Chapter 4

Relevance of Research at Gorgas Memorial Laboratory to Health Problems in Tropical America

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This technical memorandum considers the term tropical diseases to refer both to those classically defined as tropical diseases, such as schistosomiasis, and to those in a broader definition of the term, such as tuberculosis and malnutrition (see ch. 1). Socioeconomic status (e. g., malnutrition, poverty) defines the Tropics and, to a very large degree, tropical diseases, Otherwise life in urbanized tropical America presents the same hazards to health as life in North America or Europe. The intimate relationship between health status and economic and social progress means that some health problems in tropical America will only succumb to long-term socioeconomic advancement, yet tropical diseases, by their enormous impact on health status, simultaneously and seriously affect the economies of tropical countries. The *six* tropical diseases singled out by the World Health Organization (WHO) for special programmatic research support—malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis, and leprosy—together affect between 700 million to *800* million people. The first three each affect more than 200 million people worldwide (5).

The resulting amount of human suffering and disability is enormous. This argues for urgent humanitarian action where feasible interventions exist. Significant costs are involved in treating such diseases and in implementing public health programs for their prevention and diagnosis, even though health services are usually underfunded and inadequate in most of the less developed countries. However, the most substantial economic impacts may be the indirect ones affecting a country's human resources and productivity.

Health problems in the region of tropical America cover a broad range because of the great variations in climate, geography, socioeconomic conditions, and culture. Modernization, population growth, and rapid rural-to-urban migration cause many diseases of the developed world to have growing significance in tropical and developing America, especially among affluent, middle-aged, and urbanized persons. For example, heart disease, stroke, diabetes, cancers, and accidental injuries are all emerging as major causes of morbidity and mortality in statistics for the Latin American and Caribbean regions. *

Even as diseases of the developed world acquire increasing importance as major causes of mortality in tropical America, the nonfatal diseases caused by parasitic and infectious agents remain a critical drag on developmental progress and the quality of life. Furthermore, in the developing countries, life expectancy at birth is much lower than in the developed world. This is a direct result of high infant and childhood mortality. The major killers of infants and children are three groups of diseases: diarrheal and enteric infections (fecal-borne), respiratory infections and measles, and malnutrition.

This chapter will first describe some of the major tropical diseases and conditions of ill-health of tropical America. Following that, the Gorgas Memorial Laboratory's (GML) research and related activities will be discussed in light of the information on regional health problems and research needs.

Evaluation of research relevance quickly becomes subjective. Research by its nature is open-ended. If science administrators and researchers could predetermine all lines of productive research, they would do so. The reality is often a simpler hope—for good judgment and good luck.

*Caution is necessary, however, in interpreting these statistics, because they derive from health care systems that are weighted (because of the training of physicians, the availability of health facilities, the logistical problems of data collection, etc.) towards the diagnosis and recording of acute, traumatic, or degenerative disease presentations in urban areas.

In evaluating the relevance of research at GML, OTA depended on identified health problems and needs, resulting research questions and opportunities, and the relationship of GML's research to those health problems and research needs.

TROPICAL DISEASES: DESCRIPTION AND STATUS

Acute Respiratory Infections

Acute respiratory infections (ARI) area major cause of mortality in children under 5 and the elderly. The group includes many viral and bacterial infections: influenza (myxoviruses, type A, B, C), parainfluenza (paramyxoviruses), measles (paramyxovirus), respiratory syncytial viruses, adenoviruses, rhinoviruses, *Streptococcus pneumonia* and other bacteria, chlamydia (congenital), and mycoplasma. Influenza and pneumonia are among the top five causes of death in children under 5 in every country of the Pan American Health Organization (PAHO) region (75). In addition to the serious mortality risk for the very young and the very old, these infections are a tremendous social burden in terms of work productivity lost and demands on the health care system by all age groups.

These infections are aggravated in conditions of malnutrition and substandard living conditions, and in combination with other infectious diseases. A principal epidemiological factor of ARI transmission is close, overcrowded associations that promote inhalation of aerosolized pathogens by coughs, sneezes, and personal contact.

For most of these diseases there is no treatment other than symptomatic and supportive relief, though bacterial infection can be effectively treated with antibiotics. Vaccinations for measles, whooping cough, and diphtheria are feasible and promoted under the Expanded Program on Immunization of WHO. Vaccines against influenza and pneumococcal pneumonia are available but have reduced usefulness in developing countries: Pneumococcal vaccine is not very effective in children under 2 years old; influenza vaccines must be renewed periodically according to the currently prevalent strain.

Improved access to health care is a critical factor, but also needed are field-based epidemiological studies. ARI control is largely ignored in most developing countries. This is a function of difficult diagnosis (of the etiologic agent), lack of effective treatment, lack of definition as a tropical disease, and as an entity worthy of focused research. Longitudinal studies on the epidemiology of ARI using rapid diagnostic techniques are needed. These studies could simplify the prevention and treatment of ARI by precisely identifying the important etiologic agents in geographic areas and by determining the risk factors which 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. With risk factors defined, intervention against them could be initiated. At the same time, such studies would produce baseline prevalence data for subsequent evaluation of intervention measures taken.

Diarrheal and Enteric Diseases

Diarrheal diseases are the leading cause of death in children under 5 years of age in over half the countries of Latin America and one of the top five for all other countries. Data from several countries indicate that the typical child below 5 years of age experiences four to eight diarrheal episodes annually. 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 (76).

A comparison of death rates in children under 1 year of age is startling. For North America (United States and Canada), the mortality rate in infants in 1979 was 21.9 per 100,000; for Latin America it was 914.6 per 100,000, 40 times higher, almost 1 in 100 infants dying of diarrheal disease. Because underreporting from rural areas is still a problem, it is likely that the statistical number of diarrheal cases will increase as health services are extended to rural populations.

Diarrheal diseases constitute a clinical syndrome of varied etiology, all of which are transmitted by human feces. These include bacilli, viruses, and parasitic and helminthic parasites, such as shigellae, salmonella, Escherichia coli, Cam*pylobacter, Yersinia,* rotaviruses, amoeba, giardia, ascaris, and ancylostoma. Poliomyelitis is also a fecal-borne disease.

Rotaviruses, which in recent years have been found responsible for almost half of infant diarrheas in the developing world, were first detected in humans in 1973. Serologic studies have shown that by the age of 2 years, nearly all children have had the infection. A Guatemala community study indicated that rotavirus accounted for 10 to 20 percent of all diarrhea there.

Escherichia coli is a second important cause worldwide of diarrheal disease. Only certain strains which are classified in three groups cause disease: enterotoxigenic *E. coli,* enteroinvasive *E. coli,* and enteropathogenic *E. coli.* Each group has a distinctive physiological and pathological symptomatology. Serotyping based on bacterial cell wall antigens is a second classification system.

Other important diarrheal pathogens are *Shigellae, Salmonellae* (both typhoid and nontyphoid), *Campylobacter, Entamoeba histolytica* (amebiasis), and *Giardia lamblia* (giardiasis).

Although acute diarrheal diseases remain a leading cause of childhood morbidity and mortality in most of the Americas, prospects for their control are steadily improving. Intensive research in recent years into almost all aspects of diarrheal disease has led to a number of breakthroughs and technical innovations, such as oral dehydration therapy (ORT), which has become the main strategy of the WHO/PAHO diarrheal disease control program. Therapeutic studies continue to document the effectiveness of this simple, safe method which uses a single specific orally administered water solution of electrolytes and glucose. An ORT trial project begun in 1978 in Costa Rica has proved an effective lifesaver in both bacterial and rotaviral infant diarrhea (70,72,83). A recent study (95) demonstrated that even in well-nourished children in developed countries, ORT is a safe and effective treatment for acute diarrhea (regardless of etiologic agent) and could replace the use of intravenous fluids in the majority of such children.

In addition to ORT, four other major strategies comprise the diarrheal disease control program: 1) improved child care practices, including promotion of breastfeeding, proper weaning, and personal hygiene; 2) health education; 3) improved water supply, environmental sanitation, and food hygiene; and 4) epidemiologic surveillance. A medium- to long-term objective is to integrate diarrheal disease activities into existing primary health care systems.

With the growing evidence of rotavirus importance in diarrheal disease, further epidemiologic, clinical, and basic research is needed. A major objective now is to develop a vaccine for humans. Such a vaccine exists for animals. Immunological diagnostic testing exists which can be utilized for field studies of prevalence and incidence in geographic localities.

Childhood mortality is the highly visible tragic aspect of enteric disease, but the chronic and debilitating effects of these parasitic and infectious diseases (e.g., chronic anemia due to intestinal hookworm) rob a nation of productivity, vitality, and initiative. 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 amoebiasis, and 350 million people with whipworm (trichuriasis) (99). Fecal-oral transmission is the common denominator of all these diseases. Lack of safe and adequate water supply and of proper excreta disposal, two of humankind's most basic needs, are the critical deficiencies that promote these diseases. In rural Latin America, 68 percent of the population lack access to water supply service, and 98 percent lack sewage service of any type. In urban areas, 22 percent lack access to water supply service, and 57 percent have no sewage service.

Malnutrition

Malnutrition is a primary cause of death of children under 5 years of age in Latin America. Though not a disease per se, it is so intimately involved in disease processes and ill-health to warrant specific mention in this overview. The Inter-

American Investigation of Mortality in Childhood showed that low birth-weight (2,500 g or less) and nutritional deficiency were the direct cause of 6 percent of deaths 'before age 5 and an associated cause in 57 percent of all deaths (85). Death is the final outcome in a chain of events that begins before birth and then involves the pernicious interaction of malnutrition and infectious disease. Maternal malnutrition (together with maternal age and parity, two other determinants in infant mortality (86)); produces premature birth and low weight at birth, both serious risk factors for the newborn. Infants who survive the neonatal period tend to thrive for the first 6 months of maternal feeding, but then come to risk from varying degrees of kwashiorkor and marasmus, the two poles of protein-energy malnutrition. According to Gueri (48), in a great majority of cases the problem results not from lack of food in the home but rather from maldistribution of food within the household, from lack of knowledge about child feeding, from an unsanitary physical environment conducive to infectious diseases (particularly gastroenteritis) that increase the child's energy requirements while decreasing its appetite, from early replacement of breastfeeding with highly diluted and contaminated milk formulas, and in some cases from sheer neglect.

Though malnutrition as a primary cause of morbidity and mortality is less prevalent in adolescents and adults, it still must be considered a major contributing factor in infectious diseases. Immunologic defense mechanisms are seriously compromised by malnutrition. The synergistic interaction of malnutrition and disease is well documented. For example, Scrimshaw, Taylor and Gordon (101) observed that, except where populations are malnourished, or otherwise uncommonly susceptible to disease, the incidence of tuberculosis is significantly lower than would be expected by the widespread presence of the tubercule baccilus. Mortality due to measles was 274 times higher in Ecuador than in the United States in 1960-61, a time before the development of immunization to the disease (85). Thus in all analysis of tropical health problems, protein-energy malnutrition must be considered a contributing cause in the disease process, and as a primary cause in children under 5 years old.

Important research and intervention experiments have been carried out under the auspices of PAHO. The principal research centers are the Institute of Nutrition of Central America and Panama (INCAP), the Caribbean Food and Nutrition Institute (CFNI), and the Latin American Center for Perinatology and Human Development.

Malaria

Malaria is a disease caused by a protozoan blood parasite transmitted by various anopheline species of mosquitoes. It is one of the most widespread and destructive diseases in the world and has made a resurgence in the last decade with a more than two-fold increase in world prevalence (127,128). The incidence of malaria in developed nations, such as England and the United States, has also been increasing due to imported cases. Estimated malaria incidence worldwide is 300 million cases per year. In 1982, 702,000 confirmed cases were reported from the Americas. These statistics are large but undoubtedly underreported, because the disease is contracted in rural areas remote from medical facilities. An estimated 64.9 million people live in areas of tropical America where the risk of contracting malaria persists. The countries of worst malaria incidence are Haiti, Guatemala, Honduras, El Salvador, Colombia, Bolivia, and Brazil.

The resurgence of malaria in the last decade is a setback due to the failure of the global eradication campaign based on DDT house-spraying and supplementary mass drug distributions. Early successes led to overconfidence that ignored the complexity of a disease caused by four different species of parasite and transmitted by many different species of mosquito vectors, each with peculiar behavior patterns in widely varying ecological and sociological settings. The serious consequences of that failure are insecticide-resistant mosquito vectors and drug-resistant strains of the parasite.

Malaria research is in a new period of vigorous activity, like most of parasitology. Molecular biologists, geneticists, and biochemists have begun to apply their research skills to the many important questions that were ignored during the eradication era. Metabolic studies can identify parasite-

specific enzyme pathways that can be exploited to kill the parasite without harming the human host, Membrane research can reveal how the parasite finds, attaches to, and invades 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.

The spread of drug-resistant malaria (by the species *Plasmodium falciparum)* is of great concern worldwide. Regular monitoring of local parasite strains is necessary to keep abreast of therapeutic changes that may be needed, both in type of drug and dose. In Latin America, serious drug-resistance has still not moved north of the Panama Canal. Renewed effort to develop new drugs is producing results, but takes years to move from laboratory screening through animal testing to human trials.

Vector biology studies are critical to any rational mosquito-control effort. Cytogenetic research which analyzes insect chromosomes has identified species complexes that were previously unrecognized by conventional taxonomy. As an example, *Anopheles gambiae,* the notorious malaria vector in Africa, is now known to be a complex of several distinct species all identical to the unaided eye. Cytogenetic differentiation of the various species has explained the different behavior patterns of the *A. gambiae* complex and defined the important vector species. Research on physiological resistance mechanisms can aid the development of better insecticide methods. Behavioral resistance, the avoidance of insecticides by insects, is important for two opposite reasons—the killing effect is reduced, but transmission may still be interrupted, if vectors avoid human habitations.

Field- and community-based studies are needed to assess the impact of antimalarial interventions. The ecological impact of vector intervention is critically important. The selection of insecticide-resistant vectors has seriously handicapped current control efforts. The effect of antimalarial activities on population immunity levels still 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 need to evaluate the importance of sociological and human behavioral factors and the usefulness of health education, community self-help, and volunteer collaborators.

Significant progress is being made on the development of a vaccine against malaria, including the identification of surface antigens and their production by bacteria. If animal testing confirms the feasibility of immunization against this parasite, extensive human and field trials will be required, before there is widespread usage of vaccines in the control of this disease. The wide usefulness of a vaccine is also debated considering the many difficulties associated with implementing other disease immunization campaigns.

Chagas' Disease

Chagas' disease (American trypanosomiasis) is caused by a protozoan parasite of the blood and tissues and transmitted by reduviid bugs ("cone-nosed" or "kissing" bugs), common blood-sucking insects in the Americas. It is a disease of poor rural areas with substandard housing that provides harboring sites for the bugs to live and breed. About *150* species of mammals have been incriminated as reservoir hosts, including dogs, cats, guinea pigs, rats, opossums, and other rodents and *marsupials*. The parasite has two life stages in the mammalian host, one that circulates in the blood and another that proliferates intracellularly in tissues.

In 1974, WHO estimated that out of 50 million exposed, a total of 10 million persons were infected with the Chagas' disease parasite Trypanosoma *cruzi* (discovered by Carlos Chagas of Brazil). Studies in Brazil have shown Chagas' disease to be a significant cause of mortality in those under 45 years of age (84) and a heavy social burden due to high rates of hospitalization (with unsatisfactory outcome) and disability assistance (78).

After initial infection by the reduviid bug, the acute phase of the disease varies in severity according to age. Cardiac arrhythmias, myocardial insufficiency and collapse, or central nervous

system damage may result in death. The younger the individual, the greater the severity. Mortality is high in children under 2 years of age, while adults may show no symptoms. The acute stage may resolve completely in a few weeks or months, or may pass into a subacute or chronic stage. There is no effective cure. Long-term sequelae are cardiomyopathy leading to heart failure and grotesque enlargement of the digestive tract (megaesophagus and megacolon).

The transmission threat in rural areas is great, but transmission by blood transfusion is also a major problem for blood banks in Latin America.

The disease is found in every country of the Western Hemisphere, except Canada and the Caribbean. Opossums and other mammals harbor the disease in the Southern United States, and a small number of indigenous human cases have occurred in recent years (e.g., two in California in 1982).

Control measures concentrate on insecticide spraying of houses and upgrading of housing construction (adobe, mud, cane, thatch, or otherwise poorly constructed rural homes with cracks in the walls are the usual harborage of the insect vector).

An effective drug cure is a critical research need. With a therapeutic drug in hand, a simple effective test for early diagnosis would be essential—the long-term effects once they appear are irreversible. Vaccine research is underway, but this disease has a complicating factor—the long-term pathology seems to result from the body's immune response reacting against the parasite and cross-reacting to its own heart and nerve tissue. Vector bionomics remain important research topics for defining transmission areas, vector behavioral characteristics, and improved control measures.

Leishmaniasis

Leishmaniasis is a disease with three clinical presentations depending on the leishamanial parasite species. In each case, the protozoan parasite species is transmitted by bloodsucking phlebotomine sandflies. Cutaneous leishmaniasis is a self-limiting and usually self-resolving sore at the point of infection. Mucocutaneous leishmaniasis is caused by a different *Leishmania* species that begins as a sore but commonly metastasizes and proliferates in the nasal and pharyngeal mucous membranes. Gross destructive disfigurement of the nasal passages occurs. Visceral leishmaniasis (kala-azar) is a third type of disease in which spleen, liver, bone marrow, and lymph glands are the sites of parasite proliferation. Fatal outcome in children is common.

The disease exists in all Latin American countries except Chile, and in some the number of cases is increasing because of agricultural colonization in jungle areas, In the late 1970's, cutaneous leishmaniasis seriously impeded a Bolivian scheme to relocate people outside the overcrowded alti*piano.* Many of the colonists abandoned their land. More than 60 percent of those who did said that leishmaniasis was their reason for returning to the mountains. It has also significantly hampered both oil exploration and roadbuilding in several Andean countries (76).

Epidemiologically, most forms of the disease are transmitted to humans from animals in the jungle (zoonoses), representing a health hazard to anyone working there, and rendering control unsatisfactory or impracticable.

Specific treatment is now limited to antimony compounds that are not always effective and often have adverse toxic side-effects. Another disadvantage is that they require daily injections over 10 to 20 days, which makes 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 the patient who cannot afford to leave work or farm for an extended period. For these reasons, improved treatment of the tens of thousands of existing cases is a priority research goal. PAHO/WHO currently has a structured effort to develop new therapeutic drugs. Allopurinol is a promising compound of current research activity (119).

In other PAHO investigations of leishmaniasis epidemiology, a seroepidemiologic survey in Panama revealed an apparent focus of leishmaniasis transmission without clinical infection. Completely subclinical leishmaniasis was previously unknown and may be important to vaccine development. Rapid species diagnosis of leishmanial sores may be soon possible by a recently published technique of DNA hybridization (124).

This would permit early treatment of the destructive mucocutaneous form of the disease, as well as facilitate precise epidemiologic field studies.

Arthropod-Borne Viral Diseases (Arboviruses)

This large group of diseases is caused by viruses (currently about 80 in humans) defined by ecological, epidemiological, and clinical parameters. Strictly speaking, arboviruses replicate in and are transmitted by arthropods (predominantly mosquitoes, but also ticks, sandflies, midges and gnats). There are some arbovirus- like diseases whose vector is still unidentified and some whose early epidemiological profile incorrectly suggested arthropod transmission; their symptoms (e. g., Argentinean and Bolivian hemorrhagic fevers) must be differentiated from those of true arboviruses. The number of arboviruses is growing rapidly as research resolves the etiologic agent of many fevers and brain inflammations (encephalitis) of unknown origin and elucidates transmission cycles. Examples of arboviruses include: yellow fever, dengue fever, eastern equine encephalitis (EEE), western equine encephalitis (WEE), St. Louis encephalitis (SLE), Venezuelan equine encephalitis (VEE), California encephalitis (CE), Colorado tick fever, Chagres fever, and Oropouche fever. (Locality names denote the source of first isolation; range of each is far wider.)

Clinically these diseases are classed in four groups *(6): 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 (WEE, EEE, CE/LaCrosse encephalitis, SLE); 2) acute benign fevers of short duration, many resembling dengue with and without a rash (exanthem), although on occasion some may give rise to a more serious illness with central nervous system involvement or hemorrhage (yellow fever, dengue, VEE, Oropouche); 3) hemorrhagic fevers, including complications of acute febrile diseases (previous group), with extensive hemorrhagic involvement, frequently serious, and associated with shock and high-fatality rates. One of them, yellow fever, also causes liver damage and jaundice; 4) polyarthritis and rash, usually without fever and of variable duration, benign, or with arthralgic sequelae lasting several weeks to months.

Most of these infections are diseases of animals (zoonoses) accidentally transmitted to man, though epidemics can occur with man; the principal source of vector infection, In 1981, an epidemic of dengue fever swept through Cuba with 344,208 cases and 158 deaths. The *1977-80* pandemic of dengue in the Caribbean and Central America caused a half-million cases.

Laboratory diagnosis can identify arboviruses and define antigenically similar groups, but great geographic and climatic diversity is found in each serologic grouping. This emphasizes the complexity and challenge of arbovirus research and control. There is no cure for these diseases, only symptomatic and supportive relief. Early diagnosis of serotype has three important values: to differentiate ambiguous presenting symptoms; to anticipate life-threatening complications, as in yellow fever and dengue fever; and to target the type of vector which then determines control strategies. Current control efforts rely on identifying epidemic outbreaks early in order to institute vector-control measures such as insecticide fogging. However, disease surveillance is not well developed in many tropical countries of the region.

Only yellow fever has an effective vaccine. There are experimental vaccines for certain strains of dengue fever, VEE, and WEE. The general utility of arbovirus vaccination is doubtful, though, because of the complexity involved. The wide variety of arboviruses, most occurring only sporadically in humans, and without inducing cross-immunity, raise many questions about implementation and bring the realization that vaccination is unlikely to be a panacea. Vector control will remain the primary intervention method. Entomologic research on vector bionomics together with surveillance of sentinel populations (animal reservoirs and vectors) are activities for emphasis. Especially important is elucidation of the vector-bridge concept—the factors permitting transmission of these zoonoses to humans when the principal vector arthropod is not a human-biter.

Yellow fever was the first arbovirus disease of the Tropics to be recognized and elucidated. It was William Gorgas who eradicated the disease from the Panama Canal Zone and Cuba in the early 1900's. Further success was recorded throughout Latin America against urban yellow fever, such that no cases were documented in the Americas for the past four decades. Jungle yellow fever, however, remains a major threat in tropical America. It is the same virus maintained by transmission through a number of jungle mosquitoes with monkeys and possibly certain marsupials serving as reservoirs. Recent research has demonstrated that transovarial transmission (passage of the virus from the female mosquito to the egg) occurs in vectors of yellow fever *(26)* (and other arboviruses). Thus, the mosquito may function not only as a vector, but also **as a** reservoir. Human cases are associated with man invading the jungle habitat. In recent years, however, an outbreak in Colombia appeared 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 or vectors is of concern. *Aedes aegypti* the vector of urban yellow fever remains abundant throughout the hemisphere (including the United States), posing a persistent threat of epidemic outbreaks in large population centers.

The disease occurs in periodic cycles stretching over several years which depend on the buildup of nonimmune individuals in a population who are then swept by an epizootic of the virus leaving an immune population of survivors.

Vaccination of human populations near endemic jungle areas is one strategy. Surveillance of monkey populations and jungle mosquitoes by sampling for virus isolation is an important control measure that gives early warning to institute remedial action.

Dengue fever is a. disease caused by four different serotypes of the dengue flavivirus. 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 1940's occurred. The virus is endemic in the Caribbean and is transmitted by mosquitoes of the genus *Aedes,* including the common urban vector *Aedes aegypti* which is found as far north as St. Louis, Mo, It breeds in small containers of water such as discarded tires, cans, and jars. A serious, sometimes fatal, complication of dengue fever is dengue hemorrhagic fever (or dengue shock syndrome).

Oropouche fever is emerging as a very important type of arbovirus disease, because of its debilitating symptoms that reduce productivity due to convalescence. The virus is transmitted by biting midges *(Culicoides* spp.) in urban and periurban areas. There is probably also a silent transmission cycle in forested areas.

Filariasis

Several species of filarial nematode worms can inhabit the skin, other tissues, or the lymphatic system causing disease in humans. These parasites are transmitted by bloodsucking insects. In Latin America only two worms are considered public health problems, *Wuchereria bancrofti* and *Onchocerca volvulus.*

The bancroftian filariasis was introduced from Africa. It is transmitted by several species of mosquitoes including common household pest species. The adult worms live in the lymphatic system and cause pathology depending on the immune response of the host. Inflammation and gross obstruction results in varying degrees of swelling of the lymph glands up to frank elephantiasis of the legs, breasts, or scrotum. Adult worms release immature forms (microfilariae) that circulate in the blood which then infect feeding mosquitoes to complete the transmission cycle. Chemotherapy and vector control are currently imperfect and need more research.

Onchocerciasis is also known as river blindness, because the blackflies *(Simulium* spp.) that transmit it live and breed in or near waterways. The disease occurs in well-defined parts of Africa and in the Americas, in discrete foci in Guatemala, Brazil, Colombia, Ecuador, Mexico, and Venezuela. Ecuador's onchocerciasis focus was only discovered in 1980. A Panamanian blackfly has recently been shown to be a potential vector of **O. volvulus.**

The adult worm lives in the tissues of the body and often forms large nodules where an intertwined clump of worms localizes. Microfilariae released by the adults migrate through the body in the subcutaneous tissues where they can be picked up by feeding black flies. If microfilariae reach the eye, lesions and blindness can result. Control measures focus on vector control and blindness prevention (imperfectly achieved by chemotherapy and nodule removal),

Schistosomiasis

This debilitating disease is caused by a fluke. The worm-like adult parasite lives in the human host's bloodstream, Eggs are deposited *in* the blood vessels and escape into the bowel or bladder, or lodge in other organs, where they produce inflammation and scars. The complex lifecycle involves excretion of the eggs into water sources, an intermediate snail host in which proliferation occurs, and an immature stage that can penetrate the unbroken skin of persons who enter infected water. Three major species of the fluke occur worldwide, only one in the Americas, Schistosoma *mansoni,* which was introduced from Africa.

S. *mansoni* is now established in suitable snail hosts in more than half the States of Brazil, where 10 million people are believed infected, in Surinam, where 10,000 people are probably infected, and in parts of Venezuela, where 10,000 more people are thought to have the infection. Foci in the Caribbean occur in the Dominican Republic, Guadaloupe, Martinique, and St. Martin. A few cases have been detected in Montserrat. The disease is declining in Puerto Rico and Saint Lucia due to intervention measures *(76).*

Chemotherapy against the disease is effective and relatively safe. Total and complete coverage in endemic areas can be difficult to achieve requiring other measures to complement control efforts, particularly attention to water and excreta sanitation and anti-snail treatment of breeding sites (molluscicide against the snail host).

Schistosomiasis is spreading worldwide due to 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 deserve special surveillance and assessment.

Leprosy

Leprosy is a chronic bacterial disease that continues to be an important public health problem in the Caribbean and Latin America. A quarter-million cases are registered in the region, perhaps twice that number are prevalent. As case-finding and notification improved, reported incidence increased with extension of anti-leprosy efforts. Depending on the host's immunologic response, leprosy can range from the benign tuberculoid form with localized skin lesions and some nerve involvement to the malign lepromatous form that causes spreading lesions which become nodular and disfiguring, destruction of the nose, involvement of the vocal cords and eyes, and severe nerve damage. Over half the cases in Latin America are the lepromatous form.

Research on the epidemiology of leprosy is still needed. A number of useful drugs are now available for treatment. Drug-resistant strains of *Mycobacterium leprae* have resulted in recommendations for combination chemotherapy which will shorten the treatment period. If organized and administered well, this will lighten the workload of health services, improve patient compliance, and result in better *prognosis.* Vaccination against the disease is in human trials but still years from routine use. The PAHO-associated Pan American Center for Research and Training in Leprosy and Tropical Diseases (CEPIALET) in Caracas, Venezuela, carries out a full research agenda on leprosy, as does the U.S. Public Health Service in Carville, La. Other philanthropic institutions provide support to leprosy control either directly to the countries or through PAHO.

Tuberculosis

Tuberculosis is a mycobacterial disease transmitted mainly by airborne droplets. The lungs *are* first involved, after which infection can spread to all parts of the body. Though the disease is decreasing slowly in the Americas, it is still a serious problem in most countries of the region.

Even countries such as Canada and the United States, with highly developed coverage for diagnosis and treatment, have significant numbers due to immigrants from tuberculosis-prevalent areas.

Control methods based on BCG (bacille Calmette-Guerin) vaccination, diagnosis from those with productive cough and treatment for those with sputum positive, is the policy of PAHO and the health ministries of Latin America.

BCG vaccination of uninfected persons can produce high resistance to tubercule bacilli, nonetheless, the protection conferred has varied greatly in field trials. Because some trials have shown high protection, BCG is still recommended in areas of high-transmission risk. The resolution of the question of BCG effectiveness needs further evidence.

Cancers

Cancers deserve mention in the context of this technical memorandum. They are already one of the leading causes of death in Latin America. This is an unhappy indicator of progress against other causes of mortality, because to die of most cancers, one must survive past middle age.

Epidemiologic research has identified varying patterns of site-specific prevalence in the region. This points out areas for research on risk factors as possible causes. Extremely high rates of cervical cancer and penile cancer, compared to the rest of the world, occur in several of the Latin American countries, including Panama.

RELEVANCE OF RESEARCH AT GORGAS

The relevance of GML research maybe evaluated in comparison to the health problems of Panama, the tropical Americas, the United States, and to biomedical research in general. The broad range of pressing health problems in Latin America and the modest amounts of research support available dictate that careful stewardship and rational integration of resources and activities take place so that research programs do not overlap unproductively and that the restricted resources are used efficiently.

Historically, GML has concentrated on vector-borne parasitic and infectious diseases. Consequently, it is not surprising to note that GML has no active research program on malnutrition, leprosy, or tuberculosis. These health problems, however, are under active research and study by other institutions in the region. For example, malnutrition is the focus of a longstanding agenda of research and intervention studies by INCAP in Guatemala, by CFNI in Jamaica, and others. Leprosy research is carried out by CEPIALET in Venezuela, and the U.S. Public Health Service in Carville, La., while PAHO and philanthropic institutions also provide other support for research and intervention in several countries of the region. Tuberculosis research and training is also funded by PAHO. Thus, a lack of GML activities in these areas, by itself, does not indicate low relevance.

On diarrheal disease, GML has researched Campylobacter-caused diarrhea in Panama which was found to be very prevalent in hospitalized cases. Another recent study examined epidemiologic features of Norwalk virus and *Escherichia coli*. This work complements other diarrhea disease work in the region, such as rotavirus research by INCAP and the Caribbean Epidemiology Center.

A recent GML collaborative clinical study of oral dehydration therapy (95), published in the New *England Journal of Medicine* and also in Spanish in the *Revista Medica de Panama*, documented the wide applicability of this technique that was highlighted by an accompanying editorial (12). Thus, GML exploited the availability of a health problem to expand basic scientific understanding, to test clinical therapy, and to disseminate the knowledge in Latin America and the United States.

Malaria research utilizes the GML monkey colony to test experimental drugs. The spread and multiplication of drug-resistant malaria is a cause for concern throughout the world emphasizing the need for discovery and testing of new therapeutic drugs. GML research has identified several promising compounds. This work is not only relevant to the countries with high-malaria prevalence, but

also to the U.S. military, which in fact supports much of this research.

The *Aotus* monkey also appears to be a good animal model for leishmaniasis, which has been used at GML to test therapeutic treatment with allopurinol (119) of this disfiguring, sometimes fatal, disease. The GML monkey colony constitutes a resource to conduct screening of promising anti-leishmanial drugs.

Cancer is a growing concern in Panama, as well as the rest of Latin America, to which GML has responded by assisting in the development of a cancer registry utilizing the computer facility at GML. One result is the identification of a focus of strikingly high prevalence of cervical and penile cancers. Continuing research has since examined various epidemiological parameters, and has also shown a very high prevalence of a cancer-associated virus (HTLV) in this population. This is being investigated under a grant from the National Institutes of Health (NIH) and the National Cancer Institute (NCI). This work appears to be highly relevant to the region and especially to Panama. This finding was corroborated by the Minister of Health of Panama *(34).*

Epidemiological capability at GML is available to assist in epidemic outbreaks, such as occurred in 1981, with aseptic viral meningitis and with acute hemorrhagic conjunctivitis. GML's laboratory expertise for diagnosis of viruses complemented these investigations. GML maintains one of the few viral diagnostic capabilities in the tropical Americas. This type of activity is very important to Panama and the region.

Current research on Chagas' disease is surveying the human populations in two geographical areas of Panama in which different vector species transmit the T. cruzi parasite to determine epidemiological differences in the transmission cycles, This is under a grant from WHO.

Arbovirus research, especially on the vectors and reservoirs, is a major GML activity. A large effort is expended to monitor jungle yellow fever, using a system developed by GML, in the belief that surveillance can give early warning of epidemic potential. Urban yellow fever has not occurred for several decades in Latin America, but the vector *Aedes aegypti* is abundant throughout the region, including the United States. When an epizootic of jungle yellow fever flares, there is a probability of spillover transmission to humans, but, worst of all, would be involvement of *A. aegypti* in the transmission. Furthermore, there still remain questions about reservoirs and vectors of this disease. For Panama and Latin America, the relevance is obvious. For the United States, too, the relevance is not just theoretical or abstract. There are *20,000* U.S. Government employees and dependents in Panama, another *20,000* U.S. citizens in neighboring Costa Rica (51).

St. Louis encephalitis is another focus of arboviral research. GML is attempting to elucidate how the virus is maintained in tropical areas, the vectors and reservoirs, in order to expand knowledge of this arboviral disease that is prevalent throughout Latin America and the United States.

Research on insect vectors and animal reservoirs of other diseases is carried out as well at GML. Two important functions of entomologic field studies are discrimination of vector and nonvector species in various localities of actual and potential transmission (different species have varying transmission capabilities in different habitats), and elucidation of vector behavior and bionomics (e. g., biting times, resting habits, insecticide susceptibilities) in order to develop intervention strategies and to understand the interaction of host, parasite, and vector. Work at GML has recently demonstrated that a common blackfly of Panama, *Simulium quadrivittatum,* can function as a vector of onchocerciasis, though the disease is currently unknown there, Endemic foci of this disease occur in neighboring countries, thus the disease could spread. Recent work at GML demonstrated that transovarial transmission of yellow fever occurs in one of the mosquito vectors. Thus, the vector may also function as a reservoir of the virus, that may explain the persistence of the virus in the absence of disease in animal hosts. Identification of reservoir hosts is an important adjunct activity. Reduction of disease is sometimes feasible through control of animal hosts (e.g., China claims to have reduced leishmaniasis through control of dogs that harbor the parasite.) These activities have relevance to possible intervention in

Panama and the region, as well as to basic understanding of disease processes.

GML maintains a reference capability (available to the region as a WHO Collaborative Research Center) for the identification of blood meals in suspected insect vectors. This is used to determine host-preference from field-collected specimens throughout the region.

Investigation by isozyme electrophoresis' of disease vectors is carried out by GML. Identification of these biochemical markers improves the differentiation of vectorial status, especially where species complexes are involved. GML is examining sandfly vectors of leishmaniasis. Isozyme identification was also developed to differentiate the *Leishmania* species isolated from cutaneous sores. This can diagnose the mucocutaneous type before the destructive pathology develops.

Recently, ecological studies on the effects of impoundment of the Bayano River on insect populations and arbovirus activity have been carried out on contract. Also, environmental and disease impact assessments were carried out in connection with the Tabasara Hydroelectric Project. Relevance seems obvious given that the work was carried out under contract with a third party (the Government of Panama), but the relevance is several-fold:

1. the scientific merit and addition to scientific knowledge;
2. that environmental concern is being addressed and promoted in a developing country;
3. related to the development of environmental concern in Panama is the significant role that environmental preservation plays in the continued function and maintenance of the Panama Canal, a gravity-flow, natural watershed-fed navigational waterway; and
4. that GML was contracted, recognizing it as a body of expertise, within Panama, competent to do the work,

GML's work in sexually transmitted diseases (STDS) has focused on forms of STD that are of high prevalence in Panama, as well as surrounding countries of the region. STDS are epidemic in tropical America, as they are in the rest of the world, but very little public health activity is currently underway in Latin America or the Caribbean:

> With the exception of the four nations mentioned above [Canada, United States, Costa Rica, Cuba], few countries have been able to carry out well-organized STD control efforts. Although most countries have developed guidelines and standards for diagnosis and treatment, few programs to carry them out exist, especially outside large cities **(76).**

GML research on STDS in tropical America is an early and unique effort. For a problem of large magnitude with very little current information or other research underway, relevance to the needs of Panama and the region seems to be very high.

GML physicians see about 1,000 patients each year. These are people suffering from a variety of tropical diseases for which GML can provide expert and specialized services lacking among local physicians and clinics. This clinical service not only adds to the research effort at GML but also supplies a superb and unique teaching facility, and evidently creates much good will among the general, and health professional, population in Panama.

*Isozyme electrophoresis is a method of separating and identifying variant proteins in apparently similar organisms which then permits differentiation and classification. This is most useful when it correlates with geographic, pathogenic, or other varying characteristics of the organisms.

SUMMARY

Overall, the work of GML appears to have high relevance to tropical Latin America, especially to Panama, to tropical disease research in general, and to the United States' interests. Not every activity of GML has obvious relevance. * Nonetheless, the Office of Technology Assessment finds that there is no major problem relating to the relevance of GML's areas of research. This finding is supported by the information presented above, by the personal statements of officials of Panama's Ministry of Health and other health professionals in Panama, by award of grant and contract funding of research projects by NIH, the Department of Defense, WHO, and the Government of Panama, by Fogarty International Center (FIC) site visit reports, and by NIH/FIC testimony before congressional committee. *

*Clearly stated objectives and goals for the institution, as well as individual projects, together with regular, at least annual, formalized intramural review procedures could improve this situation.

*House of Representatives, Committee on Appropriations, 98th Congress: Subcommittee on the Departments of Labor, Health and Human Services, Education, and Related Agencies, Appropriations for 1984, National Institutes of Health, Part 4B, April 1983, pp. 1635-37, 1641-43.