosy ranges from benign tuberculoid leprosy, with localized skin lesions and nerve involvement (sometimes severe peripheral neuropathy) and the presence of few M. *leprae* bacteria, to lepromatous leprosy, with spreading lesions that become nodular and dis-

Figure 4.13. -Geographic Distribution of Major Filarial Diseases: Infection With Onchocerca volvulus, Brugia malayi, **and** Wuchereda bancrofti



SOURCE V Zaman and L. Keong, *Handbook of Medical* **Parasitology (Australia: ADIS Health Science Press, 1982), used by permission.**

m

figuring, resulting in destruction of the nose, involvement of the vocal cords and eyes, and often severe nerve damage, with a heavy infection of *M. leprae.*

Questions about why leprosy has such varied effects on its victims have not been fully answered. Researchers are not even sure how the disease is transmitted. The latent period, the time between infection and the actual appearance of symptoms, often lasts for many years. The individual is capable of unknowingly infecting others during this time. Leprosy is more likely to be spread by chronic exposure to dried skin lesion matter and nasal secretions from the lepromatous and more severe borderline patients. The general consensus seems to be that *M. leprae* bacteria enter the human body through the respiratory system, although some researchers suspect entry may also be through the skin (406).

Immunologic diagnostic techniques have shown that people with tuberculoid leprosy have a strong and effective cell-mediated immune response (via lymphocytes) that controls the infection, whereas lepromatous leprosy patients do not. There is some evidence to suggest a genetic basis for this difference. The nerve damage in patients with lepromatous leprosy seems to result from an absence of cellular immune response. Characterization of this defect in Iepromatous leprosy patients is being investigated with MAbs that can identify lymphocyte subsets and also by analysis of the patients' genetic type.

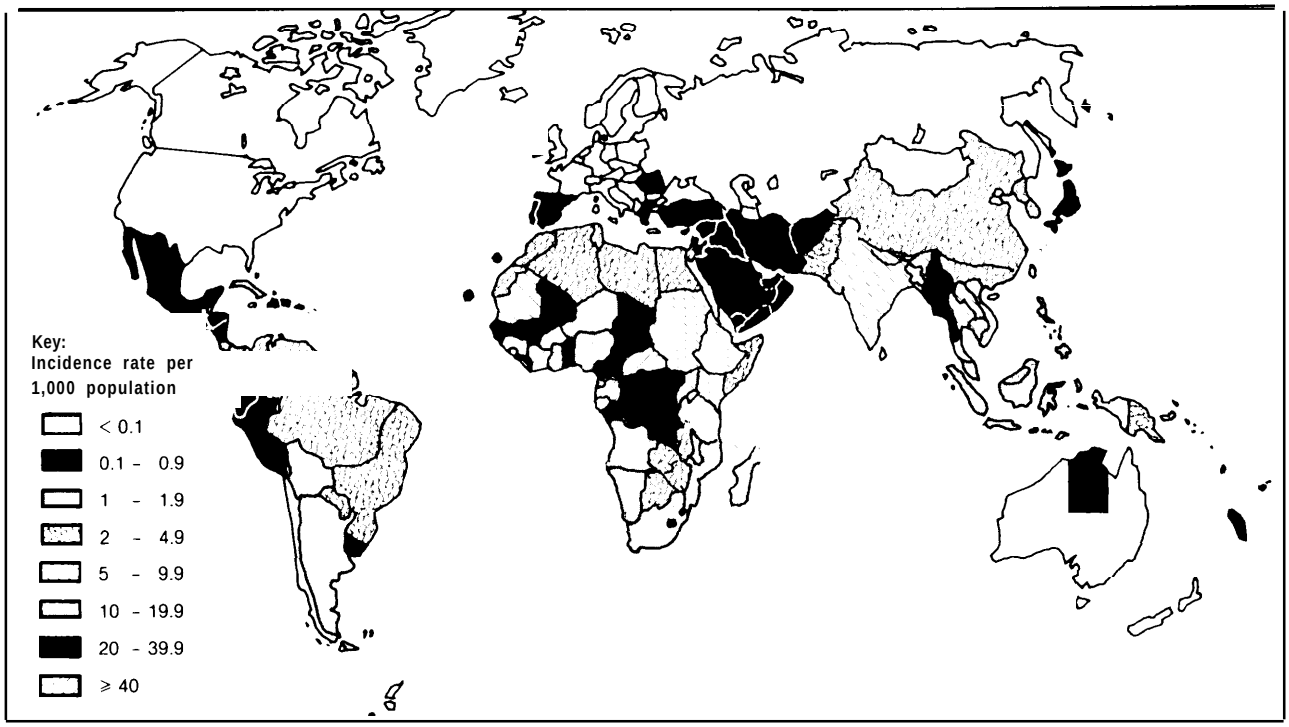
Incidence and Prevalence

Worldwide there are an estimated 15 million leprosy cases (307). The prevalence of leprosy has been reduced in many places, but the overall incidence (i.e., the number of new cases per year) has not changed with advances in science (see fig. 4-14). In some very small, isolated communities in parts of Africa and Australia, the prevalence of leprosy may be as high as 1 out of every 50 inhabitants. The disease is also common in southern Asia, especially India (210). In China, an estimated 500,000 cases of leprosy occurred in the early 1950s, but fewer than 200,000 cases were reported in 1984 (307). As of 1984, there were 2.5 million cases in Southeast Asia alone (135).

In the Americas, there are about 400,000 cases of leprosy, 80 percent of the new cases occurring in Argentina, Colombia, and the Amazon area of Brazil (265). The recorded incidence of leprosy in the Americas has almost doubled in the last 10 years, but the increase is thought to reflect improvements in case finding and notification of authorities, rather than to be a true change. Over half the clinical cases are of the more severe lepromatous form. However, as many as four-fifths of those infected with M. *leprae* never get sick, though they may transmit the disease to those with more susceptible immune systems (210).

About 20 cases of leprosy acquired in the United States are diagnosed each year, occurring in Texas, Louisiana, California, Florida, and Hawaii. Of the 250 new cases of leprosy diagnosed in the United States in 1982, 233 were immigrants

Figure 4-14.—Geographic Distribution of Leprosy



SOURCE: L. M. Bechelli and V. Martinez Dominguez, "The Leprosy Problem in the World, " Bull. W.H.O. 34:811-826, 1966

who had contracted the disease in their homelands. In the past, most cases have come from Mexico and the Philippines, but in recent years immigrants from Cuba, Haiti, El Salvador, Nicaragua, and Southeast Asia have entered the United States with leprosy (135).

Why leprosy occurs more in some parts of the world than in others is not fully understood.

Interventions

A number of useful drugs are now available for leprosy treatment. The most effective drug is dapsone. Unfortunately, however, strains of *M. leprae* **have** developed resistance to dapsone (217). This situation has resulted in new recommendations for combination chemotherapy for leprosy that will shorten the treatment period and increase the likelihood of effective control of the disease. If organized and administered well, combination chemotherapy will lighten the workload of health services, improve patient compliance, and result in better prognosis.

Vaccination against leprosy is in the human trial stage, but still years from proof of its effectiveness and routine use. Research on the epidemiology of leprosy is still needed to improve intervention strategies.

Recent Progress

A small number of laboratories in the United States, probably fewer than 10 (including the U.S. Public Health Service in Carville, LA) specialize in leprosy research. Past leprosy research efforts were hampered by the inability of researchers to grow *M. leprae* in culture and also by the lack of a suitable animal model. The introduction of the armadillo model of infection in the early 1970s has helped both in the characterization of the disease and in the development of serodiagnostic procedures and a potential vaccine (307). The fairly recent discovery of the susceptibility of mangabey monkeys (217) may also help research efforts. The problems at this point are the slow growth rate of *M. leprae* in culture and the inability of arma-

dillos to breed in captivity, necessitating their continual trapping from the wild.

Despite the paucity of workers, the tools of biotechnology are being applied to *M. Ieprae.* At **least** three investigators are preparing MAbs as part of studies on the immunochemistry or antigenic structure of the bacterium (16).

TUBERCULOSIS

Aspects of Natural History

Tuberculosis is caused by the bacterium *Mycobacterium tuberculosis,* transmitted mainly by airborne droplets from person to person. There is no insect vector or animal reservoir. Tuberculosis remains a major threat to health in many parts of the world, causing several million deaths annually. Though basically a chronic respiratory disease, tuberculosis can spread into the cardiovascular, endocrine, and genital systems, and into the lymph nodes, bone, brain, kidneys, and other organs (406).

Incidence

A 1982 worldwide estimate put the number of tuberculosis cases at 11 million (265), with some 3.5 million new cases occurring each year (92). Tuberculosis is still a serious problem in most countries of the world. About 500,000 deaths are attributed to the disease each year.

Even in countries such as Canada and the United States, with highly developed coverage for diagnosis and treatment of tuberculosis available, a significant number of cases of tuberculosis are encountered each year. Often the disease is present among immigrants arriving from tuberculosis-prevalent tropical areas. From 1962 to 1975, prior to the current wave of immigrants to the United States from Indochina, the tuberculosis case rate among children under 14 in the United States decreased from 10.4 to 3.7 per 100,000, representing a 9-percent decline per year. But this downward trend has not continued, and the rate in 1984 was about the same as that of 1975 (281). In 1980, some 30,000 new cases of pulmonary tuberculosis were reported in the United States (70).

Interventions

In the past, control of tuberculosis was based on the identification, isolation, and treatment of patients with active disease, since these patients are the source of continued transmission and spread. More recently, with the advent of effective chemotherapy and reduction of active cases, developed countries with lower prevalence of tuberculosis have emphasized identification of newly infected persons via the tuberculin skin test and treatment of these individuals, in addition to identification and treatment of persons with active disease. Developing countries continue to emphasize identifying and treating patients with active disease, who account for most of the transmission. Tuberculosis is generally diagnosed by sputum microscopy or culture.

Treatment of tuberculosis patients consists of daily administration of one or more drugs in combination for 6 to 12 months. The drugs most commonly used include isoniazid (INH), streptomycin, Para-aminosaliqlic acid (PAS), pyrazi.namide, and rifampicin. If the course of treatment is followed properly, cure rates can be as high as 100 percent (406). Because of the practical problems of long-term treatment, however, a 100-percent cure rate is seldom realized.

Unfortunately, some strains of *M. tuberculosis* have developed resistance to INH, the most effective drug available. Cases of INH-resistant tuberculosis are commonly reported in tropical areas from Asia to Latin America. Patients infected with resistant strains must take several chemotherapeutic drugs, and for a longer time period, before the infection is arrested.

A factor strongly contributing to the resistance problem is the high cost of rifampicin. This drug, when used with INH, is highly effective in controlling tuberculosis, but it costs about 400 times as much as INH (see ch. 9). Developing countries that cannot afford to use rifampicin in their treatment regimes often opt for other less expensive drugs. The short-term savings, are lost, however, because patients often do not complete long-term regimens. Partial treatment that does not eliminate the infection encourages the proliferation of drug-resistant organisms, as the most susceptible are kiIIed off even with an incomplete course of therapy.

Despite the availability of a vaccine for tuberculosis, Bacillus Calmette-Guerin (BCG), there is considerable controversy as to its effectiveness. BCG vaccine is derived from a live, attenuated bovine tubercle bacillus, isolated from a single strain by the Pasteur Institute 50 years ago. BCG vaccination of uninfected persons can produce high resistance to tubercle bacilli, but the protection against tuberculosis has varied greatly in field trials. Since the vaccine was made years ago against only one isolated strain, it may not be capable of immunizing individuals against all currently active strains of *M. tuberculosis. Never*theless, some trials have shown very effective protection, and BCG vaccine is still recommended in high-risk areas.

Recent Progress

The tuberculin skin test is not an adequate predicter of infection or active tuberculosis, particularly for research purposes. The use of antigen probes and ELISA methods may be helpful in more accurately characterizing the state of an infection (16).

DIARRHEAL AND ENTERIC DISEASES

Aspects of Natural History

Diarrheal diseases, all of which are transmitted by fecal contamination of food and water, constitute a clinical syndrome of varied etiology. Such diseases are caused by a variety of viruses (primarily rotaviruses), bacteria (Shigella, Sahnonella, *Cryptosporidium, Escherichia coli, Campylobacter,* and *Yersinia),* protozoa *(Entamoeba* and *Giardia),* and worms *(Ascaris, Ancylostoma,* and *Necator),* interacting in a complex fashion within the susceptible host. Diarrheal diseases are distributed worldwide.

Diarrhea is primarily a disease of infants and children. The great danger in diarrheal disease is the dehydration and subsequent shock caused by tremendous losses of fluids and electrolytes (salts). Severe dehydration is the most frequent cause of diarrheal deaths. Although treatment directed at the disease-causing organisms may or may not be effective, there now exists effective treatment for most cases of dehydration caused by diarrhea. Oral dehydration therapy (ORT) for diarrheal diseases is considered one of the most significant therapeutic advance in the past several decades (see ***Case*** *Study A: Oral Dehydration Therapy for Diarrheal Diseases).*

In 1980, WHO conservatively estimated that among children under the age of 5, 750 million to 1 billion diarrheal episodes occur yearly in Africa, Asia (excluding the People's Republic of China), and Latin America (324). Data from several developing countries indicate that children under 5 years of age in these countries typically experience four to eight diarrheal episodes annually (23,215,216). In contrast, infants in the United States and other developed countries experience one or two diarrheaI episodes yearly. In some countries, up to 45 percent of all hospital visits during the months of highest diarrhea prevalence are due to childhood diarrhea, and case fatality rates as high as 40 percent have been recorded (249).

A comparison of death rates between children under 1 year of age in Latin America and North America is startling. For the United States and Canada, the mortality rate due to diarrheal disease among infants in 1979 was 21.9 deaths per

100,000 infants; for Latin America, it was 914.6 per 100,000. The Latin American figure is 40 times higher, which means almost 1 in 100 infants born there dies of diarrheal dehydration. Wherever the infant mortality rate exceeds 100 per 1,000 births, at least one-third of the deaths can be attributed to diarrhea (216,257).

Viruses

The complex of diarrheal diseases caused by viruses-rotaviruses, Norwalk-like agents, adenoviruses, astroviruses, enteroviruses, coronaviruses, calciviruses, and others, perhaps not yet identified—present extreme difficulties in diagnosis (15). Viral agents cause a significant amount of diarrheal illnesses in the tropics, but very little is known about any of them except rotaviruses.

Rotaviruses, the most frequently isolated group of viruses, have a worldwide distribution. They were first detected in humans in 1973. Rotaviruses, which are believed to cause one-third of all diarrheal disease in the world, may cause up to 40 percent of diarrheal disease in children in developed countries. Serologic studies have shown that by the age of 2, nearly all children have been infected with rotaviruses.

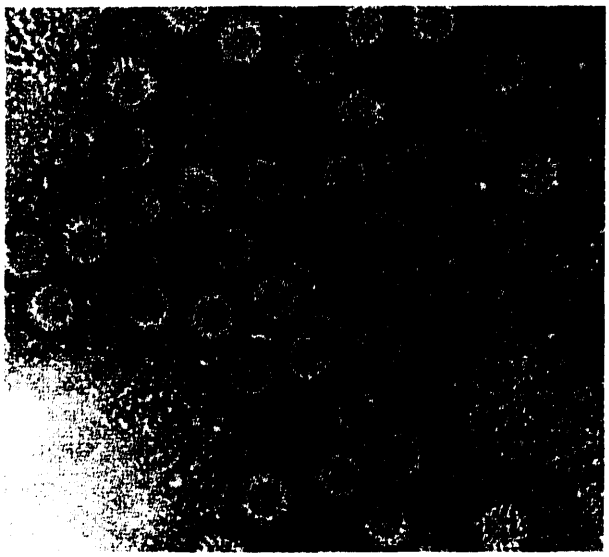


Photo credit: S. S. Raphael, "Lynch's Medical Laboratory Technology," W. B. Saunders Co., 1983. Reprinted by permission.

Electron micrograph of a rotavirus, a major cause of diarrheal disease in children.

In Australia, Canada, the United Kingdom, and the United States, a large percentage (40 to 60 percent) of all children hospitalized with diarrhea are infected with rotaviruses; the percentage in countries like Guatemala and El Salvador is smaller (20 to 40 percent) (371,420). However, since the incidence of all diarrhea] disease is much higher in developing countries than in developed countries, the toll due to rotaviral infection in these developing countries is actually much greater than the percentages indicate.

Growing recognition of the importance of rotaviruses emphasizes the need for further epidemiologic, clinical, and basic research. Rotavirus biology currently is studied at the National Institutes of Health, where each of the rotavirus genes has been cloned into bacteria and identified (117). Immunologically based diagnostic testing can be used for field studies of prevalence and incidence. Since a rotavirus vaccine exists for animals, a major objective now is to develop one for humans.

Bacteria

Numerous bacteria are known to cause diarrheal illness, and the list continues to grow as laboratory identification methods improve. In many areas of developing countries, the facilities needed to identify the agents responsible for diarrhea are not available. The question of causality is complicated by the wide variety of bacteria which live harmlessly in the intestine. This large "intestinal flora" confounds efforts to isolate and identify the important pathogens, among them enterotoxigenic (toxin-producing) *E. coli, Shigella* **spp. (which cause dysentery),** ***Salmonella*** **spp. (which cause food poisoning and typhoid fever),** *Vibrio cholerae* (which causes cholera), and ***Campylobacter.***

At present, there is a great deal of concern about the apparent rise in antibiotic-resistant bacteria. Two separate factors may be responsible for the increase. One factor is the widespread misuse of antibiotics both in the United States and abroad, due to ineffective dosing of individuals, indiscriminate prescribing of drugs (regardless of the etiologic agent), and the availability of antibiotic drugs over-the-counter in many developing countries. As a result of this misuse, many

intestinal bacteria, both pathogenic and nonpathogenic, are being exposed to antibiotics. Most intestinal bacteria are killed by antibiotics, but those bacteria that have some sort of resistance mechanism, often genetically determined, survive and are passed on.

The second factor is the ability of many intestinal bacteria to exchange genetic material among different strains, species, and even genera through the transfer of DNA. Bacteria that survive antibiotic exposure may transfer the genes that code for their resistance to previously susceptible bacteria, and these bacteria in turn incorporate them into their genetic material and pass them on to both pathogenic and nonpathogenic bacteria. Thus, in the past, a cholera infection might have been successfully treated with a few highly effective doses of tetracycline, but now larger doses of two or more other antibiotics may be required to combat the disease. Strains of E. *coli, Shigella,* and *Vibrio cholerae* have all been shown to be antibiotic resistant.

Escherichia coli.—E. *coli* is second to rotaviruses as an important cause of diarrheal disease. For the American traveling abroad (or the foreign visitor touring the United States), *E. coli* is frequently the source of the infamous travelers' diarrhea.

Ironically, although *E. coli* is one of the most intensely studied of all organisms in the laboratory, little is known about its disease-causing abilities. Most strains are harmless inhabitants of the intestine, and only certain strains cause disease: enterotoxigenic E. *coli* produces toxins that result in excessive fluid production; enteroinvasive *E. coli* invades the cells of the intestinal wall; and enteropathogenic *E. coli* produces a toxin similar to that of *Shigella,* which causes diarrhea in infants. Investigators are currently studying the genetic basis for disease-causing properties of different *E. coli* strains.

Shigella. —In 1981, there were 19,859 cases of diarrhea due to *Shigella* reported in the United States (366). Infections by *Shigella dysertteriae* result in bacillary dysentery, a serious and sometimes fatal disease. Most *Shigella* infections, however, are by species other than S. *dysenteriae (e.g., S. sonnei* and S. *flexneri),* and the symptoms are not as severe. *Shigella* is difficult to study because it colonizes only primates; thus, research on its pathology is very expensive. The genes coding for the attachment factors (which allow the organism to adhere to the intestinal wall) have been cloned and inserted into *E. coli.*

Salmonella. —This genus is frequently divided into *Salmonella typhi,* the cause of typhoid fever, and the nontyphi species. In general, the nontyphi species of *Salmonella* cause self-limited gastrointestinal distress, although some species may cause bacteremia bacteria in the blood. The wide variety of symptoms associated with *Salmonella* infection, ranging from mild flu-like stomach upsets to severe food poisoning to typhoid fever, make the collection of accurate incidence and prevalence statistics almost impossible.

In 1981, there were 39,990 cases of salmonellosis food poisoning reported in the United States (367). Salmonellosis is usually associated with the consumption of contaminated livestock or poultry products. In that year, there were approximately half of the 510 cases of typhoid fever reported in the United States, about half of which were acquired during travel abroad. During the period 1970-80 while the incidence of typhoid fever in Latin America increased, the number of cases remained stable in North America and the Caribbean region (265).

Sahnonella spp. usually cause endemic diarrhea, but they may cause epidemics. The need for improved sanitation and new antibiotics was brought forcefully home during a nontyphoid epidemic in Mexico in 1972-73, when it was discovered that the strain causing the epidemic was resistant to chloramphenicol, the drug of choice, and to other antibiotics (265).

Recently, researchers at the Walter Reed Army Medical Research and Development Command cloned *Shigella* genes into an attenuated live typhoid vaccine developed by a group of researchers in Switzerland. The result was a vaccine that produced immunity to both Shigella and Salmo*nella* (126,423).

Vibrio cholerae. -Cholera occurs in both endemic (in parts of China and India) and epidemic forms (in Asia and Africa). Because of improved

sanitation in many countries, cholera epidemics are not as common as in the past, although one reached the U.S.S.R. as recently as 1970 (406). For unknown reasons, cholera epidemics have spared the Western Hemisphere.

The severe diarrhea characteristic of cholera is caused by the action of a bacterial toxin on the gut wall. One of the factors that makes cholera so virulent is the number and variety of transmissible genetic elements, which vary from one strain to the next. Researchers have been collecting cholera strains from endemic areas around the world, and recombinant DNA libraries, consisting of segments of genes from wild-type organisms and laboratory-grown strains, have been created. By studying and comparing the gene segments of toxigenic and nontoxigenic strains, scientists hope to pinpoint exactly which genes are responsible for cholera's virulence **(16).**

Campylobacter. —Various species of *Campylobacter* **are** commonly the cause of sporadic diarrhea in developing and developed countries (45). Following rotavirus and enterotoxigenic E'. *coli*, ***Campylobacter*** is the third most common cause of diarrhea in developing countries (297). ***Campylobacter*** also is a "frequent, cosmopolitan risk to travelers" (278). Epidemics sometimes affecting thousands of people, have been caused by *Campylobacter* contaminating unpasteurized milk, chicken carcasses, and water (194).

Protozoa and Other Agents

There are several protozoal diarrheal pathogens, among them ***Entamoeba*** spp., Giardia *Jamblia*, and *Cryptosporidium* spp.

Giardiasis is now recognized as significant and ubiquitous throughout the United States, but is more prevalent in tropical countries. Outbreaks, such as occurred in Aspen, CO, and Rome, NY, have been well publicized (313). G. *lamblia* is a well-known hazard to camping and backpacking enthusiasts, who are becoming aware that wilderness water may not be as pristine as it looks. Many other less publicized outbreaks have occurred in preschool day care centers (400).

Cryptosporidium spp. are common diarrhea-causing agents in individuals whose immune systems are compromised, and they have also been found in some otherwise healthy individuals. *Cryptosporidium* **was** first described in 1907, but its oocysts (spherical egglike cells) were not recognized in animal feces until **1978. The importance of** *Cryptosporidium* spp. has been appreciated only recently. Investigators using a simple diagnostic procedure developed in the last few years have estimated that the organism accounts for 1 to 4 percent of all cases of diarrhea in human beings (400).

Not much is known about chronic low-level enteric infections by bacteria such as *Yersinia* (the agent of plague). Multiple infections by several different pathogens frequently occur, making diagnosis difficult. One study of people living in a poor rural area of Panama with substandard sanitation showed that 90 percent of the 202 people examined were infected by one or more parasites, the majority of which were either *Ascaris lumbricoides* (roundworm), E. *histolytica*, or G. *lamblia (88). WHO* estimates there are at least 650 million people in the world with roundworm (ascariasis), 450 million people with hookworm (ancylostomiasis), 350 million people with amebiasis, and 350 million people with whipworm (trichuriasis) infections (318).

ACUTE RESPIRATORY INFECTIONS (ARIs)

Aspects of Natural History

ARIs are among the most important causes of preventable deaths in the world. They are a major cause of mortality among children under 5 and the elderly, sometimes exceeding the mortality rate due to diarrheal diseases. The ultimate consequences of an ARI depend on the organism(s) responsible for the infection and the patient's nutritional status and age.

All of the ARIs are aggravated by malnutrition and substandard living conditions, and the presence of other infectious diseases. A principal epidemiologic factor of ARI transmission is close, overcrowded conditions that promote inhalation of pathogens aerosolized by coughs, sneezes, and personal contact.

ARI agents include viral, bacterial, chlamydial, and mycoplasmal organisms, all transmitted to humans by airborne droplets. For medical purposes, ARIs are usually characterized as upper or lower respiratory tract infections (URTIS or LRTIs); then as community- or hospital-acquired; and then grouped by etiologic agent. Many of the same organisms cause infections in both the upper and lower respiratory tracts, however.

Incidence and Prevalence

Data about the frequency of ARIs are not generally available, making a discussion of incidence and prevalence of this important group of diseases difficult. Surveys in India, Guatemala, the United States, and the United Kingdom suggest that the incidence of ARIs is similar throughout the developing and developed countries, averaging four to eight separate episodes per year (175). However, mortality rates for ARIs in India are thought to be 30 to 75 times higher than those in the United Kingdom or the United States (175). What might cause inconvenient days out of work or school in a developed country might well kill a person in a developing country.

Some 12 percent of all deaths of children living in Africa, Central America, and Asia are attributed to ARI (289), and most of these children die of either pneumonia, bronchiolitis, or acute obstructive laryngitis (croup) (370). Among infants, mortality from ARI can range as high as 1,500 per 100,000 in areas of Egypt, Paraguay, and Mexico—a figure 30 times higher than in the United States and Canada (57)—or even higher to the 4,000 to 4,400 per 100,000 observed in areas of Bolivia and Brazil (370). The incidence of pneumonia, 70 to 100 cases per 1,000 per year, in children under 5 in developing countries, is double that of the United States. Among children who are suffering from malnutrition, almost half will also contract pneumonia during any given year (370).

WHO data, collected from 88 countries on five continents, representing a quarter of the world's population, reported over 660,000 deaths from ARIs in 1978 (35). Extrapolating this figure to the world population suggests that there are more than 2.2 million deaths from ARIs per year, a significant number of which could have been prevented. In addition to presenting a serious mortality risk for the very young and the very old, ARIs impose a tremendous social burden in terms of lost productivity and demands on the health care system by all age groups.

Viruses

Viruses cause most URTIS and some important infections of the lower respiratory tract. Most viral infections of the upper respiratory tract—infections with respiratory syncytial virus (RSV), adenoviruses, rhinoviruses, coronaviruses, and influenza, parainfluenza, measles, and Epstein-Barr viruses, for example—are self-limiting, eliminated by a healthy immune system. In weakened individuals, particularly children, who may be malnourished and have other infections, however, even normally benign URTIS can be life-threatening.

Measles is one of the few URTIS against which a highly effective vaccine exists. The vaccine's use is not universal, however, and measles remains a major cause of death among children in the developing world. Worldwide, 900,000 people, mainly children, died from measles in 1979 (392). The high death rate may be due to concurrent infections, or overcrowded living conditions, which result in heavy exposure of the susceptible individual to the virus whenever several members of the same household are infected (118).

In general, LRTIs cause more serious health problems than do URTIS, though they are caused by many of the same viruses. RSV, measles, and influenza are major causes of pneumonias, which often lead to death in developing countries.

Bacteria

Bacteria cause a host of infections in and around the upper respiratory tract including the sinuses, throat, tonsils, epiglottis, larynx, and trachea. Four types of bacteria are particularly significant

causes of URTIS. *Corynebacterium diphtheria,* is the cause of **diphtheria, an infection of the pharynx. A second, *Bordetella pertussis,*** is the cause of **pertussis (whooping cough). Effective vaccines to prevent diphtheria and whooping cough are routinely given to newborns in developed countries and are included in WHO's Expanded Program on Immunization. Immunization is much more effective than treatment for these two diseases.**

A third bacterium, *Streptococcus pyogenes,* commonly infects the pharynx, but is also the organism responsible for rheumatic fever. The fourth is *Hemophilus influenzae,* which causes ear infections and the more serious condition of meningitis in children.

Bacterial pneumonias (LRTIs) area major cause of morbidity and mortality in developing countries, as they are in developed countries. *Streptococcus pneumoniae* is one of the most common causes of bacterial pneumonia affecting all ages. Other causes of bacterial pneumonia are S. pyogenes, *Staphylococcus aureus, H. influenza, Klebsiella pnemonia, E. coli,* and *Pseudomonas pseudomallei.*

Most bacterial ARIs respond to treatment with antibiotics. Important exceptions are many hospital-acquired pneumonias, which are often caused by drug-resistant organisms, a problem in developed as well as developing countries.

Other ARI Agents

Other less known ARI agents include *Chlamydia* spp. (congenital) and ***Mycoplasma* spp., usually responsible for URTIS and atypical pneumonia among adolescents and adults.** *Chlamydia* spp. appear similar to bacteria, but their size is close to that of viruses. ***Mycoplasma*** spp., a group of organisms which lack a rigid cell wall, are considered by some to be primitive bacteria.

Interventions

For most viral ARIs, there is no treatment other than symptomatic and supportive relief, though bacterial infections can be effectively treated with antibiotics. Vaccinations for measles, whooping cough, and diphtheria are effective and are promoted for vaccinating children under the Expanded Program on Immunization of WHO. However, use of the vaccines for these diseases is frequently limited by the cost of vaccines, the ability of the health infrastructure to maintain a vaccination program, and the problems inherent in maintaining a "cold chain" for certain vaccines. (Cold chain is the name given to the means for continuous refrigeration of vaccines from production to vaccinee.)

Measles is an example of an ARI which could, like smallpox, be eradicated by vaccination. Prior to the development of the measles vaccine in 1962, 481,530 cases were reported in the United States, 46 resulting in deaths. In 1979, after several years of widespread use of the vaccine, there were only 13,597 cases and only 1 death (366). In many developing countries, however, vaccinations against measles have been infrequent. Among children under 1 year of age in 1982, only 8.3 percent in Mexico, 15.9 percent in Bolivia, and 22.4 percent in Colombia (265) were immunized. Measles vaccine must be administered after maternal antibodies lose their effectiveness, but prior to the child's first exposure to a virus, in order for it to work—a critically short time span.

Vaccines against pneumococcal pneumonia (due to S. *pneumonia)* and influenzas are available, but their usefulness in developing countries, is limited because pneumococcal vaccine is not very effective in children under 2 years old and influenza vaccines must be renewed periodically according to the currently prevalent strain. Because of the high cost of annually manufacturing a different strain of influenza vaccines, influenza vaccines are generally available only to high-risk groups.

Improved living conditions and access to health care are critical factors in controlling ARI, but field-based epidemiologic studies are also needed. ARI control is largely ignored in most developing countries. This situation is a function of several factors: difficulty in identifying the etiologic agents of ARIs, lack of effective treatment for many ARIs, and failure to define ARIs as tropical diseases, or to recognize ARIs as worthy of focused research.

The prevention and treatment of ARIs could be simplified through studies precisely identifying the important etiologic agents in different geographic areas and determining the risk factors that make ARI mortality so high. Practical management of ARI depends on differential diagnosis of viral from other bacterial, chlamydial, and mycoplasmal agents for which specific treatments are effective.

Biotechnology and ARIs

The tools of biotechnology are slowly being applied to the many viruses that cause ARIs in humans, but bacterial agents are being largely ignored.

ARI viruses are being isolated, identified, and characterized. A few laboratories are working on the molecular biology of influenza are studying mechanisms of immunity (76) as well as the effectiveness of immunization (271). All of the influenza genes have been identified and sequenced. Recently, some of the influenza genes have been cloned into the vaccinia virus used to inoculate against smallpox. Hamsters were inoculated with the vaccine and immunity was produced against both smallpox and influenza (319). There is hope that all the genes from the various types of influenza can eventually be cloned into the vaccinia virus to produce a single vaccine effective against every strain.

ARBOVIRAL AND RELATED VIRAL INFECTIONS

Aspects of Natural History

Arboviral infections constitute a large group of diseases caused by viruses (currently about 80 known in humans) defined by ecologic, epidemiologic, and clinical, rather than taxonomic, characteristics. The term “arbovirus” is a contraction of “arthropod-borne virus. ” Strictly speaking, arboviruses replicate in and are transmitted by arthropods (predominantly mosquitoes, but also ticks, sandflies, midges, and gnats) (a generalized arbovirus life cycle is shown in fig. 4-15). However, there are some arbovirus-like diseases whose vector is still unidentified (e.g., those caused by the Arenaviridae family) and some whose early epidemiologic profile incorrectly suggested arthropod transmission (e.g., Argentinean and Bolivian hemorrhagic fevers). These exceptions are noted, but for lack of a better characterization system, they are discussed here.

Arboviruses are widely distributed throughout all areas of the world and cause significant endemic and epidemic disease. Most arboviral diseases are infections of animals accidentally transmitted to humans (zoonoses), although epidemics of human-to-human transmission, via insect vectors, can occur.

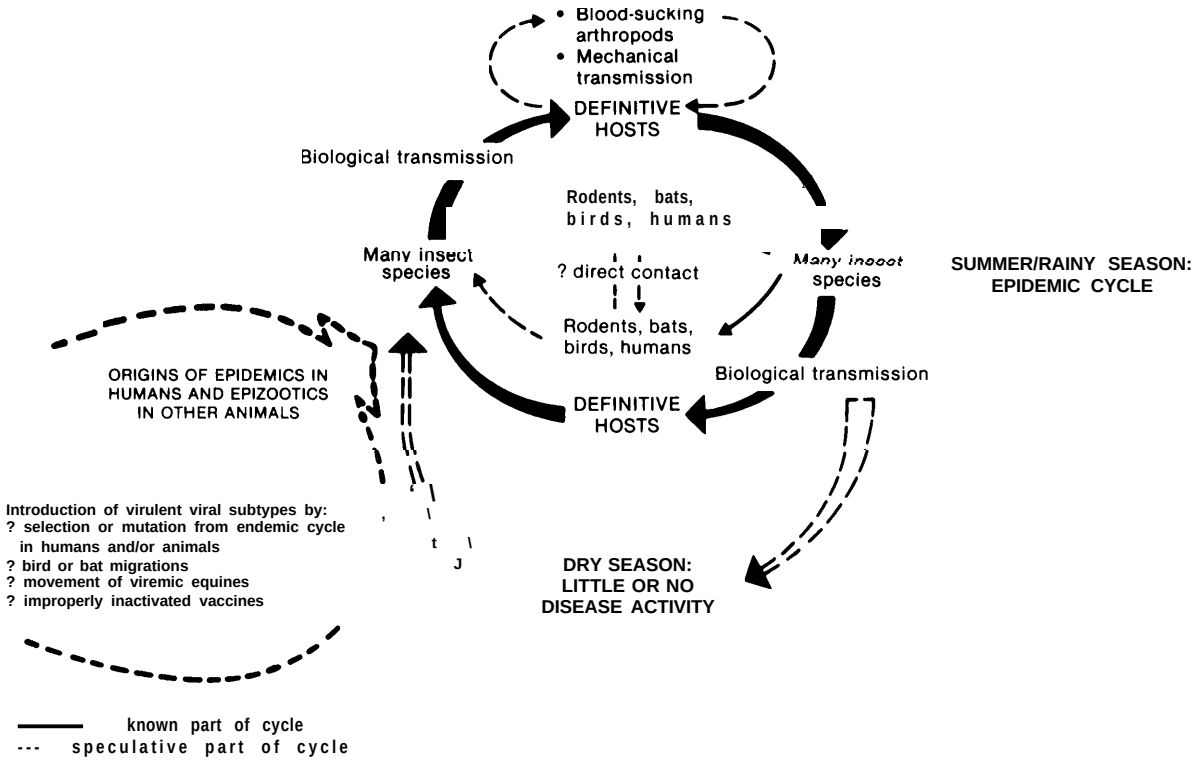
The number of known arboviruses has grown rapidly as the etiologic agents of many fevers and brain inflammations (encephalitis) have been identified and their transmission cycles elucidated. The major groups of arboviruses are classified by their biochemical and physical properties into the Togaviridae, Bunyaviridae, and Arenaviridae families.

The Togaviridae family is divided into two groups. There are about two dozen “alphaviruses” (formerly known as Group A), including the agents of Eastern, Western, and Venezuelan equine encephalitis frequently found in North and South America, Chikungunya of Africa and the Far East, and Sindbis and Semliki Forest viruses of Africa; and three dozen or so “flaviviruses” (formerly Group B), including the agents of yellow fever, dengue fever, Japanese B encephalitis and Saint Louis encephalitis (found in the United States). About *a* third of the flaviviruses are tick-borne and cause various febrile and hemorrhagic illnesses.

The Bunyaviridae family includes several hundred distinct viruses, among them the agents of California encephalitis, Oropouche fever of Brazil, Crimean hemorrhagic fever, and Rift Valley fever of east Africa.

The Arenaviridae are not arboviruses, although the possibility remains that arthropod vectors will someday be identified for the group. Included here

Figure 4-15.—Generalized Transmission Cycle of an Arbovirus



SOURCE: Adapted from G. T. Strickland, *Hunter's Tropical Medicine* (Philadelphia: W, B. Saunders Co., 1984), used by permission

are some of the most deadly infectious agents known, such as the Lassa fever agent, as well as the more common lymphocytic choriomeningitis and various South American viruses, such as Junin (Argentine hemorrhagic fever) and Machupo (Bolivian hemorrhagic fever). Lassa and Machupo fevers are carried by rodents, but the rodent-to-human connection has not been made. Work with the more dangerous arenaviruses is restricted to the very few laboratories in the world with adequate containment facilities, among them the Fort Detrick facility of the U.S. Army in Frederick, MD.

Four basic types of clinical conditions are caused by arboviral infections. Two are generally benign and self-limited: 1) fevers of short duration, with or without a rash; and 2) painful joints and rashes of a short duration. Complications can develop from either of these two conditions, but they are the exception. The two much more serious clinical syndromes caused by arboviral infections are: 1) acute central nervous system disease usually with inflammation of the brain (encephalitis), ranging in severity from mild aseptic meningitis to coma, paralysis, and death; and 2) hemorrhagic fevers, with extensive hemorrhaging, associated with shock and high case fatality rates (liver damage and jaundice accompany these symptoms in yellow fever).

Yellow fever was the first arboviral disease of the tropics to be recognized, by Walter Reed, as a mosquito-borne disease. William Gorgas led the campaign to eliminate the disease from the Panama Canal Zone and from Cuba in the early 1900s. Further success occurred throughout Latin America. Although the virus is maintained in monkeys in the wild, yellow fever has not occurred in urban areas of Latin America since the 1920s.

Symptoms of yellow fever include rapid onset, high fever (l03°F), headache, nausea, vomiting, and muscle pain. The disease in a population occurs in periodic cycles stretching over several **years.** The cycles depend on the buildup of nonimmune individuals in a population, who are then

swept by an epidemic of the virus, leaving an immune population of survivors. Safe and effective vaccination of human populations near endemic jungle areas is one control strategy and provides immunity for at least 10 years. Surveillance of monkey populations and jungle mosquitoes by sampling for virus isolation is an important monitor, providing early warning of high levels of infection.

Yellow fever still remains a major threat in tropical America and Africa (see fig. 4-16), because the virus is maintained by transmission through a number of jungle mosquitoes, with monkeys and possibly certain marsupials serving as reservoirs. Recent research has demonstrated that passage of the virus from the female mosquito to the egg (transovarial transmission) occurs among the vectors of yellow fever. Thus, the mosquito may function not only as a vector, but also as a reservoir (100).

Cases of yellow fever in humans are associated with humans invading the jungle habitat. In recent years, however, an outbreak appeared in Colombia where there were no apparent *known vectors* or reservoirs, and in Trinidad where no cases had been detected for almost 20 years. The possibility of unknown reservoirs is of concern, as *Aedes aegypti,* the vector of yellow fever in the urban setting, remains abundant throughout the

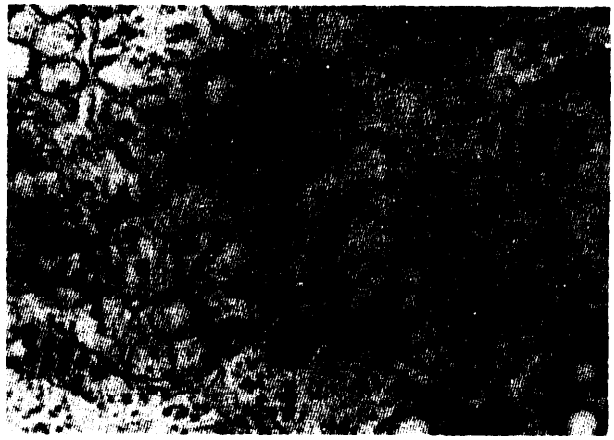
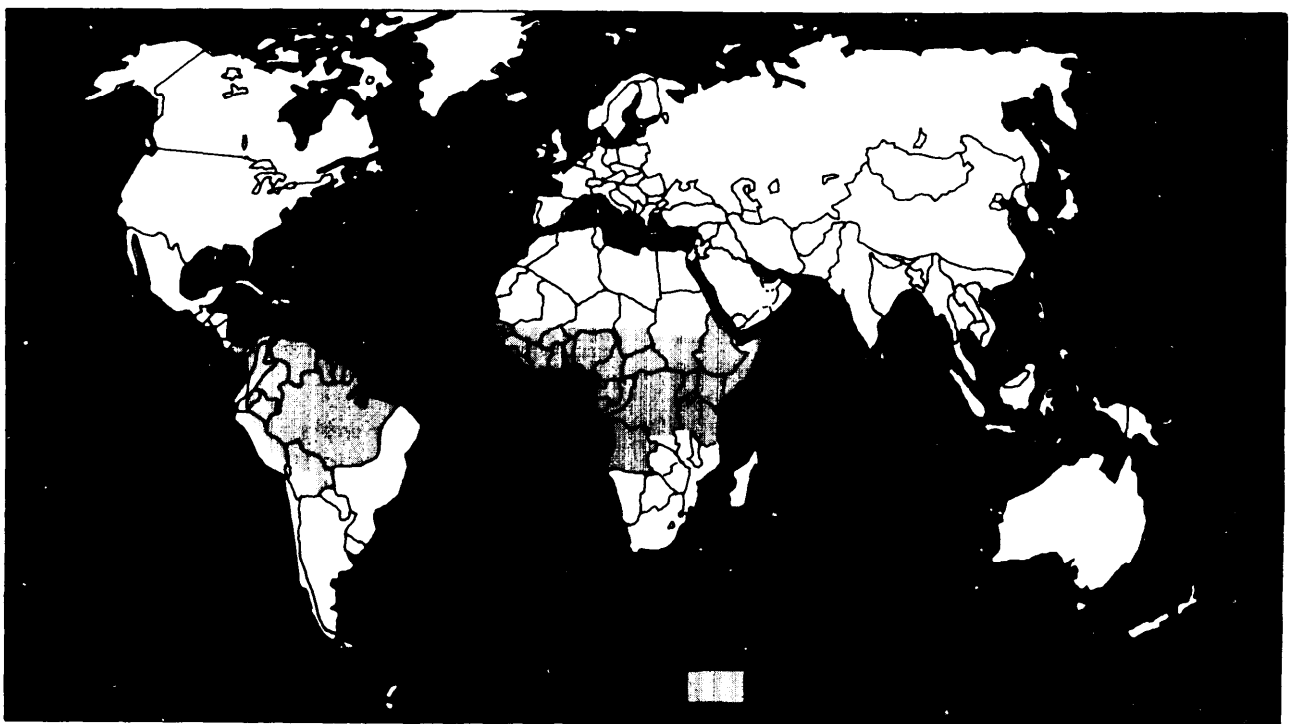


Photo credit: K.S. Warren and A.A.F. Mahmoud "Tropical and Geographical Medicine, " McGraw-Hill Book Co., 1984. Reprinted by permission.

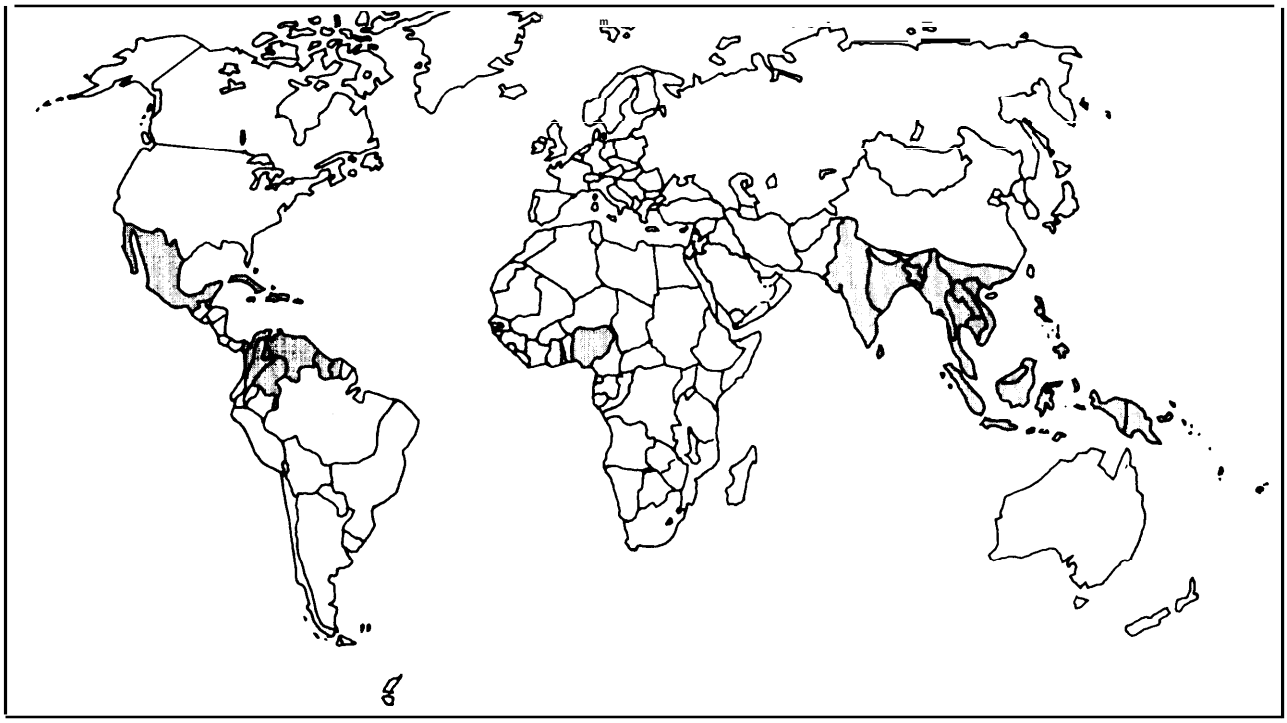
Electron micrograph of the dengue virus, agent of dengue fever.

Figure 4-16.—Geographic Distribution of Yellow Fever



SOURCE: U.S. Department of Health and Human Services, Centers for Disease Control, *Health Informat/in for International Travel,* **HHS Publication No. (CDC)840-8280 (Washington, DC: U.S. Government Printing Office, 1984).**

Figure 4-17.—Geographic Distribution of Dengue Fever



SOURCE: World Health Organization, Geneva, Switzerland.

world (including the United States), posing a persistent threat of epidemic outbreaks in large population centers.

Dengue fever is a disease of worldwide distribution (see fig. 4-17) caused by four serotypes of the dengue flavivirus. The disease is usually mild, characterized by a rash resembling measles or scarlet fever, accompanied by generalized swollen lymph glands. Convalescence is long and distressful (406). **Serious, sometimes fatal complications of dengue fever are dengue hemorrhagic fever and dengue shock syndrome. Dengue hemorrhagic fever usually affects children. In recent years, large epidemics of this virus have swept the Caribbean and Central America. In** 1981, the first indigenous cases in the United States since the 1940s occurred. The virus is endemic to the Caribbean and is transmitted by mosquitoes **of the genus *Aedes,* including the common urban mosquito *A. aegypti,* which is found as far north as St. Louis, MO.**

Oropouche fever, found in Trinidad and Brazil, is e-merging as an important arboviral disease because of its debilitating symptoms, which include anorexia, rash, and joint and muscle pain. The virus is transmitted by biting midges (Culicoides spp.) in urban and suburban areas. There is probably also a transmission cycle in forest animals away from populated areas, as in the case of yellow fever.

Rift Valley fever was first characterized in the Rift Valley of Kenya in 1931. Sandflies and mosquitoes are the suspected vectors, and while they have been shown capable in the laboratory, transmission has not been established in the field. Until 1977, Rift Valley fever was geographically limited to sub-Saharan Africa. Human fatalities were not known until the 1975 epizootic (epidemic among animals) in South Africa (KM). Currently, the disease is present throughout Africa, but has not yet spread to other continents. In 1977-78, a

widespread epizootic and epidemic of Rift Valley fever occurred in Egypt. Some 18,000 human cases were officially reported, and almost 600 people died of the disease (209). The disease in animals has a serious economic effect, causing cattle to abort and high fatality rates among newborn lambs. In humans, infection usually results only in mild dengue-like febrile illness, although it can result in severe ocular (inflammation of the retina and blindness), encephalitic, or hemorrhagic complications.

Lassa fever is endemic to some regions of West Africa. Symptoms include prostration, severe sore throat, tonsillitis, chest pain, and pneumonitis (inflammation of the walls of the air sacs in the lung). There is evidence that mild or subclinical infections occur, but among those hospitalized with Lassa fever, fatality rates range from 20 to 40 percent.

Research Needs

Laboratory techniques can identify arboviruses and define antigenically similar groups, but there is great geographic and climatic diversity in each serologic grouping. This situation emphasizes the complexity and challenge of arbovirus research and control.

There is no cure for arboviral diseases, only symptomatic and supportive relief. Early diagnosis of the agents responsible for potential outbreaks and epidemics identified down to the finest level possible, has three important values: 1) to differentiate ambiguous presenting symptoms; 2) to anticipate life-threatening complications, as in yellow fever and dengue fever; and 3) to target the vector, which then determines control strategies. Current control efforts rely on early identification of epidemic outbreaks of arboviraI infections, allowing the institution of vector-control measures such as insecticide fogging. In many tropical countries, however, disease surveillance is not well developed.