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A STUDY OF THE U.S. CAPACITY TO ADDRESS TROPICAL DISEASE PROBLEMS

FINAL REPORT

KAREN BELL

APRIL 1, 1986

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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FOREWORD

This report presents the results of a study conducted by a steering committee, appointed by the National Research Council and the Institute of Medicine, of U.S. capacity to address tropical disease problems.

↘ The central findings of this report can be stated simply. The next two or three decades offer a historic opportunity to make major progress against the heavy burden of tropical diseases. The diseases themselves are as damaging as ever, and some, such as malaria, are becoming more dangerous as vectors have become resistant to pesticides and parasites to drug therapy. What opens the doors to major progress is a combination of new biological research methods and new economic and social approaches to the applications of health improvements. Properly exploited, these new methods and approaches could result in large-scale reductions in the present enormous social cost of these diseases. (JMS) ←

The United States is participating significantly, in a variety of ways, in the international effort to attack tropical diseases. Nevertheless, despite long experience with tropical diseases and major national interests in helping to reduce their burden, the United States is currently contributing much less than it readily could and should.

The report makes a number of specific recommendations for improving the effectiveness of current efforts. And the report concludes that, with modest increases in resources, the United States could contribute much more strongly than at present to the international collaborative effort to develop and test new approaches for controlling tropical diseases.

→ This document is intended to be helpful to those interested in tropical disease problems, in the health and welfare of poor people in developing countries, and in U.S. foreign policy. We believe it brings together important information and presents conclusions and recommendations that will be useful to members of Congress, Federal agency and university administrators, industry and foundation leaders, researchers, health planners, and others seeking to understand resource constraints, develop program initiatives, and formulate policies in the area of tropical disease research and control.

The committee wishes to express its warm thanks to Karen Bell, study director, to her colleagues Heather Miller, staff associate, and Barbara Jones, senior secretary, and to Courtney Nelson and Timothy Baker, consultants. The committee was greatly aided by its advisors, who participated fully in its meetings and reviews. Finally, the committee thanks the many individuals who assisted with this study by providing information about specific programs, reviewing portions of the draft, or suggesting particular issues for consideration; a list of all contributors is included in the report.

David E. Bell
Chairman, Steering Committee

PREFACE

The study reported here originated from a request by the American Society of Tropical Medicine and Hygiene to the Institute of Medicine. The request was considered by a joint advisory committee to the Institute and the National Research Council's Board on Science and Technology for International Development, which felt that a broad examination of U.S. goals and resources for tropical health was both timely and needed. Further impetus for conducting the study was afforded by expressed interest among members of Congress and federal agency officials about ways to achieve rapid progress in applied biomedical research targeted on important public health problems in the developing world.

The National Research Council appointed a steering committee for the study in June 1984. The committee established the scope and nature of study activities and approved principal issues of concern and the recommendations to be included in the final study report.

The Office of Technology Assessment (OTA), in response to similar concerns expressed by the Senate Appropriations Committee, simultaneously began an examination of the status of biomedical research and technologies for controlling tropical diseases. Staff for

the two studies coordinated closely in order to achieve complementary, rather than overlapping, products. Results of the OTA examination were published in its 1985 report, Status of Biomedical Research and Related Technology for Tropical Diseases.

In viewing U.S. capacity to address tropical disease problems, the committee examined several major questions:

- o The extent of the tropical disease burden and the U.S. national interest in its alleviation.
- o Current prospects for control of tropical diseases.
- o Efforts by the less-developed countries, international organizations, and the United States to improve tools for dealing with tropical diseases and to strengthen health programs for their control.
- o The state of U.S. resources, both individual and institutional, for dealing with tropical disease questions.
- o How the United States might develop and channel its efforts more efficiently to make a useful difference, in a period of budgetary austerity, in the fight against tropical diseases.

Data on the scope and direction of U.S. efforts against tropical diseases have been scattered or lacking. The committee looked at

critically important categories of talent (clinicians, including clinical researchers; biomedical scientists in the fundamental and applied research disciplines; and specialists in public health and disease control); at training and research capacity; and at current efforts for tropical disease surveillance, diagnosis, treatment, and control.

For the purposes of this study, the committee decided to use the term "tropical diseases" to refer to those diseases of infectious etiology that occur predominantly in the poorest populations in less-developed countries. This definition, consistent with that found in the OTA report on the "Status of Biomedical Research and Related Technology for Tropical Diseases," includes the major tropical parasitic diseases (e.g. malaria, schistosomiasis, trypanosomiasis); diarrhea; acute respiratory infections; leprosy; and numerous other diseases of bacterial, rickettsial, viral and parasitic etiology. We did not find it necessary to prepare a precise and comprehensive listing. Other diseases, such as tuberculosis, AIDS, and gonorrhea, also pose significant public health threats in developing countries, but were not included in the committee's analysis of U.S. capacity, because they are still considered infectious diseases problems in industrialized countries and as such receive substantial research and control program support. Note, however, that our working definition is in at least two respects quite restrictive and does not include some major public health problems of developing countries. Problems related to population growth

were excluded, as were nutrition-related problems other than those directly related to viral and parasitic infections. The committee considers these omitted subjects to be of very great importance but clearly beyond its mandate.

Data on the scope and direction of U.S. efforts against tropical diseases have been scattered or lacking. In enumerating critically important categories of talent the committee adopted the term "tropical disease specialist" to designate a senior professional with advanced training in medicine, the biomedical sciences and/or public health who is currently dedicating his/her efforts to an infectious disease problem of developing countries. Three basic categories were identified: clinicians, including clinical researchers; biomedical scientists engaged in research; and specialists in public health and disease control. Individuals who were included in the biomedical research category had successfully competed for research funds. The committee also examined training and research programs and U.S. sponsored activities in tropical disease surveillance, diagnosis, treatment and control.

The study proceeded in the following way. The staff held preliminary, one-day meetings in Washington, Los Angeles, and Baltimore, prior to the committee's formal appointment. These meetings brought together experts from government, industry, academic institutions, private foundations, and other organizations to consider the study mandate and to suggest how to proceed. Several individuals subsequently appointed to the committee were present.

The committee met twice in 1984 to determine the issues to be addressed and to develop a work plan for staff and consultants. To obtain an overview of U.S. resources available to address problems associated with tropical diseases, the staff conducted surveys of U.S. institutions and individuals concerned with tropical diseases. Results of these surveys, conducted by staff members Karen Bell and Heather Miller, are presented in this report. Notes on survey methodology are available from the committee records maintained by the National Research Council. The history of U.S. international collaboration in dealing with tropical diseases was outlined in a commissioned paper prepared by Courtney Nelson, a consultant, and is included in this report. The committee staff director, three members of the committee, and several other U.S. scientists, met in Cairo, Egypt, April 24-26, 1985, with a dozen leading scientists from developing countries who are concerned with tropical diseases and who have participated in collaborative research activities with institutions in the United States. The group discussed past collaborative research efforts between U.S. scientists and their counterparts from developing countries and made recommendations for future U.S. involvement in collaborative work on tropical diseases.

In addition to these special activities, the staff gathered and analyzed a great deal of information on the issues confronting the committee. A draft of the report was prepared and was the subject of the committee's final meeting, October 10-11, 1985, at which the committee formulated its recommendations. The final draft was prepared by the staff, circulated to committee members for review and comment, and approved by the full committee.

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TROPICAL DISEASE IMPACTS AND IMPLICATIONS

TROPICAL DISEASE BURDEN IN DEVELOPING COUNTRIES

Tropical infectious diseases¹ diminish both the quality and duration of life of many people in developing countries. They coexist with poverty, crowding, illiteracy, malnutrition, poor sanitation, inadequate housing, insufficient clean water, and exposure to arthropod disease vectors. Acute infections, chiefly diarrhea, respiratory illnesses, and malaria are the most common causes of serious morbidity and death among infants and children under five years of age. Millions of adults and children are chronically infected with protozoan and helminthic organisms that debilitate, slow growth, destroy tissues, and impair immune function. Clinical symptoms are often mild in the early stages of infection, which in the case of some pathogens, can persist for many years. Disease manifestations in adults vary widely, but often produce chronic weakness, discomfort, or disability, depending upon the intensity of the infection and the individual's immune response.

The impact of infectious diseases in developing countries is most dramatic in children. Nearly a quarter of the children born in many developing countries will die before their fifth birthday (UNICEF, 1984). Diarrheal infections affect poor children living in developing

countries about four times as often as children living in the United States and cause about forty times the number of deaths (Congress of the United States, 1985). Acute respiratory infections (ARIs) are the most common illness in children all over the world, but the incidence of severe lower respiratory tract infections in the developing world is much higher, along with the death rate. In countries with high infant and child mortality rates, ARIs account for a major proportion of all deaths in children under five.

Measles and its complications are estimated to cause about 1.5 million deaths in children annually (Assaad, 1983). Malaria is an important cause of mortality in children in Africa (Bradley, 1984).

The World Health Organization (WHO) estimates that there are more than 200 million individuals infected with schistosomiasis, more than 10 million cases of Chagas' disease in Latin America, 30 million cases of onchocerciasis (river blindness) in Africa, 90 million cases of lymphatic filariasis, and 11 million people with leprosy. About 2.4 billion people live in areas where malaria poses a constant threat (International Health News, 1984b:33).

Parasitic diseases consume scarce resources in developing countries. Although impact measurement of parasitic diseases in its broadest sense lags far behind epidemiologic and biomedical studies, there is broad agreement that they are an important obstacle to social

and economic development. Long-term or heavy infections often lead to medical complications requiring expensive hospital care. The over-all impact of these infections on families and communities is measured more in terms of days of lost work, lost school, permanent disabilities, and economic opportunity costs than in terms of acute illness and death.

Many vaccine-preventable diseases have been eliminated from or greatly reduced in the more-developed countries but remain serious problems in poorer nations. Each year, between 3 million and 4 million deaths are caused by tetanus, pertussis, and measles alone--diseases for which vaccines already exist (Foster, 1984:119).

Much more frequently than in the industrial countries, childhood illnesses such as measles in the less-developed countries lead to serious complications or otherwise leave long-lasting, debilitating consequences; many infections are fatal. Multiple, concurrent infections, along with chronic malnutrition and lack of access to treatment or preventive measures for these diseases, have tremendous impact on morbidity and mortality in both children and adults in poorer nations.

Assessing the Disease Burden

The disease burden in the less-developed countries is clearly immense but difficult to estimate with any precision. Ability to identify and enumerate cases of specific illness varies greatly both

from country to country and by disease. Many tropical infectious diseases cause fever and respiratory or diarrheal symptoms. Without appropriate diagnostic tests, febrile illnesses remain undiagnosed or are arbitrarily labeled as malaria.

Several factors account for the lack of reliable information about tropical disease prevalence and incidence. When reported, death usually is attributed to an apparent immediate cause; contributory causes are not recorded at all or may not be included in the official death notice; deaths are usually not reported in the very rural or poorest regions. Research studies are usually published in scientific journals but may not be communicated in a useful or timely way to health officials. Rarely have studies been conducted on large segments of tropical populations to ascertain leading causes of morbidity and mortality. Tropical diseases may also not be viewed locally as very important. They often produce chronic subclinical conditions not perceived as abnormal by those affected. Accurate diagnostic tests are often not available.

In most countries only communicable diseases that pose an immediate threat to the population are classified as reportable. International health regulations require local health authorities to report diseases such as cholera, yellow fever, plague, and louse-borne typhus to WHO within 24 hours of case discovery. However, data published by WHO on these and other diseases are only as accurate as those collected in the individual countries. Most cases are not reported and the statistics do not accurately reflect the disease burden.

Much of the reliable data on morbidity and mortality are disease-specific and confined to small geographic areas. Researchers associated with the International Center for Diarrheal Disease Research, Bangladesh, have collected data on diarrheal diseases in Matlab, Bangladesh, and these data have been valuable in understanding the etiology and epidemiology of diarrhea associated with specific pathogens in that area. Surveys restricted in scope and size can provide accurate information, but generalizations to other populations and regions may not be possible.

Surveillance of communicable diseases by identifying active cases is rare in most areas. The development of effective surveillance systems is difficult and often requires diagnostic laboratories for support. Large portions of the populations in developing countries do not have access to health care systems, and, therefore, official morbidity and mortality statistics may greatly underestimate disease burden. Identification of specific health problems can embarrass governments unless control programs are planned. Nevertheless, data on disease incidence and prevalence are important for health planning. Information derived from routine case reporting, special surveys, and surveillance systems permits the identification of emerging and serious health problems as well as the monitoring and evaluation of programs to prevent and control them. Such information is critical in establishing priorities for the allocation of scarce resources. One of the committee's recommendations deals with this subject.

Etiology of Tropical Infectious Diseases

Tropical diseases are caused by the entire spectrum of microorganisms--bacteria, viruses, funguses, helminths, protozoa, parasites, and rickettsia. Ecological conditions of the tropics create a favorable environment for these pathogens. High temperature, humidity, animal and insect vectors, and human behavioral and socioeconomic problems sustain and amplify disease.

The following examples of tropical infectious diseases were selected by the committee to illustrate the diverse impact of infectious diseases on human lives in the development world. Disease-transmission pathways and pathogen characteristics together largely determine the nature of prevention and control programs needed. The diseases are discussed here according to their basic routes of transmission.

Vector-Borne Diseases

Insect vectors transmit many of the tropical parasitic and viral diseases to human beings. Arthropods are often an essential host during a portion of parasite life cycles. The Anopheline mosquitoes transmit malaria to humanbeings, by injecting the parasite with their saliva into the skin just before sucking blood. Anopheline and other mosquito species transmit filariasis and viral diseases such as dengue fever.

The reduviid bug, prevalent in many parts of Latin America, is often infected with trypanosomes that cause Chagas' disease and can in turn infect humans. Arthropod vectors occupy unique ecological niches in rural areas of the tropics; understanding of arthropod ecology is important for development of control strategies.

Historically, much progress in reducing tropical disease infection rates has been made through control of the vector or in preventing contacts between man and vector. For example, urban yellow fever has been nearly eliminated by removing or destroying the breeding sites of Aedes aegypti, a mosquito that prefers small containers. Malaria was greatly reduced in many countries through the application of DDT as a residual insecticide on household surfaces and outlying buildings, a measure that interrupted disease transmission; the emergence of pesticide-resistant mosquitoes has led to substantial increases in malaria in some countries. Vector control remains the only preventive measure available to public health authorities for many tropical diseases for which effective vaccines and nontoxic, inexpensive chemoprophylaxis are not available. Dengue fever, leishmaniasis, and onchocerciasis remain in this category.

Approximately 300 million people contract malaria each year, and at least 1 million of these cases, mostly in children, are fatal (Kolata, 1984b). Of the four species of malaria that infect humans, Plasmodium falciparum causes the most serious infection, which can lead to coagulation defects, shock, kidney and liver failure, coma, and death. The other species of Plasmodium which cause human disease--vivax,

malariae, and ovale--are less life-threatening, but vivax and ovale infections can produce relapses for up to 5 years after the initial infection; malariae infections can persist for as long as 50 years (Benenson, 1985:226).

Scientists have been optimistic about achieving dominance over malaria since the parasite and the vector were discovered at the end of the last century. Drugs to treat the infection and pesticides to control the vector were hailed as harbingers of the final chapter of the malaria story. Then drug-resistant parasites and DDT-resistant mosquitoes began to emerge.

Efforts to control the mosquito vector of malaria have met with varying degrees of success. In 1956 WHO began Malaria Eradication Programmes in affected Asian and Western Hemisphere countries. Soon thereafter, however, the vectors already were exhibiting resistance to DDT, and many operational, financial, and administrative problems were evident in some countries. Transient successes in India and Sri Lanka tell of the real frustrations in controlling this disease. In the late 1940s India had approximately 75 million reported cases of malaria per year; by 1961 the number dropped to a reported 50,000 cases. By 1976 the case total had risen again to an estimated 6.4 million (Peters, 1985:144). Some countries that have used broad-based strategies, including treatment, education, and surveillance as well as vector control appear free of the disease. Cuba apparently has been free of malaria since 1973, and large areas of Venezuela, Argentina, Brazil, and Paraguay appear to be malaria-free.

The elimination of malaria is a very complex process, and the interplay of economic, social, political, scientific, and technical factors is not fully understood. Dr. William Chin, a former employee of the Centers for Disease Control, describes the malaria problem in these terms (personal communication, 1984):

. . . [T]he irony is that in a control program, more malaria expertise is needed than during the eradication era; the availability of local competence in malariology may be the key element to the future success of malaria control. The facetious observation often quoted that the major success of the malaria eradication campaign was the eradication of the malariologist, underscores the present dilemma caused by the acute shortage of trained personnel. This problem is especially severe in the more disadvantaged countries unable to afford an organized program of malaria control. The plight of most of the African countries, south of the Sahara, where P. falciparum accounts for more than 90 percent of the malarias, is particularly alarming. After the emergence of chloroquine-resistant falciparum malaria in East Africa in 1979, such strains are spreading rapidly westward. As these strains continue to evolve and develop higher levels of resistance to chloroquine and perhaps to other antimalarials, from where will the needed expertise come to monitor the evolving situation and to devise countermeasures?

In this decade, the United States is leading efforts using the most sophisticated genetic and immunologic methods available to develop malaria vaccines. Candidate vaccines for one species of malaria are expected to enter field trials by 1988. Despite the enormous potential benefits of a safe and efficacious vaccine, its availability will not conclude the malaria story. Effective programs will be needed to administer the vaccine in a timely fashion to vulnerable age groups and populations. New drugs still will be needed to treat recurring cases, and methods for vector control will continue to be required.

Scientists, moreover, concede the possibility of the parasite modifying its antigenic determinants to elude detection by vaccine-induced immune systems (Kolata, 1984b). Malaria will continue to be a major health threat for some time to come.

African trypanosomiasis (sleeping sickness) is another vector-borne disease of serious consequence causing 20,000 reported cases annually in Central and East Africa. An estimated 45 million people are exposed to the risk of infection. Like so many tropical diseases, African trypanosomiasis has enormous socioeconomic as well as personal consequences. In humans, the disease progresses from malaise and lassitude, to daytime drowsiness with nighttime insomnia, to profound sleepiness, which precludes eating, and finally to seizures, tremors, mental deterioration, coma, and death. More importantly, livestock and other animals are prey to this disease when bitten by an infected tsetse fly. In an area of Africa that is larger than the continental United States trypanosomiasis has effectively prevented the raising of livestock (Kolata, 1984a).

A new drug, difluoromethylornithine (DFMO), has been used successfully in advanced cases of African trypanosomiasis caused by Trypanosoma gambiense infection and even has reversed coma in individuals at the end stage of this disease. Unlike other drugs used to treat sleeping sickness, DFMO achieves therapeutic concentration in the central nervous system without toxic side effects. DFMO inhibits polyamine biosynthesis in trypanosomes, thus blocking cell division and preventing the alteration of the antigenic coat (Sjoerdsma and

Schechter, 1984). Once the parasite is stabilized antigenically, the host's immune system can effectively recognize and destroy it. DFMO is administered intravenously to comatose patients and orally to all others and requires a six-week course of therapy. Originally developed to treat tumors, DFMO is currently undergoing clinical trials in Africa. WHO and Belgian health officials are collaborating with the U.S. manufacturer, Merrell Dow,² to undertake more definitive clinical trials.

Development of a vaccine to prevent African trypanosomiasis is unlikely in the near future. New, cheap, effective drugs for treatment in the early stages of infection are desperately needed. The drug DFMO represents a breakthrough in the treatment of an otherwise intractable disease.

American trypanosomiasis, Chagas' disease, is found throughout Central and South America and is caused by Trypanosoma cruzi. WHO estimates that at least 20 million people in Latin America are infected with this organism (TDR Newsletter 1983:6). Transmitted by the reduviid bug, which lives in trees and cracks of mud houses and in thatched roofs, T. cruzi is found in numerous mammalian hosts, including humans. Early infection usually goes undetected, but only at this stage is the currently available treatment effective. Unlike African trypanosomiasis, Chagas' disease usually affects the autonomic nerves of the cardiovascular system and the digestive tract rather than the central nervous system. Chronic sequelae include cardiac dilatation and arrhythmias and often grotesque enlargement of the esophagus and

colon. In adults Chagas' disease can produce a long, debilitating condition requiring hospitalization and disability assistance, further sapping the resources of both the community and the individual. The acute infection is commonly fatal in children.

Insecticides can effectively control the reduviid vector of Chagas' disease, and vector control is thought to be the best currently available means for diminishing the prevalence of this disease. Of course, improvement in the materials used to build houses also prevents vector-human contact, effectively protecting the urban middle class. American trypanosomiasis is not a good prospect for vaccine development. The antigenic protection system of the pathogen is especially complex; the cycle of infection includes an intracellular stage. Chagas' disease therefore will likely continue to be a serious problem for the foreseeable future.

Diseases Related to Water Supplies

Water supplies can affect the transmission of disease from one person to another in various ways. Water-borne infections, such as cholera and typhoid, occur as a result of ingesting a pathogen with drinking water or contaminated food. Other infections, like trachoma and shigellosis, are more prevalent and serious in the absence of abundant water for washing and personal hygiene. Most pathogens transmissible via a fecal-oral route pose hazards to persons who lack access to sufficient quantities of safe water.

Diarrheal diseases are caused by a wide variety of pathogens and primarily afflict infants and children. WHO estimates that there are three-quarters of a billion episodes of diarrhea each year in children of the developing world, and rotavirus alone is responsible for 20 percent to 40 percent of the 4.5 million deaths in children caused by diarrhea (Black, 1984:141; New Africa, 1985). Diarrheal disease is particularly dangerous in children because of its cyclical interaction with malnutrition: Intestinal infection inhibits nutrient absorption, which amplifies existing malnutrition, and malnutrition impairs the immune system, rendering these children more susceptible to infection. The danger associated with diarrhea is dehydration and shock, from fluid loss and electrolyte imbalance. Oral rehydration therapy (ORT), when used appropriately, is effective in preventing almost all deaths resulting from dehydration associated with diarrhea (Black, 1984:157).

Control of diarrheas is largely based on breaking the oral-fecal transmission route. Programs designed to attack this group of diseases must include all possible water and sanitation improvements as well as treatment. Improving household hygiene through education programs was found to reduce the incidence of diarrhea caused by Shigella (Black, 1984:157). Drugs can successfully be used to treat some diarrheas of bacterial etiology, including the various strains of Shigella. Bacteria, however, are now exhibiting resistance to more than one antibiotic. Diarrheas caused by parasites, however, are not easy to diagnose or treat: many of the drugs available for this problem are toxic and may be ineffective.

New or improved vaccines are being developed for the more important diarrheal pathogens. Several rotavirus vaccine candidates are being tested in humans in industrialized and developing countries (Robert Edelman, NIAID, personal communication), while field trials for a new cholera vaccine are underway in Bangladesh at the ICDDR,B.

While oral rehydration therapy can prevent much of the mortality related to diarrheal diseases, the therapy must be available, acceptable, and used to achieve successful management of illness. Sustained health education efforts and the development of local capacity to manufacture the rehydration powders are needed, as well as additional biomedical research to develop new tools to prevent and control these diseases.

Schistosomiasis afflicts between 200 million and 300 million people in Africa, Latin America, and Asia (Kolata 1985). The replication of schistosomes requires the presence of fresh water, the intermediate snail host and the definitive host, man. Infected humans shed schistosoma eggs in excreta. If egg-contaminated excreta reaches fresh water, the eggs will mature and hatch, releasing miracidia. The miracidia seek out snails in which to develop into sporocysts and finally cercaria. The cercaria are released from the snail and survive in the fresh water, until they find a human host. The cercaria penetrate the skin, and flukes mature in the blood vessels of the lung. Adults migrate to the venules around the small intestine where eggs are laid. These move through the gut tissue to the lumen of the intestine and are passed out in excreta, starting another cycle. Symptoms and

tissue damage depend on the strain of schistosome causing the infection and on the number of parasites. Schistosoma mansoni and S. japonicum are associated with liver and gut disease. S. haematobium lodges in the urinary tract and causes painful urination, bloody urine, and chronic infection predisposing to bladder cancer. The majority of those infected are children who live in rural settings. As the population increases in affected areas, the prevalence of schistosomiasis is likely to follow.

Ironically and tragically, schistosomiasis may increase if economic development efforts alter watercourses in certain ways. Hydroelectric dams and irrigation systems can increase the prevalence of schistosomiasis by supporting the intermediate host, the snail, and attract large numbers of the definitive host, man.

A new drug, praziquantel, is effective against all species of this pathogen but is expensive. The drug is sold by Bayer, the manufacturer, to WHO at \$2 per dose, still prohibitive for governments whose entire annual expenditure for health may be less than \$2 per capita. Praziquantel is a treatment, not a preventive agent; reinfection can and does occur.

Programs that simultaneously attack the vector, treat infected cases, provide clean water and sanitation, and educate the population at risk have dramatically decreased the prevalence of schistosomiasis in China, Japan, and parts of Egypt, Iran, Puerto Rico, Tunisia, and Venezuela (U.S. Congress, 1985:67). Few developing nations have the resources needed to carry out such programs over a sufficiently long

period of time to ensure effectiveness. There is some distant hope for a vaccine, but a successful human schistosomiasis immunization program in the near future is unlikely (Kolata, 1985).

Dracunculiasis is a parasitic worm infection prevalent in some parts of India and West Africa (National Research Council, 1983b). Unlike schistosomiasis and filariasis, which also depend upon water as the natural habitat of an intermediate host, dracunculiasis is acquired through ingesting water fleas infected with the nematode Dracunculus medinensis. Portions of India and Africa are affected severely by this disease, which cripples rather than kills when the worm penetrates the skin to extrude eggs. The International Drinking Water Supply and Sanitation Decade in 1981 endorsed the idea of using the progressive elimination of dracunculiasis as an indicator of the Decade's impact on health in regions where the disease is endemic. The last World Health Assembly endorsed country-by-country efforts to eliminate dracunculiasis.

Acute Respiratory Diseases

Acute respiratory infections (ARIs), including pneumonia, whooping cough and the complications of measles, are estimated to cause between one-third to one-half of deaths occurring in children under five in developing countries (UNICEF, 1984; Pio, 1984; and Bulla, 1978). Whooping cough (pertussis) and measles are preventable through

immunizations, while treatment for the severe lower respiratory tract infections caused by multiple etiologic agents is largely limited to supportive care and antibiotics, which are only effective for bacterias. Vaccine development is underway for several pathogens identified as responsible for serious illness (Institute of Medicine, 1986).

In 1985, fewer than 3,000 cases of measles were reported in the United States. In that same year in the less-developed countries more than 1.5 million children died of measles and its complications (Katz, 1985 and Division of Immunization, Centers for Disease Control). Complications include pneumonia, convulsions, coma, and diarrhea. The far greater mortality from measles in these countries is related to nutritional status, type and severity of infection, and shifts in the epidemiology of the disease. Unlike the pattern of infection in the United States, natural infection in these countries occurs in children as young as 6 months. Vaccines are not effective until children are at least 9 months old, when interfering maternal antibody wanes. A study in Haiti associated lower levels of maternal antibody with decreased resistance in the first year of life (Katz, 1985).

Other ARIs account for a large percentage of morbidity in children and in the elderly. A variety of bacterial and viral pathogens are responsible for serious respiratory infections in children, but not much is known about their incidence, distribution, and seasonal variation in developing countries.³ Malnutrition, poverty, and crowding contribute to the prevalence and severity of these diseases.

Mortality from acute respiratory infection is related directly to pneumonias and indirectly to prolonged coughing with attendant vomiting and anorexia, which can aggravate existing malnutrition. Mortality rates for ARIs in India, Egypt, Paraguay, Mexico, Bolivia, and Brazil are 30 to 75 times higher than they are in the United States (U.S. Congress, 1985:89). Differences in these mortality rates reflect differences in the severity of the illnesses and the adequacy of treatment.

Treatment for a limited number of viral ARIs is now available, but its use is not currently practical on a large scale in developing countries. Use of vaccines for ARIs such as whooping cough and diphtheria are limited largely by the restricted capacity of local infrastructure available to maintain widespread coverage and effective delivery programs. Case management based on standardized procedures is being evaluated in a number of countries. These protocols provide guidelines for the use of antibiotics and economic use of other expensive resources. More research is needed to determine risk factors and geographic distribution of the etiologic agents, to develop vaccines, and to improve case management.

Viral Diseases

Tropical diseases such as Ebola, Marburg, and Lassa fevers pose a serious threat both to indigenous populations and to travelers. All are

of viral etiology and to date are endemic only in Africa. Although these diseases differ significantly in their epidemiology, they are grouped together here because a major consideration in their control is the requirement of strict isolation of cases to prevent spread of infections in the hospital environment. Patients' excreta, sputum, and blood and all objects which which they come into contact must be disinfected. Secure pathogen containment facilities for research are available through the Centers for Disease Control and the U.S. Army Medical Research Institute for Infectious Diseases, which has patient-care capabilities. More research on the natural history of these diseases is needed, as are improved diagnostic and preventive tools.

Ebola and Marburg diseases are spread by person-to-person contact or through exposure to contaminated blood or secretions. Both diseases can also be transmitted sexually. An estimated 25 percent of reported cases of Marburg infection are fatal, and case fatality rates for Ebola range from 50 percent to 90 percent (Benenson, 1985:124). These viral infections involve multiple organ systems including the liver, pancreas, kidney, and, occasionally, the central nervous system and the heart.

The case fatality rates and prevalence rates for Lassa fever vary widely. Feared because of its virulence, this disease leads to shock, pleural effusions, hemorrhage, encephalopathy, and death. Lassa was once thought to be a rare disease, but improved diagnostic techniques have found the Lassa fever virus to be common in certain areas of West

and Central Africa. Nearly 40 percent of children assayed in Liberia were found to have antibodies to the Lassa virus (New Africa, 1985:63).

These are only a few of the diseases that debilitate local populations and thwart development efforts. Many other infectious diseases--other arboviruses, leishmaniasis, certain sexually transmitted infections (e.g., congenital syphilis, donovaniasis), and leprosy, for examples--impose disproportionate disability and mortality in tropical developing countries. AIDS is reportedly increasing among heterosexual populations in certain parts of Africa, indicating a transmission pattern apparently dissimilar to that observed in the United States.

Zoonotic Diseases (Zoonoses)

Zoonotic diseases are pathogens transmissible from animals to human beings. Some zoonoses, plague and murine typhus for examples, are transmitted to humans through an intermediate vector such as fleas. Some, such as echinococcosis and leptospirosis, are contracted through exposure to contaminated animal excretions. Still others, such as rabies, are directly transmitted from animals to human, in this case through animal bites. The presence of an animal reservoir complicates the control of these diseases. Many people in the developing world live in close proximity to animals, which increases the probability of transmission. While many zoonotic diseases can be controlled in human and some domestic animal species, the underlying reservoir in both must

also be attacked in order to break the transmission cycle. Veterinary public health therefore is linked closely to human public health. Zoonotic diseases threaten human directly by exposure and indirectly by the socioeconomic impact of diseased animals on agricultural productivity.

Leptospirosis, a bacterial disease caused by a spirochete, is transmitted to human by contact with infected urine and tissue of farm animals, pets, and wild animals. This febrile illness, associated with a range of symptoms, can lead to jaundice, renal insufficiency, and anemia. Case fatality rates can be as high as 20 percent in high-risk groups such as the elderly (Benenson, 1985:214). Leptospirosis occurs worldwide but is a notably more serious problem in the tropics, especially rice paddy or sugarcane areas. It is an occupational hazard to all people who work with animals and to sanitation workers and military troops. The clinical features of this disease make diagnosis problematic. Once it is diagnosed, antibiotics can be used, with difficulty, to treat leptospirosis, and vaccines are available for the three primary strains that cause clinical disease in humans (Yanagawa, 1985). The U.S. armed forces use doxycycline chemoprophylaxis for troops training in Panama. While the strains or serovars in Panama have not been associated with serious complications, deaths have been linked to this disease in other parts of Latin America and the Caribbean (Takafugi et al., 1984).

Canine rabies is an invariably fatal disease caused by a neurotropic virus. The course of this disease is hideous and well chronicled.

Fever, headache, and malaise give way to paralysis and muscle spasms, particularly in those muscles associated with swallowing, thus resulting in hydrophobia, fear of water. Finally, delirium and convulsions set in, with death resulting from cardio-respiratory paralysis. Of the 88 countries with endemic canine rabies, most are in the developing world. As dogs account for over 99 percent of all human cases of rabies, vaccination to prevent the disease in dogs and stray dog control are the most effective way to prevent the disease in man. Massive dog-rabies control programs have been employed successfully in Argentina, Chile, and Zimbabwe (Blancou and Bogel, 1985). By one estimate the cost of effective control is recovered in 2.5 years if dogs are the only reservoir. Such savings are made through the elimination of costly care for the victims of animal bites (Beran, 1979:145).

STRATEGIES FOR REDUCING THE TROPICAL DISEASE BURDEN

The burden of illness from infectious diseases has decreased in many societies both as a result of improvements in living standards and as a response to disease-control programs and preventive and therapeutic medical care. Achieving similar reductions in developing countries will require very large efforts, including, in many regions, the development of much stronger scientific, technical, and managerial capabilities to monitor and control disease problems. Developing such capabilities requires sustained collaboration among members of the international scientific community.

Health and Development

Poverty and the socioeconomic conditions associated with poverty--inadequate nutrition and housing, illiteracy, and lack of potable clean water, waste disposal systems, and education--are closely related to health status. Development programs that seek to improve economic conditions in developing countries indirectly improve the health of those populations as well.

As development programs have evolved, health has become a more visible goal for assistance efforts. While programs that have improved socioeconomic status have resulted in decreases in the disease burden, disease prevention and control may also be direct contributors to socioeconomic development. Accordingly, health is becoming a more important and integral part of development programs.

The future success of family planning programs is also linked to disease control. As children represent a form of old-age insurance, parents who choose to limit the size of their family need assurance that the children they do bear will survive to adulthood. Management of childhood illnesses thus becomes an important partner in population control programs.

Not long ago, many of the same diseases that affect developing countries were responsible for significant health problems in what are now industrialized nations. Malaria, cholera, yellow fever, and dengue were common in the United States throughout the Nineteenth Century. The

elimination and control of those diseases were brought about by a variety of factors, including public health legislation, the development of institutional resources to address public health problems, and adequate and widespread sanitation systems. The decrease in disease burden coincided with economic growth and general improvement in education and in standards of living.

The improvement of health through economic growth encounters many obstacles in developing nations. A severe economic crisis affects much of the developing world, limiting the availability of resources for the social sector. Rapidly growing populations, migration to urban areas, lack of appropriate technology and trained manpower, and lack of adequate environmental sanitation perpetuate the disease burden. As urban populations swell, crowding creates environmental conditions in which communicable diseases thrive.

Disease control in the tropics may involve the application of one or more specific strategies to reduce the chances of contact between person and pathogen. Strategies often include prevention through immunization and prophylaxis; case-finding and medical treatment; vector control; provision of clean water; sanitary disposal and treatment of excreta; improved living conditions; and health education.

Some of these measures will be effective against several pathogens at once. Adequate supplies of clean water reduce infection from diarrhea pathogens, and improved sanitation measures curb transmission of hookworm and schistosomiasis. However, other tools for controlling disease act against only one pathogen or vector at a time and are not entirely effective.

The St. Lucia experience illustrates the efficacy of multiple strategies and the need to consider tropical disease activities in terms of control rather than eradication, however desirable eradication may be.

In 1965 the Rockefeller Foundation and the government of St. Lucia began a cooperative study to assess the efficacy of three different means to control schistosomiasis: control of the snail vector with molluscicides; provision of potable water to houses; and drug treatment of infection. All three were successful in controlling the disease and in reducing the incidence rate for children under age 5 from 20-30 percent to approximately 5-10 percent. Chemotherapy dropped the infection rate the fastest but required continued participation, community cooperation, and surveillance to identify new cases. Use of molluscicides was the easiest but also the most expensive approach and presented some environmental problems. Provision of clean water was initially expensive and required continual expenditures for maintenance. Clean drinking water alone was the least effective control mechanism; education and chemotherapy were needed to reduce the incidence rate to approximately 5 percent.

The success of disease prevention and control programs depends on social and economic as well as biologic variables. The introduction of new medical technologies, however efficacious under controlled conditions, will not guarantee their effective or widespread use. More consideration is needed of the broader cultural and economic

determinants required to maximize the acceptance and impact of specific disease control strategies selected for mass application.

Applying Scientific Knowledge to Tropical Disease Control

The scientific knowledge necessary for dealing with tropical diseases is highly uneven and incomplete. Even when the necessary knowledge is available, applying it can be difficult. Many governments in developing countries do not give high priority to disease control. Although properly designed disease prevention and control programs can be the most effective measures which countries can take, they require a sustained commitment and effort and can be enormously expensive with currently available technologies. Furthermore, the populations who are most affected may be largely in rural areas, and may have limited political influence.

Actions can be taken, based on today's knowledge, to reduce mortality significantly from specific disease problems. ORT for acute diarrheal infections is one example. The principles behind ORT were developed and perfected over the past 20 years in research laboratories and clinical settings around the world. Efforts are being made to spread the use of ORT rapidly, but to do so requires modification and strengthening of health services, major improvements in present logistic and distribution systems, and large-scale training of health care personnel and family users. Even when use of ORT is accepted and

widespread, the underlying problem will not be solved; ORT is only supportive therapy, not prevention.

Immunization represents a much more complex intervention system than ORT. Successful immunization programs require refrigerated supply lines (so-called "cold chains"), appropriate equipment and personnel for their administration, substantial record-keeping for both program administration and evaluation, and flexibility so the vaccines can be used in many different social settings.

Vaccinations are rarely a one-time process. Many vaccines must be given in multiple doses at specified and finite time intervals. To vaccinate one generation of children is not enough; each new cohort of infants requires vaccination. In order for immunization programs to meet the expectations of full protection, much more research and development will be needed. Health services as well as the immunologic tools themselves must be improved in order to make immunization for a broader spectrum of diseases readily available to all children on a continuing basis.

Understanding the smallpox eradication campaign provides hope but also limits expectations. Smallpox may well remain the only example of disease eradication. By the time the eradication campaign began, governments of endemic countries were strongly in favor of eliminating this dread disease from their populations. Governmental will was sufficiently high for developing countries to offer local resources to assist in program development and execution and for the governments of more developed countries to provide money and manpower in a

well-orchestrated program. Equally important were the improved lyophilized vaccine, the development of the bifurcated needle for its delivery, and the lack of an animal reservoir for the virus. By the time the worldwide eradication campaign began, many countries had the disease under control, and vaccination programs had been in place in industrialized countries for more than 100 years. Even with a long-standing history of vaccine use and a readily available smallpox vaccine, however, additional research on strategies for vaccine delivery was necessary to ensure the success of the global program.

There is very limited potential for applying the smallpox model to other tropical diseases. Smallpox required no vector control, had no zoonotic component, could be prevented by a single vaccination that was already available and relatively easy to deliver, and the disease was sufficiently lethal to consolidate the will of governments to act simultaneously. In addition, the incubation period was short and nearly every infection resulted in a rash, making identification relatively simple. This is not the case with any other tropical disease. A lasting lesson of the smallpox eradication program is the value of surveillance for and containment of disease transmission, followed by limited vaccination campaigns, which replaced mass vaccination as the basic operational method for this disease.

Today's science is far from sufficient to assure successful control of other major diseases such as leishmaniasis. Leishmania parasites are known to occur in more than 13 different varieties, but the combination

of factors that will produce disease is not fully understood. Basic ecological and epidemiologic studies are needed to assess the role of animal reservoirs, identify individuals at risk of developing the disease, elucidate transmission patterns and pathogenesis mechanisms, and to define the genetic mechanisms responsible for the emergence of new and different strains. Molecular biologists are also contributing to basic knowledge about the parasite by developing DNA probes to identify specific leishmania strains in infected lesions; these probes will in turn greatly facilitate epidemiologic, clinical, and immunologic studies carried out by other investigators. Results of these studies could provide valuable clues to facilitate genetic engineering of drugs or vaccines that either block or mimic reactions and encounters already taking place in nature or in infected humans.

Strategies to reduce mortality and severe morbidity from infectious diseases in children have been integrated into Child Survival programs in many developing countries. These programs stress immunization and oral rehydration in the under-5-year population, along with breastfeeding and growth-monitoring. Vitamin A supplements may also turn out to be an appropriate addition to the list of simple but effective interventions.

Child Survival programs are very important, but the need will not stop in a single generation, nor will programs targeted for children alone constitute a sufficient attack against tropical diseases and their effects. Disease-control strategies for all age groups are needed for long-term improvements in health. Community survival depends on healthy adults as well as healthy children.

EMERGING TECHNOLOGIES FOR TROPICAL DISEASE CONTROL

There are important reasons to think substantial new gains can be made in the pathobiology of tropical diseases and their management. New biological knowledge and methods appear to offer hope in their application to this group of diseases. Effective tools such as diagnostic kits, drugs suitable for treating humans under field conditions, and vaccines are not available for the spectrum of tropical infectious diseases. But more are being developed.

In 1983, the Senate Appropriations Committee asked the Office of Technology Assessment to examine the status of biomedical research and technologies to control tropical diseases. That study examined the current status of the major technologies used to diagnose, treat, and prevent tropical diseases. The report of that study stresses the enormous potential of biomedical science for developing new diagnostic, therapeutic, and preventive measures against tropical diseases (Congress of the United States, 1985).

Diagnostic Tests

Diagnostics are important tools used to establish a diagnosis for an individual as well as to determine the diseases affecting a community. The diagnostics commercially available in the United States reflect the prevalent diseases of the domestic population. Some of these illnesses,

including rotavirus and streptococcal infection, occur worldwide, and diagnostic tests are readily available albeit at substantial cost. Most diagnostic tests for tropical diseases are not suitable for field use and require specially trained technicians in well-equipped laboratories.

Recent advances in radioimmunoassays (RIAs) and enzyme-linked immunosorbent assays (ELISAs) have improved serologic detection of malarial antigens and antibodies to leprosy. A second generation of ELISAs--using monoclonal antibodies--is being used to detect rotavirus infection. ELISA tests are currently being developed and tested for malaria, schistosomiasis, Chagas' disease, and a range of arboviral diseases. RIAs require expensive equipment and laboratory facilities to store and use chemically unstable radioactive reagents and therefore are unsuitable for field use. However, ELISA tests employ a series of reactions that result in color change, which can be read qualitatively by eye or quantitatively with a spectrophotometer. Several variations of this test, including one for leishmaniasis, suggest that this type of test will prove useful in areas where sophisticated laboratories and well-trained technicians are not available.

Card agglutination tests for African trypanosomiasis have also proved extremely valuable in field conditions. A fingertip-blood sample, when mixed with simple and stable reagents on a card, gives results that are easily read by individuals with little technical skill and takes only minutes to complete.

Another new and promising technology for the detection of tropical infectious diseases is nucleic acid hybridization probes. This highly

specific technique identifies the genetic material of the infectious agent, thus enabling the differentiation of species. Probes use a radioactive, fluorescent, or enzymatic tag to detect the DNA or RNA of the organism. These tests have proved simple, practical, and comparatively inexpensive. Small samples of material can be collected and stored for relatively long periods of time at ambient temperature. The technique of collecting material on filter paper has been successfully used and should prove extremely useful for large-scale epidemiologic and surveillance studies where samples are collected in the field and are sent back to a central laboratory for processing. Probes are being developed for malaria infection caused by P. falciparum and for African trypanosomiasis, Chagas' disease, leishmaniasis, and some of the agents that cause diarrhea and acute respiratory infections.

Despite these advances, much more work remains to be done in developing diagnostic tests for tropical diseases. Improvements are needed for all methods currently available to diagnose schistosomiasis and filariasis. Faster, cheaper, more sensitive, and more specific tests, usable under field conditions in developing countries, are needed for many diseases.

Drugs

Only a limited variety of drugs is available for treatment of tropical diseases. In part this reflects the many and diverse types of

etiologic agents. In general, chemotherapy for bacterial infections is safe and effective. Fewer drugs, however, are available for parasitic infections than for bacterial infections, and many antiparasitic drugs have serious side effects. For viral infections there are supportive drugs but practically no antiviral therapeutic agents.

Economic factors also seriously limit the availability of drugs in developing countries. Not only does the cost of treatment exceed the resources available to pay for care, but larger economic forces may deter industry from developing new and cheaper tools effective against tropical pathogens. Many of the new drugs now being used to treat tropical diseases were developed originally to treat nontropical diseases. While companies such as Merck, Sharp and Dohme, the developer of ivermectin, and Merrell Dow, the developer of DFMO, have been active and willing partners with WHO in clinical trials for their products already developed against diseases in the developing world, they may not feel able to afford to direct their research and development resources to produce drugs engineered specifically for tropical infectious diseases.

Some progress is being made, however. The Special Programme for Research and Training in Tropical Diseases (TDR), sponsored by the WHO, the United Nations Development Programme, and the World Bank, screens compounds that are used to treat a range of illnesses for activity against tropical pathogens. The U.S. military has a pharmacology research program to develop drugs to treat tropical diseases of military importance. Mefloquine, a drug effective in both the prophylaxis and treatment of malaria caused by all species of Plasmodia was developed by

the U.S. Army in the 1970s. But P. falciparum strains resistant to mefloquine have already been reported, demonstrating the constant need for new drugs to treat this widespread and persistent illness and underlining the importance of developing a vaccine to prevent it.

Ivermectin, a drug developed for use in veterinary medicine, has been found to be effective against a broad range of helminthic parasites. Clinical trials in Liberia in patients with onchocerciasis compared the efficacy and safety of Ivermectin to diethylcarbamazine. The group treated with Ivermectin required only one dose of orally administered drug, compared with eight days of treatment with diethylcarbamazine. Diethylcarbamazine produced more severe systemic reaction and more permanent damage to the eye than Ivermectin, and Ivermectin kept the microfilarial counts lower for six months after initial therapy (Greene et al., 1985).

Many diseases lack any effective treatment. Drugs available for Chagas' disease are of limited efficacy and cause serious side effects, including neurologic disorders, in a very high percentage of patients. Clinical management of leishmaniasis is usually restricted to expensive, hospital-based care, because drugs effective against this disease have to be administered intravenously and have frequent and serious side effects.

Vaccines

Vaccines represent a promising and practical strategy for preventing

tropical diseases. Although vaccines are available for selected bacterial and viral diseases, primarily those occurring in early childhood, no vaccines are currently available for general use in preventing parasitic infections. Moreover, of those vaccines in current use, none is fully satisfactory with respect to one or more of the following characteristics: durability of immunity, stability, efficacy, and number of doses required for immunization. Recent advances in biotechnology, including the development and use of monoclonal antibodies and recombinant DNA, give hope that more stable, safer, and less expensive vaccines will be available for a wider range of diseases. The complicated life cycles of parasites, however, make diseases such as schistosomiasis and trypanosomiasis unlikely candidates for vaccine development in the near future.

Economic factors constrain development of vaccines as well as drugs. Vaccines, like drugs, are expensive to develop, and the domestic U.S. population does not represent a market for vaccines for tropical diseases. In addition, U.S. firms involved in vaccine production have been involved in lengthy and costly litigation related to side effects of immunization. Liability has reduced incentive to manufacture vaccines for domestic diseases, and there is even less incentive for development of vaccines for diseases of the poor in the developing world. AID, the Department of Defense (DOD), and the National Institute of Allergy and Infectious Diseases (NIAID) have supported programs to develop new vaccines. However, these have been largely targeted

programs, restricted by limited resources. Long-term support for basic science is needed to understand the antigenic complexities of parasitic diseases.

The malaria vaccine candidates are among the most recent and most promising products for tropical disease prophylaxis. Antigenically active determinants have been found for three life stages of the parasite; the vaccine candidate developed at New York University with support from Agency for International Development, National Institutes of Health, and Special Programme for Research and Training in Tropical Diseases at the World Health Organization is specific for the sporozoite stage. NIAID and DOD have sponsored the development of a separate recombinant DNA sporozoite malaria vaccine candidate. Field trials and full-scale production remain to be accomplished, and neither will be easy. Few groups in the United States have the expertise to conduct clinical trials, and fewer companies have an interest in vaccine production.

The availability of vaccines is only one aspect of disease prevention strategies. For prevention to be successful, the vaccines have to be available, acceptable and administered to susceptible children. A measles vaccine has been available since the 1960s, but measles remains a major cause of child mortality around the world.

INSTITUTIONAL CAPACITY OF DEVELOPING COUNTRIES

Dealing with tropical diseases has changed radically since World

War II. Before the war control of communicable diseases was largely a function of economic activity. Diseases that impeded the building of roads or canals or otherwise restricted the work force were high-priority candidates for control programs, necessarily narrowly organized around the etiologic agent. These categorical disease-control programs were commonly housed within a ministry or agency, with little or no communication or coordination among the programs.

The new nations of the postwar era were left with limited resources and little if any successful experience in spreading health benefits widely and rapidly. Narrowly defined control programs were of limited success and demanded more resources than newly emerging nations could afford. The reliance on hospital-based, high-technology medical care and Western-style medical schools resulted in health services directed toward urban, upper-income groups. Leaders of many new nations placed top priority on industrial and agricultural development and limited the resources available for broad-based health improvement. As former colonial powers withdrew, the budgets of the new nations for tropical diseases manpower and research diminished, leaving only a limited number of well-trained scientists to oversee research activities.

Over time a different model for health care delivery and disease control emerged, one more suited to economic levels and personnel capabilities of developing countries. Community-based primary health care and the use of paramedical health personnel--forcefully advocated at the 1978 WHO conference at Alma Ata--have become the usual approach to extension of health services both to rural villages and to urban

slums. Still, it is a slow process. Despite official support for primary health care, requests for assistance continue to reflect a preference for institutional medicine (Howard, 1983).

Research capacity varies greatly among developing nations. While centers of excellence in biomedical research and training exist in a number of these countries, they are few and scattered. Much more effort is needed to ensure the growth of these institutions as well as the creation of new ones.

Scientists from developing countries have participated in and benefited from substantial international research efforts: the Special Programme for Research and Training in Tropical Diseases sponsored by UNDP, the World Bank, and WHO; the Cholera Research Laboratory, which became the International Center for Diarrheal Disease Research, Bangladesh; WHO's Special Programme for Diarrheal Disease Control, and WHO's Expanded Programme of Immunization for childhood diseases. Some of these programs have features designed to strengthen institutional research capabilities.

The climate for major efforts to reduce and control tropical diseases is improving in several respects:

- o Many governments in developing countries demonstrate a commitment to expanding primary health care facilities, which can enable disease control programs to reach a greater proportion of their populations.

- o Health personnel in developing countries are gradually increasing their competence to engage in disease control activities and, in some areas, in research and development.
- o Over half of the developing countries have experienced a steady growth in per capita income over the past two decades (Howard, 1981, p. 30.). In some cases this growth has resulted in more resources for public sector preventive health and disease control programs.

All these are limited gains, however, and for years to come, research and training activities concerned with tropical diseases, as well as some aspects of control programs, will have to draw heavily on facilities, personnel, and resources available in the industrialized countries.

NEW DIRECTIONS FOR THE CONTROL OF TROPICAL DISEASES

The problems posed by tropical communicable diseases will not disappear in the near future. Problems caused by these diseases are so complicated, affecting a large portion of the global population, that the solutions cannot come from one effort, one program, or one country alone. Long-term, global problems require long-term collaborative efforts to effect significant change. For developing nations to participate fully and equally in the solution of tropical disease

problems, additional long-term support for strengthening local capabilities will be needed.

For the most part, such help must come from experienced people and financial resources in the industrialized countries. Assistance to the developing world depends, of course, upon the political climate and economic situation obtaining in donor nations. The United States has, over the past 15 years, retained the number-one position among the seventeen Development Assistance Committee countries of the Organization for Economic Cooperation and Development in terms of total dollar contribution. However, the U.S. contribution in terms of share of gross national product (GNP) fell from 11th in 1970 (.31 percent) to 16th in 1981 (.20 percent). (Overseas Development Council, 1983). Regional ties are also important. In 1981 the United States was the fifth largest concessional aid donor for health in Latin America and the Caribbean, behind the Netherlands, the Federal Republic of Germany, Japan, and the InterAmerican Development Bank. The United States provided less than 10 percent of the total allocated by external sources (Pan American Health Organization, 1984).

There are valuable international arrangements for mobilizing and applying resources. But the largest volume of the needed scientific resources, including biomedical, epidemiologic, and social science expertise, is in the United States. On the basis of need, therefore, the argument is strong for a significant commitment of U.S. resources to address tropical disease problems. The argument of need is strongly

buttressed by the elements of extensive U.S. historical involvement in work on tropical diseases, and of strong U.S. interests in helping to achieve control over those diseases. These elements are discussed in Chapter 2.

NOTES

¹The terms "tropical diseases," "tropical infectious diseases," and "tropical communicable diseases" are used synonymously in this report. The focus here is on diseases of bacterial, viral, rickettsial, or parasitic etiology that disproportionately affect the poor in less-developed countries. Table 1 lists several of these diseases.

²Bacchi, C., Haskins Laboratories and Biology Department, Pace University, New York, New York. Personal communication.

³A collaborative research program on the causes of acute respiratory infections in children, administered by the National Research Council's Board on Science and Technology for International Development (BOSTID) should generate some of the needed data by 1987. Supported with funds from the U.S. Agency for International Development, the project involves 15 research institutions in developing countries. The project is part of BOSTID's Research Grants Program.

U.S. INVOLVEMENT

INTRODUCTION

The United States has a long history and important legacy of skills, knowledge, and institutional and legislative structures in the battle against tropical diseases. U.S. participants in tropical disease research and control come from a variety of organizations and have shared in the successes and failures of these endeavors. Their experience includes participation in multilateral programs to halt dangerous epidemics; military programs to deal with infectious diseases suffered in peacetime and in war; religious and secular voluntary groups providing health care in the tropics; disease control activities to allow overseas investments to flourish; bilateral foreign aid to developing countries; and emergency relief and assistance.

This chapter describes the historical context for this country's involvement with tropical disease problems, considers policy issues, and then discusses major national interests. Military needs, scientific interests, public health protection, foreign policy considerations, and humanitarian concerns have motivated various groups and organizations in the past. Many are still active, but today face different sets of challenges and constraints in attempting to contribute to the

reduction of infectious diseases in developing countries.

FEDERAL AGENCY ACTIVITIES

Armed Services

Historical Involvement

The U.S. military understood the importance of disease prevention long before the Panama Canal was built. In 1777, Gen. George Washington ordered smallpox inoculation of the Continental Army, because he realized that smallpox was a significant factor in the failed Quebec campaign. The technique was a primitive one and employed the smallpox virus itself. However, as Washington himself believed, the benefits clearly outweighed the hazards. (Engelman and Joy, 1975:1).

The first attempt at building the Panama Canal, in the late 1800s, cost over \$300 million, left 20,000 dead from malaria and yellow fever and bankrupted the French company responsible for the project. In the period between the failed French effort and the American attempt to dig the canal, the U.S. Army Yellow Fever Commission led by Walter Reed identified the mosquito vector of yellow fever, and control mechanisms for both diseases were tested in Cuba by Reed's colleague, William Gorgas. The Spanish-American War proved that disease control was

essential in tropical development projects, and the United States heeded this lesson in the Panama Canal project. Early U.S. efforts to build the canal included deploying 4,000 men to control mosquitoes. Swamps were drained, housing was screened, and workers were provided with bed-nets and quinine. Vector control activities continued throughout the building of the canal (Basch 1978:65-66).

George Sternberg, the U.S. Army surgeon general (1893-1902) who supervised the Typhoid Board and the Yellow Fever Commission, investigated cholera and yellow fever and was the first to demonstrate serum-associated antibody to virus, in this case to vaccinia virus. He established the Army Medical School, which today stands as the Walter Reed Army Institute of Research (WRAIR), an important federal center for research on tropical disease pathogens.

Army studies of anemia in Puerto Rico led to the discovery of hookworm as the infectious etiology and then led to development of a therapeutic agent and effective prevention and control programs. The Rockefeller Foundation later applied these findings in efforts to control hookworm in South America.

Diarrheal disease in troops stationed in the Philippines led to the discovery of two new pathogenic parasites and the development of the first serologic test for amebiasis. Army research activities in the Philippines were necessarily broadened to include entomologic studies and studies on diseases of animals in order to begin to control cholera, dengue, plague, malaria, rabies, equine encephalitis, amebic dysentery, and other infectious diseases endemic in the Philippines (Engelman

and Joy, 1975:12-15). This early work laid the foundations for a dengue vaccine candidate developed at WRAIR and for western and eastern equine encephalitis virus vaccines developed at the Army Veterinary School.

World War II presented enormous problems in the control of tropical diseases and led to important advances. A new typhus vaccine was developed by the Army, and a Typhus Commission was established to deal with epidemic and scrub typhus outbreaks around the world. The chemical DDT was used to control mosquitoes in the Pacific in 1944 to decrease the incidence of malaria, and chloramphenicol was discovered to be an effective treatment for scrub typhus and typhoid fever in Malaya.

Postwar cooperative efforts to stabilize the U.S. relationship with Japan included military assistance in controlling schistosomiasis and in elucidating the ecological cycle of Japanese encephalitis.

U.S. military presence in South and Southeast Asia since World War II exposed large numbers of Americans to tropical infectious diseases, especially malaria. More U.S. troop combat time in Southeast Asia was lost to malaria than to battle casualties. U.S. military research programs here and abroad were strengthened in response.

Military training and clinical programs today include some of the more important U.S. resources in tropical disease. The Uniformed Services University of the Health Sciences is developing an active research and training program while research units include WRAIR, in Washington, D.C.; U.S. Army laboratories in Bangkok, Kuala Lumpur, Nairobi, and Brasilia; and U.S. Navy laboratories in Cairo, Manila, Jakarta, and Lima. These laboratories have supported collaborative

relationships and research with local scientists, and the Navy's Cairo laboratory was able to continue operation at times in the 1960s and early 1970s when other government ties were severed.

Army work was important in understanding the mosquito vectors of Venezuelan equine encephalitis and developing a vaccine against the disease (Engelman and Joy, 1975). Military research on tropical diseases, including arboviral diseases, typhus, and selected diarrheal diseases, have produced diagnostic tools and the immunologic building blocks to develop vaccines. The prototype of the jet injector, making mass vaccination possible, was developed at WRAIR.

Legislative Mandate

Today, DOD involvement in biomedical research and training is restricted by law to diseases and health problems of military importance. Navy authority (10 U.S.C. 7203) to finance activities to protect the health and safety of Navy personnel has allowed establishment of Naval programs for tropical disease research at home and abroad. The Army uses similar authority (42 U.S.C. 225) for tropical disease research. While the Army and Navy both have long histories of successful programs against tropical diseases that have operated independently in the past, to minimize unnecessary duplication the Army in 1982 was designated as lead agency with regard to military biomedical research activities. Overseas military laboratories foster

training through collaboration with small numbers of host-country scientists, but the U.S. military medical mandate does not extend to building up local biomedical research institutions.

Although military programs focus on current and potential health problems of U.S. military personnel, these problems often coincide with those of the general populations in the United States and overseas. The Department of Defense (DOD) will continue to require effective means to diagnose, treat, and if possible prevent tropical infectious diseases among its own personnel and in local populations wherever a U.S. military presence is established.

Public Health Service

Historical Involvement

Communicable disease control in Latin America was a primary focus of international activities sponsored by the Public Health Service (PHS) and the Pan American Sanitary Bureau (PASB) until the 1950s. Between 1902 and 1938 the PHS surgeon general served also as PASB's director, and PHS personnel sometimes served in other countries in the Western Hemisphere. After 1938, these activities continued under PASB direction.

Reorganizations in 1943 and 1944 authorized the PHS to detail its officers to other agencies and to conduct emergency operations

overseas. PHS was authorized to fund research at home and abroad and to sponsor fellowships for U.S. and foreign scientists. By 1950, the National Institutes of Health (NIH) and other agencies of the PHS had begun hosting foreign scientists and awarding international research grants. Hundreds of PHS personnel served overseas in a variety of bilateral and multilateral arrangements through the 1950s and participated in major technical assistance missions to such countries as Liberia and Colombia. In 1954, for example, the Foreign Operations Administration had budgeted positions for 263 PHS personnel outside the United States (Corning, 1980). During the 1960's, the NIH maintained offices in Paris, Tokyo, Rio de Janeiro to support cooperative activities, exchange programs, and conferences.

Legislative Mandate

Current legislative authority for tropical disease activities in the Department of Health and Human Services (DHHS), and more specifically in NIH, comes largely from the Public Health Service Act. While the activities authorized under this act are intended to benefit or protect the domestic population, developing nations may often participate in and benefit from PHS efforts as long as the activities can also be shown to improve the health of the American people. There is no specific authorization to provide health assistance to foreign countries, though there is specific authorization to secure expertise from abroad. Section 307 of the Public Health Service Act authorizes support of

cooperative biomedical and health services research endeavors with other nations if such efforts can be shown to advance the health sciences in the United States.

The International Health Research Act of 1960 (Public Law 86-610) authorizes the President (who normally delegates this authority to the Secretary of Health and Human Services) to carry out cooperative international health research activities that "advance the international status of the health sciences." Under this Act, NIH established the International Centers for Medical Research and Training program (ICMRT), trained U.S. and foreign nationals in biomedical research, and supported research activities of paired academic institutions in the United States and abroad. Another achievement of the International Health Research Act is the U.S.-Japan Cooperative Medical Science Program. Initiated in 1965, it supports research on important health problems of Asia, including tropical diseases such as schistosomiasis, filariasis, leprosy, cholera, dengue, and other arboviral diseases (Corning, 1980). With the exception of these programs, the International Research Act of 1960 seldom has been used. Interagency conflict and lack of funding have prevented more frequent use of this legislation.

The Centers for Disease Control (CDC), another PHS agency important to tropical disease work, is authorized to support health promotion and disease prevention activities relevant to the needs of the U.S. population. Under this authority, the CDC conducts a variety of international health activities directly supportive of U.S. health needs and risks. In addition, the CDC undertakes international efforts in collaboration with AID, WHO, and other agencies and organizations,

and negotiates ad hoc agreements for reimbursement with individual countries. In the 1960s and 1970s CDC staff played a major role in executing the global Smallpox Eradication Program.

. Development Assistance

Historical Involvement

AID and its predecessor agencies have been involved in international health work since the early days of the Latin American program in 1942. Regular development assistance budgets included communicable disease control program support, and by 1974, 30 percent of the health budget of the Agency for International Development (AID) was spent on disease control. Gradual increases of funding for development assistance in health created many opportunities for wider overseas involvement of U.S. health professionals from universities and the PHS, which continued reimbursable agreements with AID. Supported in part by development assistance, hundreds of U.S. specialists in communicable diseases were involved over 10 years in smallpox eradication and malaria control programs. The U.S. financial contribution in bilateral assistance alone for malaria control since the 1950s has been enormous; the General Accounting Office estimated the cumulative total at \$678 million (U.S. General Accounting Office, 1982).

Legislative Mandate

The Agency for International Development (AID) is the only federal agency with a specific legislative mandate to support activities designed to benefit the health of developing nations. Other federal agencies can and do contribute to health programs in developing countries in the course of scientific collaboration that is justified by the benefits accruing to the health sciences and/or the health of the American people. AID programs in health are expressly authorized by the Foreign Assistance Act of 1961. U.S. foreign assistance policy regarding health shifted in the late 1970s to reflect the new worldwide emphasis on primary health care, strongly advocated at the 1978 Alma Ata conference of the World Health Organization (WHO). AID programs emphasize support of health efforts within the primary care framework, but also support applied research on diagnostic technologies, malaria, vaccine development, and diarrheal diseases.

U.S. Participation in Multilateral Agencies

International health organizations such as WHO and the Pan American Health Organization (PAHO) were established to deal with problems in disease control. Participation by the United States in WHO and PAHO is explicitly authorized by statute. U.S. membership assessments are paid by the Department of State, and additional funds for special programs, such as malaria programs and the Smallpox Eradication Program, come from AID and require separate Congressional approval.

In the 1970s, Congressional perception of disease as an obstacle to development led to increased funding to expand WHO's research programs. Multilateral research on tropical diseases receives special attention and support from the United States through the United Nations Development Programme-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR Programme), which began in 1976.

Policy Considerations

Authority for U.S. Government involvement in international health derives from ancient, common-law police powers to protect the public health and environment; from Constitutional protection of the general welfare; from statutes; and from international agreements. The mandate is very broad. Clear lines of authority for U.S. international health activities never have been established, however, and the United States has no coherent international health policy.

Communications among federal agencies and the Executive Office of the President over the last 25 years have never conclusively resolved specific questions of locations of responsibility for international health initiatives, because they are so intimately tied to broader foreign policy issues (e.g., centralization of foreign assistance programs; scientific collaboration as an instrument of foreign policy; funding of PHS international programs; and U.S. participation in multilateral organizations).

Lack of clear, comprehensive national policy for U.S. international health involvement has not prevented various federal agency administrators from considering special initiatives in this area, nor has it prevented effective interagency cooperation in specific programs. However, resource allocation tends to respond to specific agency responsibilities, which differ widely; to policy decisions, which are episodic; and to external events. Limitations of agency mandates and funding have prevented the U.S. Government from undertaking comprehensive efforts of the scale needed to make rapid progress against the communicable disease burden in the tropics.

As the Institute of Medicine Committee on International Health observed in 1978 (Institute of Medicine, 1978):

- (1) there is no U.S. Government organizational unit at present responsible for gathering and analyzing information on the nature and extent of these activities,
- (2) there is no clear U.S. international health policy to guide and relate direct investments in international health activities to bilateral program planning and U.S. participation in the international health program policy decisions of multilateral agencies,
- (3) there are no policies and no mechanism to plan and coordinate program decision-making across agencies and to take account of

the program actions of other governments and private organizations.

The situation is unchanged today.

Support for U.S. participation in international health efforts including tropical disease research, training and control has been uneven, and efficient focus of this country's international health resources has been hindered both by the existence of multiple agency mandates that can be brought to bear on the same set of problems and by insufficient effort to gear resources to needs.

Agency mandates inevitably overlap. The Department of Health and Human Services (HHS), with the bulk of the federal government's scientific and technical resources related to health, properly perceives international health as an important element of its domestic responsibilities. The Department of State and AID properly perceive international health as an aspect of foreign policy and foreign assistance.

A variety of agencies are naturally involved in international health. The principal federal agencies obviously include the Agency for International Development; the Departments of Defense, State, Health and Human Services, and Agriculture; and the Peace Corps. Other agencies, with smaller involvements, include the Veterans Administration (which has to treat patients for some of these diseases), the Department of Justice (the pertinent purview of which includes the Border Patrol, immigration, and drug smuggling), and the Treasury Department (customs inspection). Executive Branch oversight of U.S. involvement in

international health is within the ambit of the Office of Management and Budget (OMB), the National Security Council, and the Office of Science and Technology Policy. In the Legislative Branch the subject is within the jurisdiction of numerous authorizing, appropriations, and oversight committees, the Congressional Research Service, the Office of Technology Assessment, the Congressional Budget Office, and the General Accounting Office.

ROLES OF PRIVATE AND NONGOVERNMENTAL ORGANIZATIONS

U.S. foundations and private voluntary organizations (PVOs) often have led the way for federal agencies in supporting new institutions and in catalyzing federal decisions about new programs related to tropical diseases. Relationships between PVOs and the Government have been complementary or parallel rather than interdependent. Academic institutions, whether private or public, are much more dependent on public support. Predominant industry interests have shifted away from direct involvement with disease control programs and toward the supply of products needed for such programs.

Foundations

Several U.S. foundations, including Rockefeller, Edna McConnell Clark, and recently MacArthur, have provided substantial training,

research, information dissemination, and institutional support in tropical diseases research and training. Other foundations have made notable contributions to tropical disease research and training activities, but limitations of space and time precluded a comprehensive listing. Some examples can be cited: the Hooper Foundation in San Francisco supported a center for schistosomiasis research for some years; the Leonard Wood Memorial Foundation currently supports an active international research network on leprosy; and the Kellogg Foundation has made substantial contributions to medical education and training in Latin America, thus indirectly promoting tropical disease research and control activities. Foundations have rarely supported health program infrastructure in developing countries. Such support usually comes from local governments, or through multilateral organizations and bilateral assistance agencies.

The role of the U.S. foundations is still vital. Foundations can provide innovative and important programs, moving quickly to identify unmet needs and recognize scientific opportunities. Foundations can base their programs on the best international scientific expertise, and can remain engaged with important issues for long periods of time. They can also help countries whose problems elude official governmental efforts, perhaps because of political disputes, or because they do not qualify for development assistance. These countries may have excellent biomedical centers that with appropriate support could make important contributions to the control of tropical diseases.

The Rockefeller Foundation, established in 1909, has as a stated purpose the enhancement of human welfare around the world. The foundation's early efforts focused on hookworm, malaria, and arboviral diseases, including yellow fever. The foundation played an active role in the control of hookworm and malaria in the southern United States and South America. Rockefeller research programs funded the work that led to development of the yellow fever vaccine in 1936 and has supported first-class medical education in Thailand, Lebanon, Brazil, and other countries. The educational program's most famous product was the Peking Union Medical College, in China. The foundation established the Great Neglected Diseases program in 1977 to deal with training and research issues in applying the latest biological research techniques to the control and treatment of parasitic and diarrheal diseases. The Clark Foundation supported a large program in schistosomiasis for more than a decade, and the MacArthur Foundation in 1984 established a consortium of twelve research groups to investigate the molecular biology of parasitism as related to potential means for preventing, treating, and controlling parasitic diseases.

Foundations have demonstrated their capacity to support innovation. Compared with the governments of the industrial countries, however, the foundations control relatively small amounts of money.

Academic Institutions

Universities provide training in international health both for U.S.

citizens and for a limited number of foreign nationals. More important, they employ technical and scientific experts who teach and conduct research, and are vital resources of knowledge and talent. Despite the risk and hardship that work on problems of tropical diseases in developing countries often entails, the interest of faculty and students in working on these problems far outweighs available opportunities.

Most U.S. university-based research in tropical diseases is funded by the federal government (primarily NIAID and DOD) through contracts and grants. The government also provides limited support for training activities. Increased competition for federal biomedical research grants and decreases in research funds have made academic participation in international health a riskier proposition for universities. The short-term nature of this kind of financing is incompatible with hiring personnel and establishing laboratories. Federal policy uncertainty and unstable funding constitute little incentive to academic administrators. Faculty who wish to participate in health activities overseas sometimes risk their tenure status and pose administrative problems because a replacement must be found to assume teaching responsibilities while they are away.

Private Voluntary Organizations

Working largely independently, many U.S.-based PVOs strive to improve health abroad. Few work exclusively with tropical disease

problems, although many sponsor service programs that include prevention, diagnosis and treatment of infectious diseases. The American Medical Association has identified more than 170 organizations that recruit U.S. physicians for assignment overseas (Journal of the American Medical Association, 1984). Some organizations have broad-based assistance programs, of which health is one part. Others focus exclusively on health. Some have both domestic and international programs. Some restrict participation by country or geographic area. While many organizations provide health care service, some groups have also trained local people in paraprofessional capacities and have contributed to institutional strengthening by building hospitals and clinics. The contributions of PVOs are difficult to quantify; they go far beyond financial support.

The National Council for International Health (NCIH), active since 1980, has mobilized a broad constituency for international health, including many of the PVOs. The annual conference and numerous special meetings provide a forum for PVO health workers to exchange ideas, learn from other program experiences, and meet with federal agency officials. NCIH does not carry out its own health projects; rather, it serves the distinctive needs of its members. It is a meeting place for individuals and organization staff whose shared concerns include coordination of efforts.

The capacity of PVOs to work abroad is limited by funds, number of volunteers, receptivity of host governments and communities. Their impact on health problems remain unknown as their performance has not

been evaluated or assessed. Congress expressed its support of PVOs in legislation that directs the President to "encourage and support to the maximum extent practicable, the international assistance efforts, aims and activities of U.S. voluntary organizations qualified for such service" (Bourne, 1978:88). Assistance has been provided in the form of grants, contracts, goods, equipment, and advice and guidance through U.S. embassies and missions.

An additional role for PVOs is emerging. Recent Congressional approval of additional funds for Child Survival programs included the designation of PVOs as eligible recipients. At least 15 different organizations have received more than \$13 million to provide selected primary health care services--immunizations, ORT, growth monitoring, and promotion of breastfeeding--in addition to their regular programs. This relatively new type of AID-PVO partnership could facilitate expanded future participation by PVOs in coordinated efforts to reduce childhood mortality and morbidity. However, it is important to point out that as private enterprises, PVOs remain independent of national strategies and do not constitute a panacea for decreases in federal involvement.

Industry

Involvement of industry in the health problems of the developing world has stemmed from economic interests. Since World War II, U.S. investment abroad has increased both in industrial countries and in

less-developed areas. Initially, industry provided health care for workers to ensure a stable workforce. This coverage was extended to include dependents, and many corporations established local hospitals and clinics.

Several U.S. and transnational corporations have demonstrated more than minimum interest in health in the developing countries in which they operate. Examples include medical facilities, malaria control, health education, housing, running water, waste disposal systems, medical screening, vaccination, nutrition programs, maternal and child health programs; and training for paramedical personnel (Franz, 1967:41). A corporate contribution helped to establish the Liberian Institute of the American Foundation for Tropical Medicine as an international, multidisciplinary research center for tropical diseases. The center operated until 1969, when major contributors withdrew support and the center closed (Corning, 1980:316).

Since the 1960s, U.S. corporations working overseas have shifted away from direct corporate health care and toward community-based care where possible. Occupational health issues generally remain direct company responsibilities, including minimizing risks from worker exposure to disease vectors, while the broader health needs of employees and dependents are handled by local public and occasionally private systems, sometimes subsidized by the corporation. Corporate support often is negotiated by the ministry of health, which may attempt to coordinate the health planning goals of the country with those of the corporation (U.S. President, 1978).

While economic forces stimulate corporate involvement in international health activities, they also constrain participation. Providing health care is expensive, and every corporation has to show a return on its investment. In addition, government forces (tax structures are an example), both U.S. and host country, shape the nature of corporate contributions to health. The roles of multinational corporations in local health are changing and idiosyncratic.

U.S. pharmaceutical and biotechnology companies represent a special case of private sector involvement in tropical diseases. Many U.S. firms have expanded distribution of their products to include developing countries. These products, however, were developed largely to meet U.S. domestic health care needs. With few exceptions, the research and development programs in U.S. biomedical industries are not aimed at tropical disease problems. Very few drugs used in the treatment of tropical diseases have been developed by the U.S. pharmaceutical industry. Several of these drugs were designed to treat other diseases and were found incidentally to be active against tropical pathogens. Such is the case with difluoromethylornithine (DFMO), used both to treat certain tumors and to treat sleeping sickness. Lack of international activity of U.S. biomedical companies has been ascribed to several factors, including the critical role of profit margins in the support of research and development and the lack of historical and economic ties of these firms to developing countries.

Although U.S. domestic vaccine producers have decreased in number

and capacity, the science underlying vaccine development has advanced notably (Institute of Medicine, 1985b:30). Recent advances in biotechnology point to the development of safer, more uniform, perhaps cheaper and more stable vaccines through bioengineering. Identified antigenic determinants of a pathogen which can stimulate antibody production in humans, are produced using recombinant DNA technology or polypeptide synthesis. Recent advances in the immunology of parasites indicate that even organisms with great antigenic variability may now become targets of immunization programs. The malaria vaccine candidates, for example, hold great promise.

STRENGTHENING U.S. INVOLVEMENT

Numerous U.S. interests are served by reducing or preventing mortality and morbidity from tropical diseases. Many of these interests are explicitly stated in the legislation authorizing federal activities. Others are implicit in programs of private institutions and industry. All of these interests relate directly to the national security and welfare. Population movements, modern transportation, and the interdependence of biological systems on this planet have blurred the old distinctions between domestic and foreign policy needs in health. The mystery of the origins of acquired immune deficiency syndrome (AIDS) and its emergence as a major new disease threat to all human populations argue for a new era of worldwide collaboration in

communicable disease research and control. Increasing cooperative activities built on trust and close communication among health professionals and scientists, irrespective of political differences, could go a long way toward alleviating world tensions and achieving measurable progress in controlling diseases.

Protecting U.S. Public Health

The need to protect the health of the U.S. population is greater than is commonly recognized and in many respects is rising. Exposure of U.S. citizens to tropical diseases is steadily increasing and is expected to continue to do so as more and more citizens reside, work, and travel abroad. In 1980, the U.S. Census Bureau estimated that approximately 1 million citizens were residing abroad (U.S. Department of Commerce, 1982:8). Air travel has enabled Americans to explore distant and exotic places. In 1983 almost 9 million U.S. citizens traveled to the Caribbean, Latin America, Africa, Asia, and Oceania; this was a fourfold increase from 1968 (U.S. Department of Justice, 1976, 1983). Many travelers are unprepared for the health challenges abroad. Lacking both information and appropriate immunizations for international travel, and adequate drugs for malaria chemo-suppression or management of diarrhea, they often become ill while abroad and return to the United States well within the incubation period of serious diseases such as malaria. The second group in particular represent a

hazard to the domestic population and a diagnostic challenge for their physicians, who are unlikely to be prepared to diagnose or manage such problems.

The number of foreign nationals visiting the United States from less-developed countries has also been rising. In 1983 almost 6 million people from the Caribbean, Latin America, Africa, Asia, and Oceania traveled to the United States, a fivefold increase from 1968 (U.S. Department of Justice, 1976, 1983). While the number of refugees from Asia, Latin America, and Africa has dropped from approximately 125,000 in 1978 to 75,000 in 1980, the number of immigrants from those regions has risen from 300,000 in 1975 to 400,000 in 1979 (U.S. Department of Commerce, 1982:89).

Health hazards to U.S. travelers and the domestic population exposed to tropical pathogens are evident. A small but continuing number of cases of trypanosomiasis, cholera, malaria, schistosomiasis, dengue, and other tropical diseases are reported to CDC. Aedes aegypti, the mosquito vector for dengue, is found in many Southern states. A total of 351 cases of leishmaniasis were reported in the United States from 1975 through 1984. Of the four cases of visceral leishmaniasis reported in the past two and a half years, two proved fatal (Pearson and de Sousa, 1985). Americans who travel and reside abroad face increasing exposure to malaria as mosquito vectors increasingly resist pesticides and more of the parasites resist antimalarial drugs. Between 1973 and 1983, 2,575 cases of malaria were identified in U.S. citizens traveling abroad; 31 cases were fatal (Morbidity and Mortality Weekly Reports,

1984:388). The 26 cases of transfusion malaria reported in the United States from 1972 through 1981 may be accounted for by foreign origin of 17 percent of U.S. blood donors in this period (Bruce-Chwatt, 1985). There were 45 confirmed cases of dengue reported in 1982 (Morbidity and Mortality Weekly Reports, 1983:145). While no vector-borne transmission of malaria within the last decade has been confirmed in the continental United States, the Anopheles malaria vector is plentiful in many parts of the country, and therefore the potential for reintroduction and transmission of malaria exists. Sporadic locally transmitted (autochthonous) cases and mini-epidemics still occur, most recently in irrigated farming areas of California.

U.S. military interests in tropical disease problems are obvious and compelling. At the height of the Vietnam war in 1967, disease accounted for 70 percent of the admissions at U.S. Army medical facilities, battle casualties for 16 percent, and nonbattle injuries for 14 percent. Malaria was by far the most common disabling disease. The similar experience of World War II led General MacArthur to say he needed three divisions in the South Pacific to do the job of one: One doing the fighting, another in the hospital with malaria, and a third convalescing. U.S. military personnel are stationed in many parts of the world, including the tropics, and the continuing possibility of larger-scale involvement is a reminder of the strong need to develop better methods of prevention and disease control--for the benefit both of the United States and potential allies, many of whom do not have resources for research and development.

Advancing Biomedical Science

Research on tropical diseases not only contributes to scientific knowledge needed to prevent or control them but also broadens basic understanding of important biological phenomena. Current investment in research on trypanosomiasis is justified both because of the need to control and treat this disease and because the parasite is an excellent model for investigating a variety of questions in immunology and molecular biology. There are important scientific and clinical gains to be made from tropical disease research. However, it should be noted that encouragement will be required for U.S. companies to develop the requisite technology to permit large-scale production and the building of a capacity for such production.

While the United States has tremendous capacity in biomedical research, there are other countries in both the developed and developing worlds whose contributions to medicine and biomedical research have been outstanding. The United States benefits directly from their efforts. Oral rehydration therapy, developed and perfected primarily at Dhaka, is now the treatment of choice for severe diarrheas of diverse etiology. This treatment, applied in the United States, has saved substantial costs for hospitalization and administration of intravenous rehydration solutions. Studies on the epidemiology, natural history, pathology, and risk factors of AIDS in regions of the world where the disease is epidemic may shed light on transmission patterns and other unresolved issues pertaining to its prevention and control. Research to deal with

the AIDS crisis is contributing substantially to knowledge of the human immune system.

The U.S. research community has clearly benefited from grants and contracts available through national and international organizations. Of the total of 2,046 TDR projects through 1984, U.S. citizens have been awarded 351, about 17 percent, representing in dollar terms more than their Government's contribution.

Assisting Developing Countries
to Achieve Measurable Health Objectives

The United States has contributed widely to disease control activities in developing countries. U.S. support for the public projects largely comes from AID. Some programs, most notably the smallpox eradication campaign, have saved the United States large sums of money. The smallpox effort eradicated the disease, lowered the disease burden caused by this illness to zero, and saves approximately \$300 million per year by eliminating the need for immunization programs. When effective disease prevention exists, it is cheaper and more effective than treatment or rehabilitation. A variety of infectious diseases, such as polio, have been controlled in the United States but not in many developing countries. New paralytic cases of poliomyelitis occurring in the United States now usually come from cases acquired abroad. Each outbreak is expensive to identify, treat, and contain. The cost-saving incentive to help lower the prevalence of these diseases in other countries is clear.

Effectiveness of programs to control communicable diseases can be measured only in terms of numbers, location, and age of new and old cases. Ability to measure disease rates is essential for evaluating program strategies. The epidemiologic skills required for disease surveillance and program evaluation, however, are lacking in most developing countries.

Assisting developing countries to improve their capabilities in monitoring the incidence or prevalence of important communicable diseases has economic and health benefits for the United States as well as for the people of those countries. Knowledge of changes in disease rates enables directors of control programs to target scarce resources toward populations at greatest risk and to consolidate gains in regions where disease is diminishing.

International health agencies and bilateral assistance agencies of many countries, notably including the United Kingdom, France, the Scandinavian countries, and Australia, have been helping developing countries to achieve health objectives.

Responding to Humanitarian Needs

The United States has always expressed its humanitarian concern, in both public and private ways, for the poor and deprived in other countries. The United States has responded generously with money and

people to aid victims of hurricanes, typhoons, and earthquakes, to assist refugees, and to collaborate in dealing with epidemics. Disasters will certainly occur, in some instances with higher risks of damage because of larger populations living in steadily more crowded conditions. In the case of epidemics of tropical diseases, preventive action and advance preparation and training can greatly reduce the human toll of disease and the cost of emergency response. The long-term need is for a continuing commitment to health activities that support increased local capabilities to prevent and respond to disasters and disease outbreaks.

CHANGING THE U.S. ROLE

The prospects for control of tropical communicable diseases appear brighter today than two decades ago. Pathogens are yielding the secrets of their molecular structure and immunologic properties, new surveillance and control strategies have been successful against targeted diseases in selected areas, and scientific and professional capabilities have increased in developing countries. Increased knowledge of disease etiology, epidemiology, and vector ecology, combined with the newly emerging vaccines, improved diagnostic tests, and better drugs, hold great promise for highly specific and effective control approaches. In fact, in many cases application of control

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measures on a wide scale in developing countries actually or potentially represent the most cost-effective intervention for reducing the burden of illness.

The current U.S. strength in biomedical research, training programs, trained manpower, public health programs, and tools to control communicable diseases could benefit many of the poorest developing nations. A few of the more advanced developing countries have biomedical research centers and trained people, and their requirements are very different from those countries totally lacking in resources.

Programs and policies to deal with a dynamic disease burden need to be flexible and responsive. The United States has a good record of rapid response to requests for assistance in epidemics and outbreaks of infectious diseases overseas but lacks a central mechanism for dealing with endemic tropical diseases in developing countries. What is appropriate U.S. involvement is partly a function of the capacity, or lack of capacity, of the developing countries to deal with problems associated with tropical infectious diseases. The assistance required by one country today may not be needed by that country in the future.

U.S. policies and programs in international health, as in other fields, have not kept pace with the many, changing needs in developing countries or with the wide range of opportunities for collaboration and assistance. A middle-income country in Latin America, for example, may require small amounts of money to fund exchange visits of scientists and industry technicians, improve vaccine production, train epidemiologists, or begin collaborative projects to develop new chemotherapeutic agents.

Yet AID may not have missions in such countries, and the PHS has no funds or personnel available to respond to specific needs or identify appropriate U.S. experts.

The poorest countries, where AID missions are located, often lack the resources to assess their communicable disease burden and formulate specific requests. The poorest countries also are mostly likely to lack the necessary infrastructure to make the best use of assistance. On the other hand, those countries which have developed that infrastructure are frequently not eligible for AID assistance. The AID missions, in turn, have difficulty providing U.S. technical experts or supporting training if the problem appears to fall outside the current priorities of the particular country program. Due to budget cuts, AID has had to reduce the number of technical personnel both in Washington and abroad, thus reducing its capacity to analyze problems and formulate programs. Of course, the gaps in U.S. efforts may be bridged very effectively by other nations. Japan, for example, supported onchocerciasis control in Guatemala for over eight years, contributing a team of experts and insecticides to suppress the blackfly vector. Norway supports leprosy research and control in Africa from Addis Ababa, where the Armauer Hansen Institute is located.

What the United States needs are long-range, stable program commitments within which flexible adjustments could be made to respond to new opportunities and to evolve new forms of support and collaboration. Such long-range commitments would support the development of steadily rising scientific competence on tropical

diseases in developing countries, and encourage the increasing growth of scientific collaboration between U.S. and developing country scientists.

Increased opportunities for scientific collaboration and the relationships of friendship and trust thereby developed can only help to serve U.S. national interests. International collaboration represents the most efficient way to proceed because the work of scientists in many countries can enlarge the total scientific effort. For this to be an effective process the United States cannot simply be a recipient of the results of work conducted elsewhere but must be a contributor as well.

There is a straightforward, strong U.S. interest in joining the international effort to understand and to control tropical diseases, on a sustained and systematic basis. This requires a long-term commitment to institutional development and training programs for scientists from a variety of disciplines.

U.S. TROPICAL DISEASE SPECIALISTS

Concern has been expressed both in the United States and abroad that the number of people with expertise in tropical human diseases may be shrinking. Who and where are the U.S. tropical disease specialists? How are they trained? Are there enough? Is the talent pool being renewed? Are skills adequate? The field is not easily defined, and it is seldom assessed. Results of a survey by this committee suggest several reasons for concern.

The number of this country's tropical disease specialists is small, diagnostic capability is not strong, research employment opportunities are very limited, many researchers in the field cannot give it their full attention, many work outside the country's more productive research centers, financial support is shaky, and training requires increased attention in several respects. Still, the attractiveness of the field is high, and young people are continuing to enter it.

The term "tropical disease specialists" as used here refers to individuals who have received advanced training in and have direct experience working with tropical diseases of infectious etiology and who are still active in the field. These specialists include:

- o physicians who currently work on tropical diseases and who have experience with clinical management of tropical communicable diseases and/or additional experience in related research and public health activities
- o biomedical research scientists with an advanced degree in a physical science or medicine and postdoctoral training who have successfully competed for grants to conduct research on tropical disease pathogens; many have participated in collaborative research activities abroad
- o public health and disease control specialists who have an advanced degree in public health or medicine, who teach courses related to tropical diseases or are otherwise employed in related international public health activities, and who may have also participated in tropical disease control activities abroad.

The committee recognized that many individuals working, for instance, in infectious diseases, on research methods of possible applicability to tropical disease pathogens, or on public health issues related to domestic poverty, were capable of making important contributions to this field. However, in the opinion of this committee,

they constitute potential expertise. The evaluation of tropical infectious disease expertise for the purpose of this study, whether clinical, biomedical research or public health, was determined to be dependent upon knowledge of the problem in its setting. An appreciation and first hand knowledge of the interactive effects of climate, socioeconomic factors, culture and local medical infrastructure on health are vital to the understanding of tropical infectious diseases and therefore the definition of tropical disease expertise. These criteria greatly reduce the number of individuals who, in the opinion of the committee, qualify as tropical disease experts.

The committee recognized that other individuals, including advanced students, postdoctoral research fellows, and various consultants, are important to international health work. While many of these people are health professionals, very few are regularly involved in tropical disease research and control activities and therefore are not included in the committee's statistics.

For example, social scientists are contributing to tropical disease research and control efforts. A small, growing number of social scientists and other professionals interested in tropical disease problems were not included within the survey categories. The committee guesses that several dozen such individuals serve as advisors, consultants, and evaluators. These include medical sociologists and anthropologists, health economists, medical geographers, psychologists, and public health behavioral scientists who have had first-hand tropical disease research experience. This is an increasingly important talent pool.

DEMOGRAPHY

Data on the number of tropical disease specialists and information on their training and employment have been scarce. This report comes nearly a quarter of a century after the last major effort to look at the state of U.S. human resources in tropical disease work (National Academy of Sciences--National Research Council, 1962). Disease definitions and occupational categories of occupations in the previous study were much broader than those used here, so data from the two surveys are not comparable, and judgment about trends is difficult.

To count and characterize the human resources available in the United States to address problems of tropical diseases, the committee first drew from a variety of sources to compile a roster of individuals and their institutional affiliations. Sources include catalogs of schools of medicine and public health; membership directories of the American Society of Tropical Medicine and Hygiene (ASTMH) and the Infectious Disease Society of America (IDSA); Government employee lists; grantee lists from the Special Programme for Research and Training in Tropical Diseases (TDR) and Diarrheal Disease Control Programs at the World Health Organization (WHO), National Institute of Allergy and Infectious Diseases, Department of Defense, and the Rockefeller, Clark, and MacArthur Foundations; and the directory of the Epidemiological Intelligence Service of the Centers for Disease Control (CDC).

A random sample drawn from the roster was surveyed by questionnaire, as were participants at an annual meeting of the ASTMH. Response rates for the roster sample of 112 and the ASTMH sample of 700 were 90 and 37 percent, respectively. Respondents classified themselves by type of work (clinical work, biomedical research, disease control), and allowance was made for overlap. Replies were counted only if respondents met these criteria: U.S. citizen or permanent resident; directly relevant advanced degree (MD, PhD, DSc, DVM, MPH or DrPH); and directly relevant career status. Students and trainees, including postdoctoral trainees, were excluded. A total of 347 responses are included in the analysis of the sample data presented here: 258 from the ASTMH distribution, and 89 from the random sample.

Size of the Work Force

The number of U.S. specialists in tropical communicable diseases probably does not exceed 2,500. This estimate, based on the roster (in which 1,935 persons were counted), allows for probability of a small undercount and for narrowness of the definitions used.

Age

A common perception, shared by the committee at the outset of this study, was that the population of specialists in tropical diseases was aging and would decrease by attrition. This perceived loss of expertise was attributed to the recent death or retirement of tropical disease specialists who trained and worked during World War II.

The gross survey results do not support that perception. The mean age of survey respondents was 46.9 years, with a range of 26 and 83 years. The distribution shows a peak in the middle years, similar to other data on the ages of the large population of U.S. medical and biological scientists (National Research Council, 1985). The similarity argues for (1) validity of the survey age data, and (2) a likely tendency of the age distribution of U.S. tropical disease specialists to mirror that of the larger scientific community. See Table 1.

However, there is no doubt that the nature of expertise available has shifted. Younger persons entering the field are more likely to be narrowly trained in a specific area of biomedical research, and are less likely to encounter career opportunities that permit them to broaden their experience. This situation is especially true in academic institutions with few tropical disease specialists.

TABLE 1 Age Distribution in U.S. Biomedical Research Personnel^a and Tropical Disease Specialists^b

Age (Years)	1983 Survey ^a		1985 Survey ^b	
	Number	Percent	Number	Percent
25-29	N.A.	1.9	3	0.9
30-34	N.A.	14.8	42	12.3
35-39	N.A.	20.3	58	17.0
40-44	N.A.	19.8	70	20.5
45-49	N.A.	12.5	48	14.0
50-54	N.A.	10.0	34	9.9
55-59	N.A.	9.0	30	8.8
60-64	N.A.	5.4	28	8.2
65+	N.A.	6.5	27	8.0

^aData from National Research Council, 1985. Science, Engineering and Humanities Doctorates in the United States, 1983 Profile. Washington, D.C.: National Academy Press, p. 21. It includes doctorates in both medical and biological sciences.

^bData from manpower survey conducted for this study.

Education and Training

More than one-third of the respondents reported that they had received no training specific to tropical medicine or tropical public health. Formal or specific training as defined here included but was not limited to: course(s), such as those offered at the Walter Reed Army Institute of Research, tailored to issues of tropical medicine or tropical public health; postdoctoral training on a tropical disease problem; or a research doctorate in parasitology or medical entomology. Over half of those reporting specialized training had participated in formal programs lasting six months or more. Generally, the specific training was relatively short.

Nearly half the respondents hold an M.D.; just over half hold a Ph.D. or D.Sc. Fewer than 20 percent hold degrees in public health. The numbers exceed 100 percent because some respondents hold multiple degrees.

The distribution of schools conferring degrees is very broad. Physicians reported degrees from 58 different schools, Ph.D. and D.Sc. holders from 74, and M.P.H.s and Dr.PH.s from 16. While there was some clustering for physicians and research doctorate holders, no single institution trained 10 percent or more of the total (Table 2).

TABLE 2 Source of Graduate Degrees Held by Survey Respondents

n	M.D.	n	Ph.D. or D.Sc.	n	M.P.H./Dr.P.H.
13	Harvard	17	Hopkins	11	Harvard
11	Hopkins	13	University of	11	Tulane
9	Cornell		California at	7	University of
8	Chicago		Berkeley		California at
6	Yale	10	Illinois		Berkeley
5	University of	10	Tulane	6	Hopkins
	California at	9	Wisconsin		
	San Francisco	5	London & Liverpool		
146	Total M.D. Reporting Alma Mater	185	Total Ph.D. Reporting Alma Mater	59	Total M.P.H./Dr.P.H. Reporting Alma Mater

Professional Specialization

Parasitology, infectious diseases, and epidemiology were the areas of specialization most reported by the survey respondents, who were asked to choose from among 20 fields and indicate those in which they were active professionally. There is considerable versatility:

TABLE 3 Fields of Specialization Among Survey Respondents
(In partial activity units)^a

Parasitology	192	Biochemistry	38
Infectious Diseases	137	Pathology	29
Epidemiology	126	Pediatrics	23
Immunology	95	Taxonomy	19
Public Health	83	Pharmacology	15
Virology	70	Mycology	13
Vector Biology	63	Nutrition	11
Entomology	50	Malacology	8
Molecular Biology	42	Dermatology	5
Bacteriology	40	Ophthalmology	1

^aThese units represent the number of individuals indicating an unspecified degree of participation, not necessarily a full time-commitment to the field.

80 percent reported working in two or more specialties; only 20 percent reported working in one specialty. See Table 3.

Despite the diversity of specialties and the relatively good distribution of activity, there are worrisome lows (defined here as 5 percent or fewer respondents reporting any activity in the particular specialty): ophthalmology, dermatology, malacology, nutrition, mycology, pharmacology, and taxonomy. The low level of reported activity in nutrition can probably be ascribed to the criteria used in developing the roster of tropical disease specialists, and representation of professional specialties at the ASTMH; ASTMH membership factors might also explain low levels of activity reported in dermatology and ophthalmology. The low levels of activity in taxonomy, pharmacology, mycology, and malacology, however, are of particular concern. These four fields had disproportionately fewer younger people reporting involvement, indicating that fewer people may be entering

these fields. In all other fields, approximately half the respondents were under 44 years of age. A greater percentage of malacologists, taxonomists, and pharmacologists were over 44 years of age.

The different professional disciplines require quite different lead times for expansion. The number of people working on tropical diseases in certain specialties could readily be expanded if additional funds were available. Molecular biologists, virologists, bacteriologists, biochemists, and immunologists, for examples, could be recruited to work on tropical disease pathogens and could become productive rapidly with proper guidance from and collaboration with experienced scientists. In other specialties, such as vector biology, mycology, dermatology, and pathology, the number of people working on tropical diseases cannot quickly be expanded; several years of postdoctoral training and dealing with tropical diseases in their natural settings are essential.

Type of Work

The total distribution of activities reported by respondents is highly skewed in favor of biomedical research, in terms both of time and numbers of persons. Of the total time devoted to tropical disease work, about 72 percent was spent on biomedical research, 18 percent on public health activities, and 10 percent on clinical research and patient care. Biomedical research related to tropical diseases is more likely than clinical and public health work to be a full-time pursuit. See Table 4.

TABLE 4 Mean Percent Time Devoted to Activities Among All Surveyed and Mean Percent Time Devoted to Three Activities Removing Other Category

	<u>Biomedical Research</u>	<u>Clinical</u>	<u>Public Health</u>	<u>Other</u>
Percentage For All Surveyed	41.6	5.6	10.3	42.3
Percentage To Three Activities Removing Other Category	72.3	9.7	17.8	

Survey respondents were asked to estimate the proportion of their time devoted to biomedical research, public health, and clinical work related to tropical diseases, as well as unrelated or "other" activities. A high proportion of these specialists reported activity in more than one category, with many also reporting time spent in an "other" category, which includes teaching and administrative duties as well as clinical, research, and public health activities not related to tropical diseases. Without considering the "other" category, mean, full-time equivalent (person) units were calculated for the three categories.

Similarly, most of the respondents identified themselves primarily as biomedical researchers. See Table 4. Of those who reported clinical work, 78 percent also reported research or public health activities or both. Of those reporting public health activities, 72 percent also participated in research or clinical activities or both. Only 116 (45 percent) of those reporting biomedical research also did clinical or public health activities or both (because of overlap the total exceeds 100 percent).

TABLE 5 Types of Activity Reported by Tropical Disease Specialists^a

Activity	Survey	
	Number	Percent Total
Clinical work	111	32
Biomedical research	259	75
Public health and disease control	105	30
Other	249	71

^aBecause of overlap, total percentages exceed 100.

Tropical disease specialists considered to be clinical experts are essential for patient care, and for diagnostic, drug, and vaccine trials, in addition to clinical research. Most internists with some training in infectious are capable of diagnosing and treating a wide range of infections. However, they usually contact CDC or a tropical disease specialist known to them personally if the diagnosis and treatment are problematic. In addition to internal medicine, clinical specialties such as dermatology, pathology, and ophthalmology are legitimately required to handle some types of infections.

The number of clinicians recognized as U.S. clinical specialists working in the area of tropical diseases varies according to estimation methods but is clearly low. In the survey, 30 percent of respondents reported clinical work of some type. Another method used to estimate the number of tropical disease clinical specialists in the United States involved peer judgment by a small panel of experts. They reviewed the roster, adding and deleting names of clinicians, and produced a final list of 181 individuals who, in their judgment, had sufficient training

and experience in clinical tropical medicine to qualify as specialists. This method identified physicians recognized by the medical community as the leading experts of this field. The major deficiency with this method of estimation might be undercounting of younger individuals not known to the panel.

The most conservative estimate generated from expert opinion would put the number of U.S. clinical specialists in tropical diseases at fewer than 200 physicians. The most liberal estimate based on the 30 percent response rate in the survey would put the total number of clinical experts closer to 600; however, this would include non-physician specialists, biomedical researchers conducting some type of clinical investigation, and diagnostic service personnel. A realistic estimate would be that the United States has fewer than 300 clinical specialists capable of diagnosing, treating, and studying tropical infectious diseases. Concern was expressed that fewer individuals who are broadly knowledgeable of clinical tropical medicine are active today than was the case 20 years ago, and that this subgroup in particular, represent an aging population.

Employment

Over half of the United States' tropical disease specialists work in academic institutions. Federal agencies employ more than a quarter. Very few are employed by industry. See Table 6. The data from the

questionnaire substantiate the basic findings from the roster.

Hospitals and clinics may appear underrepresented because physicians with academic appointments were placed in the academic category rather than hospital/clinic.

TABLE 6 Employers of Tropical Disease Specialists by Type

	Individuals Represented on Roster		Institutions Represented on Roster	
	Number	Percent	Number	Percent
Academic	1,122	58	155	54
Hospitals/Clinics	21	1	16	6
Federal ^a	288	15	10	4
Military	259	13	13	5
Industry	40	2	33	12
Other ^b	<u>205</u>	<u>11</u>	<u>58</u>	<u>20</u>
Total	1,935	100	285	100

^aIncludes all Federal agencies except those in the Department of Defense.

^bInstitutions in "Other" include private research institutes, state departments of health, international organizations, private voluntary organizations, foundations, associations, museums, and scientific academies. The majority of individuals in this category are working by themselves either as consultants, private practitioners of medicine, or with organizations employing no other tropical disease specialists.

A strikingly small percentage (2 percent) of U.S. tropical disease specialists are employed by industry. See Table 6. In sharp contrast to these results concerning tropical disease specialists, a 1983 National Research Council survey of the larger U.S. scientific community found 24 percent of all medical science doctorates and 18 percent of

biomedical science doctorates employed by industry (National Research Council, 1985:36). Medical science doctorates include parasitologists and pharmacologists as well as public health scientists. Biomedical science doctorates include graduates from programs training particular scientific disciplines (e.g., biochemistry, cell biology, immunology, bacteriology, entomology). The database for the 1983 survey did not

TABLE 7 Distribution of Specialists by Size of Tropical Disease Program and Type of Employer (In Percent)

Size ^a	Institutions Represented on Roster		
	Academic	Civilian Government	Military
Small	62	17	23
Large	37	84	77

^aSmall is defined here as an institution or organization employing 9 or fewer specialists in tropical medicine, and large is defined as 10 or more.

include information on graduates of professional schools, and physicians therefore were not included.

In government agencies, specialists tend to be concentrated in organizations employing more than 10. On the academic side, however, the disaggregation is marked. See Table 7. The majority of U.S. tropical disease specialists in academic institutions are at schools employing fewer than 10 tropical disease specialists. Three-quarters (119 of 155) of the academic institutions included in this survey employ 9 or fewer tropical disease specialists. This relative lack of

concentration of academic talent may have adverse consequences for (1) multidisciplinary, team research, (2) collegial interaction and breadth of disciplines that can be focused on a particular problem, and (3) achievement of a critical mass for training.

The majority of clinical specialists work in academic settings and in the Federal Government. More than half of those employed by the Federal Government are employed by the CDC, and these have very limited involvement in patient care and followup. Few specialists see more than 50 patients with tropical diseases per month, and many provide consultation by telephone. Only a very small number of U.S. clinical specialists (21 in the survey) have a regular practice in hospitals, clinics, and private practice devoted primarily to tropical infectious diseases.

Financial Support

Nearly half (47 percent) of the individuals identified as conducting biomedical research indicated they work for or receive external funding from Federal agencies, including the military. See Table 8. Almost 20 percent receive money from foundations, and 16 percent receive research support from WHO. Industry provides contracts for 8 percent.

Respondents were not asked to report the amounts of support they received; therefore no conclusions can be drawn as to relative size of funding from the various sources. Obviously, however, both the Federal

Government and other sources are very important. Over half of the tropical disease specialists conducting biomedical research rely at least partly on nongovernmental support.

A large share of university-based specialists in tropical diseases depend on Federal grants and contracts. In addition, and not shown in Table 8, tropical disease work is undertaken directly for the government by Federal employees, and this of course depends also on Federal budgeting. The net result is that the nation's corps of

TABLE 8 Funding Sources for U.S. Tropical Disease Research

Source	Number of Respondents Holding Grants	Percent Total Grant Holders
U.S. Government Grants and Contracts	145	47
Foundations	60	19
Industry	24	8
World Health Organization	48	16
Other ^a	32	10

^aOther includes seed funds from employing institution and donations from private individuals, state governments, and organizations not otherwise categorized here.

tropical disease specialists depends heavily on Federal funding, and budget cuts, personnel freezes and cutbacks may bring about a critical loss of vital U.S. expertise.

Experience with Developing Countries

Residence Abroad

Although a substantial portion of the U.S. community of tropical disease specialists has resided in developing countries, such experience is not necessarily being continued for younger members, and the amount of overseas experience is not distributed evenly among types of activity. See Table 9.

Of 347 respondents, 52 percent reported having worked in developing countries for one year or more. In addition, 40 percent of a smaller sample (n=89) reported being abroad for shorter periods totaling one

TABLE 9 Developing Country Experience Reported by Survey Respondents

Age	20-29	30-39	40-49	50-59	60-69	70-79
Percent w/ LDC Experience	0	34	56	58	65	61
Total for Age Cohort	3	100	118	64	43	13

year or more. (Only those individuals who were randomly selected from the roster and were mailed a copy of the questionnaire were asked to provide information on shorter periods of time devoted to research activities abroad.)

Respondents working in universities had about the same foreign experience as the total group surveyed; of respondents working in universities, 46 percent reported spending more than one year abroad in developing countries, and an additional 39 percent reported spending shorter periods totaling one or more years overseas.

Of the respondents reporting overseas work, almost half reported activities in biomedical research, one-third in public health and disease control, and roughly one-sixth in clinical work. Numerous respondents, of course, engaged in more than one of these types of activities during their overseas stays. The extent of the overseas experience in developing countries reported by the current U.S. biomedical researchers overall is reassuring, but the number of clinicians with solid overseas experience is quite small.

Respondents under 40 years of age had much less overseas experience than their older colleagues. Fewer than 35 percent of individuals 30-39 years old reported such experience versus 57-64 percent of respondents 40 years of age and older. This survey finding is not easy to interpret, but it raises the question of whether sufficient numbers of the current 30-39 year cohort will acquire overseas experience to meet the 56 percent level reported by their older colleagues. An alternative explanation for the low figure for this cohort might be the obvious difficulties in identifying potential survey respondents who are spending several years out of the country.

Collaborative Experience

Collaborative relationships between U.S. tropical disease specialists and their counterparts in developing countries appear to be both numerous and broad in geographic scope. A total of 141 survey respondents (41 percent) reported participating in collaborative relationships lasting at least three years with colleagues in developing countries. Individuals reporting current participation indicated relationships with institutions in 36 different countries, including 10 institutions in Africa, 12 in Latin America, and 7 in Asia. The countries with the greatest number of U.S. collaborative partners reported in this survey included Egypt, Thailand, and Brazil.

Demographic Stability

There are well-qualified, young U.S. specialists at work on problems of tropical diseases of the less developed countries, as indicated by a healthy spread in most age categories of training, overseas experience, and recipients of research grants among survey respondents. These specialists do not seem to be older than their colleagues in other, comparable fields. Within the field of tropical disease work, clinical, biomedical research, and public health groups are attracting well-trained younger scientists. Confirming survey findings, committee members are aware of many young scientists who express interest in the

field while in training, and there is no difficulty in attracting able applicants when a career position does open up. The job market evidently is not expanding, and the number of qualified applicants exceeds tenure-track or career opportunities. The U.S. labor force in this field appears to be neither shrinking nor growing.

Not everyone in this labor force is there because of absolute career commitment; there are in-and-outers. People enter and leave the field at different stages of their careers for a variety of reasons and at various ages. Working for long periods where these diseases are endemic can entail considerable personal hardship and family sacrifice. Employment opportunity and research support are obvious factors. Research scientists require grants and contracts to fund their work, and shifts in allocation of money among research programs result in scientists moving in and out of specific areas. Biomedical research and development funds designated specifically for tropical infectious diseases amount to not more than 1 percent of all public and private monies from U.S. sources (U.S. Department of Health and Human Services, 1985; and Congress of the United States, 1985). Decreases in research funding for tropical diseases have resulted in the movement of scientists to more financially stable research areas.

Identification of individuals who have left the field is difficult. There is anecdotal information on the temporary surges in number of U.S. tropical disease specialists, including clinicians, during World War II and the Vietnam War. At the height of the antimalaria campaign in the 1960s, several dozen malaria specialists were hired by CDC and AID to

work abroad. Many have retired, never replaced, and as a result few malaria control specialists remain in these agencies.

There is considerable variation in the length of time required to complete the various training programs associated with tropical disease specialties, and individuals begin such training at different times in their lives. Other studies on personnel in biomedical sciences compare the percentages of individuals entering a field (ages 25 to 35) with those leaving through death or retirement (ages 60 to 70) (Tu, 1985). Table 1 shows 13.2 percent of tropical disease specialists to be in the 25 to 35-year-old group and 16.2 percent to be 60 years of age or older. The sample here is quite small, limiting the interpretation of these data. Still, entry rate evidently is approximately equal to the exit rate.

Anecdotal evidence suggests that there has been a decline in the number of U.S. tropical disease specialists over time, but no quantitative trend is apparent.

ADEQUACY

The committee finds elements of strength and of weakness in the characteristics of the current group of U.S. specialists in tropical diseases.

Field Experience

Although half of the survey sample (which totalled 347) have overseas experience, the age distribution of those who have worked abroad may indicate a decrease in opportunity for field experience. Lack of such opportunity and experience is a serious problem for individuals who wish to pursue a career in tropical medicine, biomedical research, and public health. The decline results not only from the end of the Vietnam War but also from reductions in National Institutes of Health and AID funding and positions for research, training, and operational posts overseas. If U.S. citizens are to make appropriate contributions to the solution of tropical disease problems, more opportunities for training abroad will be needed.

Career Stability

The high proportion of U.S. tropical disease specialists working in academic institutions presents both advantages and problems. On the positive side, academicians can be readily identified and mobilized if given sufficient lead time and support. Indeed, anecdotal information indicates that this group is anxious to participate in overseas activities. Moreover, this group is training the next generation of specialists. On the negative side, academicians are vulnerable. Many survive on small amounts of shifting, soft money, and there is little

incentive for young faculty members to pursue and sustain a career in this area.

The U.S. military maintains strength in all three areas--tropical disease research, tropical medicine, and tropical health. By design, its focus is on its own needs. The military has its own training programs and so does not have to depend on outside specialists. This is especially important because so few U.S. clinicians specialize in tropical medicine.

Military medicine has among its inadvertent employment drawbacks the services' up-or-out personnel structure. Personnel are expected to advance while at the same time the number of job slots at senior levels are limited in number. The military's pyramidal system makes it difficult to retain senior military researchers, clinicians, and tropical health experts who are concerned primarily with tropical disease problems.

Very few jobs for tropical disease specialists can be found in U.S. industry. This weakness reflects the inability or unwillingness of U.S. pharmaceutical companies to compete with their European counterparts in the production of drugs and vaccines for tropical diseases (Institute of Medicine, 1979b, 1985b).

Clinical Skills

U.S. tropical clinical specialists report extensive direct experience in the past but now spend a much smaller proportion of their time in clinical tropical medicine and see few patients with these diseases. Half the clinicians responding to this survey were seeing eight or fewer patients per month with suspected or actual cases of tropical diseases, raising the question whether this patient load is sufficient for maintaining first rate clinical skills.

As noted earlier, the number of broadly trained U.S. clinician specialists in tropical diseases is fewer than 300. Despite widespread student interest in international medicine, a larger supply of clinical specialists cannot be generated quickly or without access to large numbers of patients with a range of tropical diseases. Opportunities for such training clearly are not adequate. The current number of specialists will not be sufficient if events increase the need for their services.

Diagnostic Laboratory Skills

In the United States most people suspected of harboring a tropical illness never encounter a clinical specialist in tropical medicine. Instead, their regular physicians send blood or fecal specimens to a clinical laboratory for testing. The committee sought assurance that

clinical laboratories in the United States are capable of correct diagnosis of tropical parasites. Parasitology proficiency testing programs are scheduled regularly, and the results over the last 15 years show improvement in accurate diagnosis. In laboratory qualification trials, about 90 percent of clinical laboratories correctly identify most parasitic organisms in stained test specimens. In ordinary practice, however, the sensitivity and specificity of laboratory diagnosis may be much lower because the physician may not order the appropriate tests.

Federal and state licensing bodies require that clinical laboratories participate in programs that independently assess their performance. Independent laboratories as well as those receiving Medicare funds and those in interstate commerce are required to participate in an assessment program. Such programs are run independently in the United States by CDC, the College of American Pathologists (CAP), and the American Association of Bioanalysts (AAB).

The low U.S. prevalence of parasitic diseases and the difficulty of distinguishing among some of the parasitic agents make ability to diagnose parasitic illnesses a sensitive indicator of U.S. ability to deal with tropical diseases.

In general, parasitology proficiency testing programs send approximately 5 samples 4 times per year to participating laboratories. A sample can be concentrated or unconcentrated feces fixed in formalin, a polyvinyl alcohol fixed slide of fecal material, blood smears as well as specimens containing no parasites. Because only 20 or so samples are

sent each year, it is not possible to survey for the range of parasitic pathogens. Each agent might be surveyed only several times in a decade. Therefore, it is important to note in interpreting the following data that the total number of challenges for a given etiologic agent varies.

Table 10 compares data collected by the CDC Parasitology Proficiency Testing Program to that of the AAB and CAP over past 15 years.

There is some variation among these programs for some pathogens. This could be explained by differences in the sizes and types of laboratories subscribing to each program as well as by differences in sample preparation. Although U.S. prevalence of parasitic diseases is very low, data from public health laboratories indicate that 18.2 percent of fecal specimens examined were positive for parasites (Smith, 1979:371). However, smaller laboratories not serving high-risk populations (immigrants, travelers, homosexual men, and institution-alized individuals) may see substantially fewer positive specimens.

The trend in parasite identification is improving for all organisms listed in Table 10, perhaps with the exception of malaria. Data on parasites other than those in Table 10 confirm this trend. More complete data on the identification and speciation of plasmodia (Rogers, 1982:669) show considerable variation over time but no discernible trend. See Table 11.

Although the overall trend in the correct identification of parasites is improving, it is important to note that results of proficiency testing represents the best capability of any given

laboratory. It is, after all, an anticipated test that could have implications for the future operation of that facility, and is therefore handled carefully. In consequence, these data must be interpreted with caution.

TABLE 10 U.S. Laboratory Identification of Parasites in Test Specimens
(Percent Correct)

		1970-74	1975-79	1980-84
E. histolytica	CDC	68	75	86
	AAB	46	61	62
	CAP	-	75	79
Ascaris	CDC	99	95	98
	AAB	84	97	97
	CAP	85	92	88
Filaria	CDC	-	-	85
	AAB	-	-	-
	CAP	-	-	-
Hookworm	CDC	94	98	94
	AAB	68	76	88
	CAP	89	93	96
Trypanosome	CDC	96	-	-
	AAB	-	-	94
	CAP	-	-	-
Malaria	CDC	97	-	91
	AAB	-	91	-
	CAP	-	-	-
Schistosomes	CDC	92	90	96
	AAB	-	68	-
	CAP	98	85	90
Giardia	CDC	81	90	94
	AAB	74	67	87
	CAP	67	81	93

SOURCE: Compiled from information provided by the CDC, AAB, and CAP.

TABLE 11 Identification of P. vivax (One of Malaria Species)

Year	Laboratories	Percent correctly identifying P. vivax
1973	291	90
1976	399	31
1978	511	45
1979	572	51*
1979	540	71*
1980	594	60
1981	587	75

*Same specimens, different lots of Giemsa stain.

(From: W. Rogers, Am. J. Clin. Path 78(4): 669, 1982).

Biomedical Research Capacity

Biomedical research specialists appear to be strong in numbers and laboratory bench skills. However, programs to support travel to developing countries where the problems are endemic are needed to provide more opportunities for younger scientists to conduct field research. Heavy reliance on the Federal Government and limited opportunities in the private sector provide tenuous career support. While most fields of specialization are reasonably well covered by the present set of U.S. scientists, fewer young people trained in tropical vector taxonomy, pharmacology, mycology, and malacology are working on tropical disease problems. These fields will need special attention for the foreseeable future to assure a minimum reserve of expertise to protect the health of the domestic population and to meet unforeseen needs.

Productivity and Disaggregation

Few U.S. tropical disease researchers are employed in large groups; many work alone or nearly so. Does such disaggregation affect research productivity? Were researchers at the larger centers more productive? Or less? Was their work more important to other scientists? Or less?

Statistical analysis of research publications and citations does not necessarily characterize quality or quantity of effort. It may provide useful clues, however. Such analysis applied to the U.S. tropical disease research community shows more publications from investigators working in larger groups, and it shows that published work by investigators in the larger groups is cited more often by other scientists.

A sample of 100 biomedical researchers was selected at random from the survey roster. Half were from schools employing 10 or fewer tropical disease specialists (small groups), and half were from larger schools employing 20 or more (large groups). Index Medicus listings for each person in the sample were checked for the years 1979-1983, and the number of articles by each was counted. In addition, each person was followed for the years 1980-1984 in Science Citations Index to find the total number of times the work of each was cited.

Individuals working in larger academic groups produced a significantly larger number of articles and were cited more often than those working alone or in smaller groups (student's T test). The results with this small sample suggest that investigators working in

larger centers are demonstrably more productive than their colleagues in smaller groups and that the work produced in larger groups may have more impact on the field. See Table 12. Many explanations are possible. The results support the supposition that good collaborative relationships among scientists working on tropical diseases are fostered by proximity.

TABLE 12 Research Publications and Citations for U.S. Academic Tropical Disease Specialists, by Size of Working Group

	Mean Number of Articles Cited in Index Medicus 1979-1983	Mean Number of Times Cited in Science Citation Index 1980-1984
Small Group (n=50)	1.7	19.4
Larger Centers (n=50)	3.5	60.0
Difference*	1.8	40.6
Standard Error	0.2865	5.970

*p .005

Future Personnel Needs

Supply and demand forces operate differentially upon the pools of tropical disease specialists who have careers in biomedical research, clinical investigation, and public health. Survey results, which reveal only a partial picture of these forces, were augmented by committee discussions in assessing their implications for continued U.S. participation in tropical disease work around the world.

Clinicians

The current supply of clinicians who are specialists in tropical diseases appears adequate to meet current domestic health needs, though the quality of expertise may be compromised due to the very small number of patients seen on a regular basis. However, this number may be too small to sustain a focus of interest for training a future generation of U.S. tropical disease specialists who have the breadth of clinical skills and depth of experience required to resolve diagnosis and treatment problems for diseases occurring predominantly in the tropical developing countries. Career opportunities must be perceived early in the course of physician training, and role models are essential. At least five years of clinical research training following a basic post-M.D. residency program is needed to produce one junior-level clinical specialist for a specific group of diseases. Seven or eight years will be required to increase the number of trained U.S. clinical specialists.

Demand for clinical specialists is also linked to opportunities emerging from basic biomedical science for developing and testing diagnostic methods, drugs, and vaccines. The acceleration of discoveries with potential clinical application should increase demand for clinical specialists within the next five years by at least 50 percent from Federal agencies, academia, and possibly private industry. In the committee's judgment, the supply of U.S. clinical specialists is insufficient to respond to increased demand, and remedial steps are needed.

Biomedical Researchers

The need for biomedical research on tropical diseases is high, but need has no direct influence on the numbers of U.S. biomedical research specialists. The supply of researchers who are available to work on tropical disease problems responds to two major factors: (1) employment opportunities in academia, government, industry, and elsewhere, and (2) funding made available through grants and contracts.

A large pool of talented young scientists trained in basic biomedical science disciplines is potentially available from United States academic institutions to work on tropical disease problems. However, a quick response to funding increases or expanded employment opportunities does not necessarily correspond to an increased capability to make rapid progress in developing new approaches for controlling tropical diseases. Relatively few doctoral candidates or postdoctoral fellows are linked to programs that possess the laboratory infrastructure, clinical, or field research capabilities required for comprehensive study of pathogens, hosts, and vectors.

Long-term support of institutional programs is essential for maintaining an adequate supply of multidisciplinary biomedical research groups capable of addressing tropical disease problems. Support for individual investigators who bring fresh approaches to intriguing scientific questions possibly relevant to tropical diseases is just as important.

Career opportunities for biomedical research specialists will probably not increase without a significant shift in Federal agency priorities. Two factors are responsible. First, institutional program support is often more difficult to justify within Federal agency budgets than are research grants to individuals. Institutional support does not increase dramatically without a change in agency program emphases. Second, a large portion of all biomedical research support comes from the Federal Government, and the types of research emphasis (e.g., cancer, AIDS) influence perceived career opportunities in certain fields.

Public Health Specialists

U.S. public health and disease-control specialists work in Federal agencies, academic institutions, and consulting firms. Demand for their services is generated by Federal agency programs and international and multilateral organizations. Supply of these specialists depends on employment opportunities and training programs. Of the three types of specialists considered in this study, the public health and disease-control group appears to respond more elastically to supply and demand pressures, and larger numbers move in and out of the work force.

Within this group, however, senior-level professionals with training and experience in specific areas are in short supply. Applied or field epidemiologists, parasitologists, vector biologists, and virologists

with program management and language skills are not available when needed, or they are seriously overcommitted with academic responsibilities and multiple consultancies. Their numbers will increase only in direct response to the creation of additional training opportunities and career positions within Federal agencies and academic institutions.

Public health and disease control specialists are the most underutilized resource that the United States has to contribute to international tropical disease control. They have helped to protect the U.S. population from epidemics and have helped other governments to protect their peoples. Shortages of money and mandate have limited the extent to which these specialists have been used. There is great potential to advance U.S. foreign policy interests, which include economic and humanitarian interests, through better disease control abroad, and public health specialists are uniquely qualified to assist the less developed countries to achieve measurable health objectives and to assist in training local health personnel. Increasingly, schools of medicine and public health in developing countries are seeking collaborative relationships with U.S. schools to improve skills of their faculty members.

U.S. public health specialists are especially valued by many of the developing countries, some of which completely lack the specialists and career structures needed to address control problems. Foreign governments frequently request assistance in solving specific disease outbreaks from the public health and disease control authorities of the

United States. The response has largely come from CDC, which has been able to meet the demand to date, by organizing advisory services on a case-by-case basis. Mechanisms allowing CDC and academic institutions to train and mobilize a larger cadre of specialists would be helpful, and will be needed if the demand for such advisory services increases in the future.

ACADEMIC INSTITUTIONS

Academic institutions play several roles in international health. Approximately 150 U.S. universities employ more than half of the nation's tropical disease specialists. Universities conduct a large portion of the research on tropical pathogens, generate new knowledge, and contribute to technology development. Several U.S. academic medical centers have the capacity to attend to the special clinical needs of patients with tropical diseases. They provide technical assistance to Federal agencies, foreign health ministries, and international organizations. The universities train future U.S. and foreign specialists in tropical health work. Assuring continuing U.S. competence and expanding the ability of developing countries to take measures against these diseases are important investments.

U.S. TRAINING CENTERS AND PROGRAMS

Training in clinical work, research, and public health and disease control varies among schools and fields of study. Clinical training

may emphasize individual patient care, and it may extend to include management of health problems of the community. Biomedical research is conducted on a range of tropical pathogens from the perspective of many disciplines. Schools with limited resources may focus on a single pathogen; other schools may do more. The schools of public health also have a diverse array of interests and resources for dealing with problems in international health.

This committee's survey (Table 1) of U.S. schools of medicine and public health found eight institutions that could be categorized as tropical health centers. A center, by the committee's criteria, is involved in clinical work on tropical diseases and in pertinent biomedical research and public health and disease control. This range of activities requires:

- o Facilities of both a school of medicine and a school, department, or division of public health;
- o Collaborative relationship(s) with similar institutions in developing countries for training and research activities of both faculty and students; and
- o Integrated training programs in each of the three activities associated with tropical medicine and tropical public health.

TABLE 1 Academic Training Related to Tropical Disease

University	Trop Dis Training in:				Faculty	Level of	Diversifi- cation of Support*
	Clin	BioRes	Pub Hlth	Has LDC Collab	Size	Activity	
Harvard	X	X	X	Yes	+++	Center	11
Johns Hopkins	X	X	X	Yes	+++	Center	15
Tulane	X	X	X	Yes	+++	Center	6
U California	X	X	X	Yes	+++	Center	
Berkeley		X	X		+		7
Lc; Angeles		X	C		++		4
San Francisco	X	X	C		+++		5
U Hawaii	X	X	X	Yes	++	Center	4
USUHS	X	X	X	Yes	+++	Center	4
Yale	X	X	X	Yes	+++	Center	13
Case Western	X	X	X	Yes	+++	Center	13
Columbia		X	X	Yes	++	Program	7
Cornell	X	X		Yes	+++	Program	8
Loma Linda			X		++	Program	1
LSU	C	X		Yes	++	Program	2
Michigan State		X		Yes	++	Program	8
NYU	C	X		Yes	+++	Program	9
Tufts	X	X		Yes	+++	Program	8
U Maryland	X	X	C	Yes	+++	Program	6
U Michigan		X	C	Yes	++	Program	4
U N Carolina		X	C	Yes	+++	Program	6
U Pennsylvania	X	X		Yes	++	Program	6
U S Carolina		X	X	Yes	++	Program	3
U Texas	C	X	X	Yes	++	Program	4
U Virginia	X	X		Yes	++	Program	8
U Washington	X		C	Yes	+++	Program	7

X = formal degree program(s)

C = courses only

+++ = 20 or more

++ = 10-19

+ = 1-9

*Units here represent the number of sources of institutional support and individual investigator grants and contracts. Each institutional grant awarded to a school was given a weight of 2; grants awarded to an individual faculty member were weighted as 1. Sources used for this table are: Lists of U.S. academic institutions receiving grants and contracts were provided by donor agencies and organizations as follows: NIH training grants in parasitology and infectious diseases, FY 1985; National Institutes of Health/National Institute of Allergy and Infectious Diseases International Collaboration in Infectious Disease Research program or Tropical Disease Research Units program awards, FY 1984; MacArthur Foundation Consortium on Parasitology member, FY 1984; Rockefeller Foundation GND awards, FY 1984; NIAID institutional grants and contracts in tropical diseases of \$300,000 or more, FY 1984; NIAID Tropical Disease Study Section awards, FY 1983 and FY 1984; DOD contracts for tropical disease work, 1979-1984; TDR and CDD grants, 1975-85; Clark Foundation, 1983; and AID contracts, 1983-1984.

The survey found 15 institutions not qualifying as centers but offering tropical health programs--that is, conducting clinical, biomedical research, or public health training, including postdoctoral training, leading to a degree or certificate in a discipline related to tropical diseases. Special resources of these programs include collaborative relationship with institutions in developing countries; clinics for travelers and refugees; and special laboratory facilities to produce reagents or to maintain pathogens for research.

Biomedical research training had the strongest showing among U.S. academic institutions. Of the 23 institutions with centers or programs, 21 offered formal biomedical research training, 14 offered clinical training in tropical medicine, and 13 had degree programs in tropical public health.

Two indicators of strength and diversity in academic activities are the size of faculties and the amount and sources of financial support. Good correlation was demonstrated between the extent of training opportunities and both faculty size and level of support. Not surprisingly, schools that receive funding from multiple sources have larger faculties and offer a wider range of training activities.

With one exception, centers employed 20 or more tropical disease specialists. Most universities with programs employed 10-19 tropical disease specialists.

To summarize, quantify, and compare relative strength and range of support for tropical disease activities in academic institutions, a "diversification of support index" was created. This index reflects the number of sources

contributing money for tropical diseases research and training. It does not indicate the total amounts given to each school or the total number of grants or contracts received by each institution, since estimation of actual dollar amounts would be both time consuming and inaccurate. Each school was given a score of 1 for each source of grant or contract monies awarded to individual faculty members; a score of 2 was given for each institutional award. The higher score for institutional grants was used because they represent an institutional commitment to the field and offer core support as well as support for specialized capabilities. Such monies also provide opportunities for obtaining additional support from other sources. In addition, they facilitate career development for faculty and training for students. The maximum possible score for an individual school is 15, the total sum attained if support is received from all funding sources included in the analysis.

As expected, the highest scores for diversification of funding were found for the most part in centers.

This is an indicative, not exhaustive, summary. Training activities may be unreported because of limitations of definition. This survey apparently undercounted U.S. programs that train vector biologists. Significant, related efforts in progress outside the schools of medicine and public health have been assessed in other recent studies (National Research Council, 1983a and 1983c).

Clinical Training

Current initiatives to train clinicians in tropical medicine display

enthusiasm and inventiveness in affording exposure to clinical cases of tropical diseases as well as didactic training. A variety of courses is available to medical students and practicing physicians. The presence of travelers clinics and refugee clinics affiliated with university teaching hospitals provides additional clinical experience. However, students need to see a range of tropical diseases at different stages of the illness in order to develop good diagnostic skills. Domestic clinics can provide only limited training opportunities; the patients are fewer, and the range of diseases is much narrower than where tropical diseases are endemic. Unfortunately, opportunities for travel to such areas are limited, and time allotted is short. By the time a trainee masters language skills and begins to acquire clinical skills the tour is over. This has been frustrating for both U.S. trainees and the host organizations.

Clinical training takes place during medical school and in residency and postdoctoral programs. While the range of possibilities is broad, there are, in fact, very few programs that provide for specialization in tropical diseases, and very few individuals are in such programs at any one time. These resources may be sufficient to train clinicians for current needs of patients in the United States but do not support a role of U.S. leadership in reducing the wider disease burden. The U.S. military appears to be able to meet its own clinical needs, through didactic training in the United States and specialized clinical and research facilities overseas. Although this is an excellent model, the

limited resources in academic institutions make it inappropriate for the majority of training programs, and training slots in the military are available to a very limited number of nonmilitary personnel.

Better ways to train U.S. physicians in clinical tropical medicine are needed. Within the United States, the domestic didactic programs can be strengthened, and regional systems for centralized patient referral that concentrate cases for teaching and treatment purposes in this country would enhance the quality of medical care. More important, the low prevalence rate and the sparse distribution of communicable tropical diseases in the United States suggest that training be done where the diseases are endemic. Unfortunately, few academic institutions in developing countries have clinical tropical medicine services with the financial and faculty resources to care adequately for a wide range of cases.

Current opportunities for clinical training abroad are limited both in scope and number. Students generally depend on individual referrals by people they perceive to be experts. This is not in the best interest of the student, the overseas host institution, or the referring specialist--who can be inundated with requests and have little or no resources to match people to institutions in an appropriate fashion. A referral system was recently established in Canada with support from the International Development Research Centre (IDRC). The Canadian Society for Tropical Medicine and International Health, the Canadian Public

Health Association, and the Medical Research Council of Canada, cooperate in sponsoring a collaborative research and fellowship program in tropical medicine. This program matches Canadian medical students to institutions in developing countries and provides funds for travel and subsistence. In addition, scientists from developing countries are afforded training in Canadian institutions. Information on program results and impact is not yet available, but the experience should be examined for applicability to U.S. training programs.

Clinical residency programs that provide suitable training abroad are urgently needed. There is no lack of interested potential trainees from industrialized as well as developing countries. Resources are needed to develop and support programs of a scale and quality comparable with first-class clinical teaching programs in other fields of medicine. These programs should be collaborative, providing for the joint training of physicians from the sponsoring as well as the host country. Programs should also include research cooperation between faculty members, with opportunities for specific short-term training available to faculty from developing countries.

Didactic Instruction in Tropical Medicine

Historically, tropical medicine was taught as a separate course and included in the second-year medical curriculum. Over the past 40 years

the numbers of courses and hours of instruction in parasitology offered to medical students in U.S. academic institutions have fallen considerably. Paralleling this trend, fewer medical students perceive career possibilities in clinical care or research aspects of parasitic diseases.

Of the 81 schools responding to a 1945 survey by the American Association of Medical Colleges, 35 reported allotting 20 hours or more to tropical medicine. The 1950s brought integrated medical curricula and a decrease in the number of hours devoted to tropical medicine, with the eventual demise of this area as a distinct subject. The National Research Council tropical health resources survey found that 67 of the 76 responding medical schools had training in tropical medicine but only 8 percent taught this separately (National Academy of Sciences--National Research Council, 1962).

A total of 141 educational institutions responded to a 1978 survey by the American Society of Parasitologists (ASP). The range of interests reflected in course titles was wide, but the majority of schools were teaching general courses, such as medical parasitology, and few schools offered specialized parasitology courses.

Material formerly in the classical tropical medicine curricula may today be offered through occasional lectures by scientists or professionals trained in the field's various disciplines (e.g., microbiology, infectious diseases, pathology, preventive medicine, immunology, medicine) or through an integrated course linking

clinical, research, and epidemiologic aspects of these diseases.

Harvard University and Case Western Reserve University offer medical students a range of courses from an international perspective: Medical parasitology, biology of parasites, nutrition, rural medicine, and international health, among others. New York University and the Medical College of Pennsylvania focus on parasitic infection.

Residency Programs in Tropical Medicine

This committee's survey found 10 medical schools reporting physician residency programs in tropical medicine. Of these, the University of Hawaii, Yale University, Johns Hopkins University, the University of Maryland, Tulane University, and the Uniformed Services University of the Health Sciences offer residency programs, primarily in preventive medicine, that allow for specialization in international health or tropical medicine.

The University of Maryland's program is interdepartmental, involving the Department of Epidemiology and Preventive Medicine and the Division of Geographic Medicine. The University of Hawaii has a residency program in epidemiology as well as collaborative research links with various institutions in countries of the Pacific, Asia, Africa, and Latin America. Tulane participates in a program with the Pan American Center for Research and Training in Tropical Diseases, in Venezuela, to

assess the adequacy of treatments for patients with onchocerciasis. Most of these training programs can arrange for short-term experiences in less-developed countries. Several schools, including Yale and the Uniformed Services University, incorporate in these residencies an MPH program with emphasis on tropical medicine.

Postdoctoral Training for Physicians

U.S. university postdoctoral training for physicians in the field of tropical diseases focuses on research problems. The diversity of interests is tremendous. Although the programs are few, some offer opportunities to gain experience working in developing countries on a specific research problem.

For example, Tufts University offers postdoctoral training to approximately eight M.D.s and Ph.D.s per year, including several foreign nationals. The research deals with a broad range of pathogens--giardia, amoeba, schistosomes, leishmania, trypanosomes, diarrheal pathogens--and with vector-parasite interactions. Tufts is participating in the planning of a multi-institutional collaborative program in the Gambia to study the epidemiology and efficacy of a vaccine candidate for hepatitis B.

Postdoctoral training in tropical diseases for physicians at the University of Maryland includes a year of clinical training in

infectious diseases followed by a year or more of research. Research interests of postdoctoral fellows have included the pathophysiology and epidemiology of enteric infections; infant growth and nutrition; respiratory infection; and vaccine development and testing. The university has research links with groups in Chile and Peru. The University of Washington has a similar program, on parasitic and chlamydial diseases and leprosy.

Similar programs at other universities combine clinical training with infectious disease research. Faculty interests cover a broad spectrum of diseases as well as experience with drug and vaccine trials in developing countries. Postdoctoral training for physicians is also offered at the University of Washington, University of Virginia, the University of California at San Francisco, Cornell University and Case Western University.

First-hand Clinical Training: Illustrative Examples

Primarily because of the low prevalence of these diseases in the United States, medical students normally see few if any patients with tropical diseases and get little first-hand experience in their care and clinical management.

In 1955, Louisiana State University began a program to provide clinical training opportunities in neighboring developing countries to

faculty from all U.S. medical schools and schools of public health and to microbiologists. These opportunities later were made available to 3rd- and 4th-year medical students and to PhD candidates in microbiology and those interested in zoonotic diseases. Experience was concentrated in hospitals, rural clinics, public health laboratories, and research laboratories of Latin America for periods of 8 to 12 weeks (Swartzwalder and Thurber, 1974). This program ended more than a decade ago, but it reportedly influenced many participants to seek careers in tropical disease work.

Cornell's collaborative program with Brazil has had a large impact on clinical training in tropical medicine. Beginning in 1964, this program which is supported by ICIDR funds from NIH (see Chapter 5 - NIAID, Extramural Activities Collaborative Programs) has provided clinical training to nearly 200 U.S. medical students at facilities in Brazil. This program, scheduled to end in 1990, concentrates on endemic forms of cutaneous, mucocutaneous, and visceral leishmaniasis and Chagas' disease.

Today, several schools use travelers' and refugees' clinics to supplement courses. Others, such as the Uniformed Services University and the University of Virginia and the University of California at San Francisco, provide a few students and house staff with opportunities for clinical experience in less-developed countries.

While several schools reported ties with clinical facilities suitable for training medical students in the tropics, there was a

universal need for funding for travel. In most instances students have to pay all their expenses. Grants and departmental and university funds rarely provide money for this purpose.

Biomedical Research Training

Both public and private support for training and research in tropical diseases have produced excellent programs in tropical disease research in the United States. However, very little of the biomedical research funds are directed to research training. Foundations such as Rockefeller, Clark, and recently MacArthur have actively supported programs for research training in the field of parasitic diseases, which has received less attention from other funding sources. The U.S. Government, largely through the National Institute of Allergy and Infectious Diseases (NIAID), supports a limited number of collaborative research programs with institutions in developing countries; these monies also support research training.

Academic research and training programs address domestic needs and wider national interests. The breadth of research training programs offered in this country is important in the development of new tools and technologies against tropical diseases. With adequate support these programs have the capacity to respond to a variety of problems and can provide training in a wide range of scientific disciplines.

Biomedical research gives an illusory appearance of permanency to the training activities often associated with it. Neither research programs nor research training have any permanency in U.S. academic institutions, however. The recent decision to close the Naval Biosciences Laboratory associated with the parasitology program at the University of California at Berkeley is one example of the instability of resources. Biomedical research and training constitute the strongest of the fields of activity examined in this study but warrant close monitoring nevertheless to maintain U.S. competence.

Training in biomedical research is directed to master's degree and doctoral candidates and to postdoctoral fellows and is provided by a number of departments with interests in tropical diseases. Training for students involves lecture and laboratory courses as well as supervised independent research at the dissertation stage. Postdoctoral training frequently is less structured.

Many schools offer interdisciplinary degree programs, and there is opportunity to study a variety of pathogens. Several schools offer students the chance to pursue research interests at collaborating institutions in developing country institutions.

Most current U.S. academic research in tropical medicine is on parasitic diseases, rather than on diseases of viral, bacterial, or rickettsial etiology. This emphasis reflects both the complexity of parasitic organisms, which necessitates lengthy and detailed study by researchers who may focus on just one parasite, and the relatively

smaller numbers of investigators working on bacterial diseases (e.g., cholera, plague) and arboviruses of special importance in the tropics.

Parasitology Research Training

Curriculum Changes Several surveys of parasitology training programs substantiate descriptive reports of changes occurring in this field in U.S. academic institutions. In the 1974 ASP survey of parasitologists teaching at various levels in U.S. colleges and universities, 61 percent were teaching a course in general parasitology and over 40 percent were the only member of the faculty at their institution with any teaching responsibilities in parasitology. Parasitology has not been regarded as an important part of the undergraduate curriculum in basic sciences. This omission may limit the numbers of students ultimately selecting parasitology for advanced study and subsequent careers, and it may indicate that those deciding on an advanced degree in this field need basic courses in this field before pursuing graduate instruction.

Changes in the parasitology training curriculum have paralleled changes in the life sciences; emphasis in the traditional areas--e.g., morphology, biology and life cycles, pathogenicity, and epidemiology--has shifted to molecular and genetic study of parasites. See Table 2.

TABLE 2 Non-traditional Parasitology Courses at U.S. Universities, 1978

<u>Course</u>	<u>Number of Institutions</u>
Advanced parasitology	19
Fine structure of parasites	4
Immunology of parasites	26
Intracellular parasitism	1
Physiology and biochemistry of parasites	20

SOURCE: Weinstein, P.P. 1981. Teaching parasitology: The current scene. In K.W. Warren and E.F. Purcell, eds., The Current Status and Future of Parasitology. New York: Josiah Macy Foundation, 57.

A review of the 1978 ASP survey and parasitology teaching (Weinstein, 1981) concluded that molecular biology and biochemistry, cell and developmental biology, endocrinology, immunology, neurobiology and neurochemistry, as well as the use of tools of molecular and population genetics, DNA and isoenzyme biochemistry, statistics, and computer applications should be added, if not already in the curriculum, which should continue to include its classical subfields (e.g., life cycles, systematics, and evolution).

Illustrative Examples Many U.S. academic parasitology training programs reflect research advances. The MacArthur Foundation has helped training programs to incorporate advanced research methodologies in tackling complex problems associated with parasitic life cycles and infection. The MacArthur Research Consortium on the Biology of Parasitic Diseases supports programs in foreign institutions and at seven U.S.

universities: Case Western Reserve University, Harvard University, Johns Hopkins University, Yale University, Columbia University, New York University, and the University of California at Berkeley.

For example, the program of the University of California at Berkeley has drawn on resources of several campuses of the University of California system, and originally on the Naval Biosciences Laboratory. This broad-based, interdisciplinary program focuses on the genetic regulation of parasites that have evolved alternative strategies for evading the immune system. Doctoral students come from the Departments of Microbiology and Biochemistry and from other domestic and foreign universities.

While programs at Harvard, Hopkins, Case Western Reserve, Yale, and Columbia have wide interests, the parasitology program at New York University is more concentrated, devoted largely to malaria (as is a program at University of Pennsylvania). New York University has had a large malaria program, active in the development of a malaria vaccine. Representatives from New York University and NIAID recently conducted field trials in the Gambia to determine sporozoite infection rates in Anopheles gambiae mosquitoes. The university's malaria program has trained a number of scientists from developing countries.

Rockefeller University does not have a formal parasitology program. Its lack of conventional departmental structures and its admission of PhD and MD students to a university-wide graduate program, rather than to individual specialties, offer several opportunities for involvement in advanced basic research in parasitology. Students who choose to do a

thesis on some aspect of parasitology are required to take qualifying courses in at least three basic biological disciplines (e.g., biochemistry, cell biology, molecular biology, virology, immunology). Parasitology itself is not a qualifying subject, although a lecture-and-discussion course is offered. The Laboratories of Molecular Parasitology, Medical Biochemistry, Cellular Physiology and Immunology, and Biochemical Cytology have major commitments to parasitology.

The Uniformed Services University of the Health Sciences provides its medical students with more classroom and laboratory instruction in preventive medicine and parasitology than any other U.S. medical school, in keeping with its mandate to train physicians for the Armed Forces and the Public Health Service. The Department of Preventive Medicine and Biometrics offers a Master's Degree in Tropical Medicine and Health and a Ph.D. in parasitology and vector biology to military personnel and civilians.

Research Training on Other Infectious Diseases

Although most U.S. tropical disease research training programs concentrate on parasitic illnesses, several also investigate viral and bacterial diseases. The following universities are only a few of many reporting training opportunities in their schools of medicine and/or public health.

The University of California at San Francisco offers doctoral and postdoctoral training through its Departments of Epidemiology and International Health, Pharmacology, and Ophthalmology. The tropical disease interests in the Departments of Pharmacology and Epidemiology and International Health include research problems associated with parasitic, arboviral, and chlamydial infections and leprosy. Leprosy is also a focus at Wayne State University, which recently received an International Collaboration in Infectious Disease Research, program grant to collaborate with the Armauer Hansen Research Institute in Ethiopia in research on the immunology of leprosy.

The University of Texas School of Public Health trains for research on diarrheal diseases of bacterial, viral, and parasitic etiologies. This program provides training for approximately four graduate students and postdoctoral fellows per year and has collaborative ties with institutions in Mexico and Egypt. Similar programs at the University of Michigan and the University of Maryland include many interests while emphasizing development of vaccines for a variety of tropical pathogens.

Training in Public Health and Disease Control

U.S. training programs can prepare students for many career paths in international public health. Strong programs can be found in such varied subjects as vector biology and control, epidemiology of infectious diseases, and health planning and evaluation. The student who is seeking training has few choices within any subfield, however.

That U.S. academic tropical public health programs are few and generally small mostly reflects unstable and limited funding for research and training activities. These programs, too, must be watched to ensure that capacity to train new generations of public health and disease control specialists is not lost.

Careful attention to science infrastructure is also warranted, especially if cutbacks are faced. Specialized facilities--for examples, possibly unique insectaries and taxonomy libraries necessary to vector biology--should not be dismantled without careful consideration of the long-term impact.

Opportunities for field training, limited in biomedical research, are more limited yet in public health. Such limitations seriously weaken U.S. capacity to train specialists in international public health.

Most U.S. training in public health and disease control is offered through schools of public health. Like clinical training, it ranges from individual courses to degree-granting programs. These programs are designed to train people for a variety of careers, some related to service, others to research. Substantive areas of training include vector control and environmental health, general tropical public health, or health program design and evaluation. The program examples mentioned here are in schools of public health or medicine. A number of other U.S. universities have programs in vector biology (National Research Council, 1983a).

The University of Hawaii Department of Public Health Sciences offers an MS-M.P.H. program for engineers who wish to work in less-developed countries. This program provides training to cope with problems of water supply, wastewater collection, treatment, and disposal, and control of disease vectors. Vector biology and control programs are also offered at the University of Hawaii, the University of South Carolina, Harvard University, Johns Hopkins University, and Tulane University. Medical entomology and zoonotic disease epidemiology are emphasized at Yale University.

The University of Hawaii and Tulane offer M.P.H. programs dealing with management, development, and evaluation of programs in developing countries. Tulane's program is tied to the Institute for Health Services Research, which seeks to develop more efficient methods for the organization and delivery of health care. Harvard School of Public Health's Takemi Program in International Health supports a 10-month fellowship for research and advanced training in critical issues of international health. This program concentrates on how resources are allocated and used for health purposes.

The public health program at Loma Linda University is broad, but the emphasis is clearly on service. This Seventh Day Adventists' university sees itself as a resource center for missionary programs, and the M.P.H. program reflects the diverse needs of this effort.

The University of California at Berkeley and the University of California at San Francisco jointly offer a unique program in medical anthropology and epidemiology. The San Francisco component is based in

the Department of Epidemiology and International Health. Doctoral students in anthropology on either campus normally obtain additional training in epidemiology and various other public health and biomedical disciplines. Some elect to undertake dissertation research on tropical disease problems.

The School of Public Health at Johns Hopkins University provides administrative support and coordination for the tropical disease activities conducted by this university. With more than 55 faculty members involved in tropical health and with an overall operating budget of more than \$11 million, the School of Public Health represents the largest aggregate of tropical disease specialists in an academic setting in the United States. The School of Public Health trains U.S. citizens and foreign nationals; foreign students represent 67 countries and comprise 20 percent of the student population.

Training for Foreign Nationals

Training of tropical disease specialists from the less-developed countries serves many interests. Contact with U.S. educational institutions and students fosters improved international understanding and a common language of science; it promotes collegial and collaborative relationships that represent the most fruitful, mutually beneficial form of scientific exchange between the United States and

developing countries; it fosters the establishment of a wide network of expertise in the monitoring and surveillance of communicable diseases. Training health specialists from the less-developed countries is increasingly important.

Students who come here from less-developed countries for training in tropical health are not always matched to schools that would best meet their needs. The training needs of students who have come from less-developed countries and who will return home to far different settings to engage in clinical, research, and public health work differ in many ways from those of U.S. citizens who anticipate careers in international health. The technology associated with clinical and research training in the United States may impart skills of little use in the developing countries; curricula may take U.S. health care and its support systems for granted.

Although the United States obviously has participated in training of foreign specialists in tropical diseases, data fully measuring this participation do not exist. Few schools provide information on their alumni, and fewer have data available for tropical disease training programs. Anecdotal information and statistics provided by WHO indicate that U.S. training programs, especially those for biomedical research and public health, are filling unmet needs for students from developing countries. The international Special Programme for Research and Training in Tropical Diseases (TDR) program has sent trainees to 29 U.S. academic institutions.

The stage at which a student from a less-developed country might enter training in the United States or another developed country will vary according to the training capacity available at home. It is more logical for the student to take advantage of local resources first, after which further training in the United States or another industrial country might be desirable. This may be for the master's degree, the doctorate, or postdoctoral training, depending on the trainee's interest, local training capabilities, and the local need. Suitable training programs are available at U.S. academic institutions as well as at agencies of the federal government, including NIH; capacity varies. Overseas U.S. military laboratories provide research training to a very few local scientists.

Clinical Training

With the possible exception of specialized programs for high-technology clinical subspecialties, clinical training in tropical diseases for foreign nationals is best given where the diseases are endemic. That is where the need and experience are greater. A logical strategy for clinical training could capitalize on the strengths of local institutions and foster the development of regional training centers for clinical tropical medicine and research. The International Center for Diarrheal Diseases Research, Bangladesh, is one example of a successful training center which is able to link field work, research,

and the provision of clinical care. The combined hospital-research laboratory located where tropical diseases are endemic could provide excellent training, and might also be amenable to collaborative programs with the United States, facilitating training of U.S. citizens as well. What is needed is a stronger U.S. commitment to clinical training in tropical medicine, with sufficient funds to support such activities.

Biomedical Research Training

Relevance is an important issue in U.S. research training for individuals from less-developed countries. Are they training for work that can't be done in their home countries? The research problem and the technologies used to solve those problems must pertain to issues and capabilities back home if the trainee is to return and contribute to problem-solving efforts there. Such trainees may do best with two preceptors--one at an institution in the United States or another developed country and one back home. If these advisors have a common collaborative relationship, the definition of a suitable research problem and the selection of appropriate research methods will increase the benefits both to the trainee and the home-country institution. Scientists who have trained in the United States share a common experience and perhaps perspective on science with their U.S. colleagues. They also become familiar with the resources and people important to the establishment of collaborative relationships.

Public Health Training

U.S. public health training for students from less-developed countries should take account of the problems and resources of those countries. Because U.S. public health training programs typically and understandably concentrate on U.S. conditions and options, foreign students who seek public health training in this country must take care and may need help in selecting their academic programs.

In addition to academic training, opportunities are available to small numbers of public health specialists from less-developed countries to study applied epidemiology with the Centers for Disease Control (CDC). Special, problem-oriented short courses, which can be tailored to important issues of less-developed countries, also are available from CDC.

Returning Home

The question of students who do not return home upon completion of training must be raised. Does their U.S. training discourage foreign students from returning home?

Lack of opportunity to continue at home in a career or research quest begun in the United States is an effective disincentive to returning. When the clear purpose of a visiting student's work here is to prepare for research or service at home, special attention must be paid to match the student with the appropriate course of training.

The Rockefeller Foundation has an innovative program to encourage foreign students to return home to work. Its Career Fellowship Program provides funds for graduates of U.S. training programs from developing countries to return to their training laboratory once a year for three months to maintain technical skills and personal relationships and learn new methods. Rockefeller pays for travel and living expenses, and the training laboratory pays for research costs. The student can maintain U.S. contacts while carrying the benefit of his training to his home community. Very few programs systematically follow their alumni to monitor career development and relevance of training. The Johns Hopkins School of Hygiene and Public Health, which has developed a system for alumni follow-up, reports that the majority of foreign medical school graduates receiving U.S. public health training return home (U.S. Department of Health and Human Services, 1983b). Samples of alumni taken in 1970, 1975, and 1980 found that 90 percent returned to their home countries.

ACADEMIC RESEARCH AND TECHNOLOGY DEVELOPMENT

Development of diagnostic tests, drugs, and vaccines for tropical diseases usually requires the cooperation of Federal agencies, universities, and industry. Academic investigators make many of the breakthroughs in basic knowledge, but they are often not in a good position to carry out those phases of technology development that

require production of drug or vaccine candidates and their clinical testing. When, as with drugs for treatment or prevention of tropical diseases, commercial incentives to develop a product apparently are not high, industry is reluctant to invest in applied or developmental research. Federal agencies such as the U.S. Army Research and Development Command, NIAID, and AID are bridging this gap with contract and grant programs.

Academic institutions have great strengths in basic science research. The survey undertaken for this report indicates that more than 150 U.S. universities conduct research on tropical pathogens. Basic science at universities is a foundation for applied research.

Academic research scientists have done well in the competition for funds provided by investigator-initiated grants programs, and this support system is well suited for investigators working in institutions with few other tropical disease specialists. Scientists in academia are well prepared to respond to increases or changes in basic science research funding, and it is expected that these individuals will continue to participate in significant efforts in this field.

Fewer academic biomedical research groups can respond well to proposed applied research efforts. Contracts typically target a product, such as a diagnostic test or a drug. Development of these products or tools requires a broad range of expertise. Ability to respond requires capability in a variety of disciplines in research, clinical, and public health and disease control work. Drug or vaccine trials for tropical diseases require not only general clinical expertise

but also appropriate overseas experience in program design, execution, and evaluation. Contacts in the country where the testing is to occur are invaluable and are usually established through long collaborative relationships. Ability to respond to targeted research contracts requires flexibility to tap or acquire expertise for the short term of a contract. This is not feasible for smaller academic groups, which lack the needed diversity of personnel. Unless links can be quickly established with other schools or industry, most schools are unable to compete. The seven centers noted earlier in this chapter would be the most likely candidates for participation in applied research.

Cooperative biomedical research relationships between industry and academia (especially the larger universities) have proliferated in the past five years. In 1985 Yale University had cooperative research contracts in all fields with 22 companies, while 32 members of the medical school faculty had corporate research grants totalling \$2.2 million (Kezerian, 1985a:17 and 1985b:19). Most of these are for research on cancer, genetics, and hormones, but it is not unreasonable to imagine similar arrangements for work on tropical diseases if the serious problems from industry's point of view, such as lack of financial incentives, were overcome.

Sources of Funding for Biomedical Research

Biomedical research on tropical diseases overlaps with so many other fields that its funding can only be estimated. The total approximated

\$100 million for fiscal year 1983 but has fluctuated greatly and generally has been much lower. Its primary sources clearly are few, and they support work within federal agencies as well as work in private and state institutions (see Table 3). More than half the money for U.S. basic science and training in tropical disease work comes from one agency--NIAID, which supports academic research training, biomedical research, and limited career development programs at U.S. academic institutions. NIAID also supports collaborative research programs with institutions in developing countries, through the ICIDR program. AID and the Department of Defense (DOD) support academic research through grants and contracts. A small group of foundations, including Rockefeller, Clark, and MacArthur, have programs in this field. In addition, U.S. universities have received support from international agencies, especially through the TDR program.

Academic institutions are not the sole recipients of these funds. Universities compete with private research institutes, industry, and other organizations conducting research. Grants and contracts for research projects account for the largest share of financial support for tropical disease work, and securing such funding demands a great deal of time and attention from researchers as well as administrators.

Of the more than 150 academic institutions surveyed for this study, all but 30 received some external funds for tropical disease research. NIAID awarded grants and contracts to 97 U.S. institutions. The TDR and WHO's Control Program for Diarrheal Diseases provided support to 72 U.S. institutions over the past 2 years through individual grants.

The DOD provided support to approximately half as many schools over a 5-year period. AID awarded research awards to approximately 20 U.S. academic institutions in the past 2 years.

ADEQUACY

The United States has some superb academic resources for work on tropical diseases. Adequacy is another matter. Measured against global needs and scientific opportunities, the tropical health resources of U.S. universities fall far short. Broadly based programs

TABLE 3 Distribution of Biomedical Research Funds by Funding Source
(millions of dollars in FY 1983)

NIAID (tropical diseases)	33.158
(ARI and diarrhea)	22.000
DOD	14.111
USAID	13.800
CDC	4.929
Foundations	2.600
WHO	4.200
Other	5.202
 TOTAL	 100.000

SOURCE: U.S. Congress. 1985. Office of Technology Assessment. Status of Biomedical Research and Related Technology for Tropical Diseases. Chapter 3, Tables 5-17.

in tropical medicine and tropical public health are few, and they would not be able to respond quickly to a sudden increase in demand for training and services, particularly because of requirements of time,

money, and dedication to train new clinicians and public health specialists. Largely because of inadequate institutional support and the lack of appropriate career structures, U.S. academic resources are severely limited in their capacity to make long-term or comprehensive commitments to reducing mortality and morbidity from tropical diseases despite recognition of the relatively stable foreign assistance policies of improving human welfare in the developing world.

The research community serves both as critical reviewer of programs and policies in international health and as participant in study and service efforts attached to those programs and policies. This is a difficult position in any event. There are program imbalances, and the array of resources is not optimal.

Although the primary task of faculty is teaching, academic success comes more often from research activity. At the same time, financing research through intermittent grants and contracts cannot ensure the adequacy of a continuing base of ability. Tenured positions in international health are needed to sustain faculty and to encourage talented individuals to go into this field. The most vulnerable individuals in academia are lower-level, untenured professionals who have to teach, submit grant proposals, conduct research, and, if they are physicians, provide clinical service for the institution. Little time and no support are left to generate initiatives in tropical health.

U.S. effort to strengthen the health research and training institutions of developing countries is insufficient. Those institutions that could most benefit from U.S. collaboration in research

and training are not regularly identified and optimal use of resources is not assured.

U.S. universities are great potential resources for direct efforts to decrease the disease burden in the developing countries. Only the largest centers can afford to have faculty members overseas, however. So most such contributions by U.S. academics are short-term. Very few U.S. schools are expanding their international work, and there are no signs of prospective increases in the small number of major U.S. centers for tropical health work. Expansion depends on investment in availability of clinical, research, and public health experts, all with significant experience overseas and all with a willingness to train others.

U.S. GOVERNMENT, INTERNATIONAL, AND PRIVATE RESOURCES

Much of this nation's capacity to deal with tropical diseases is in the federal government; predominantly in the Public Health Service (PHS), the military services, and the Agency for International Development (AID). Federal agencies conduct training, research and disease control activities themselves. In addition, they channel funds to international organizations, which in turn support special programs of the World Health Organization (WHO).

The United States is both a supporter and beneficiary of the disease control work of international organizations.

Private industry appears willing to respond to requests from governments and international agencies but believes it lacks sufficient market incentive and legal protection to warrant making major investments in this field.

Several private foundations have provided leadership both in the identification of tropical disease problems and in the stimulation of innovative attacks on these problems. The roles of foundations go well beyond the relatively small research efforts they sponsor.

This chapter brings together information on the nature and scale of resources devoted to tropical diseases from these several sources together with some comments by the committee.

FEDERAL AGENCIES

Federal agency programs and activities for tropical disease research and control are concentrated within the Departments of Defense and Health and Human Services and the Agency for International Development. Other agencies, such as the Department of Agriculture, National Science Foundation, and the Peace Corps, are involved in related activities, but do not have a continuing, specific commitment against human diseases of the tropics.

The particular mandates of each federal agency with tropical disease interests govern the structure and scope of its programs. AID justifies its antimalaria and oral rehydration therapy (ORT) programs on the basis of enhancing child survival in developing countries. The National Institutes of Health (NIH) funds research on malaria and in order to advance biomedical sciences and to protect the health of the American people. The U.S. Army supports research on arboviruses in Africa because of its need to be prepared for disease exposure anywhere.

Although the mandates differ, the programs, quite properly, overlap significantly in technical and general objectives, and often require the same kinds of resources and skills. The Walter Reed Biosystematics

Unit, at the Smithsonian Institution, receives nearly all of its support from the military, yet has the world's most complete mosquito-vector taxonomic reference facilities and is used widely by academic investigators from the United States and abroad. Epidemiologists employed by the Centers for Disease Control (CDC) are often loaned to other parts of the PHS, to WHO, and to AID. CDC, NIH, and the military cooperate closely in many research activities.

Among questions of interest in the examination of Federal programs are these:

- o Are resources utilized fully? Is there unmet demand?
- o What are the major strengths and limitations of each program?
- o What are the potential capability and likelihood for future growth and renewal of resources within each program?
- o What is the career structure within the federal agencies for tropical disease research and control? Do the agency programs support careers outside the government?
- o Are Federal programs flexible enough to deal with the changing needs of developing countries?
- o To what extent are activities within programs organized in light of specific objectives and, where appropriate, targeted toward measurable outcomes?
- o To what extent do program planning and budgeting take into account consequences of omissions and changes in emphasis?

National Institutes of Health

Established in 1930, the National Institutes of Health conduct and support research in biomedicine and the life sciences and to train

physicians and scientists. NIH is a complex of 11 institutes, a clinical center, 4 research divisions, the John E. Fogarty International Center for Advanced Study in the Health Sciences (FIC), and the National Library of Medicine. Its budget of \$5.5 billion supports research and research training in its own laboratory and extramurally in private, industrial, and academic laboratories, while also creating informal global networks of communication among scientists. Of this total, a little more than \$50 million supports research and research training on tropical diseases.

The International Health Research Act of 1960 (Public Law 86-610) authorized NIH to "advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, research planning, and research training." While tropical diseases have a limited direct impact on the health of the American people, research on tropical pathogens has advanced the health sciences significantly and will continue to do so.

Because of the geography of tropical diseases, cooperative efforts with other countries are very important to development of sound, pertinent science. The FIC coordinates the international activities of the NIH concerned with health sciences internationally.

Fogarty International Center

The Fogarty International Center administers and/or supports several postdoctoral fellowship programs for research training in the United

States and abroad. Two of these specifically relate to tropical diseases, although scientists supported through the others may work in the field. The International Tropical Diseases Research (ITDR) Fellowships, managed by FIC with the cooperation of NIH's National Institute for Allergy and Infectious Diseases (NIAID) and the UNDP/WB/WHO Special Programme for Research and Training in Tropical Diseases (TDR), sponsors postdoctoral training for scientists from countries where the six tropical diseases targeted by TDR are endemic; these diseases are malaria, schistosomiasis, filariasis, trypanosomiasis, leishmaniasis and leprosy. No new awards have been made since fiscal year 1983 due to limitations in NIAID research training funds. The Senior International Fellowship (SIF), with an emphasis in Tropical Diseases, is a special competition within a broader SIF program for mid-career and senior U.S. scientists to spend three to twelve months in cooperative research projects in tropical medicine outside the U S. This program also has been affected by NIAID budget limitations and made no awards for tropical medicine fellows in fiscal year 1983.

The International Research Fellowship Program is for scientists, from around the world, who are at the postdoctoral stage of career development. This program provides training in research for up to 2 years in U.S. institutions, sometimes NIH. Upon completion, awardees must return to their home countries. Approximately one fourth of the International Research Fellowships have been awarded to scientists from developing countries, and several awardees each year may work on problems related to tropical diseases.

The FIC also channels core support earmarked by Congress of approximately \$2 million annually to the Gorgas Memorial Laboratory in Panama. Gorgas offers training for graduate and medical students who can obtain financial support from other sources. Its diverse research program includes work on viral and parasitic diseases of importance in Central America and studies of effects of environmental change on disease vectors and transmission.

National Institute of Allergy and Infectious Diseases

While most NIH institutes sponsor international health activities, the overwhelming volume of NIH research in tropical diseases occurs within the National Institute of Allergy and Infectious Diseases. NIAID categorizes activity in tropical entities according to the following groups:

- o Tropical diseases--leishmaniasis, trypanosomiasis, leprosy, malaria, schistosomiasis, and filariasis, the six diseases targeted by TDR.
- o General parasitology--including cestodes, nematodes, protozoa, and trematodes.
- o General tropical medicine--tropical virology (arboviruses, rabies virus, and the exotic viruses such as the Lassa virus), tropical bacteriology (cholera, tuberculosis, spirochetes, yersiniosis), tropical mycology (histoplasmosis and coccidioidomycosis), tropical rickettsia, and vector pathogens (mosquitos, flies, ticks, and snails).

These categories are somewhat narrower than adopted by the committee elsewhere in this report and would exclude some NIAID-supported work on

acute respiratory infections and diarrheal pathogens.

NIAID awards grants and contracts to U.S. scientists and a limited number of foreign scientists through NIH's extramural activities. Intramural activities support in-house studies and research training for U.S. and foreign scientists.

The institute participates in two bilateral programs with Japan. One, the U.S.-Japan Cooperative Medical Science Program, focuses research attention of both countries on diseases of importance in Asia. These include cholera and other diarrheal diseases, arboviral infections, leprosy, tuberculosis, and parasitic diseases. The program facilitates contact and exchange among scientists and in the opinion of an NIAID administrator has stimulated successful applications for NIAID research grants.

In fiscal year 1985, slightly over \$42 million of NIAID's \$295 million extramural budget was allocated to extramural grants in tropical diseases, general parasitology, and general tropical medicine. The extramural activities received approximately 78 percent of the tropical disease related funds for the past 4 years, with the remaining 23 percent going to the intramural work. See Table 2. The largest increase in funding for tropical disease research between fiscal year 1983 and fiscal year 1985 was for extramural activity.

Intramural and extramural research funded by NIAID (and for all NIH institutes) can be categorized generally as:

- o Basic--exploratory, with no specific, predefined goal;
- o Applied--goal-oriented, practical; or
- o Developmental--product-targeted, mostly contract-supported.

TABLE 2 National Institute for Allergy and Infectious Diseases Funding for Tropical Disease Research, 1982-85 (Thousands of Dollars)

Fiscal Years	1982	1983	1984	1985
Tropical Diseases - Intramural	5,627	5,182	4,953	5,066
- Extramural	10,042	16,211	19,127	23,836
Gen Parasitology - Intramural	1,854	1,245	965	735
- Extramural	3,502	2,908	3,526	7,151
Gen Trop Medicine - Intramural	1,991	1,430	2,734	2,864
- Extramural	7,659	6,182	10,095	11,428

SOURCES: U.S. Congress. 1985. Office of Technology Assessment. Status of Biomedical Research and Related Technology for Tropical Diseases. National Institute of Allergy and Infectious Diseases. Annual Reports of International Activities at NIAID, Fiscal Years 1982-1985, Karl Western, personal communication.

NIAID administrators told this committee their retrospective analyses of work that the institute supports show a noticeable decline in developmental effort since fiscal year 1980, and such modest increases in basic and applied research. The shift reflects protective concern, in years of tight budgets, for the investigator-initiated basic research that they feel is the heart and soul of the field. Developmental work that is necessary and timely might therefore be deferred.

NIAID's tropical diseases activities have maintained funding increases on a par with total NIAID budget increases for the period fiscal year 1980 to 1985. The NIAID budget increased by 72 percent from \$215 million in fiscal year 1980 to \$370 million in fiscal year 1985, while NIAID programs related to tropical diseases rose by 72 percent,

from \$29 million in fiscal year 1980 to \$51 million in fiscal year 1985. (Personal communication, Yvonne DuBuy, Budget Office, NIAID, and Karl Western, NIAID).

Intramural Programs Of the 13 laboratories in NIAID, the Laboratory of Parasitic Diseases (LPD) and the Laboratory of Infectious Diseases (LID) perform most of the institute's tropical disease studies and research training.

Research LPD's intramural research is on a broad spectrum of parasitic pathogens. LPD maintain collaborative relationships with research institutions in Brazil, England, the Dominican Republic, Venezuela, the Netherlands, Israel, Germany, Egypt, and India.

Research Training Intramural programs throughout NIH provide laboratory and clinical research training for physicians and PhD scientists at the postdoctoral level:

1. Medical Staff Fellowships provide physicians with clinical and research training in areas targeted by individual laboratories within NIH. Appointments are made for a period of 2 or 3 years and require FTE authorizations.
2. Staff Fellowships provide postdoctoral training in research for periods ranging from 2 to 7 years. Each fellow requires an FTE.
3. Visiting Fellow Program provides 1 to 3 years of postdoctoral training in research for foreign citizens who have a doctoral degree or its equivalent. Participants receive fellowship awards, which do not carry FTE status.

4. Visiting Associate Program provides research experience for up to 7 years for foreign scientists who have had 3 to 6 years of postdoctoral research experience. These positions require FTEs.
5. Guest Researcher Program provides facilities to U.S. and foreign scientists. It provides no salary and does not require an FTE.
6. Visiting Scientist Program provides scientists from all over the world the opportunity to conduct research at NIH, sharing NIH resources and learning techniques used in these laboratories.

Infectious disease research training opportunities at NIH for U.S. citizens and foreign nationals are heavily concentrated within NIAID laboratories. Foreign nationals from developing countries have usually occupied close to one third of the available Visiting Fellow and Visiting Associate positions at NIAID, a higher proportion than that calculated for these programs overall at NIH.¹ The total number of new positions available each year is subject to two constraints. First, each laboratory at NIH has a personnel ceiling, against which each permanent employee position--scientist or technician--is charged. Only visiting fellows and guest researchers do not count toward this ceiling. The 1985 ceiling for LPD at NIAID, for example, was 56 and was to be cut to 55 in fiscal year 1986. Second, some intramural programs require FTE authorizations for participants.

Research trainees at LPD took up 21 FTEs (Table 3). This represents 37.5 percent of that laboratory's personnel slots. The number of FTEs is being reduced throughout the Federal Government. Owing to the unique resources of NIH and the very limited numbers of positions allotted for individuals interested in tropical disease problems, reductions at NIH could have serious consequences for this field of study. Cuts in FTEs

are expected to hit Medical Staff and Staff Fellowships in the near future, with less impact on the programs for foreign scientists which are independent of FTEs.

TABLE 3 Research Training at the Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases

	1983	1984	1985
Medical Staff Fellows	6	6	7
Staff Fellows	11	7	9
Visiting Fellows*	6	6	8
Guest Researchers*	19	21	23
Visiting Associates	1	2	3
Visiting Scientists	1	2	2

*Slots exempt from FTE.

Through the Medical Staff Fellowship program at LPD, physicians receive, in addition to research training, staff-supervised clinical training in the management of known or suspected cases of tropical diseases that are under active research protocols. These diseases include giardiasis, schistosomiasis, cryptosporidiosis, leishmaniasis, Chagas' disease, filariasis, ascariasis, strongyloides, hookworm, malaria, and amebiasis. The other intramural programs offer research training only.

Research and research training in tropical diseases at LID focus on viral pathogens of diarrhea (primarily rotavirus) and dengue. While there have been no medical staff fellows recently, two staff fellows have been working on dengue projects and one on rotavirus. LID usually also has one or two visiting fellows and visiting associates as well as

several guest researchers. LID has collaborative research projects with research institutions in Australia, India, Venezuela, and Belgium. Administrative staff at LID indicate that cuts in FTEs have made it difficult for them to maintain research training.

Extramural Activities NIAID's extramural activities include research support and participation in research fellowship programs.

Research As noted above, most of the institute's science program is conducted extramurally, principally under grants for investigator-initiated research.

Most of the proposals for tropical disease research are reviewed by the Tropical Medicine and Parasitology (TMP) study section, which is managed by NIH's central Division of Research Grants. Ad hoc review groups have been added; for example, clinical trials and vector or arbovirus studies have been reviewed separately since 1984. Priority scores are calculated for each proposal on the basis of scientific review, following which the proposals are assigned to appropriate institutes at NIH for funding decisions. About 95 percent of the proposals reviewed by TMP are sent to NIAID, which also receives tropical disease-related bacteriology, mycology, and virology proposals from other study sections.

NIAID has applied uniform priority score criteria to funding investigator-initiated proposals, rather than weighting program or subjects to promote selected areas. Table 4 compares the numbers and

proportions of approved and funded proposals considered by the TMP study section and ad hoc research groups with proposals funded by NIH and NIAID. Overall, TMP proposals received scores that gave them

TABLE 4 Investigator-Initiated Research Grants Approved by Tropical Medicine and Parasitology Study Section and Funded by NIAID, compared with NIH and NIAID data, Fiscal Year 1979 to Fiscal Year 1985

Proportions Funded in Parentheses					
	NIH	NIAID	TMP	Ad Hoc TMP	Total TMP Approved
FY 1979	5944 (51.6)	537 (48.6)	70 (44.9)	---	156
FY 1980	4875 (42.3)	452 (38.3)	64 (32.3)	---	198
FY 1981	5109 (39.2)	433 (34.9)	50 (28.7)	---	174
FY 1982	5027 (34.7)	411 (28.6)	78 (34.5)	---	226
FY 1983	5389 (37.2)	522 (37.1)	76 (37.9)	---	200
FY 1984	5493 (37.3)	507 (36.0)	56 (29.2)	13 (48.1)	218
FY 1985	6246 (37.3)	549 (36.5)	70 (33.5)	12 (38.7)	240

SOURCE: Ms. Geraldine O'Rose, Division of Research Grants, SAB.RAPS.-1 National Institutes of Health, U.S..

lower priority , and consequently lower funding rates, than all proposals received by NIAID, with the exception of fiscal year 1982 and

1983. The number of proposals approved by the study section increased by 54 percent between fiscal year 1979 and fiscal year 1985, indicating a significant rise of scientific interest in tropical medicine and parasitology. Unfortunately, however, the number of new grants funded annually by NIH and NIAID was lower during the 5 years 1980-84 than it had been in FY 1979, before rising again slightly above the FY 1979 level in FY 1985.

Nearly all of NIAID's extramural funds go to U.S. institutions. Very small amounts have been awarded to foreign institutions primarily on a competitive basis. In other industrialized countries, in fiscal year 1984, Mexico received direct grant monies from NIAID for a total of \$34,675. However, many U.S. research projects funded by NIAID involve collaborative activities with scientists in lesser developing countries.

NIAID funds several centers that focus on specific issues relating to tropical medicine. In fiscal year 1984, Johns Hopkins University received over \$500,000 to establish a center for the study of infectious enteric disease, and the University of Maryland received almost \$1.5 million to maintain its vaccine center for infectious diseases. Both are funded through research development and service contracts. Yale University received a grant for approximately \$150,000 to support its world reference center for arbovirology; an additional \$470,000 was awarded to study the control of arbovirus infection. These awards provide support for a university-based center of excellence in tropical virology. A virology training grant at Yale for

a 5-year period provided 3 postdoctoral fellowships, some in areas related to tropical virology. Generally, however, research grants provide no money for training per se.

Research Training and Fellowships NIAID programs support comparatively little research training in tropical diseases. In fiscal year 1985, for example, the institute expended only \$718,743 for research training related to tropical medicine-1.7 percent of the NIAID combined intramural and extramural budget for tropical medicine in that year. (U.S. Department of Health and Human services, 1985: Tables 1,2)

NIAID awarded 67 research training grants to U.S. academic institutions in fiscal year 1984; total expenditure: \$6,780,494. Of these grants, only 6 were identifiable by title of award (e.g., parasitology) as specifically pertaining to tropical disease. (University of Massachusetts, Johns Hopkins, Case Western Reserve, Yale, Notre Dame, Michigan State) These awards amounted to \$445,443--6.6 percent of the total. Other research training grants may also support work related to tropical medicine. This committee's survey of training programs in schools of medicine and schools of public health identified 9 additional NIAID research training grant-recipient institutions with tropical disease or international health programs (University of North Carolina, University of Texas, University of Washington, University of Virginia, Columbia, Stanford, Harvard, Tufts, and University of California at Los Angeles).

Collaborative Programs

The International Health Research Act (Public Law 86-610), of 1960, expanded NIH's ability to participate in international cooperative research activities. The law authorized NIH to set up the International Centers for Medical Research and Training program to provide long-term overseas sites for research and training. A major goal of ICMRT was to produce U.S. scientists with expertise in biomedical research and health problems of international importance. Over the 20 years of this program, 4 universities (University of Maryland, Tulane, Johns Hopkins, and the University of California at San Francisco) actively maintained continuing programs in academic and research institutions in Asia and Latin America. Louisiana State University was dropped in 1970 because of cuts in ICMRT funding.

In 1973, Congress and the Office of Management and Budget placed considerable pressure on NIH to reduce its training activities. Fearing further loss of funds for ICMRT, NIH officials deleted its training component. The surviving International Centers for Medical Research (ICMR) program operated until 1980, without training and with a narrower research focus that reflected its administrative relocation to NIAID from an NIH-wide Office of International Research.

NIH sponsored another, shorter-lived program to provide young physicians with research experience overseas. This program was in operation from 1963-1969 and placed clinicians in overseas military laboratories, ICMRs, and the Cholera Research Laboratory, in Dhaka. A total of 23 physicians participated in this program.

When the ICMR program was dismantled in 1980, three award mechanisms were instituted to provide support for international research:

International Collaboration in Infectious Disease Research Program (ICIDR), Tropical Disease Research Units (TRU), and the International Tropical Diseases Research fellowships. These programs vary in their training capacity.

The ICIDR program was designed to develop peer relationships between U.S. research institutions and those in developing countries. Most of the funds allocated to recipients of these grants must be spent overseas. In fiscal year 1985, ICIDR grants were active with the following sets of institutions:

Harvard School of Public Health	Federal University of Bahia, Brazil
University of Illinois	Chiang Mai University, Thailand
Cornell University	Federal University of Bahia and University of Brasilia, Brazil
Michigan State University	Ministry of Health, Khartoum, Sudan
Tulane University	Colciencias, Colombia, and Institut Francais, Haiti
Yale University	Ministry of Health, Bogota, Colombia
Johns Hopkins University	Universidad Peruana Cayetano Heredia, Lima, Peru
Wayne State University	A. Hanson Research Institute, Addis Ababa, Ethiopia

A total of \$2.7 million was budgeted for these programs for fiscal year 1985. Approximately \$300,000 was allocated for exploratory grants

that link individual investigators in the United States with colleagues in developing countries. These grants allow investigators to explore the possibilities for long-term collaborative relationships between their institutions. The training component of ICIDR grants varies from school to school. In general, overseas research facilities provide students and postdoctoral fellows with unique opportunities including field research. However, travel expenses, which are not included in the grants, may present problems for students and program administrators.

The TRU program was intended to provide block grants, through NIAID, to support collaborative research, strengthening the ability of U.S. institutions to conduct multidisciplinary research in tropical medicine. These were to include research training, as well as career development, for U.S. and foreign scientists. In fiscal year 1985, there were three active TRU awards, to Harvard through the Peter Bent Brigham Hospital, to Case Western Reserve University, and to New York University. The focus of the program at Harvard is the immunology of parasitic diseases; the program at Case Western is a multidisciplinary program in parasitic infections with an emphasis on schistosomiasis; and the program at New York University is on the immunology of malaria. Total funding for these programs was \$1,437,000.

Adequacy

Research grants, contracts, and research training awards related to tropical diseases have accounted for a considerable and steady

proportion of NIAID's total extramural program over the past decade. Offsetting the maintenance of investigator-initiated awards, however, has been a loss in development contracts that may lead to new technologies. Integrated, targeted programs for applied research on tropical diseases never have been emphasized at NIH, although recent efforts to set priorities for vaccine development may presage more coordinated efforts in this area.

The extent to which NIH support for collaborative research on tropical diseases helps to strengthen research capacity in developing countries is unclear. No formal connections exist between the ICIDR or TRU programs, which link academic groups with overseas institutions, and the intramural training fellowships awarded to nationals of the less-developed countries.

NIAID has a remarkable diversity in its extramural programs for tropical disease research and related training. The total number of awards is very small in relation to need and could be increased rapidly if funds were available. The major gap in the programs is the lack of any explicit mechanism to strengthen research capability of institutions in the developing countries. This weakness could lower the long-term productivity of any collaborative award.

ICMR(T) and ICIDR funding has been relatively constant (temporary increase in 1979 reflects the overlap of these two programs as one

replaced the other) (See Table 5). However, evaluation of such constancy in funding levels must take inflation into account. The same amount of money is now being spread among twice as many projects, thus significantly decreasing the amounts of individual grants.

TABLE 5 National Institutes of Health International Awards for Research Training and Research

<u>Year</u>	<u>ICMR(T)/ICIDR*</u>		<u>Training</u>	
	Number of Grants	Amount**	Number of Grants	Amount*
1957	0	0	1	13
1958	0	0	1	17
1959	0	0	2	30
1960	0	0	3	39
1961	0	0	7	251
1962	5	2,093	13	380
1963	7	2,093	16	536
1964	6	2,484	17	544
1965	6	2,491	22	615
1966	5	2,423	18	559
1967	5	2,360	15	506
1968	5	2,360	16	449
1969	5	2,294	11	187
1970	4	2,070	4	46
1971	5	2,285	0	0
1972	4	2,399	0	0
1973	4	2,244**	0	0
1974	4	2,360**	0	0
1975	4	2,411**	0	0
1976	4	2,400**	0	0
1977	4	2,400**	0	0
1978	4	2,117**	0	0
1979	13	4,699**	0	0
1980	10	2,756**	0	0
1981	10	2,585**	0	0
1982	8	2,384**	0	0
1983	9	2,741**	0	0

*training component deleted **in thousands of dollars

From National Institutes of Health's Annual Reports of International Activities for Fiscal Years, 1975-1983.

NIH supports a large group of scientists who work on numerous health problems from the perspective of every discipline related to medical science. This extraordinary aggregation of expertise and laboratory resources makes training at NIH a special experience. The

potential loss of research training for young scientists at NIH is therefore special cause for concern. Constraints posed by FTE restrictions will affect Americans more than foreigners, as foreign scientists are afforded some protection under programs that do not require FTEs, but the reduction in training opportunities at a time of such need and opportunity is regrettable.

The potential loss of research training for young scientists at NIH is cause for concern. Constraints posed by FTE restrictions will affect Americans more than foreigners, as foreign scientists are afforded some protection under programs that do not require FTEs, but the reduction in training opportunities at a time of such need and opportunity is regrettable.

Centers for Disease Control

Founded in 1946 as a continuation of the U.S. Government's program for Malaria Control in the War Areas, the Centers for Disease Control uniquely among federal agencies originated from specific concern with tropical disease. Today CDC encompasses five centers, the National Institute for Occupational Safety and Health, and three program offices.

CDC's major mandate is disease prevention and control to protection the U.S. population. To carry out that mandate it is necessarily and substantially involved in international health, although it has no

separate budget designated for research and disease control in developing countries. Its international activities are mostly in collaboration with and funded by AID, WHO, other international organizations, and other countries.

The agency's international programs and activities, coordinated by an assistant director for international health, include an International Health Program Office. The committee estimates that approximately 140 CDC employees, located throughout the agency, are engaged at least partly in research, training, or technical assistance related to tropical diseases. This is about 17 percent of the number of CDC's employees who work on infectious disease problems broadly. (Personal communications with Dr. Donald Hopkins, Assistant Director, CDC, and Mr. Billy Griggs, Assistant Director for International Health, CDC). CDC's potential for greater involvement in tropical disease work depends on availability of outside funds, as well as on Federal hiring restrictions. Approximately 1 to 1.5 percent of CDC's annual budget can be attributed to international activities. In addition, approximately \$8 to 10 million are channeled to CDC through reimbursable agreements with other agencies, primarily USAID. (Personal communications with Mr. Billy Griggs, CDC).

Research

The International Health Research Act (Public Law 86-610) authorizes CDC to conduct any research potentially beneficial to the

health of the American people. Most research at CDC is of an applied nature, although substantial amounts of basic research are conducted in its Atlanta laboratories and overseas. Outside support sometimes is obtained for research projects, for example the CDC Center for Infectious Diseases' study of the molecular biology of dengue virus.

Visiting scientists frequently spend several months at CDC in Atlanta, bringing specimens from the field for analysis. Collaborative research with scientists from developing countries is extensive; relatively few CDC staff are stationed abroad. Often, consultative help is provided to design epidemiologic studies, research protocols, and select and improve diagnostic techniques.

Outside the 50 states, CDC maintains: The Medical Entomology Unit in Guatemala, conducting research on malaria and onchocerciasis transmission; a small unit in Bilbeis, Egypt, that has been conducting enteric disease studies; a dengue laboratory, in San Juan, Puerto Rico, monitoring the Caribbean area for changes in dengue transmission patterns and providing assistance to local laboratories; and a Sierra Leone unit, supported in collaboration with NIAID, studying Lassa fever.

Research is being conducted on most of the pathogens listed in Table 1, Chapter 1. Many of these studies are designed to improve surveillance techniques, to monitor drug sensitivity of pathogens, to evaluate the efficacy of new vaccines, to identify risk factors for infection, or to assess the clinical efficacy of drug treatments. In

recent years about 200 articles concerning international health have been published annually by CDC staff; of these, approximately half concern tropical disease problems. (U.S. Department of Health and Human Services, 1983c, 1984b)

Training

Each year about 200 foreign citizens participate in CDC training courses and/or programs based in Atlanta. A few physicians from developing countries are enrolled for 2 years in the Epidemic Intelligence Service (EIS) officer training program. Several training programs (mostly funded by AID) operate in the tropics, with CDC staff stationed in 14 developing countries.

CDC work under the AID-funded Combatting Communicable Childhood Diseases (CCCD) program includes development of training materials for mid-level managers of antimalaria, immunization, and ORT programs in 11 African countries. Courses are developed in close cooperation with the WHO Africa Regional Office in Brazzaville, where a CDC liaison officer is stationed, and have been conducted in several countries.

Field Epidemiology Training projects have been started in Thailand, Indonesia, Mexico, Taiwan, and Saudi Arabia. These provide a two-year period for training and on-the-job experience for young physicians (and occasionally other health professionals) at health ministries under the

1

supervision of an experienced CDC epidemiologist. Trainees learn to investigate disease outbreaks, to prepare reports, to collect and to interpret data for special epidemiologic studies, surveys, and surveillance requests and in some cases to improve laboratory diagnostic services. The Thailand program, begun in 1979, has produced more than a dozen graduate, most of whom are now working in public health.

Emory University has started a Master's of Public Health program linked to CDC, from which it will draw many of its faculty members. Opportunities for student research and special training through CDC are anticipated.

Disease Control

CDC's range of involvement with tropical disease problems is wider than that of any other Federal agency. Contributions by CDC to disease control in developing countries are largely accomplished through short-term consultative visits or provision of training courses in Atlanta and abroad. Most of these trips are funded by AID or WHO, and a few are funded by private foundations, UNICEF, or other international agencies.

International family planning, reproductive health, and nutrition programs at CDC have received stable support over the last decade or so by AID's Office of Population and Nutrition. CDC's disease control

activities abroad have been increasingly important in AID-CDC relationships over the last five years; consultations funded by the Agency have doubled.

Initiated in 1982 and scheduled to continue through 1989, the largest disease control program managed directly by the agency is the AID-funded CCCD--to improve the ability of African nations to prevent and control childhood infectious diseases. The program eventually will include all sub-Saharan countries eligible to receive AID assistance. The major targets are immunizable diseases of childhood; diarrheal diseases; and malaria. Of the CDC staff assigned to the project, about 5 are stationed in Atlanta and 10 in Africa. CCCD program components include management training, operations research, health information and disease surveillance systems, health education, and country assessments.

Emergency Assistance CDC has had a major role in helping to cope with emergencies around the world. Natural disasters, industrial accidents, famine, and disease outbreaks prompt official requests for assistance that come directly to CDC, through the Department of State, or through international agencies. CDC's International Health Program Office assembles a team to provide short-term consultation or long-term assistance. The number of consultations in response to emergencies overseas has risen to more than 20 per year.

Survey Methodology CDC has increased its international work to upgrade survey methodology. Nutrition and fertility information have been major foci for nearly a decade. Morbidity and health care behavior now are addressed in multipurpose surveys. National surveys have been designed and conducted with technical help from CDC in more than 10 developing countries, including Morocco, Senegal, Guatemala, Egypt, and Peru. Support has come from AID, which is interested in identifying national morbidity and mortality levels for children under 5, in detecting high-risk groups, and in identifying family-planning needs.

Surveillance CDC's international concerns include aspects of disease surveillance. The agency's laboratories conduct research to assess and improve diagnostic methods and develop standard procedures for handling pathogens. CDC serves as a U.S. national reference laboratory for many pathogens. More than 30 CDC laboratories have been designated as WHO Collaborating Centers for Reference and Research on subjects important to developing countries.

About five years ago, CDC began coordinating global surveillance of dracunculiasis (Guinea worm), highly endemic in certain regions of Asia and West Africa. This initiative and associated activities, in collaboration with WHO, AID, and the United Nations Children's Fund (UNICEF), have stimulated countries to consider national programs against this disease.

Adequacy The principal limitation on CDC's ability to contribute toward the solution of tropical disease problems in developing countries is the agency's lack of an international mandate. Budget and personnel decisions are made within the structures of PHS domestic concerns; planning for international work is opportunistic rather than strategic. This situation discourages long term career commitments and opportunities for tropical disease work.

Expertise within CDC for infectious disease surveillance and mortality and morbidity surveys is unparalleled anywhere in the world. Most developing countries lack the abilities to measure the prevalence and incidence of diseases and their trends over time, as a basis for planning health programs and measuring their results. CDC has begun to assist a few developing countries to improve their epidemiologic intelligence services, but years of sustained effort and interaction are needed to train a cadre of experts. Relatively small funds (and personnel positions) could substantially enlarge these much needed services, possibly with cooperation from academic institutions, and enable the United States to realize a unique and effective advisory role for tropical diseases.

U.S. Agency for International Development

Historically, much of AID's disease-control work concentrated on malaria, with many malaria advisers stationed overseas and enormous

efforts expended on the purchase, distribution, and residual spraying of insecticides. With the change from time-limited malaria-eradication efforts to long-term malaria-control programs in many countries during the late 1960s and 1970s, AID shifted its emphasis to building health care infrastructure and training health workers. Nutrition, maternal and child health, and family planning became major emphases.

Concomitantly, as many staff members who had acquired tropical disease expertise reached retirement age they were succeeded by public health and development generalists. Support for tropical disease research and control did not wane entirely. Grants were awarded to WHO for onchocerciasis control and the TDR program, schistosomiasis control was initiated in several countries, immunization programs were supported in many countries, the smallpox eradication campaign was completed with a large proportion of AID support, and the AID Office of Health began a malaria vaccine development program through a series of contracts to U.S. institutions.

By the late 1970s, official policy in U.S. foreign assistance stressed basic human needs. AID health policy was consistent with the new philosophy, favoring primary health-care systems programs over disease-control. As a result, laboratory infrastructure, diagnostic capability, applied epidemiology, and disease surveillance were not supported as discrete projects or training programs.

Within the last several years AID has given much more attention and support to activities related to disease control. These additional

disease control efforts are within the framework of primary health-care delivery. AID supports vaccine trials (such as the new oral vaccine candidate for cholera) and delivery programs and has launched a large program to enhance child survival. Like the UNICEF program for Growth Monitoring, Oral Rehydration Therapy, Breastfeeding, and Immunizations (GOBI), the AID program uses current technology, primarily ORT and vaccination, as well as nutrition education and birth spacing. The Agency's policy guidance on malaria control signed in July 1984 provides support to anti-malaria efforts and their inclusion in primary health care programs receiving support.

AID is the only U.S. agency with a legislative mandate to support activities aimed at controlling disease among populations in developing countries and building of local competence toward that purpose. The AID program makes funds available to U.S. and local private organizations and international organizations as well as other Federal agencies to carry out its program activities.

Budget for Tropical Disease Research and Control

The Agency for International Development is the largest U.S. Government resource for health, nutrition, and population assistance to the developing world. AID's annual Health budget averaged \$138 million in the early 1980s. Appropriations rose to \$223 million for fiscal

year 1985. About 20 percent of what AID has identified as its Health budget supports activities related to communicable disease research and control. The percentage is much lower if the denominator is expanded to include all of the agency's health-related activities, such as those covered under the Nutrition and Population budgets and the health projects funded with Economic Support funds.

AID's Bureau of Science and Technology funds and manages most of the research. Funding for disease-control projects comes mainly from other budgets within the agency. Missions located in 48 countries may assist national governments to formulate requests--in the form of applications for loans and grants--for health assistance. Such requests are then transformed into health projects, through a process that typically takes two years and involves visits of technical consultants and multidisciplinary teams. The projects may include support for training (usually short-term), technical assistance, purchase of supplies and vehicles, salary support, and often a resident project management staff from the United States.

The Office of Health, in the Bureau of Science and Technology, with a professional staff of about 20, together with the Regional Bureaus supplies technical support to health offices in country missions, and makes grants of its own to U.S. groups and international organizations working to develop tools and methods to control disease in developing countries. Fewer than 10 direct-hire AID staff based either in Washington or in the field have had specialized training in tropical disease research and control.

Total AID annual support for tropical disease research is difficult to determine, because of multiyear commitments. The agency estimated \$36 million for fiscal year 1985. [Personal communication with Ann Van Dusen, Office of Health.] This amount excludes applied research components of projects originating from regional bureaus or country missions. Still, it represents more than a twofold increase from an estimated \$13.8 million in fiscal year 1983 for tropical disease research (U.S. Congress, 1985). The rise is attributable in part both to increases in the Health account and to AID's shift of priorities to research and technology development.

In fiscal year 1984 and fiscal year 1985 Congress voted AID an extra \$25 million, for a Child Survival Fund, \$50 million more for its health budget, and \$10 million to launch the Child Survival Action Program. The broad goal of child survival naturally includes attempts to reduce mortality and morbidity from major communicable disease problems--including diarrhea, acute respiratory infections, and malaria. Applied and operational research on these problems will also receive increased emphasis.

Research

AID is funding an increasing array of research activities on tropical diseases. AID is one of 30 donors to the TDR program (Through WHO), supporting worldwide research and training on six major tropical

diseases. AID's Diarrheal Disease Project helps support WHO's Special Programme for Control of Diarrheal Diseases (CDD) and the International Center for Diarrheal Disease Research, Bangladesh. A separate cooperative agreement with Harvard University's Institute for International Development will fund small applied research grants in less-developed countries on diarrheal diseases. AID has contributed to WHO's Onchocerciasis Control Program.

AID also supports research on communicable diseases through two programs of its Office of the Science Advisor. The Science Advisor's Program in Science and Technology Cooperation manages a competitive grants program that includes applications of biotechnology to parasitic, diarrheal, and respiratory diseases. The National Research Council's Board on Science and Technology for International Development (BOSTID) manages an AID-funded program of research grants to institutions of the developing countries. Proposals for research on communicable disease are considered in three categories: Mosquito Vector Field Studies, Acute Respiratory Infections in Children, and Rapid Epidemiologic Assessment for Health Planning and Decision Making. As of August 1985 about \$4.5 million had been awarded by BOSTID in support of research carried out in developing countries.

AID's Malaria Immunity and Vaccine Research program began in 1964 with a grant to the University of Illinois to establish the feasibility of developing vaccine(s) against the several forms of human malaria. The agency's program has grown into a large, collaborative network of research laboratories working on several aspects of malaria

immunology. Significant research breakthroughs attributable to the program include the in-vitro culture of Plasmodium falciparum, the completion of the exorythrocytic cycle of P. falciparum in tissue culture, the development of prototype vaccines against the mosquito-stage P. falciparum and P. vivax using synthetic peptide chemistry and recombinant-DNA technology respectively. The agency has initiated development of a strategic plan for clinical field testing of malaria vaccines--as they are developed--in malaria endemic areas.

In late 1985 the Office of Health announced several new large projects, totaling more than \$20 million over 5 years, to promote integrated vector control, applied research for diarrheal diseases and immunizations, and development of diagnostic tests for diarrheal infections, malaria, and acute respiratory infections in children.

Disease Control

AID's disease control projects attack malaria, schistosomiasis, immunizable childhood infections, and diarrhea. The agency's 1982 Health Policy Statement mentions disease control specifically as part of a larger objective--"improving health programs through better program design, management, and implementation." (U.S. Agency for International Development, 1982) In supporting disease control activities mostly through primary health-care programs, AID gives highest priority to diarrheal disease control through ORT and

immunizing children against polio, diphtheria, tetanus, and measles, AID missions support separate malaria and schistosomiasis control programs only when the governments request such assistance specifically, and they must provide evidence of long-term commitment to control and willingness to assume recurrent costs associated with such programs.

AID funded relatively few large-scale communicable disease control programs in developing countries in the last decade. Recently, however, new malaria control projects have been initiated in Ecuador, Belize, and Peru. AID's new antimalaria strategy plus serious parasite and insecticide resistance problems have increased the number of government requests for AID help in malaria control.

Adequacy

Diarrheal diseases, malaria, and diseases preventable through immunization, all major causes of illness and death in children, command highest priority among AID's concerns with control of communicable diseases. Specific strategies to reduce mortality from respiratory illnesses will be developed slowly, because basic etiologic information across widely varying cultures and geographic regions is not yet available. On a global basis, these priorities are consistent with WHO's emphasis on primary health care, in the sense that selected strategies based on technologies of known efficacy constitute the core

of community health programs. Current AID priorities and programs may not meet the specific needs for communicable disease control considered locally important in a particular country, however.

AID programs and priorities are less static than those of other donor agencies and organizations, and any shift in its priorities can have a large impact. Unlike the other Federal agencies discussed in this report, AID does not have its own research and training staff or infrastructure and must rely heavily on other individuals and organizations within the United States for advice and program management. It is primarily a funding agency for foreign assistance. Except to the extent necessary to carry out its mission, AID has no mandate to strengthen U.S. institutions for tropical disease research and control. The agency uses expertise; it is not a significant producer of expertise.

Viewed as a whole, the AID budget for communicable disease research and control funds a highly diverse portfolio of programs based in a wide variety of institutions. This diversity can be viewed as both a strength and a disadvantage. The agency retains flexibility and avoids reliance on a single approach or set of institutions. However, AID policies over the past decade have not tended to support the development of U.S. centers of expertise and training for tropical disease work in developing countries.

A strength of the agency is its ability to concentrate sizeable resources on specific, long-term goals. The December 1985 conference on ORT reviewed progress made over the last four years and helped to

build collaborative networks and a sense of camaraderie among program directors around the world. The accelerated progress on the malaria vaccine to date is due in large measure to AID, which began funding immunological research more than a decade ago.

Several small research grants programs and projects funded by the agency are strengthening capabilities of developing country scientists to conduct applied research on tropical diseases. These efforts have the most impact on younger professionals, who are encouraged to participate in collaborative networks or visit colleagues in the U.S. for short periods of training in specific techniques. Although most of these programs are in their beginning stages, anecdotal evidence suggests that AID can make an enormous contribution to building tropical disease research, and eventually control capacities in developing countries.

As in most technical fields in which it works, the agency does not provide career opportunities for U.S. tropical disease specialists. Like many federal agencies, AID has experienced severe staff reductions and hiring freezes. The impact on health programs is difficult to calculate, but AID was urged in the Senate to "allocate funds from its 1986 operating expense appropriation to increase its staff of health professionals." (Martin, 1985: 10)

Department of Defense

The Department of the Defense (DOD) has established and maintained

a variety of research and development programs here and abroad to protect the health of troops stationed in tropical areas. The Army has run overseas laboratories since the early 1900s. The Navy Medical Research Unit (NAMRU) system began in 1934. The United States has had 20 military laboratories overseas since World War II; 4 laboratories under U.S. Army direction and 3 U.S. Navy laboratories currently operate in the developing countries.

The preponderance of tropical disease research funded by DOD is managed by the Army Medical Research and Development Command. The following figures reflect these expenditures: In fiscal year 1983, DOD allocated \$14 million dollars to research on tropical infectious diseases (U.S. Congress, 1985). This is approximately half the amount spent by the department in 1977 for tropical disease research (U.S. President, 1978:146). Army and Navy personnel conduct a significant portion of DOD-funded tropical disease research; contract research both here and abroad supplements in-house activity. In fiscal year 1983, 63 percent of all funds earmarked for tropical disease research went to the intramural programs. Approximately 20 percent of the extramural funds went to organizations in less-developed countries, and 70 percent of the extramural funds went to U.S. organizations.

Army

Most of the U.S. Army's intramural research and training in tropical diseases is at the Walter Reed Army Institute of Research

(WRAIR), Washington, D.C., at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Ft. Detrick, Maryland, and at overseas Army laboratories.

The WRAIR tropical disease research program is broad, covering most of the naturally occurring disease threats to the Army. Research includes parasitology (including malariology and work on leishmaniasis), bacteriology (including work on diarrheal diseases), virology, studies of rickettsial diseases, drug and vaccine development, and a special vector biology program, which is located at the Smithsonian Institution.

The USAMRIID mission is to investigate the pathogenesis, diagnosis, treatment, prevention, and epidemiology of infectious diseases of importance to the military, especially those due to agents that may be encountered as biological weapons. Because of its P-4 (the highest U.S. government-prescribed safety level) containment facilities, USAMRIID can study high-hazard organisms, such as the Lassa fever virus.

Most research activities at WRAIR and USAMRIID provide training opportunities for military and civilians, including foreign scientists. Both offer seminars, symposia, and meetings on topics of importance to scientists. WRAIR sponsors research fellowships, veterinary preceptorships, residence programs in preventive medicine and some clinical subspecialties.

Through WRAIR's division of preventive medicine, the Army offers an annual 6-week course in tropical medicine, with each class open to about 30 students. Because of the lack of patients, the course includes no clinical instruction. Military personnel, including residents and fellows working on infectious disease, preventive health, and community medicine, comprise most classes. The 1984 class included one Brazilian physician and one Kenyan medical officer, both civilians associated with U.S. Army overseas research units. In the past, 1 to 5 slots have been available for civilian physicians. An administrator for this program reported a significant demand for attendance (up to 50 applicants and many more telephone requests), primarily from missionary doctors.

Four U.S. Army overseas laboratories are involved in biomedical research on tropical diseases. These laboratories are in Brazil, Kenya, Malaysia, and Thailand, (the largest). These laboratories act as small, overseas branches of WRAIR, and each has a limited number of projects.

The U.S. Army Medical Research Unit (USAMRU) in Brasilia was established in the early 1970s to develop and identify drugs for the treatment of schistosomiasis. The program has been expanded to study the transmission and treatment of leishmaniasis and malaria. This laboratory is currently a part of the Tropical Medicine Center at the University of Brasilia.

The research program at USAMRU-Kenya, also started in the early 1970's, initially functioned as a WRAIR extension to study African trypanosomiasis where the disease is endemic. In 1978, the program was expanded to include visceral leishmaniasis. It is currently associated with the Kenyan Medical Research Institute and the Kenyan Trypanosomiasis Research Institute. The program was recently expanded to include malaria.

USAMRU-Malaysia, started in 1948, focused first on the development and testing of drugs to treat scrub typhus, still its primary research interest. The program now includes malaria studies as well. This laboratory is an integral part of the Malaysian Institute of Medical Research.

The Armed Forces Research Institute of Medical Sciences in Bangkok is a collaborative operation with the Royal Thai Army. Scientific personnel evaluate new drugs to treat malaria as resistance to currently used drugs emerges. They are also evaluating dengue virus vaccine candidates and generally monitor the range of tropical diseases endemic in that part of the world.

Navy

About 15 percent of the U.S. Navy's biomedical research on tropical diseases is conducted in the United States. Most of the effort is in overseas laboratories--NAMRUs. U.S.-based research on tropical diseases

is conducted at the Naval Medical Research Institute, in Bethesda, Maryland. The focus of research here is development of vaccines and diagnostic tests.

NAMRUs in Egypt, Indonesia, and the Philippines address tropical disease problems and appear to be larger, more broadly based in their research programs, and more self-sufficient than their Army counterparts. A small Naval detachment conducts infectious disease studies in Peru. Unlike the Army overseas units, the NAMRUs report to the Navy Research and Development Command rather than to a laboratory. This arrangement affords more autonomy but limits scientific support from U.S.-based colleagues.

NAMRU-2, formerly located in Taiwan, was moved to Manila in 1979. Its research focus is the infectious diseases of importance in the Western Pacific and Southeast Asia. NAMRU-2 has been involved in studies on the epidemiology of hepatitis-B infection, immunodiagnosis of parasitic diseases, surveillance for drug-resistant malaria, and epidemiologic surveys in the Philippines. A NAMRU-2 detachment in Jakarta works on scrub typhus, diarrheal diseases, filariasis and dengue.

NAMRU-3, in Cairo, Egypt, has remained in full operation since the late 1940s despite fluctuating relationships between the U.S. and Egyptian governments. NAMRU-3 has new laboratory facilities and a large medical library, which serves limited numbers of the local medical community. The unit's research targets tick vectors, schistosomiasis, diarrheal diseases, rapid diagnostic methods for meningitis, and epidemiologic studies of Rift Valley fever.

Air Force

The Air Force conducts blood chemistry and oxygen studies, obviously related to its mission, and conducts epidemiologic surveillance and provides health care to military personnel here and abroad. Occasionally Air Force personnel extend medical care to populations surrounding an overseas base.

While involvement of the Air Force in the study of tropical diseases is largely restricted to service and epidemiological surveillance, some training is also provided. The School of Aerospace Medicine, at Brooks Air Force Base, Texas, offers a 2-week course in global medicine. Currently, it is offered once a year to 100 individuals involved in clinical care, public health, or environmental health. Civilian physicians may take the course if space is available; an administrator for this program reported little outside interest in it. The course emphasizes clinical recognition, diagnosis, treatment, control, and prevention of tropical diseases. Photographic presentations are used to teach disease recognition; Brooks seldom encounters actual cases of tropical diseases.

Armed Forces Institute of Pathology

The Armed Forces Institute of Pathology (AFIP), on the Walter Reed Army Medical Center's campus in Washington, D.C., is a joint agency of

the three armed services and is administered by the Army. It is the services' central pathology facility, performs medical and veterinary analyses, serves military and civilian needs, and has diagnostic consultation as its primary mission, followed by education and research. Resources include laboratories, expertise, and extensive biological sample collections.

Its Department of Infectious and Parasitic Diseases houses tropical disease research. The department provides extensive consultation services to military, Veterans Administration, and civilian hospitals in the United States and foreign countries. Specimens from hospitals in developing countries are regularly received directly or referred by other AFIP departments. Thousands of reference specimens of more than 130 varieties of bacterial, mycotic, protozoan, and helminthic pathogens are filed in three pathology registries.

Tropical disease research efforts cover a broad range of clinical and pathologic interests, concentrating especially on filariases, leprosy, Buruli ulcer, malaria, tungiasis, rickettsial infections, deep fungal infections. While AIDS is not classified as a tropical disease in the present report, it is noteworthy that AIDS research has intensified recently, with the establishment of a WHO collaborative center within the department and the development of a program to study AIDS patients in Zaire and Ethiopia.

Department members conduct a research training program for domestic and international fellows and trainees. International fellow and

visiting scientists have recently included nationals of Egypt, Ethiopia, the Federal Republic of Germany, the German Democratic Republic, India, Nigeria, People's Republic of China, Peru, and Singapore.

Federal Agencies: Strengths and Weaknesses

Federal resources for tropical disease research and disease control have expanded modestly over the past three years. However, this expansion has not been accompanied by increases either in career positions or in opportunities for research training or research collaboration overseas. The net result has been a loss of career opportunities within the federal government as a whole, and within federal agencies a reduced flexibility to develop and manage new programs.

For the most part, U.S. government resources to address tropical diseases are well utilized. They are adequate for sustaining a biomedical research base and for maintaining a small cadre of specialists capable of protecting the health of the U.S. population and the military. However, none of the current federal programs is of the scope and scale needed to initiate strong collaborative research and training activities with scientists and public health officials and specialists in developing countries.

Resources available to federal agencies are sufficient to deal with occasional domestic cases or outbreaks of infectious diseases that are much more prevalent in the tropics. Both the PHS and the military seem moderately well equipped to respond to occasional requests from foreign governments for assistance in coping with infectious diseases.

Federal agency resources are insufficient to enable the U.S. government to cooperate with developing countries as extensively as it might--in its own interests as well as those of others--to reduce the burden of infectious disease and its consequences. The reasons are partly financial, partly organizational. They include having to respond to sometimes conflicting requirements and to seemingly narrow mandates. From time to time this subject has been addressed--broadly but episodically. No continuing review of U.S. tropical health capacity is evident.

Viewed as a whole, the federal response to tropical disease problems is uneven, lacks a comprehensive policy, and suffers from serious weaknesses. The legislative mandate for assisting the least-developed countries to control infectious diseases clearly resides with the Agency for International Development. The human resources, clinical, research, and research training programs related to tropical diseases, reside for the most part in the Public Health Service and the Department of Defense. Arrangements for sharing resources between agencies are program or project specific and do not usually require consideration of broader agency goals or mandates. Notable gaps in Federal programs include the absence of any career structure for tropical disease

specialists to work with developing countries in disease control programs, as well as the absence of a clear mandate for any of the agencies to work cooperatively with and to strengthen capabilities in the more advanced developing countries on tropical disease problems.

Federal agencies can respond quickly to crises or new scientific opportunities. NIAID, for example, has channeled some of its budget increases through existing contract and grant mechanisms for promising areas of tropical disease work. Malaria vaccine development supported by AID, WRAIR, and NIH has intensified, as has vaccine development for several diarrheal disease pathogens.

Federal agency programs related to tropical diseases compete within the budget track and mandate for each agency, not the entire spectrum of U.S. interests. This situation, although self-evident, periodically engenders funding or extinction crises for programs that have fallen to the bottom of a single agency's priority list, even though that program may serve constituencies or interests much wider than those usually considered by agency directors. Gorgas Memorial Laboratory, whose budget was assigned to the Fogarty International Center by Congress, does not rank high among priorities at NIH, which closed its own tropical disease laboratory in Panama in 1971 because of budgetary considerations. The military periodically compares infectious disease or basic biomedical science research programs with other health risks (e.g., drugs, chemical weapons) and makes budget decisions that have an enormous impact on military scientific careers as well as university contractors. AID projects that support tropical disease research and

training programs in international agencies often face close scrutiny from a skeptical Congress, despite the enthusiastic involvement of many scientists from other federal agencies and U.S. universities, and the many developing country institutions that participate in these programs.

U.S. RELATIONSHIPS WITH INTERNATIONAL HEALTH AGENCIES

U.S. public contributions to health and development activities include participation in multilateral agencies, through so-called regular programs (long-term programs and support of the organizations themselves) as well as through special programs of the international organizations. The Department of State, in cooperation with Department of Health and Human Services, has responsibility for representing the U.S. government's membership interests in and assessed contributions to the World Health Organization. The Agency for International Development makes decisions about funding special programs managed by WHO and UNICEF.

Generally, the U.S. contribution to both regular and special programs has increased, but it has been uneven. The U.S. government provided over 90 percent of the total contributions for the Malaria Eradication Program and has provided additional monies for community water development and medical research. The global smallpox eradication campaign has been the best known and most successful of the WHO special programs. The United States contributed \$27 million and 300 PHS employees, primarily from CDC, to the smallpox effort.

Special Programme for Research and Training in Tropical Diseases

The TDR program began in 1976 as a cooperative endeavor of several international agencies and a small group of donor countries, with Denmark and Sweden in the lead. It is a joint program of WHO, the World Bank, and the United Nations Development Programme, and it is based in Geneva with WHO, although its scientific direction and policy decisions are largely independent. A standing committee from the sponsoring agencies provides general managerial and financial direction. Government representatives from donor countries and from countries where the targeted diseases are endemic meet in a Joint Coordinating Board. A Scientific and Technical Advisory Committee selected on the basis of professional and scientific achievement sets priorities and develops TDR policies. TDR's two principal goals are:

- o Research and development of new and improved tools to control six major tropical diseases--malaria, schistosomiasis, filariasis, the typanosomiases, the leishmaniases, and leprosy; and
- o Strengthening of national institutions, including training, to increase the research capabilities of the tropical countries affected by these diseases.

In general, TDR research is goal-oriented, based upon strategies developed by 14 scientific working groups (SWGs) and their respective steering committees.

Several TDR features have contributed to its successes thus far: An ample, capable secretariat with stable leadership; some of the field's

best talent from around the world, enlisted to develop scientific objectives and award research grants; adequate budget; and flexible mechanisms for cooperation with governments, private institutions, other funding agencies, and industry. A scientific staff of approximately 30 individuals administers TDR from WHO Geneva. Over the past decade the TDR budget grew to \$25 million in 1981-82, declining to \$20 million in 1982-83. TDR has allocated \$150 million over 9 years in support of the work of 3,700 scientists in 125 countries.

The United States contributed \$20.3 million to TDR through 1984 and in 1985 was planning to contribute \$10 million more through 1989. U.S. citizens represent about 30 percent of the SWG steering committee membership of 131 individuals. As of 1984, U.S. citizens had been awarded 351 out of a total of 2,046 TDR projects, about 17 percent of the total; in dollar terms these projects represent more than the U.S. Government's specific TDR contribution since 1976.

Research

Research project awards are judged and approved by the SWG steering committees on the bases of scientific quality and relevance to the program's plans. Average award size is about \$50,000, with the more expensive projects mostly located in more developed countries. Salary support for the principal investigator is generally discouraged.

Research plans are reviewed annually by the SWG steering committees, which document progress, point out new scientific developments, and phase out less-promising areas of investigation. The SWG committees, together with TDR staff, actively promote or facilitate cooperation among groups with complementary strengths and interests. Collaboration occurs among investigators in developed and developing countries, in industry, and in other donor agencies.

Overall budget allocations are recommended by the Scientific and Technical Advisory Committee, which also reviews the quality and effectiveness of the research on the several diseases. Malaria has the highest priority among the six diseases targeted by TDR and receives the largest proportion of research funding. Drug development has focused on two new compounds. Mefloquine, discovered by WRAIR, was recently registered after field testing coordinated by TDR. Qinghaosu (artemisinin), rediscovered from a herbal remedy long known in China, yields highly active derivatives that are being safety-tested with TDR support. Immunological studies of the malaria parasite have been supported by TDR since its inception. TDR's role is increasingly that of coordinator except for aspects of the work (e.g., sexual stage vaccine) that depend on TDR support. Malaria field research includes studies of epidemiology and vector ecology as well as the appearance and spread of resistance to antimalarial drugs and insecticides.

TDR supports research on problems of common interest that affect the control of more than one disease. The program has trans-disease working groups in epidemiology, biological control of vectors, and social and

economic research. These groups stimulate research that crosses the boundaries of disease-specific research plans.

TDR research goals go well beyond the publication of scientific discoveries; useful products and technologies are the objective. Much effort is devoted to evaluating, testing, adapting, and promoting promising new tools for understanding or controlling tropical diseases. In addition to work on the new antimalarial drugs, advanced clinical trials of ivermectin for onchocerciasis with Merck, Sharpe and Dohme are proceeding, as are trials, with Merrell Dow, of difluoromethylornithine (DFMO) for African sleeping sickness. Diagnostic methods developed with TDR support include the card test for sleeping sickness and an agglutination test to be used in screening blood banks for Chagas' disease. In vector control, Bacillus thuringiensis *i.* has proven very effective against the blackfly in the Onchocerciasis Control Program.

Training

Nearly a third of TDR's budget has been spent on activities designated as training and institution strengthening. The funds are intended to help national authorities develop the capacity to carry out research and training for disease control where these diseases are endemic. The strategy is to strengthen the ability of institutions to conduct needed research. To this end, funds have been awarded to academic and government institutions in developing countries for staff

development and support and to build laboratory infrastructure. Grants are awarded for long- and short-term institutional support, courses, workshops, and degree programs, and individual training grants. Since 1976 more than \$18 million has been spent on institutional grants, and about \$10 million has been awarded to individuals for formal and informal training.

Institution strengthening is the least documented, least evaluated aspect of TDR and was expected to be a major focus of the formal evaluation scheduled for completion in 1986. Criteria for judging the productivity and effectiveness of scientific institutions in developing countries are difficult to set, because the process of establishing and maintaining a viable and productive institution in the face of severe economic problems and occasional political upheaval may easily require decades rather than a few years.

More than 48 institutions in developing countries received long-term grants in the years 1975-1983. Individual training grants, now totaling close to 400, have enabled young scientists from developing countries to obtain doctoral and master's training abroad, to learn new laboratory techniques, and to return to their home countries with some research funding in hand following long training absences. An objective has been to discourage brain drain by encouraging young scientists to remain in their own countries or region for training rather than spending several years in a developed country. Relatively few awards have been given for doctoral training.

Nearly 150 young scientists had earned advanced degrees as a result of TDR support through 1984, over one-third of them funded under research-strengthening grants.

Special Program for Control of Diarrheal Diseases

This WHO special program (CDD) with an annual budget of \$6 million, promotes the use of and assists in the production of oral rehydration mixtures to manage diarrhea episodes, and it supports epidemiologic, biomedical, and operations research related to diarrheal infections in children under 5 years of age. CDD has set the target of reducing the annual number of childhood deaths (estimated to be 6 million) by 25 percent between 1984 and 1989, primarily through increased use of ORT in countries that have implemented CDD programs. Such progress will be difficult and, if achieved, dramatic, for ORT use was estimated in 1984 to be under 5 percent in populations around the world.

Until recently, the U.S. contribution was mainly in the form of personnel; a PHS officer served as the program's director. Other major contributors include the United Nations Development Program, UNICEF, and Sweden. The program is managed by 7 full-time staff in Geneva; time is contributed from other WHO offices and regional staff. CDD's biomedical research activities are directed by steering committees for bacterial (and parasitic) enteric infections, viral diarrheas, and drug development and management of acute diarrheas. Operational research is

managed by WHO's four regional offices, each of which has organized a steering committee. By the end of 1984, nearly 200 biomedical research and about 100 operational research projects had been funded, 60 percent of them in developing countries.

Clinical management is the largest component of CDD technical training and management activities. A "comprehensive programme review" methodology for assessing national CDD programs uses a joint national-external evaluation team to collect and analyze information on all aspects of a program within three weeks.

More than 40 U.S. investigators have been active in CDD research. U.S. nationals have participated in about 16 percent of the research projects funded in the program's first four years. Several of the projects build on collaborative efforts established earlier under other auspices between U.S. institutions and those of developing countries. Research groups from Johns Hopkins University and Peru's Cayetano Heredia University are testing an attenuated live rotavirus vaccine, are studying the role of weaning foods in diarrheal disease transmission, and are conducting pathogen-specific studies. WRAIR, the University of Maryland, and Chile's Ministry of Health are conducting field trials of an oral vaccine against Salmonella typhi.

International Center for Diarrheal Disease Research, Bangladesh

The International Center for Diarrheal Disease Research, Bangladesh, (ICDDR,B) was established in 1979 under an international charter from

the government of Bangladesh. The commissioned paper by Courtney Nelson (appendix to this report) describes the center's origins and accomplishments as the Pakistan-South East Asian Treaty Organization Cholera Research Laboratory. Today the ICDDR,B stands as the only international institution devoted entirely to the study of the causes, prevention, and treatment of diarrheal disease. A professional staff of over 500, including about 20 foreign nationals, directs the work of the center.

The centre, which includes an urban and a rural research treatment center, trains researchers and health care personnel from Bangladesh and other countries. Workshops and training courses aim to improve clinical skills in the diagnosis and treatment of diarrhea and in program management and evaluation. Research working groups are organized around five areas: community services research, pathogenesis and therapy, disease transmission, host defense, and nutrition. The Matlab thana disease surveillance system has been in operation for more than 20 years; it offers rich research opportunities for studying the etiology of diarrheal diseases and their interaction with other social, cultural, economic and physiologic factors. The center is also well-equipped to conduct large-scale vaccine trials; in 1985, 65,000 persons in rural Bangladesh participated in an oral cholera vaccine trial. Preliminary results indicate that a combined killed B submit-whole cell vaccine confers a high level of short term protection against cholera.

Support for the scientific work of ICDDR,B comes from many donor countries and agencies, including AID, which contributed more than \$10

million from 1979 through 1984. Recently the institution was designated one of 11 WHO collaborating centers. Project support at ICDDR,B is obtained from a wide variety of granting agencies; however, obtaining core support for the clinical care and surveillance programs is a recurrent problem.

INDUSTRY

U.S. pharmaceutical companies are this country's largest repository of talent and infrastructure required for the development, testing, and marketing of new drugs and vaccines. While the industry employs many researchers in development of antibiotics and antivirals that might be widely applicable, it employs very few who concentrate their efforts on the infectious diseases that occur predominantly in the developing countries.

Most of the research and development for new drugs to treat parasitic diseases is concentrated in the European laboratories of multinational pharmaceutical companies. (United Nations Development Program, World Bank, and World Health Organization, Special Program for Research and Training in Tropical Diseases, 1983). Lepetit in Italy, Hoechst and Merck in Germany, Wellcome, Beecham, and S. Ross in Britain, Janssen in Belgium, and Roche and Ciba-Geigy in Switzerland were among firms invited to send representatives to a TDR meeting concerned with drug development and testing. In the United States the larger pertinent

efforts are located in Sterling-Winthrop, Merck, Pfizer, and Warner-Lambert/Parke-Davis and Smith Kline & French.

Some of these companies long have been involved in tropical disease drug research. Parke-Davis began parasitology work in 1935, concentrating on malaria, and after World War II expanded its efforts to other parasitic and bacterial infections of the tropics. Through the 1960s it invested about \$16 million, about 10 percent of its total research and development budget, in antiparasitic research. During the 1950s and 1960s the company developed and marketed 7 different drugs for malaria, 1 for leishmaniasis, and 2 (a sulfone) for leprosy. This research was scaled down during the 1970s, when some activity on malaria and schistosomiasis continued with support from WRAIR and the Clark foundation. The Brazilian affiliate of Johnson & Johnson set up a research insititute in Sumare to conduct research on indigenous diseases. Subsequently the company helped in the development of mebendazole, a treatment for schistosomiasis (Pharmaceutical Manufacturers Association, 1984).

Merck, Sharp and Dohme, is working on filaricides. Smith, Kline, and French, is working on malaria chemotherapy and a malaria vaccine. Burroughs-Wellcome, in North Carolina, is working on malaria chemotherapy. Merrell Dow is working on African trypanosomiasis.

A 1979 conference (Institute of Medicine, 1979a) explored the scientific opportunities, research and development issues, and market incentives for the pharmaceutical industry in development of products to treat and control infectious diseases in the tropics. The report that followed (Institute of Medicine, 1979b) notes decreasing drug

to increasing costs and time needed to bring therapeutic compounds through testing for toxicity and efficacy. Perceived regulatory barriers, market limitations, and inadequate patent protection further discourage companies from targeting their efforts on drugs for tropical diseases. Further, many countries require clinical tests to be conducted with their own populations prior to licensing and marketing approval. The report also noted lack of a formal policy or mechanism within the U.S. government to facilitate or encourage the development of drugs for developing countries through targeted research by some combination of industry, academia, and Federal agencies.

The situation does not appear to have changed much in the last few years, despite passage of an Orphan Drug Act and establishment of programs to encourage small businesses to invest in research and development for biologics (U.S. Congress, 1985). This committee did not attempt to survey efforts of U.S. firms to develop and test new drugs for tropical diseases. In conversation with the committee, pharmaceutical company personnel maintained that the industry faces powerful disincentives to substantial new investment in development of antiparasitic compounds. Several companies have small units that are active in clinical testing or marketing of promising new drugs, and these examples are described below. For the most part, however, the new compounds that have recently emerged represent the fruit of research conducted more than a decade ago; they represent no assurance of a continuing trend.

In the last two decades more than half the U.S. vaccine manufacturers ceased vaccine production, and now many vaccines have no more than one producer (Institute of Medicine, 1985b:46). Disincentives to vaccine innovation and production were reported to include "complexity of development, production, and quality control"; "cost of research and development in relation to anticipated sales"; "perception that vaccines . . . have received less effective patent protection"; and "apprehension over the liability situation" (Institute of Medicine, 1985b:7). Export sales for vaccines manufactured in the United States are small, compared with foreign drug sales, because many governments subsidize vaccine production (Institute of Medicine, 1985b:34).

Given the current uncertainties about vaccine manufacture, few U.S. companies are participating actively with the government to develop and test vaccines with potential for reducing the communicable disease burden in developing countries. An early malaria vaccine candidate developed by WRAIR and NIH is being produced by Smith, Kline, and French.

Several promising new drugs for parasitic diseases have emerged from collaborative work sponsored by academia, multinational pharmaceutical companies, government agencies, and WHO. International cooperation of this type will become increasingly important to assure that potentially useful compounds initially developed for veterinary use or cancer treatment will receive evaluation for tropical diseases.

These experiences illustrate roles of multinational pharmaceutical companies, including U.S.-based firms, in the development and testing of new antiparasitic drugs:

- o Praziquantel: Collaborative work beginning in 1968 between Bayer (Germany) and E. Merck/Darmstadt concentrated on compounds active against schistosomiasis. Initial clinical trials were conducted by the London School of Hygiene and Tropical Medicine and the Schistosomiasis Research Unit in Belo Horizonte, Brazil. Later, intensive clinical trials were conducted in Zambia, Brazil, Japan, and the Philippines, with some coordination from WHO (especially in Brazil). This work found the drug safe for humans.
- o Mefloquine: This compound was one of many synthesized by the Walter Reed Army Institute of Research antimalarial drug program. Phase I, II, and III clinical investigations by WRAIR over the next four years demonstrated the promise of the drug for treatment and prophylaxis. In 1976, the TDR, the U.S. Army and Hoffman-LaRoche initiated a collaborative effort for further development. WRAIR and Hoffman-LaRoche conducted additional drug trials. Then TDR organized additional Phase I, II, and III clinical trials in Brazil, Zambia, and Thailand. TDR and Hoffman-LaRoche have worked together to establish clinical guidelines for use of the drug formulations, marketing, and distribution in ways intended to delay the spread of parasite resistance as long as possible. By 1985 mefloquine was registered for use in adult males only, with use in women and children expected shortly. (Behrman, 1980; A. Lucas, personal communication; TDR/JCB(7)84.7, 1984)
- o Difluoromethylornithine: In 1977 a Merrell Dow (Cincinnati) researcher met a Pace University faculty member (Cyrus Bacchi) at a Gordon Research Conference, where he learned about a compound from a Dow cancer screening program that showed remarkable activity against African trypanosomiasis in mice. Then a TDR grant awarded in 1978 to Bacchi led to further collaboration between Merrell Dow and Bacchi. By 1985 early clinical trials of DFMO were carried out in Africa, where the drug's low toxicity and rapid action apparently led to surprising recoveries of comatose patients (A. Lucas, personal communication; Altman, 1985).
- o Ivermectin: This compound is a derivative of avermectin B, a lactone produced by an actinomycete. It was first discovered in the fermentation broth of a culture sent by the Kitasato Institute in Japan to investigators at Merck, Sharp & Dohme

Research Laboratories, Rahway, N.J., who were engaged in an intensive search for natural products with antihelminthic activity. The first activity was demonstrated against dog heartworm and *Onchocerca microfilariae* in horses, and subsequently against nematodes and arthropods. (Campbell, et al., 1983). Merck and the TDR program are collaborating in the development of ivermectin as a microfilaricide. A research center in Ghana in collaboration with the Liverpool School of Tropical Medicine is conducting Phase III clinical trials with the drug as a treatment for onchocerciasis.

WHO did not take an active role in the development and testing of new therapeutic agents until relatively recently. Officials at the organization now realize that market forces do not provide sufficient incentive for pharmaceutical companies to develop new antiparasitic compounds for commercial sales. Accordingly, WHO has revised its patent policy for new pharmaceutical products. The general objective is now to make available to developing countries and to the wider public sector products conceived or developed under WHO auspices. A second important objective is to make product development commercially attractive, so that at least the costs of research and development can be recovered.

Full disclosure and publication of discoveries was originally contemplated, but then it was realized that commercial exploitation would be discouraged. In 1982, a flexible patent policy was adopted, allowing for various arrangements between WHO and public or commercial enterprises. Basically, the specific arrangements will be decided case by case. WHO can decide to obtain patents or inventors' rights in patentable health technologies where such rights are necessary to ensure development of the new technology, or such rights can remain vested in the commercial enterprise, with a specific agreement on conditions under

which WHO can promote the product or make it available.

(TDR/IMMAL/SC/IND/83.3 1983.)

In October 1985 Senator Orrin Hatch reintroduced a bill that would, among other provisions, allow the export of drugs not approved by Food and Drug Administration to developing countries if they were for the treatment of tropical diseases. (Sun, 1985) Such legislation might help to make drug development for tropical diseases more attractive to U.S. companies, especially the smaller biotechnology firms, by removing a regulatory obstacle.

Diagnostic tests are another area in which U.S. companies could make an important contribution to tropical disease control. Currently, however, the major impetus, albeit on a modest scale, for development of diagnostic tests has come from federal agency efforts.

The U.S. military has begun a program to develop rapid and simple diagnostic tests for a range of tropical infectious diseases that may threaten military personnel. AID has initiated a program to develop field kits for diagnosis of malaria, diarrhea, and ARI. Many small biotechnology firms in the United States have both the capability and interest to develop these tests, but they require support and incentive for these endeavors. Because there is no identifiable market in the developing world that can afford these important tools, a different set of incentives or guarantees will need to be built into the research and development systems for diagnostics if the private sector is to play an active role.

FOUNDATIONS

The work of private, philanthropic foundations in tropical disease research and control has had more impact than their modest cumulative financial contributions to the field would suggest. Earlier, this report noted programs supported by the Rockefeller and Clark foundations and more recently by the MacArthur foundation. These institutions, together with others, have provided imaginative leadership, sustained support, often financial leverage, and recognition to work on a set of problems that fall outside the mainstream of American medicine.

Today, only the Clark foundation retains the title Tropical Diseases for its program in this field. The Clark program targeted schistosomiasis and now focuses on trachoma and onchocerciasis. The Rockefeller foundation campaign against the Great Neglected Diseases is supported within its health sciences division. The MacArthur foundation, a younger organization, has chosen to launch a carefully structured program in molecular parasitology research. These programs typically define a particular area and facilitate communication and collaboration among scientists from the United States and developing countries. They also seek to stimulate interest in a particular problem area by talented investigators from outside the field, by offering incentives and even by brokering collaboration between groups.

NOTES

¹These are approximate estimates derived from fiscal year 79-83 figures of NIAID expenditures for the Visiting Fellow and Associates Programs. "Developing countries" included Argentina, Bangladesh, Brazil, India, Korea, Lebanon, Peru, Sierra Leone, and Venezuela. Source--Dr. Karl Western, NIAID.

CONCLUSIONS AND RECOMMENDATIONS

This report states the results of the committee's examination of U.S. capacity to deal with tropical diseases. Is this country's biomedical research, clinical, and public health expertise in tropical diseases sufficient to meet its needs and concerns at home and abroad? Are recruitment, training, career structures, and collaborative work adequate to maintain a reservoir of competence? Are they sufficient to strengthen health and biomedical research institutions in the developing countries?

The committee found the concerns that led to its study to be well warranted. Despite a wide array of U.S. interests and involvements, tropical health is outside the mainstream of U.S. health concerns, the maintenance of competence in tropical diseases tends to be taken for granted, and the state of the field is seldom assessed.

Tropical diseases continue to be major world health problems, causing millions of deaths, especially among children, and many more cases of sickness each year. The burden is felt most directly and most heavily by the less-developed countries. In interacting cycles, disease incidence increases with population growth, poverty, and social

turmoil. For strong reasons of risk of disease, of humanitarian concern, and of international security, the United States shares an interest in reducing this burden.

Reliable information on the prevalence, incidence, and distribution of infectious disease pathogens is not available in most developing countries. Special surveys, conducted for a single region, and prospective etiological studies have permitted inferences about the public health implications of specific disease problems. Routine surveillance of communicable diseases for disease control or planning purposes is rarely maintained; lack of trained epidemiologists and lack of diagnostic facilities are major problems.

The trends toward control of these diseases are unclear; the reports are mixed. Malaria is resisting the standard drugs and control measures in many areas of the world; cases are increasing especially in Latin America and Africa. Filariasis, schistosomiasis, and leishmaniasis infections may also be increasing as irrigation and jungle-clearing activities bring more people into contact with disease vectors. Clinical symptoms resulting from these parasites often develop years after the initial exposures, producing disability or requiring costly hospitalization. Vaccine-preventable diseases are decreasing in many areas; the international donor-supported childhood immunization programs are reaching larger proportions of the population and monitoring of coverage is improving. Diarrheal infections still account for much of the serious illness among babies and small children, but oral rehydration programs have reduced the number of deaths from diarrhea.

More epidemiologic studies are needed to assess the extent of the disease burden and identify population groups at greatest risk of acquiring tropical diseases. Disease-control programs can have an impact if given adequate national priority and funding.

The prospects for scientific progress are encouraging. New drugs show promise in dealing with schistosomiasis and onchocerciasis. The new biological techniques offer hope for new vaccines and diagnostic methods.

These advances could revolutionize approaches for disease surveillance, especially in inaccessible rural areas. Finger-prick quantities of blood, collected on filter paper, can now be stored and sent to a central diagnostic facility, or in some cases processed for diagnosis in the field. Heat-stable vaccines, a research priority, could multiply protection from communicable diseases.

Scientific and technical competence in tropical disease research, medicine, and disease control are growing in the less-developed countries, although slowly. Developing-country researchers are acquiring formal training in the biomedical sciences at a fast rate, but opportunities and facilities for them to apply their skills are often lacking. Collaborative research programs with U.S. and other developed-country institutions are essential to a solid human resource and institutional base for tropical disease work.

The United States has not been working alone to control tropical diseases. Several of the Scandinavian and European countries have supported tropical disease research and control programs with

relatively large proportions of their foreign assistance budgets, including initial critical support for the Special Program on Tropical Disease Research and Training, based at the World Health Organization. The World Bank, the United Nations Children's Fund (UNICEF), and other international donor agencies have contributed financially to research and/or disease-control measures; many of their programs now consider infectious diseases as major impediments to human resource development. National leaders in the developing countries are increasing their support for health measures. Still, there are areas where half the children do not survive to school age and where infectious diseases produce chronic health impairments in adults, making economic and social progress and self-sufficiency goals yet more distant.

Among U.S. interests in reducing the incidence and impact of tropical diseases are the following:

- o The health of this country's population, its travelers, diplomats, and armed forces, in a time of increasing international trade and travel.
- o Scientific advancement likely to be realized in immunology, molecular biology, and other disciplines from the study of such tropical pathogens as trypanosomes and schistosomes.
- o Humanitarian interest in reducing morbidity and mortality and in alleviating suffering.
- o Increased international security that would result from economic and social progress.
- o Insuring against sudden, costly need to rebuild U.S. international health capacity, a task requiring five to ten years.
- o Poor health inhibits development, and development of other countries is important to the U.S. for economic, social, and political reasons; the still-widening gap between the developed and the developing countries should not increase.

In meetings in the United States and overseas and through surveys, statistical analyses, interviews, staff investigation, examination of technical, administrative, and policy reports, and a commissioned review of experience with collaborative tropical health research endeavors, the committee sought a fresh census (the first in a quarter-century) of the field. Who and where are the researchers, clinicians, and public health and disease control specialists? How are they trained? Are there enough of them? What do they do? What might contribute to their effectiveness in meeting long-term goals of advancing scientific knowledge, strengthening indigenous research capabilities, and reducing the infectious disease burden in developing countries? What, where, and how adequate is the institutional base?

The numbers were difficult to obtain. U.S. capacity to deal with tropical disease problems of the developing countries is spread among private and public agencies, national and international, and is to be found in a variety of disciplines. It is the purview of no single institution or professional organization.

The number of persons who can be characterized as U.S. tropical disease specialists, with research, clinical, or public health skills, is low--less than 2,500. Comparable data from the past are unavailable. Most U.S. tropical disease specialists are in research, fewer in public health and disease control, far fewer in clinical work. On the whole, the population of U.S. tropical health specialists is not an aging one. However, the committee noted that broad based knowledge and specialized training in clinical research on tropical diseases is

increasingly lacking in the younger age cohorts, who are more likely to have a narrow biomedical research specialty.

Generally, except for several important areas of the field, the population of specialists is being renewed, and its age distribution is the same as that of the broader U.S. scientific community. The number, however, is not expanding, nor does it represent career commitments. Although the total may be relatively steady, the wealth of experience brought to this field by veterans of major campaigns against communicable diseases worldwide is irreplaceable. Individuals are entering and leaving the field at various ages and for a variety of reasons, including employment opportunity or its lack. Opportunity for clinical and research apprenticeship with preceptors who have extensive experience is declining. Recruitment lags in several research areas including vector taxonomy, mycology, and malacology, all important in tropical health studies. More than half this country's tropical health specialists are employed by universities and nearly a third by government (including the military). Few are in industry. Most U.S. research in tropical diseases is sponsored by the federal government; little is supported by industry. Several private foundations make a unique contribution, important not so much in relative dollar volume as in catalytic effect.

The committee identified eight U.S. universities that have substantial programs in tropical disease research, tropical medicine, and tropical health. In addition to these major centers, perhaps seven additional academic institutions have large commitments to tropical disease research and training. Federal agencies--especially the Centers

for Disease Control, the National Institute of Allergy and Infectious Diseases, the Army, and the Navy--are engaged in tropical health research and in training of specialists for research or other work in tropical health. U.S. opportunities for clinical training in tropical diseases are not widely available. Direct experience obviously is more likely to be gained where these diseases are endemic. Collaborative activities that would foster such training, giving U.S. specialists and their colleagues the chance to learn from each other, are few.

The United States probably has fewer than 300 clinical specialists in diagnosis, treatment, and study of tropical infectious diseases, and the ability of U.S. diagnostic laboratories to recognize tropical diseases should be strengthened. The role of the laboratory is often very important in the diagnosis of any infectious disease. In the event of a rise in the prevalence of tropical diseases in the domestic population, the need for well-trained and knowledgeable laboratory technicians and clinicians will increase.

The committee found it more difficult yet to judge the adequacy of these resources and programs against concrete measures of need, disease trends, incidence, or prevalence. There is no benchmark against which to compare current programs and numbers of people. The conclusions here are unavoidably judgmental. Nevertheless, the committee is convinced that the United States could have a greater impact on the burden of infectious diseases, that doing so is in the national interest, and that neglect of the state of U.S. resources in tropical infectious diseases may be very costly.

The U.S. biomedical research base for dealing with tropical diseases is substantial but needs stronger collaborative research and training

Infectious Diseases, for example, has consistently supported tropical disease research, and institute administrators have demonstrated creativity and flexibility in promoting previously neglected areas as well as scientific opportunities. However, the absence of a specific mandate to fund applied research primarily relevant to diseases of developing countries as well as budgetary considerations have limited the impact of the institute's programs. Support for research training lags behind support for research. Younger scientists find it difficult to broaden their skills and experience in tropical disease research.

Current U.S. career structures in much of this field are unstable, heavily dependent on otherwise unrelated Federal financial and personnel policies. The number of U.S. tropical health specialists who are broadly trained in science, medicine, and public health and disease control and who have direct experience in dealing with these diseases in the less-developed countries need not be large. But this country must ensure that such people are available.

The importance of international collaboration to U.S. capacity to cope with tropical disease problems is very great. Only through collaborative relationships in research and training in biomedical science, clinical work, and public health and disease control will U.S. specialists develop the first-hand experience they need, to be able to contribute strongly to disease treatment and prevention. The right kind of collaboration can assist in building health institutions and self-sufficiency in the developing countries. It is an investment both in reducing the disease burden and its consequences and in building

flexible, collegial, worldwide networks of cooperation in detection, surveillance, treatment, and control of communicable diseases. Collaboration is essential to the most efficient and economical use of resources to maintain U.S. capacity in tropical health. It could also become the price that the United States must pay to be able to conduct research where tropical diseases are endemic.

The United States can and should contribute more to training and development of foreign competence, particularly in research and in disease monitoring. The infrastructure necessary to effective work against these diseases is too often lacking in the developing countries. Not only are diagnostic equipment, supplies, and pathology reference materials needed; diagnostic talent must be attracted and retained. Health science and technology require sustaining infrastructure.

In considering the U.S. capacity to deal with tropical diseases, the committee examined several specific components it believes are integral to sustained or accelerated progress:

- o support for basic and applied research
- o development and testing of new preventive, therapeutic, and diagnostic technologies
- o career structures for tropical disease specialists
- o capacity to train U.S. tropical disease specialists and those from the less-developed countries research and public health service
- o development of disease surveillance capabilities
- o strengthening institutional capabilities in developing countries

- o flexible, responsive administration of programs and activities to avoid unnecessary duplication, to maximize efficient use of resources, to minimize gaps and imbalances, and to meet needs of individual countries--including the United States.

By these criteria, U.S. capacity is barely adequate, but with improvements in policies and modest additional funding could make a substantially stronger contribution.

RESEARCH AND TRAINING

Tropical disease research, like many rapidly advancing fields in science, is international. The diseases and their impacts cross many national boundaries. Progress in research depends on communication, cooperation, and collaboration among scientists from many nations. Research institutions recruit scientists from around the world, and students seek placements in accord with the concentration of talent in areas of their interest. The United States has maintained a favorable climate for basic research on tropical diseases, and it has attracted able scientists from other developed and developing countries.

In most of the world, national research budgets typically accord relatively low priority to tropical diseases. The United States supports more than half of the world's biomedical research, by some estimates, including work on infectious diseases.

U.S. capacity to conduct basic biomedical research on tropical diseases corresponds closely to availability of funds. Disciplines in

the forefront of the biomedical sciences--molecular biology, biochemistry, and immunology--have attracted funding. Other specialties, traditionally associated with tropical medicine and public health, have lagged in research-funding competitions. Fewer individuals are applying for ecological and field research positions; universities have not been hiring many vector biologists, taxonomists, and parasitologists.

The committee discerns disproportionate emphasis on laboratory research, in contrast to field research that takes advantage of improved epidemiological techniques and developments in social science methodology.

Clinical research is an area of concern. Training and career opportunities are scarce, and long lead times are required to produce clinical specialists with the requisite experience in the tropics. The committee therefore suggests that the Department of Health and Human Services establish a physicians' fellowship program in clinical research on tropical diseases for physicians trained in the United States. Such a program would be consistent with the department's domestic responsibilities for public health protection. Competitive awards should be made to three U.S. medical schools for developing collaborative programs with counterpart institutions overseas. U.S. residents, together with young physician trainees from developing countries, would spend one or two years at the collaborating institution working under the supervision of at least one U.S. faculty member and local faculty colleagues in clinical care and research. Such programs would be best

undertaken where other collaborative research and field programs are in place and should be undertaken with long-term commitment in mind, to build a foundation of trust and confidence.

Training is underemphasized. Basic and applied research and research training capacities in this country represent the strongest component of total U.S. efforts related to tropical diseases. However, research training and career development in several fields need to be strengthened significantly in order to maintain an appropriate balance between field and laboratory-based research.

Active intervention is warranted in order to maintain at least a minimum level of expertise in vector ecology and infectious disease epidemiology, which have fared poorly in the competitive grants process and have received relatively little Federal support. Lack of adequate support for field investigations of tropical disease pathogens and their interactions with human hosts and vectors will impair the ability of U.S. scientists to work collaboratively with scientists from developing countries and will handicap the United States in a critically important area of defense against tropical diseases.

Several federal agencies have interests in maintaining national expertise. An efficient way to build expertise in vector ecology and infectious disease epidemiology would be the establishment of a jointly funded program, managed by one agency, of at least 10 career development fellowships in tropical vector ecology and 10 in tropical infectious disease epidemiology for junior faculty in U.S. universities. Such a program should provide incentives and support to academic institutions

to create faculty positions for individuals whose scientific interest is the study of arthropod vectors and snail intermediate hosts in endemic settings or in developing better approaches for the collection of population-based data on infectious diseases.

A seemingly entirely new disease--Acquired Immune Deficiency Syndrome (AIDS)--adds considerable weight to arguments that it is imperative for the U.S. to maintain a cadre of individuals capable of carrying out epidemiologic and clinical studies under conditions prevailing in tropical countries. This disease, while first described in the United States in the early 1980s, appears to have existed in Central Africa at least at that time (probably much earlier) and may have arisen by transfer of the etiologic agent (a virus) to man from a non-human reservoir. Cases have now been reported from over 100 countries and initiation of a major WHO program attests to the current and future problem it poses. A large number of questions remain to be answered in the pursuit of control and treatment, many of which may be best addressed in tropical countries.

Restrictions of full-time employee equivalent position authorizations in research training fellowships unnecessarily limit training opportunities for U.S. scientists at the National Institutes of Health. These constraints affect U.S. scientists more than foreign nationals, who are afforded some protection under other programs. Limitations imposed by head counts are an inadequate substitute for budgeting and administration to ensure optimal mix and scope of research

training in relation to funds, space, and supervision available.

National Institute of Allergy and Infectious Diseases research training fellowships for investigators working on problems related to tropical diseases are much more likely to accomplish their purposes if not counted against the full-time authorization ceiling.

The social sciences represent disciplines and skills much needed and underused in tropical disease research and control. Investigators trained in health economics, medical sociology, medical anthropology, health, psychology, and health education have demonstrated their ability to participate in tropical disease research and intervention (i.e., clinical services, prevention, control, eradication) programs and projects.

The potential range of sociomedical work is broad. Three areas especially need attention: Disease-transmission research, including descriptive study of human factors that influence transmission, and collection of data for modeling studies; baseline and continuing studies of the consequences (economic and psychosocial) of disease and of continued transmission; and intervention studies, including assembling of sociocultural, ecological, and other background data, research on potential for community involvement in control or other interventions, studies of planning, ethical issues, policy-making, operations, monitoring and project evaluation, and research and planning for health education.

Operational studies of disease-control programs contribute to our

knowledge about the administrative, economic, and cultural factors that contribute to successes and failures. In the committee's opinion, the Agency for International Development would find it useful to increase its involvement of U.S. social scientists in research programs related to communicable disease control.

Training Capacity

Eight U.S. multidisciplinary centers associated with schools of medicine and/or public health offer specialized training in tropical medicine and tropical public health. Four have concentrations of 30 or more tropical disease specialists. Only one has more than 50 faculty members full- or part-time in tropical health work. Large, multidisciplinary centers of excellence are essential for training clinical and public health specialists in tropical disease problems and in contributing to technology development. Size and diversity do not appear to be as crucial for sound doctoral programs in the biomedical sciences.

In the committee's view, at least four centers--each with participation of at least 60 faculty members from a broad range of health and social science disciplines--are needed to sustain a core of U.S. expertise and leadership to deal with tropical disease problems. This judgment assumes that Federal career positions are unlikely to

increase, that up to 50 percent of the faculty will be traveling or residing abroad at any one time, that mechanisms will be found to enlist academic personnel in the activities of government agencies, and that a larger number of smaller programs will continue to coexist and cooperate with the larger centers. Institutional support to academic groups of tropical disease investigators in the United States should be increased and clinical and public health as well as biomedical aspects of problems selected for study should be encouraged. The National Institute of Allergy and Infectious Diseases already supports a program Tropical Research Unit that promotes faculty career development and research on tropical diseases, but it supported only three university groups in Fiscal 1985. Strengthening and expanding the range of interests at existing centers would be an appropriate place to being. The Committee recommends increasing both the size and number of National Institute for Allergy and Infectious Diseases Tropical Research Unit awards over the next five years. These awards facilitate postdoctoral training, tropical disease research, and collaboration abroad.

The Public Health Service and the Department of Defense maintain research and training establishments. With the exception of the Uniformed Services University of the Health Sciences, however, none is a center that provides clinical training, confers a public health degree, and offers biomedical research training. Most of the tropical disease research and training conducted directly by Federal agencies does not duplicate that provided by academic institutions and cannot easily be conducted by academic institutions. Interests and activities of both are complementary and interdependent.

NEW TECHNOLOGY

The application of new approaches to the study of tropical diseases could produce an array of preventive and therapeutic agents as well as better tools for the study of disease transmission in populations. Promising new approaches in chemotherapy include use of antimetabolic drugs, specific to a particular parasite's metabolic pathways; creation of large, hybrid molecules that reduce toxicity and enhance the efficacy of compounds developed as antiparasite drugs; and targeting drugs by attaching carrier antibodies that recognize and attach to a particular parasite. Vaccine development may increasingly employ synthetic antigens and adjuvants, or viral subunits and liposomes. Peptide sequences corresponding to the protein molecule covering the virus have been synthesized and have produced immune responses to hepatitis B in rabbits. Monoclonal antibodies will be used in a variety of diagnostic techniques that are highly specific to parasite stains and that can be used with squashed and dried mosquitoes as well as blots of blood on filter paper. Monoclonal antibodies might also be used in reverse; instead of targeting the pathogen, anti-idiotypic monoclonals might mimic the antigen and replace it for vaccination purposes. Certain immunization procedures elicit specific antibody responses, some of which could be used to trigger a protective immune response before the parasite has altered its outer coat or changed to the next life stage.

Technology development has become an expensive, complex process, on a scale much larger than is usually found in academic institutions.

Bioprocess engineers and multidisciplinary teams are a prerequisite for scaling up production of a new vaccine, drug, or diagnostic test. With appropriate support and incentives, the nation's emerging small biotechnology firms could operate more prominently within the field of tropical diseases. Links to academic centers might be especially desirable; most new firms lack knowledge specific to tropical pathogens. At the same time, the nature of new relationships between universities and industry is the subject of uneasiness. The obligations of each must be clear and acceptable to both sides.

Private companies in Europe and Japan and the overseas offices of multinational pharmaceutical corporations increasingly dominate in bringing new products through the developmental and clinical testing phases to a commercial marketing stage. The World Health Organization also has demonstrated potential for leadership in this area, especially for products that have no apparent commercial market.

U.S. capacity for new product development and testing is severely limited by forces and trends beyond the field of tropical diseases, by lack of obvious commercial incentives for many drugs and diagnostics, and by regulatory and logistical barriers. Officials of developing countries may be wary of authorizing clinical tests without obvious benefit to the participants. Possibilities for remedial action include more direct Federal funding of developmental research, Federal sharing of product development risk, and Federal assistance in logistical arrangements for clinical and field testing. Development of a malaria

vaccine will certainly require such intervention from the U.S. Government. Some of these steps already have been taken.

An additional limiting factor in the role assumed by the United States in developing and testing new technologies is the lack of overseas clinical research and training opportunities for U.S. physicians. Clinical trials of new drugs and vaccines in developing countries require active participation and management from local institutions and government authorities. Training in clinical research methodology is also essential; the Rockefeller Foundation's clinical epidemiology training program is building such expertise in several developing countries. When long-term collaborative relationships of trust and understanding have been established well before the development of a technology, plans for a clinical trial can be made rapidly and the trial carried out expeditiously.

Problems of development of diagnostics, drugs, and vaccines require sustained attention.

CAREER STRUCTURES

The committee found no stable career structure for tropical public health and disease control specialists in the Federal Government, with the possible exception of the military, which has its own personnel policy problems in this regard. Although the military is an important reservoir of tropical health talent, its personnel slots, too, are

subject to classification changes, the raison d'etre of overseas laboratories is the subject of occasional controversy, and change in assignment may be a condition for higher rank. Nor, in times of financial trouble in the public sector, is there promise of reasonably stable careers in research and teaching.

Extraordinarily rewarding in an ethical sense, work in tropical health has undeniable drawbacks of frustration, health risks, loneliness, inadequate resources, limited job opportunity, and having to work apart from conventional reward structures.

Small already, the field is unusually vulnerable to adverse effects of Federal financial and personnel policies stemming from Government-wide budget considerations rather than from any specific consideration of tropical health or of U.S. weaknesses in the field. The result has been erosion of the possibilities of sustaining and expanding a cadre of sufficiently experienced Federal tropical health specialists.

Personnel ceilings established for all Federal agencies and limitations on the numbers of Federal employees stationed abroad diminish opportunities for long-term research and training where tropical diseases are endemic. The current supply of Federal employee specialists in tropical diseases is barely sufficient to sustain continuity in research programs, diagnostic services, and short-term technical assistance missions overseas. Federal agency positions for personnel engaged in tropical disease research and control should not be reduced further; they should be expanded.

Academic institutions are structured to support research careers, and individuals whose talents are more in the administration of disease control programs, applied epidemiology, or clinical practice and teaching do not receive priority in hiring or promotions. Few academic institutions can support faculty members who spend several months each year working in the tropics and who wish to maintain their ties to the university during years abroad. Only those universities with the largest concentrations of faculty and diverse funding resources can afford to maintain career positions for a multidisciplinary group of tropical disease specialists.

The private consulting firm or research institute that employs tropical disease specialists may increasingly provide career opportunities, although not stability. The financial base for such organizations may be exceedingly narrow, and individuals are employed only when a government contract is won. Private firms are often established in close physical proximity to university centers to facilitate relationships with faculty members, and one effect may be to draw attention of faculty away from their primary commitments.

The career structures similarly are shaky for tropical disease specialists who have skills in public health and infectious disease control. Demand and supply do not always match, and program budget increases do not guarantee availability of required personnel or career positions. The nation's ability to mobilize trained personnel when needed, when it has not maintained an adequate permanent base of Federal employees is of obvious and crucial concern.

Several options might ease this situation somewhat. Each involves temporary assignments or exchanges of tropical disease specialists among Federal and state agencies and academic institutions, but not necessarily at the cost of budget increases. Federal agencies with responsibilities for tropical health programs should seek ways to develop a national framework for career service in tropical disease work. Several mechanisms already exist for personnel exchanges, but they are not linked to tropical disease specialists.

The long-term objective of any career initiative should be to create a network of institutions both in the United States and abroad that would host visiting tropical disease specialists with limited assignments from participating U.S., foreign, and international agencies. Such assignments would increase the usefulness of private, state, and academic scientists to Federal programs and vice versa, while broadening their skills and contributing to competence in the agencies. Mechanisms to be explored or expanded include:

- o A competitive program using positions exempt from Federal ceilings.
- o A fellowship program administered by a national scientific association.
- o Contractual service agreements with selected universities.
- o An improved mechanism for joint career assignments by universities and the Agency for International Development. There is a well-established program between land-grant colleges and the Agency for International Development in the agricultural sector.
- o Increased consideration, in service-project contracting, of potential for building long-term academic and governmental capacity to address tropical disease problems.

DISEASE SURVEILLANCE

Disease control is linked inextricably to disease surveillance. Knowledge of disease incidence, prevalence, seasonal variations, transmission patterns, and distribution in populations, is essential to development of disease control strategies, whether for a country, region, or continent. Reliable surveillance data for most tropical diseases are lacking, as are adequate epidemiologic surveillance methods and epidemiologists to test and use those methods. Reference laboratories for a wide range of bacterial, viral, and parasitic organisms are lacking. So are skilled diagnostic staff in many countries, which makes confirmation of suspected outbreaks of communicable diseases more difficult. Moreover, governments may be sensitive about dissemination of data on problems that might have been preventable.

The United States possesses the world's largest number of well-trained epidemiologists and could, were opportunities expanded, exercise global leadership in training epidemiologists and assisting in the development of reliable surveillance systems for tropical diseases. The Global Epidemic Intelligence Service training program of the Centers for Disease Control has led to increased disease surveillance capability in several tropical countries and should be expanded.

The Department of Health and Human Services should establish a program to assist developing countries in improving the quality and increasing the number of overseas reference laboratories capable of

diagnosing tropical disease pathogens. The program should include short-term training, provision of reagents and equipment on a limited basis, and quality control arrangements. Currently, the Centers for Disease Control assist developing countries when requested, but the Public Health Service does not have the budget to establish such a program on its own. Universities and private companies also have much relevant experience but no mechanism exists to tap this expertise.

STRENGTHENING CAPABILITIES OF DEVELOPING COUNTRIES

Research capabilities in many developing countries have increased significantly over the past two decades. U.S. Government and academic institutions have contributed substantially in terms of graduate and postdoctoral training, generating a wide network of professional and personal relationships that have continued long after the formal training. Many more U.S. scientists would like to maintain links with former trainees or visitors from abroad but lack the opportunity.

In developing countries, most institutions with responsibilities for tropical disease research and control suffer chronically from outdated or non-functioning equipment and lack of resources to carry out studies. Many of their investigators have received graduate training in the United States and Europe. Some are able to maintain collaborative relationships with U.S. academic institutions, but their ability to

obtain funding for collaborative research is limited by the small numbers of donors interested in collaboration in applied and field research. The institution-strengthening program of the international Special Program for Research and Training in Tropical Diseases supports some centers in less-developed countries. They are few in comparison to need, and the quality of much of the research could be greatly improved by strong collaborative relationships with institutions in industrialized countries.

Some developing countries have established considerable infrastructure for research on communicable diseases and can take better advantage of U.S. resources that are already available. An unusual and outstanding case is Thailand which has: A Centers for Disease Control epidemiology training unit in the Ministry of Health; links to the Rockefeller Foundation's Great Neglected Diseases and Clinical Epidemiology programs; support for research in universities, in the form of several grant awards from the Office of the Science Advisor of the Agency for International Development and the Research Grants program of the Board on Science and Technology for International Development; and a U.S. Army unit (of the Armed Forces Research Institute of Medical Sciences) that does communicable disease research. In countries like Thailand, local authorities are well trained and for the most part equipped to make their own decisions about control program needs. U.S. resources can make an important difference in certain areas, however, provided that there is flexibility in their use. For example, a

national advisory board has been established for control of communicable diseases. This board represents an important step in consolidating progress toward developing an epidemiologic surveillance system, strengthening laboratory infrastructure, and improving local training programs.

Collaborative programs that combine research and training (not necessarily degree-granting) components are the most appropriate ways for the United States to assist in strengthening capabilities of developing countries to deal with tropical disease problems. This conclusion is based on several observations. Trained scientific and technical personnel in developing countries are more numerous than before, and many are now receiving graduate training in their own countries. U.S. institutions clearly benefit from collaborative relationships in terms of field research and training opportunities. Institutions of the less-developed countries also benefit enormously from participation in collaborative research programs, provided that relationships have continuity and generate scientific opportunities for both sides. Formal U.S. academic degree programs are not always appropriate to needs and conditions in developing countries. Substantial resources are not likely to be available in the future from U.S. donor agencies for support of research in less-developed countries without a collaborative component that involves U.S. scientists.

In a commissioned review for this committee, Courtney Nelson recounted U.S. experiences in tropical disease research in a variety of

circumstances and arrangements. Nelson considered the scope of each program along the spectrum of basic, applied, and developmental research needed for disease control, the extent of collaboration between U.S. and host-country scientists, the impact of the program in reducing disease burden, and the effects on institutional capacities of the developing countries. Of the programs considered, only two--International Collaboration in Infectious Disease Research, funded by the National Institutes of Health, and Great Neglected Diseases, funded by the Rockefeller Foundation--were designed from the outset to promote collaboration between institutions of the industrialized countries and the less-developed countries. Even these programs are limited in funds, problems addressed, and purposes of research.

This committee held a workshop in Cairo, Egypt, immediately following the 1985 Congress on Infectious Diseases, to discuss these issues with scientists from developing countries. Workshop participants endorsed problem-oriented collaborative research on tropical diseases both as a development tool and as an effort that will yield scientific and practical benefits to the U.S. public. The workshop noted that collaboration serves numerous U.S. interests, including opportunities for basic ecological and clinical studies and for testing new vaccines and pharmaceutical products for tropical diseases. They did not view U.S. involvement as only technical assistance or expert advisory services; effective collaboration was seen as a long-term partnership.

Participants observed that collaborative relationships with U.S. scientists function best when relative parity exists between the

partners, even though each contributes different but complementary assets, with mutual appreciation of good science. Critical factors in this respect include three basic components--time available to devote to research, scientific equipment and reagents, and access to the scientific literature. U.S. collaborative programs should assist their partners in the developing countries to build this kind of capability.

Information on U.S. tropical health programs and their purposes is not easy to obtain in the United States, and the problem is compounded by distance and lack of access to adequate reference sources. Moreover, as workshop participants noted, the administrative styles and managerial requirements of various agencies differ markedly. These are issues to which donor agencies, public and private, and science attaches might usefully give attention. Improvements in the confusing situation that prevails currently could be achieved at modest cost by adding staff, communications and data base facilities to an existing program.

All U.S. donor agencies should consider ways to restructure current tropical disease research and control programs to include or improve the three basic components--collaboration, research training, and institutional support. Agencies could restructure existing programs by using interagency agreements to cofund and/or cosponsor, with personnel sharing, additional activities that would mutually benefit the sponsors.

The National Institutes of Health program of International Collaboration in Infectious Disease Research should be expanded to a constant level of at least 10 Part A (Program Project) and 10 Part B

(Scientist to Scientist) awards, with appropriate funding levels. The program should be changed to include provisions for making additional funds available to developing country institutions for research and formal research training of their own scientists in tropical diseases within the general objectives of each award. This modification would contribute toward the strengthening of host institutions in developing countries and thereby more effectively promote the program's initial goals.

COORDINATION

An initial impetus for this study was the need on the part of the three federal agency sponsors to characterize the extent of the national effort directed toward tropical disease problems and to compare relevant functions of various agencies and private organizations. Issues of coordination of efforts and the extent of targeting toward specific objectives are inherent in this kind of review. The fact, rather than the form, of coordination is what is important. Federal agencies interpret their legislative mandates and structure their programs independently, and effective coordination to ensure that the United States is doing what it needs to do is a function of care and concern. Highly structured coordination machinery, whether with or without arrangements for lead agencies, sometimes works and sometimes does not.

Not surprisingly, this committee could not identify any single locus of responsibility for monitoring the activities and directions of national tropical disease research and technology development, for integrating knowledge with disease control programs or for tracking progress in reducing rates of infection in developing countries. However, the committee observed numerous instances of meetings to assess research needs and opportunities or to review agency priorities for a single disease or group of diseases. Coordination of the nation's research programs and activities related to tropical diseases is decentralized, and much of it is informal. People who care about these subjects seek to stay in touch with one another.

Information exchange and sharing about tropical disease activities among U.S. private organizations, academic institutions, and Federal agencies is uneven. Ad hoc personal communication and individual research generally bridge the gaps about specific country programs and activities or new Federal agency initiatives. Newsletters such as the National Council for International Health's International Health News also contribute by reporting federal initiatives and funding opportunities. A U.S. data base for tropical disease program and country activity information would be helpful for tropical disease specialists as well as program administrators if its coverage is wide rather than limited to programs of only a few agencies. The Agency for International Development, in cooperation with the Department of Health and Human Services and the Department of Defense, should consider establishing a new data base for tropical disease research and control activities.

Where there is overlap or complementarity of program objectives, the agencies may negotiate agreements for exchanging or borrowing personnel and transferring funds. For example, in Fiscal Years 1984 and 1985, the Public Health Service maintained about 20 separate agreements relating to communicable disease research and control in developing countries. These arrangements include \$47 million in program funds for the Combatting Communicable Childhood Diseases program in sub-Saharan Africa and \$3.2 million for an accelerated vaccine-development program managed by a project officer at the National Institute of Health's Fogarty International Center. The Agency for International Development has also just arranged to channel about \$3.5 million through the National Institute of Allergy and Infectious Diseases to establish a university-based facility to conduct clinical trials of malaria vaccine.

Informal personal networks of communication and cooperation in federal agencies and extending into academia and industry in this field have been extensive and have contributed substantially to its history. For the most part such networks have been built upon shared experiences--for example, service in World War II, research work at major laboratories, or participation in the global campaign to eradicate smallpox.

Internationally, of course, the World Health Organization and the Special Program for Research and Training in Tropical Diseases contribute to research coordination, information dissemination, and technology development, consistently so for the six priority diseases of the special program.

Establishing an international research and development system for tropical diseases is a worthy long-term goal for maximum impact in reducing the disease burden. However, such a system is not feasible in the short term. The multidisciplinary institutional anchoring posts are, for the most part, still lacking. Few institutions in developing countries possess sufficient multidisciplinary talent and resources to support productive collaboration along a broad spectrum of activities that range from research and technology development to disease surveillance and control. So it is unlikely that such a system will be available soon as an international coordination mechanism.

In reviewing the major programs and activities currently sponsored by private organizations and government agencies, this committee found little or no evidence of wasteful duplication of efforts as a consequence of different Federal agency mandates. However, the committee did find evidence of missed scientific, humanitarian, and foreign policy opportunities. U.S. drug development for parasitic diseases has lagged, research collaboration and training opportunities have not been emphasized, and communicable disease surveillance and control capabilities in the less-developed countries have not received systematic attention from U.S. donor organizations.

U.S. academic and military resources have been underutilized in some respects. Domestically, there is much more interest and potentially much more capacity within U.S. universities to support collaborative research and training activities with institutions of the developing

countries. Yet few universities have been able to build up the critical mass of tropical disease specialists needed to sustain multidisciplinary programs. Overseas, the military laboratories are often restricted by security or local political considerations from a more useful role in local tropical disease control.

POLICY AND PLANNING

The U.S. government does not have a strategic policy and program planning capability for tropical diseases. Responsibilities and resources to address tropical disease problems are split, for the most part, among the Public Health Service, the Agency for International Development, and the Department of Defense. Federal agency programs expand and contract within the constraints of agency mandates and budgetary pressures; no central government office monitors national goals, priorities, or activities related to tropical disease research and control and with developing countries.

The committee notes that absence of a central review office has not impeded agencies from taking important initiatives. Some, like the International Collaboration for Infectious Disease Research program, have been established with a long-term perspective, but lack the explicit mandate and funds to meet the full range of collaborative research needs. Others, like the competitive research grants programs

supported by the Agency for International Development's Office of Science and Technology, strengthen research capabilities in developing countries but do not support formal research training of U.S. or developing-country scientists. These two programs, as illustrative examples, may complement each other to some extent within a specific developing country, yet neither covers the entire spectrum of potential U.S. involvement in tropical disease problems.

Over the past decade, various government offices have assumed lead roles in international health policy formulation, each emphasizing tropical disease research and control to some extent. The Executive Office of the President, in 1977, began an ambitious review of all Federal agency involvements in international health.

The United States has not regularly reviewed its tropical health efforts in light of national interests. Arrangements are needed for regular review of U.S. and international tropical health programs in order to assess progress, to recognize innovations, to respond to resource and program gaps, and to foster economy and efficiency in these programs.

Within the United States, the Office of Science and Technology Policy and the Office of Management and Budget have broad responsibilities for review and analysis of both single-agency and multi-agency programs. The mission agencies as well have been charged by Congress with coordinating their efforts to guard against gaps, imbalances, and unnecessary duplications of effort. The Office of

Science and Technology Policy, in cooperation with the Office of Management and Budget, will find it useful to consult periodically with representatives of all federal agencies concerned with tropical health, and to meet with nongovernmental advisers also, to ensure that U.S. efforts in this field meet national needs. It would also be desirable to assess and review the international and other bilateral programs for tropical disease research and control to identify specific opportunities for U.S. contributions that could expand or strengthen existing efforts.

U.S. Government and private resources dedicated to tropical health are sufficient to sustain a substantial biomedical research base in this field and to respond to occasional public health threats from tropical pathogens in the United States. They are insufficient to ensure U.S. ability to cope with more than occasional domestic cases of these diseases. U.S. capacity and coordination of U.S. efforts in this field depend heavily on the specialized knowledge, experience and dedication of veteran tropical health specialists. That expertise is not being adequately renewed. Nor is this country adequately serving its tropical health interests abroad. Accordingly, the United States is limiting its leadership role in the control of tropical diseases at a time when scientific opportunities and humanitarian and economic concerns are greatest.

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APPENDIX

COLLABORATIVE RESEARCH ON TROPICAL DISEASES*

By Courtney Nelson

Tropical diseases are difficult to understand, definitely to be avoided, and sometimes seem not really our business. U.S. science has much to offer in the struggle against these diseases, and our national interests combine with our humanitarian impulses to make a strong case for doing more about them.

The National Research Council's study of U.S. capacity to address tropical disease problems looks at manpower available to deal with clinical, public health and disease control, and basic science aspects of tropical diseases and considers the major institutions in which these people work.

This paper describes some of the programs and overseas facilities through which U.S. capacity is or has been directed to combat tropical diseases. Emphasis is placed on collaborative processes and relationships because it seems clear that access to areas where these diseases are endemic is so vital to the maintenance of an experienced cadre of experts and must be based on genuine collaborative research with scientists of the less-developed countries.

The creation and maintenance of a cadre of experienced researchers are a minimal expenditure for a country such as ours, possessing such a disproportionate share of the world's medical research capacity. The programs described below show the ability of U.S. specialists and institutions in some circumstances to ease the disease burdens of thousands or even millions of people at rather minor cost.

CHOLERA

The cholera experience is an unfinished story of combat with a terrifying disease, illustrative of many of the programs and

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institutions considered here. (This discussion is based, unless otherwise noted, upon Cholera: The American Scientific Experience, 1947-1980, by W.E. van Heyningen and John R. Seal.)

Cholera is a disease with a definite home base and only an occasional urge to travel. The base is the Ganges Delta, northeastern India around Calcutta and areas of Bangladesh. Cholera is always present in this area, thriving in the warm, moist climate. Exactly why it bursts out into the rest of the world in brief but terrifying raids is still not known. Curiously, cholera pandemics seem not to have occurred before the Nineteenth Century, and to have occurred at all only seven times, once in the Twentieth Century.

A cholera pandemic must have been horrible, because of the suddenness of the incursion, the high mortality rate, and the awful impact it had almost immediately on its victims. The fourth pandemic of 1863 reached Europe by means of pilgrims through Mecca to Egypt, Constantinople, and thence to Italy and France, killing a half-million people in Europe. It also reached the United States for the third and last time, where it killed about 50,000 people. Earlier epidemics, in 1829 and 1849 left approximately 100,000 dead each time. Later pandemics, in 1881 and 1889, reached Europe but affected many fewer people.

Cholera was not the greatest killer of the time. In the United States many more died of malaria and tuberculosis. But it wondrously focused the medical mind because of the panic it spread. The onset of the disease is abrupt, involving diarrhea and vomiting to the point of severe dehydration. Victims appear cadaverized in a short time, their bodies drained of water so that their eyes sink into their sockets, the flesh sags and wrinkles, and the skin color becomes leaden. Yet the mind remains clear, fearfully aware of the deterioration of its surroundings.

The sudden appearances of the disease in Europe, where it was considered the worst thing to happen since the plague in the Middle Ages, led to observations and experiments of remarkable acuity; they sometimes faded from the scene like the disease itself, having to be rediscovered or re-observed. The bacterium that carries the disease was observed by the Italian Filippo Pacini around 1853, but it was discovered anew by the great German bacteriologist Robert Koch in 1883.

Koch supposed that the cholera bacterium sent a poison into the body to act in some systemic way on the patient, as was known to be the case with tetanus, diphtheria, and botulism. This turned out to be an error; the poison acts on the walls of the small intestine, inhibiting the absorption of water into the system and facilitating the flow of water into the intestine. The discovery of the cholera toxin took another 75 years after Koch began the search. Then an Indian scientist, S.N. De, conclusively demonstrated that the damage to the body was caused by an exotoxin.

For tetanus and diphtheria, the discovery of the toxins led quickly to production of a vaccine to ward off the disease. This has so far not occurred for cholera, although efforts have continued since the toxin was discovered. Prevention of cholera in Europe followed the demonstration by John Snow of Britain in 1853 that the disease was

transmitted through water contaminated by sewage. This led to important improvements in sanitation throughout Europe.

The idea of treating the disease by rehydration was also conceived during the early pandemics. In Moscow, around 1830, two German expatriates, Jaehnichen and Hermann, had the idea, based on the chemical analysis of the blood and stools of cholera patients, of injecting water and acids into the blood stream. Their attempts to do this were unsuccessful. In London, in 1831, a young physician named O'Shaughnessy proposed injecting water and salts into the blood stream. He rejected Hermann's notion that the disease caused acid loss. O'Shaughnessy took a job with the East India Company and worked no more on cholera, but his ideas were tried in 1832 by a Scottish physician named Thomas Latta. Latta succeeded in reviving an aged female patient who seemed at death's door. Within a half hour she was free of discomfort, her features restored, and was convinced that all she needed was a little sleep. Latta himself took rest. The patient soon again experienced vomiting and diarrhea; she died before Latta was informed of her change in condition. He was convinced that she could have been saved if the rehydration had continued.

These early attempts at rehydration, while promising, could not have succeeded easily. Intravenously injected water, alone or with acetic acid added, as proposed by the expatriate Germans, did not replace the essential minerals also lost from the blood. The use of unsterilized saline and undistilled water by Latta could have led to septicemia and high fever. Latta died the following year, and cholera retreated from Europe of its own accord. The medical community became convinced that rehydration merely postponed the effects of the disease and that it prolonged suffering.

Virtual disappearance of cholera from Europe and the Americas by the end of the Nineteenth Century left Western medicine with little concern for the problem, except among the few physicians and scientists working in the Orient. One of these, Sir Leonard Rogers, a professor of pathology at the Medical College of Bengal in Calcutta before World War I, thought of using an intravenous solution twice as salty as normal when rehydrating cholera patients in order to restore circulation while preventing a recurrence of diarrhea. His reasons have since been faulted, but his method halved the fatality rate in half, to 30 percent from 60 percent, of those treated in the hospital.

In Manila about this time, Andrew Watson Sellars, an American, experimented with sodium carbonate and sodium bicarbonate solutions, similar to those proposed by O'Shaughnessy and tried by Latta in 1832. Sodium bicarbonate proved effective, and Rogers used it in Calcutta to bring the fatality rate down to 20 percent, at which it stayed until after World War II. Relatively few, however, were fortunate enough to have access to intravenous treatment in sanitary conditions.

U.S. medical science had not yet come of age in the mid-Nineteenth Century. Despite three serious cholera epidemics, no major contributions to knowledge arose from the painful experience. The Marine Hospital Service dispatched Dr. Joseph Kinyoun to Europe to find ways to study cholera and other infectious diseases. He visited the famed Professor Koch, returned home with Zeiss' latest microscope, and

on Staten Island in 1887 set up the Hygienic Laboratory, a precursor of the National Institutes of Health (NIH), but its concerns soon shifted from cholera to other diseases.

A significant chance encounter between cholera and one of the key figures in this narrative took place in Cairo many years later. Robert A. Phillips, a medical scientist, joined the U.S. Naval Reserve in 1940 and was assigned in 1944 to work at a newly established Naval Medical Research Unit (NAMRU) at the Rockefeller Institute, in New York. Among his colleagues there were several scientists who were to become important to the cholera story.

Phillips, NAMRUs, and Rockefeller Institute scientists were in and out of the cholera picture for the next 30 years. At that time they were working on problems of body fluid balance in connection with transfusions. Their studies required a reliable method to determine the specific gravity of blood. The tests had to be made in field conditions with minimal equipment. The techniques they devised later played a critical role in determining the degrees of dehydration of cholera patients.

Later in 1944, Phillips was assigned to a U.S. facility in Cairo to work on typhus. After the war, this laboratory was turned over to the Navy and was designated NAMRU-3. Phillips returned to Cairo to become its first head in 1947. His return was followed within three months by the first outbreak of cholera to hit Egypt since 1919.

The disease raged through the Nile Delta to Cairo and up the Nile Valley, causing 30,000 cases and 20,000 deaths in under three months. Phillips and NAMRU used the field-tested specific gravity techniques and biochemical analysis to determine the amounts of rehydration necessary and appropriate; they reduced the death rate of those treated from the 20 percent achieved by Rogers to 5 to 7.5 percent, a relatively quick return on the transfer of technology.

Phillips had wanted to do more accurate balance studies on the patients, which would have required limiting fluid intake to intravenous means so it would not induce vomiting and so the loss of fluids could be measured carefully. His colleagues considered it inhumane to deny drinking water to patients, so this experiment was delayed until 11 years later in Bangkok, when Phillips, assisted by Raymond Watten, balanced intravenous input with measured fluid output and reduced the mortality rate to 0.6 percent. Here again, work on cholera benefited from a transfer of technology. Watten had worked in San Francisco on one of the first artificial kidneys, which required very careful studies of the balance of intravenous input of electrolyte and fluid and output by the kidney and of losses through respiration and perspiration, with nothing given by mouth.

The possibility of bringing knowledge and experimental techniques developed for other purposes to bear on tropical diseases is of course one of the main reasons that U.S. involvement can be so beneficial. Two other notable examples occurred in Bangkok in 1959. Eugene Gangarosa had worked with Col. W.H. Crosby on the development of a device that could be passed through the mouth, esophagus, and stomach into the small intestine and to obtain a lining biopsy sample for microscopic and biochemical studies. Use of the Crosby capsule helped settle the

debate over what actually happened to the wall of the intestine during active purgation.

The other example is that of NIH scientist Robert Gordon, who had been studying the intestinal tract permeability to proteins in a variety of diseases. By intravenous injection of a radioactive molecule about the size of a protein molecule, he showed that the intestinal wall remained sufficiently intact to block protein passage. The conclusion of Gordon's and Gangarosa's work was that the lesion of the intestine which occurred in cholera was biochemical and invisible.

What brought all of these knowledgeable people to Bangkok in 1958 and 1959? Certainly not the size of the outbreak, or its rarity. Cholera outbreaks occurred every year in the Ganges Delta, often twice a year and of greater magnitude, but they attracted little Western scientific attention. The Bangkok outbreak, in two seasons, killed 2,372 people, a significant but not by earlier experience a startling number. The incursion of cholera into Thailand a decade earlier had resulted in 13,000 deaths.

Van Heyningen and Seal offer clues to the motivations of several of the actors in the Bangkok outbreak but no satisfactory explanation of the magnitude of the U.S. response. It is clear, however, that these events heralded an explosion of knowledge about cholera and other diarrheal diseases and revolutionary advances in therapy. Who was there from the U.S. medical establishment, and why?

The first year Phillips and his NAMRU crew were there, and the renewed outbreak in 1959 brought teams from the Walter Reed Army Institute of Research (WRAIR), the NIH, and the Jefferson Medical College, of Philadelphia.

Phillips had been interested in cholera since his first trip to Cairo. In the mid-1950s he went to Taipei to set up a Pacific NAMRU to work on tropical diseases. There was no cholera in the area of interest at the time, but in 1958, a year after the unit was commissioned, Dacca experienced an unusually heavy outbreak, which was expected to and did spread to Thailand. NAMRU-2 was ready when cholera hit Bangkok on May 23. The team in collaboration with the staff of Chulalongkorn University quickly succeeded in learning rehydration procedures, which reduced the mortality rate of those treated to 0.6 percent.

There are different versions of how the other organizations came to Bangkok when the disease broke out. Phillips is reported to have alerted other Federal services to the recurrence and to have invited their participation. The Army perhaps felt its unit in Malaysia should have been involved in the first place because it was closer to the scene. A personal friendship between Kenneth Goodner of the Jefferson Medical College and one of its graduates who was then a high official in the Thai Ministry of Public Health prompted an official invitation for assistance.

Who invited whom is unclear. More important, who authorized the expenditure of time and money, and why? The answer to the first question goes back to the Rockefeller Institute, where Phillips got his start. The talented group of medical researchers working there during World War II went on to become influential policy-makers and

administrators in the Washington medical research establishment. Seal refers to them as the inner circle, a group held together by common experience and interest in tropical diseases. They included James Shannon, director of NIH; Joseph Smadel, associate director of NIH for intramural research; Colin MacLeod, then a professor at the University of Pennsylvania and later deputy director of the White House Office of Science and Technology; Theodore Woodward, professor at the University of Maryland; and Goodner. Tangential to the inner circle were Richard Mason, director of WRAIR, and several members of the Armed Forces Epidemiological Board.

The importance of this group's interest in cholera to the size of the subsequent U.S. research effort is indisputable. What prompted the original interest is not so clear. Some of them had been involved in devising a cure for scrub typhus and an immunization procedure that was found to be highly effective against both typhoid and scrub typhus. As participants and leaders of the great NIH take-off, after the war when its budget was growing by 15-20 percent per year, they may have been uncomfortable with the overwhelming emphasis placed on degenerative diseases to the near total neglect of tropical maladies. They may have been intrigued by communications from another of the old boys from the field, Robert Phillips. They simply may have perceived opportunities to benefit mankind. Their interest in cholera, first evident in the U.S. response to the Bangkok outbreak, continued throughout their careers.

It seems most likely that Thailand's proximity to Vietnam explains the extraordinary attention paid to the relatively minor outbreak of cholera there, compared to apparent indifference to its annual occurrence on the Subcontinent. Vietnam split in two in 1954, and by 1958 was clearly destined to become a trouble spot. An American build-up occurred in Thailand in 1955-1957.

The Southeast Asia Treaty Organization (SEATO), formed in 1956 to give Western backing to the Asian front-line states, Pakistan, the Philippines, and Thailand, was broadened in 1958 to include economic and social as well as military cooperation. That was also the year of the cholera outbreak in Bangkok. This new clause in the treaty gave rise to a suggestion by Phillips to the State Department officer handling SEATO affairs in Thailand that a medical laboratory modeled on NAMRU be set up in Bangkok for research on cholera. Phillips, in response to encouragement, drew up a proposal for such a center including a budget of \$400,000, half for buildings and half for equipment.

This amount was soon earmarked by the International Cooperation Administration (ICA) for the laboratory, but confusion arose over how to spend the money. ICA did not wish to pay the recurrent costs of a laboratory for years. NIH, informed of the earmarked sum by Clifford Pease of ICA, formed an ad hoc committee and devised a cholera research program that would use the money over three or four years for university-based research in the United States under contract to NIH, for field studies combined with laboratory work on cholera epidemiology, and for field trials of cholera vaccines. The field work might best be done in Calcutta in collaboration with the World Health Organization (WHO).

Two things were wrong with this idea: India was not a member of SEATO, so the funds could not be spent there, and the State Department wanted visible evidence of U.S. concern about the disease. The department wanted something in a SEATO country, not a research program in U.S. universities. Creation of an institution was almost certainly more beneficial to the struggle against the disease than a research program alone would have been. Research programs can quietly dry up and disappear when the initial funds run out. An institution, particularly a productive one, creates continuing demands of its own, as ICA feared.

A team of six from the ad hoc committee toured the region in late 1959 and decided that the laboratory should be in Dacca, where cholera was endemic. An excellent building was found, empty because of a fall in the price of jute, and the Pakistan government was eager to supply the space and local personnel. ICA funds held over from a previous year could not be spent on personnel, so three positions from the National Heart Institute were assigned to the project. ICA, which became the Agency for International Development (AID) in 1961, passed its funds through NIH for administration. The recurrent cost problem was in part met by funds from the AID office in Pakistan, but a more important source turned out to be blocked currency, newly available to NIH through Public Law 480. Thus the Pakistan SEATO Cholera Research Laboratory (PSCRL) was launched, without SEATO funds. SEATO deserved its spot in the title, however, because without its political-military rationale the PSCRL would not have come into existence.

Other SEATO member nations were invited to contribute to the PSCRL. The United Kingdom and Australia did so, earning seats on the Directing Council. The structure of the PSCRL was modeled by its first director, Fred L. Soper, on the Institute for Nutrition for Central America and Panama (INCAP) which he had earlier founded. This provided an autonomous organization with its own Directing Council and Technical Committee.

People in the Washington medical inner circle moved from the original ad hoc committee to a new Cholera Advisory Committee established to advise the Director of NIH on technical aspects of the project. Smadel was the first chairman.

PSCRL really became operational in 1962. By then the Seventh, and current, cholera pandemic was spreading in Asia.

Pandemic Number Seven broke out in 1961 in Celebes, Indonesia, and hit China and the Philippines the same year. At first it was called para-cholera because the infecting organism was not the classical vibrio, but a variety called El Tor. The El Tor vibrio, discovered in the bodies of hajis who had died of other causes, was named for the Sinai Peninsula quarantine station where it was found in 1907. It appeared to cause only a mild variety of diarrhea, not real cholera.

In 1937, El Tor showed up in the Celebes, where, although the infection rate was low, the mortality rate exceeded 50 percent. The disease did not take on epidemic characteristics until 1961. It spread from East Asia to the Subcontinent and on to the Middle East, Southern Europe, and East and West Africa, where it seems likely to remain.

As the pandemic spread, Phillips and his team developed an efficient procedure for responding to cholera epidemics in the Philippines, South Korea, South Vietnam, East Pakistan, Malaysia, and Sarawak. The Navy offered its services as soon as news of an epidemic was received, and a team of 3 or 4 and 8 to 10 technicians was dispatched by military aircraft as soon as an invitation arrived. They first indoctrinated local physicians and nurses in the Navy method of treatment, then requested permission to conduct research.

The Navy treatment, with a mortality rate consistently under 1 percent, had evolved in Cairo and Bangkok. The specific gravity of the patient's blood was measured to determine the volume of fluid needed to restore the plasma to normal levels. Fluid balance was rapidly restored intravenously and maintained thereafter by matching inflow with outflow. The fluids used contained minerals to match those lost in diarrhea, and sodium bicarbonate counteracted acidosis. The cholera seemed to cure itself, as Phillips said, like the common cold.

This method of treatment was a definite advance over previous therapies, and Phillips consequently received the Albert Lasker Clinical Research Award in 1967. The new treatment was impractical, however, for large-scale epidemics in developing countries. The fluids had to be made from sterile, distilled water to avoid fevers, and they had to be administered under medically controlled conditions. Patients would often require infusions of more than their own weight in liquids, placing a huge burden on logistical services.

The NAMRU group knew the shortcomings of its method and sought a means of oral rehydration. The principal problems were that fluids taken orally generally induced nausea and vomiting, and even if they could be kept down the body seemed unable to absorb needed sodium and chloride from them.

In July 1962, in Manila, Phillips found, literally, the solution. Addition of glucose to the swallowed fluid allowed sodium, chloride, and greater amounts of water, to be absorbed by the body. Fluid balance was restored immediately. An editorial in the medical journal Lancet in 1978 valued the finding thus: "The discovery that sodium transport and glucose transport are coupled in the small intestine, so that glucose accelerates absorption of solute and water, was potentially the most important medical advance this century."

Credit for this momentous discovery may rightly be shared by physiologists at Oxford, Harvard, and Yale, and by the clinician N.S. Chatterjee, who in 1953 experimented with cholera patients; but in the history of science v. cholera, the accolade is assigned by Van Heyningen and Seal to Phillips. He was, for a long time, not himself convinced of the utility of his findings.

Encouraged by the initial observation, a small NAMRU team treated 40 patients with the glucose solution, after initial intravenous rehydration, in September. Five died, drowned, technically, by water drawn to the lungs from their cells by an excessively salty solution. This failure soured Phillips on the oral rehydration notion, to the point that when he received the Lasker prize in 1967 he referred to the glucose solution as a hope that did not materialize. As head of the PSCRL after 1965, he restrained experimentation on oral rehydration.

In 1962, as Phillips was experimenting with oral rehydration, NAMRU was perfecting its epidemic response procedure, and PSCRL was becoming operational in Dacca, another U.S. medical research team set up shop in Calcutta. Under an NIH grant program, Johns Hopkins University established a Center for Medical Research and Training (JHCMRT) in Calcutta. A cholera research program was initiated because the disease was important to the site, not because the grant required work on cholera or because Johns Hopkins was experienced in the disease.

The Hopkins group found pre-NAMRU procedures in effect for dealing with cholera; patients admitted for treatment at the Infectious Diseases Hospital in Calcutta, to which JHCMRT was attached, had a mortality rate of 30 percent. Phillips' work in Cairo in 1948 had gone unnoticed, perhaps because it was published in an obscure journal or, as often happens in the less-developed countries, the hospital couldn't afford the periodical in which it appeared. The major NAMRU advances during the Bangkok outbreak were more recent and hadn't been demonstrated on the Subcontinent. The Hopkins group arranged a controlled comparison of the methods used by the Indian physicians with those recommended by NAMRU. The dramatic differences in results led the Indians to abandon traditional therapy.

The Hopkins group regularly exchanged information and visits with the NIH scientists at the PSCRL. Craig Wallace, who was with Phillips at NAMRU-2 and headed the Hopkins group from 1964 to 1966, said that both Hopkins and PSCRL made important observations but each would have in time done what the other accomplished. Their working conditions differed substantially. Hopkins was primarily a research group, admitting only a few patients per day for observation but caring for as many as several hundred a day. PSCRL was a treatment center. During one period of Moslem-Hindu tension in East Pakistan, cholera broke out among a group of Hindus taking shelter in several cotton and jute mills. Patients were transported by the truckload to the Mitford Hospital, the hospital in Narayanganj, and the PSCRL, each receiving about a third of the victims. Within 48 hours all but two of the PSCRL patients had been discharged, with zero deaths, while 27 percent had died at Mitford and 47 percent at Narayanganj. Thereafter, the PSCRL was charged with treatment of all diarrheal cases in Dacca.

The Hopkins team had advantageous conditions for conducting intensive clinical studies. They were attached to a large hospital where it was possible to develop excellent laboratory facilities and their Indian colleagues, including S.N. De, who had already succeeded in identifying the cholera toxin, had vast experience with cholera. Links to the Johns Hopkins School of Medicine were also important even though some of the field staff did not come directly from the parent institution.

Among the achievements of the Calcutta group was the appreciation of the value of antibiotics in the treatment of cholera. It was known from previous experiments by Chaudhuri in Calcutta and Phillips in NAMRU that antibiotics would not alone reduce the death rate from cholera. Once the lining of the gut was damaged by the disease, the damage was done. It takes a week for the damaged cells to grow back, by which time the cholera vibrios have gone away of their own accord, so Phillips saw

no sense to using antibiotics for treatment. At Calcutta, the Hopkins group showed that with tetracycline only half the volume of replacement fluids and half the hospitalization time were required for recovery.

The Calcutta team also made important advances in identifying severe diarrhea causes other than cholera. The team noted that cholera vibrios could be identified in only about half of the patients in their care. In 1964, an unusual epidemic of non-cholera diarrhea broke out at the time of year cholera could be expected to appear. Of 145 patients studied, 86 percent did not have cholera, although they were as sick as if they did. In 1968, Hopkins workers identified the causative agent as Escherichia coli, an organism which had been known to exist harmlessly in the large bowel but was now found to act in the small bowel much like cholera. E. coli is not the only non-cholera diarrhea-producing organism, but it is one of the most dangerous worldwide for children under two years of age.

Hopkins' advantage in having facilities for intensive clinical work was balanced in Dacca by the opportunity for field surveillance and epidemiological studies. One of the important missions of the PSCRL was to test the efficacy of cholera vaccines. This task required access to an area with a high incidence of cholera and where comparisons could be made of cholera attack rates in people given a vaccine and control groups given placebos. PSCRL needed a cholera ward in which to treat those who contracted the disease, and it needed ready access to a sizable population at risk. With the assistance of local authorities, a group of 23 villages in the Matlab thana, one of the most densely populated areas of East Pakistan, was selected. The thana was a subdivision of Comilla District, about 40 miles from Dacca. The villages were most easily reached by boat through rivers and canals.

The Matlab thana surveillance area, and another developed shortly thereafter at Teknaf, remains a major resource for epidemiological research and experimental interventions in such fields as nutrition and family planning as well as diarrheal diseases. Experiments there demonstrated conclusively that it is far cheaper and more effective for a poor country to devote its resources to therapy centers and to upgrading sanitation than to large-scale vaccination programs. Vaccines then and until now available are effective at most for three or four months and must be administered a month before exposure to the disease. Therapy, particularly after an oral rehydration method became available, has become relatively inexpensive.

The Dacca and Calcutta units differed from the NAMRU approach in various ways. As a laboratory man, Phillips favored tests of blood specific gravity in order to determine the volume of replacement fluid needed. The more clinically oriented physicians at JHCMRT and PSCRL soon came to prefer quicker assessments made by judging the degree of dehydration by the fullness of the skin, assessing blood pressure by pulse, and other observations.

In 1965 Phillips was appointed to direct the PSCRL. He was at heart a laboratory scientist, with little background or interest in epidemiology. His first concern was to understand the disease process. He was a physiologist, not a clinician. His attitudes were not shared

by many of his Dacca colleagues, several of whom came from predecessor agencies of the Centers for Disease Control (CDC).

The 1962 setback in Manila apparently inhibited both Phillips and his colleague Wallace; both were extremely cautious in permitting clinical experimentation with oral rehydration in the units they ran during the next five years, Phillips in Dacca and Wallace in Calcutta. Yet the idea was far from forgotten, and Wallace continued to believe that it would work under proper conditions.

Research on the glucose transporter continued at both PSCRL and JHCMRT in the field, and at Johns Hopkins and other laboratories in the United States. Results were encouraging, and Dacca field staff interests in the oral technique were reinforced in the 1966-1967 winter by the biggest cholera epidemic the PSCRL had yet witnessed, giving rise to fear that they might run short of intravenous fluids. The first experiment, in Chittagong in 1967, was not a success, although not catastrophic as in Manila; the second attempt was more encouraging. Despite official opposition, from Phillips and NIH, a controlled field trial was conducted in 1969 in Matlab, then in the midst of an epidemic in which a shortage of intravenous fluids actually did occur. The result was a powerful affirmation of the value of oral rehydration. The need for intravenous fluids was reduced by 80 percent, and in mild cases it was not needed at all. Phillips became convinced again of the promise of the technique.

In Calcutta, the Hopkins group worked along similar lines. The group demonstrated in 1968 that oral rehydration could be used successfully to maintain balance after initial intravenous rehydration had been used, but it preferred to await further study before experimenting further. The disease broke out among a concentration of 350,000 refugees from the civil war in East Pakistan in May 1971. The death toll was huge; a fatality rate of 30 percent prevailed among patients in the refugee camps. There was no hope of producing the amounts of intravenous fluid needed for such numbers, nor of training the personnel to administer it. The Hopkins group consequently prepared packets of dry ingredients in Calcutta and sent them to the camps, where an Indian team from the JHCMRT dissolved the packets in clean drinking water and dispensed the liquid to patients. Packets for 50,000 liters of solution were prepared. In all, 3,700 patients were treated, only the most seriously ill intravenously, with a mortality rate of 1 percent among those in the JHCMRT tent, and 3.6 percent for others using the solution.

Indian resentment over U.S. involvement in Vietnam, and over U.S. policies regarding the Subcontinent in the early 1970s, made the Hopkins situation in Calcutta increasingly uncomfortable. Had the program been designed to assist Indian research and treatment efforts, and, in particular, had it been meant to train Indian scientists, it might have had more local support. But the NIH grants of the time were designed purposely and narrowly to support U.S. research and training, not to build the competence of their foreign colleagues. When cholera broke out among the Bengali refugees no Americans were permitted to participate in their treatment. The next year, relations became so strained that Hopkins staff had problems obtaining visas to visit the

unit, and they abandoned the Calcutta location. They moved the unit to Dacca and affiliated with the PSCRL.

Civil turmoil also brought research to an end at the PSCRL, as the Bengalis struggled for independence. The laboratory remained open for the treatment of patients, and the conflict brought them the greatest number of cholera patients in its history, but throughout 1971 most of the expatriate staff were kept elsewhere for security reasons.

Fortuitously, another mechanism for advancing cholera research appeared on the scene in 1965. President Johnson received Prime Minister Sato of Japan in Washington to discuss, primarily, their balance-of-payments problems. The meeting produced few positive results on that score, and the President reportedly asked Colin MacLeod to come up with a suitable topic for constructive cooperation in order to avoid too discouraging a final communique. MacLeod, working all night, came up with an idea that became the U.S.-Japan Cooperative Medical Science Program. Its announced purpose was to expand cooperation between the two countries on human health problems "of great concern to all the peoples of Asia." Malaria, cholera, schistosomiasis, tuberculosis, and stomach cancer were designated for early attention.

The program continues to be both popular and important to work on cholera. No money crosses borders under this program, and no collaborative research is supported. Each side funds its own research, and panels on each of the major diseases meet annually to report accomplishments. The program has widened to include leprosy, dengue, arboviruses, and parasitic infections.

Initially, U.S. participation in the program was guided and funded by the Office of International Research at NIH, but later it came under the National Institute for Allergy and Infectious Diseases (NIAID). In the program's first decade, 58 grants and contracts were made in the cholera field in the United States and a similar number in Japan. The program was an important source of funds for U.S. researchers during its first years of operation. It has facilitated contact and exchange between scientists with an interest in infectious diseases of developing countries, and it has stimulated research proposals that have competed successfully in the NIAID peer-review grants process. NIH no longer carries the program as a line item in its budget, although in 1983 roughly \$11 million in grants were made under its aegis. All such grants are funded from regular NIH appropriations. Abolition of the program might not affect the awards made but would adversely affect exchange of ideas between U.S. and Japanese scientists.

The program operates under the only active delegation of Presidential authority to conduct research for international health purposes. This power is given to the President in the International Health Research Act of 1960. It has been delegated only three times, including the U.S.-Japan case. Its broader use was opposed by the Department of State, but the mechanism remains as an desirable instrument to enhance U.S. capacity to conquer disease in the developing countries.

The year 1971 was difficult for the SEATO center and Dacca generally. Strikes and riots disrupted research in February, and work

came to a standstill in March when West Pakistani troops attacked the Bengalis. Months of fighting followed. The laboratory was untouched, but much of the surrounding area was bombed between March and December. The local staff, led by Deputy Director Mujibur Rahman, kept the laboratory open, working without regular salary and treating as many as 1,500 patients a month. Research was impossible, but refrigerators and deep freezers were kept going to protect specimens until they could again be studied. Most of the U.S. staff was evacuated in April and the remainder in December.

The People's Republic of Bangladesh emerged from the conflict on December 16, 1971. The immediate consequence of independence for the laboratory was the loss of its SEATO affiliation and the loss of eligibility for Public Law 480 funds. In early 1972 the laboratory was on the verge of bankruptcy.

Within a week of independence, a group of Americans who had worked at the laboratory formed themselves into a Committee for the Continuation of the Cholera Research Laboratory. The committee was led by William B. Greenough III, a physician who was among the first to serve in the SEATO laboratory and who would become director of the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B). The committee kept interest in the laboratory alive at AID and NIH, stimulating an interim AID grant of \$500,000 to maintain the institution while its future was being negotiated.

NIH's director asked the Cholera Advisory Committee to determine the scientific justification for maintaining access to a population in which cholera was endemic. He was advised that the anticipated expenditure of \$1,500,000 per year was justified. Although access to a cholera-endemic population was not necessary for physiological or pharmacological research, it was necessary for field trials of vaccines. Additional valuable studies could also be conducted in the field in search of a single method for rehydrating children and on other diarrheal diseases such as E. coli.

Negotiations dragged on until mid-1974. The new government wanted NIH participation, but wanted the institution to be a Bengali laboratory in direction and operation, responsible to the Ministry of Health. This was unacceptable to NIH. Eventually a compromise was reached under which the laboratory would continue for three years as an autonomous body with a Directing Council of three Bengalis, two Americans, and one representative each from participating nations or international organizations. NIH organized the Scientific Review and Technical Advisory Committee to advise the Directing Council and selected the director of what was now the Cholera Research Laboratory (CRL).

This was not meant to be permanent. AID was no more eager to assume a continuing recurring cost burden than was ICA in 1959. AID's motivation in seeking to internationalize the laboratory went beyond simple desire to share the financial burden. Diarrheal diseases are leading worldwide killers of children, and AID saw the potential value of developing this highly successful institution, attracting high-quality international staff, and lending permanence to the work.

Between April 1976 and February 1978 five reports recommended expanding international participation in the CRL and broadening its activities. The two most influential of these reports came from W.F. Verwey, director of CRL from 1974 to 1977, and W.H. Mosley, chairman of the Department of Population Dynamics at Johns Hopkins and successor to Verwey as director of CRL. Mosley knew the CRL well, having been the epidemiologist who set up the Matlab surveillance area in 1965.

As recommended by Verwey and Mosley, AID opted for CRL's internationalization along the lines pioneered in the agricultural field in the institutions supported by the Consultative Group for International Agricultural Research. That model involved funding from many private, international, and national sources, an international board of trustees, a technical committee, and an international mandate that transcended local concerns.

Mosley, as director, struggled to internationalize the institution. He received strong support from the resident representative of the United Nations Development Program (UNDP), who was in turn backed by the UNDP in New York. The Ford Foundation, which was along with the Rockefeller Foundation a founder of the original international agricultural research centers, backed the internationalization idea and provided funds for contingency expenses.

WHO, perceiving a marginal role of the U.N. Food and Agriculture Organization in the international agricultural research picture, was more interested in primary health care, opposed the plans for CRL. AID and the UNDP tried to keep WHO informed and out of open opposition. Within Bangladesh there were some who opposed internationalization as a drain on their country's resources; others saw the chance to take over a well-equipped institution if the broader effort failed.

Planning and negotiation went on for two years, with the scope of the laboratory, its name, and its mission constantly in debate. In early 1978 a review meeting at the CRL, attended by 20 international and 6 Bangladesh scientists and the senior staff of the CRL, examined the laboratory's scientific program, considered the arguments for internationalization, and recommended a course of action. The meeting favored a concentration on diarrheal diseases at the proposed center, with biological and demographic population studies relevant to these diseases, and nutritional studies with a focus on maternal and fetal malnutrition, breastfeeding, and weaning.

Finally, a draft ordinance to establish the ICDDR,B was prepared by an international committee consisting of representatives of WHO, Australia, Bangladesh, the Ford Foundation, the International Development Research Centre of Canada, the United Nations Fund for Population Activities, the United Nations Children's Fund (UNICEF), the United Kingdom, and the United States. The permanent representative of the UNDP chaired the committee. The Bangladesh government promulgated the ordinance on 6 December 1978. In February 1979 the UNDP sponsored an organizational meeting at WHO Headquarters, in Geneva, and a memorandum of understanding was signed by over 20 donor participants. This memorandum and the Bangladesh ordinance constitute the ICDDR,B charter. President Ziaur Rahman formally inaugurated the ICDDR,B on 26 June 1979.

The CRL's major scientific value was its ability to conduct clinical research and field investigations of high standard in disease-endemic areas. Studies at CRL revealed many of the abnormalities and intestinal functions associated with diarrhea, whether caused by cholera or not. They showed the abnormal dehydration and fluid loss that must be corrected in treatment in order to lower the mortality rate from around 30 percent to under 1 percent. Simplified treatment procedures were developed at CRL so that low mortality rates could be achieved in relatively primitive situations with minimal equipment and training.

Field trials by CRL showed that cholera vaccine may be protective in an epidemic but for only a limited time. These results led the U.S. Public Health Service to abandon the cholera vaccination requirement for travelers to the United States from cholera-infected areas. WHO also no longer recommends cholera vaccination for travel to or from cholera-infected areas.

CRL proved to be a useful facility for testing and refining work begun elsewhere. Work at CRL confirmed the Hopkins findings that tetracycline was most effective against the cholera vibrio and that oral administration of the antibiotic effectively shortened the duration of the disease. Oral rehydration therapy (ORT), initiated at NAMRU-2, was greatly refined and developed at CRL, leading to the development of a formula for the use of local materials in the preparation of soluble packets for administration by mothers or little-trained health workers. UNICEF and WHO made extensive use of this formula in their work around the world.

CRL pioneered research on the pros and cons of combining nutrition, family planning and ORT in villages. The CRL work on cholera thus extended all the way from physiological research to public health campaigns for countering the disease. This broad range of activity is extremely rare in medical institutions.

One of the greatest benefits of the PSCRL and the CRL for the United States was the field experience it afforded a generation of young researchers, who then made lasting commitments to work on tropical disease problems. Many of them now occupy senior faculty positions at Johns Hopkins, Harvard and Case Western Reserve Universities.

LESSONS LEARNED

The cholera problem is not identical to all others, but it illustrates several important points. First, the connection between basic science and the development of an inexpensive cure for the disease was fairly straightforward, more so perhaps than for most diseases. An understanding of the glucose transporter system in the gut and an awareness that it continues to function during diarrheal diseases led to the development of a cure of such simplicity that in the Nineteenth Century would have been called miraculous.

The disease was ignored by science for nearly a century at a cost of untold thousands of lives. Time lags of 75 years between Koch's

postulation of a toxin and its discovery by De, and nearly 100 years between Latta's experiments with rehydration and perfection of the technique by NAMRU would have been scandalous for a disease of greater concern to us.

A third striking feature is the speed with which progress was made when modern scientists did finally get into the fray. Among the reasons: Cholera researchers benefited from research technologies developed in other, better funded, fields. The inner circle was involved in monitoring progress, setting priorities, devising strategies, and shifting resources to combat cholera. The value of scientific infrastructure is revealed by the knowledge explosion set off by the distribution of purified toxin to the scientific community. Informal communications, seminars and workshops, and publications, also played important parts in advancing the frontier of understanding cholera.

A fourth point is the variety of justifications for official action. Phillips' work in the NAMRUs was fueled by military considerations. Diplomatic factors led to the U.S. response to the Bangkok outbreak in 1959 and to establishment of the SEATO laboratory. Political face-saving was initially behind the U.S.-Japan program. The International Centers for Medical Research and Training (ICMRT) program supporting the Johns Hopkins team in Calcutta was an effort to protect the health of Americans. Development and humanitarian factors led to the ICDDR,B. Scientific and medical concerns led to the distribution of the purified toxin and, of course, to many of the individual actions justified so variously above. All these motivations were wellsprings of action, but the picture which emerges from this history is not one of a prudent, thoughtful blueprint for the conquest of disease. The result probably would not have been as successful had it not been for fortuitous interest in cholera taken by that remarkable group of old boys from the Rockefeller Institute.

Fifth, the cholera experience illustrates the many types of research and experimentation required to learn to deal with a tropical disease, and the variety of social and economic factors that affect interventions. The process of science extends from the university laboratory researcher, who works on purified toxins and may never encounter a person with cholera, to the social scientist in Matlab thana concerned with local sanitation and nutrition.

A final point is that medical science was advanced immeasurably by work on the disease; indeed it changed the approach to study of the gastrointestinal tract.

COLLABORATIVE PROGRAMS

U.S. institutions, public and private, combat tropical diseases through a variety of mechanisms. The examples here do not represent the totality of collaborative efforts. Much collaboration between U.S. and developing country scientists is arranged informally and is often supported within the budgets of research grants awarded by the NIH extramural program. The list of formal programs is not long, however.

Examples selected include the military laboratories overseas, both the NAMRUs, which played so vital a role in the cholera story, and the Army's laboratories; the ICMRT program, of which the Johns Hopkins group in Calcutta was an example, and its successors; the ICDDR,B; Gorgas Memorial Laboratory, in Panama; and foundation research grant programs.

For convenience, the examples may be considered in three categories: U.S.-established research laboratories in less-developed countries, research grant programs, and the smallpox eradication program. The smallpox program was not primarily research, nor was it a U.S. effort, but it illustrates an effective mobilization of U.S. talent and institutional resources in an international program.

The overseas laboratories play unique roles in U.S. efforts to deal with tropical diseases. Temperate-zone laboratory research can take us only so far in the process of understanding a disease and learning to conquer or, more often, control it. Information about incidence, prevalence, and case-fatality of a disease, its natural history and patterns of transmission, can only be collected in the field. Clinical research requires ready access to a patient population. The fruits of research--drugs, vaccines, vector control--must be tested where the diseases occur. Training in tropical medicine is most effective in the tropics.

BASES FOR COMPARISON

Objectives of the programs differ significantly, different diseases dictate different approaches, and circumstances of origin sometimes shape programs in unusual ways. Bases of comparison include:

Scope Normally, research on a tropical disease must seek to increase understanding of the biological nature of the pathogen, clinical manifestations and efficacy of treatment, disease distribution and transmission patterns, and social and economic factors that constrain public health interventions to control it. Simply stated, research is needed on the nature of the disease organism, how it affects human beings, the means and extent of transmission, and the human behavior and natural environment that may need changing if the disease is to be controlled. The locus of research may be an advanced biological laboratory, a hospital, a field station, or a community. Relatively few programs span the entire range of research activities necessary to disease management, but laboratory research on tropical diseases can be part of a coherent effort and not an isolated set of activities with little potential impact on human suffering.

Collaboration with Scientists and Institutions in Developing Countries Because work on a tropical disease must be done in field conditions and not only in advanced medical laboratories, collaboration between U.S. scientists and those of less-developed countries is desirable and usually necessary if the work is to go on. Collaboration is becoming more difficult to arrange without an element of training to strengthen

the collaborating institution in the tropics. Patterns of fruitful collaboration therefore deserve special scrutiny.

Impact on Understanding and Controlling Disease Not all research or control efforts lead to progress in the control of a disease. It is difficult to know just how research on tropical pathogens will result in new methods to control the disease or treat its victims. Most of the laboratory work on African trypanosomes in humans is devoted to understanding how the body's immune system responds to the ability of the invading organism to change its protein coat. Such research is required if we are to have a protective vaccine against trypanosomiasis. More efforts designed to understand and control tropical diseases are needed.

Enhancement of U.S. and Foreign Capacities Few known diseases are, like smallpox, susceptible to eradication. We and the people of the less-developed countries will be coping with pestilences for generations. Increasingly, the battle will be waged in endemic grounds by scientists whose people suffer most, but time and careful husbandry of resources are needed for science to grow firm roots in most developing countries. The role of scientists and institutions of advanced countries in the process of building research capacity in the tropics is crucial, so value must be assigned to the growth in institutional competencies that a program represents and leaves as a legacy.

U.S. Department of Defense Overseas Medical Research Laboratories

The reasons that the Department of Defense (DOD) maintains medical laboratories overseas are fairly clear. Until this century, more combatants died from disease than from combat in every war in history. Even in every war in this century, disease still has cost the loss of more soldier-days than has combat. Military laboratories in the tropics are useful for field research on exotic diseases, for maintaining surveillance on diseases of potential military significance, for evaluating drugs and vaccines developed elsewhere, and for training medical staff to deal with diseases not generally found in the United States.

The U.S. military has had overseas medical facilities since 1900. Early efforts included the Yellow Fever Commission, with which Walter Reed was associated, and the Anemia Commission, which studied hookworm in Puerto Rico. The Army ran research laboratories in the Philippines from 1900 to 1934 and in Panama from 1936 to 1945. The Navy's NAMRU system began in 1934 with a unit on the Berkeley campus of the University of California. The first overseas NAMRU was set up in Guam during World War II. Since then a total of 20 overseas medical research laboratories, units, and teams have been operated by DOD for varying periods of time.

Nine such laboratories are functioning in the tropics. Four, in Brazil, Kenya, Malaysia, and Thailand, are U.S. Army laboratories.

Four, in Egypt, Indonesia, and the Philippines, are U.S. Navy. The Uniformed Services University of the Health Sciences has a laboratory in Pakistan. Navy laboratories are generally larger than their army counterparts, broader-based, and moderately self-sufficient. The Army laboratory in Bangkok is similarly organized; the other Army units are small, more specialized, with limited objectives. The Army laboratories are administrative elements of WRAIR. They serve as branch laboratories for WRAIR research projects, and they have their own research programs as well. The Navy units report directly to the Navy Research and Development Command, a headquarters unit rather than a laboratory. This arrangement allows the NAMRUs more autonomy in the field but limits scientific support and guidance that might be available to them if they had a home-base laboratory.

The overseas laboratories are operated by approximately 110 U.S. citizens, of whom 100 are military personnel, and 500 local staff. NAMRU-2, when operating out of Taiwan, benefited from a University of Washington contract that assigned university staff to Taiwan for up to 5 years. The scientific work was excellent. The other military laboratories have not generally used contract civilian workers.

U.S. military laboratories in the Congo, Uganda and Ethiopia have had to close because of changes in host-country political relationships with the United States. Otherwise, the military laboratories seem among the most popular of U.S. institutions abroad--as demonstrated by the continued welcome of NAMRU-3 in Egypt and of AFRIMS in Thailand.

Some of the U.S. military overseas facilities are described below.

U.S. Army Medical Research Unit-Brasilia USAMRU-Brasilia was established in 1973 to identify new drugs to prevent and/or treat schistosomiasis. In 1978 the program expanded to include a multidisciplinary study of clinical, immunological, epidemiological, and vector transmission dynamics of malaria in the Amazon Basin.

USAMRU-Kenya This laboratory was established in 1973 to pursue WRAIR research leads concerning African trypanosomiasis. The program expanded in 1979 to include study of visceral leishmaniasis.

USAMRU-Malaysia This laboratory was set up in 1948 by J.E. Smadel, then at WRAIR and concerned with tests of the efficacy of new antibiotics to treat scrub typhus. The unit has advanced the knowledge of arthropod-borne virus infections and leptospirosis. Scrub typhus remains a major concern; malaria studies also have been undertaken.

Armed Forces Research Institute of Medical Sciences AFRIMS, in Bangkok, is a joint operation with the Royal Thai Army. The U.S. Army Component was set up in 1961, an outgrowth of WRAIR concern with the 1958-1959 cholera outbreak. It was for a time a SEATO research center but completely separate from the PSCRL. AFRIMS has six research departments: Medical entomology, bacteriology, medicine, virology, veterinary medicine, and immunology. Its primary missions are to evaluate new drugs against naturally acquired drug-resistant malaria,

to elucidate immunologic and entomologic aspects of the use of dengue virus vaccine, and to monitor all tropical diseases.

AFRIMS is working closely with WRAIR in attempting to make a transition from an effective antimalarial prophylactic drug to a new vaccine. In collaboration with a children's hospital, AFRIMS has initiated work on Japanese encephalitis, which occurs seasonally among children upcountry in Thailand. An expert in virology and neurology from Johns Hopkins University has been a visiting scientist at AFRIMS, working on validation of a candidate vaccine for Japanese encephalitis. The vaccine has not been fully field tested.

NAMRU-2 Established originally at the Rockefeller Institute in New York, this unit by 1942 was located in Guam. It was deactivated at the end of the war and then revived by Phillips in Taipei in 1957. In April 1979, after the United States and the People's Republic of China established diplomatic relations, NAMRU-2 was moved to Manila. Its mission is to conduct medical research on infectious diseases of military importance in the Western Pacific and parts of Southeast Asia. The program includes the epidemiology of hepatitis B infection, immunodiagnosis of parasitic diseases, gonorrhea sensitivity, surveillance for drug-resistant malaria, and virological, parasitological, and entomological surveys in the Philippines. After Phillips left NAMRU-2, cholera work there ceased.

NAMRU-2 Detachment in Jakarta In 1968 a team was asked to investigate a plague outbreak in central Java. Subsequently, the Indonesian Minister of Health invited establishment of a permanent NAMRU laboratory in Jakarta. Research efforts have expanded to include work on scrub typhus, diarrheal diseases and enteric fever, gonorrhea, filariasis, and dengue.

NAMRU-3¹ This facility succeeded and supplanted the U.S. Typhus Commission, set up in Cairo in 1942 and instrumental in averting a serious typhus outbreak during World War II. At Egyptian government request, the U.S. Navy took over the laboratory and established NAMRU-3, which was headed by Phillips at the time of the rogue cholera outbreak in 1948. The unit has remained in full operation since that time, despite frequent conflicts in the area and fluctuating relationships between the Egypt and the United States. At one stage, in 1967, diplomatic relations were broken, and NAMRU-3 found itself the only U.S. Government agency allowed to function in Egypt.

The NAMRU-3 program is a blend of the interest of DOD with the health priorities of the Egyptian government. In virology, both have a high degree of interest in Rift Valley fever, West Nile fever, and dengue. NAMRU-3 has the only virology laboratory in Egypt with a P-3 biosafety level. Ain Shams University, which has an AID grant for trilateral research involving NIH and an Israeli institution, has plans

¹Note: The author visited NAMRU-3 in April of 1985, and subsequently expanded this description, intended to be illustrative of the operating conditions of all the overseas military laboratories.

to develop its own P-3 facility but uses NAMRU-3 laboratories now and will continue to want NAMRU collaboration when its own laboratory is functional.

On bacterial diseases, the military and government interests diverge. NAMRU-3 works on cholera in Somalian and Ethiopian refugee camps but is discouraged from working in Egypt for fear of adversely affecting tourism. In Egypt cholera does not officially exist, but summer diarrhea, an identical malady, does. Clinical trials of drugs are often sensationalized by allegations of human experimentation.

Among parasitic diseases, schistosomiasis is the major infectious disease problem for Egypt. It does not have a high military importance, but substantial research is done for the benefit of the host country. Malaria has a very high military priority but is of minor interest in Egypt, so studies are conducted in other parts of Africa.

Problems sometimes arise because of differing cost horizons. Some drugs are considered to be too expensive; experimental trials are resisted.

Government of Egypt clearance is required in all NAMRU-3 publications and field work plans. The process causes delays and can cause the laboratory to miss scientific opportunities, as in the case of unusual viral activity noted in the field.

Most of NAMRU's staff of 300 people are Egyptian. The scientific staff consists of around a dozen each of Egyptians and Americans. No area of the laboratories is off-limits to Egyptians. NAMRU is able to accept 5-10 Egyptian graduate students or interns per year, although training is not part of its mission. The students are guided by Navy scientists. The students must bring their own funding and be working on topics of interest to NAMRU; they contribute more than they cost scientifically.

The NAMRU medical library, the best in Egypt although its collection is geared to the NAMRU mission, is open to graduate students as space and staff time permit. Around 50 students per day use the library, but 100-200 would like to do so.

A new laboratory building, completed only a year ago at a cost of around \$10 million in Public Law 480 blocked currency, and \$4.5 million in hard currency for equipment, sets NAMRU-3 apart from the other military laboratories overseas. The operating budget and ceilings of NAMRU-3 were not raised to take advantage of the new facility, so it has been underutilized.

Costs and Staffing

The cost of maintaining these seven facilities abroad in 1980, including military pay and special foreign currency allocations, was approximately \$6 million. In the late 1970s, the overseas laboratory system of the military services came close to extinction. Ambassadors complained that the number of official Americans attached to their embassies from other agencies was often burdensomely high. To cut expenses and lower the official profile abroad, the Office of

Management and Budget (OMB) instituted a manpower accountability system--Monitoring Overseas Direct Employment. OMB teams reviewed the status of official representation in six of the countries in which DOD had laboratories. The reports of two of these teams did not mention the laboratories. The other four recommended that the DOD medical research laboratories' staffing not be reduced. These recommendations were disregarded, and DOD was directed to prepare for the elimination of the overseas laboratories, through closure or conversion to contractor operation. Value and quality of the laboratories were not questioned. At issue was simply the number of official Americans abroad.

DOD responded by conducting an exercise culminating in a report by Col. Phillip Winter, arguing for maintaining the laboratories under direct military control. A group of civilian scientists served as consultants to the study. They reviewed the history, missions and functions of the laboratories and some of them visited four overseas locations: Kenya, Indonesia, Egypt and Thailand.

The Winter report concluded that contracting-out the operation of these laboratories would be neither desirable nor feasible. The study found no evidence that changing the mode of operation would increase productivity and efficiency or produce savings of manpower or dollars. To the contrary, it found that contractor operation would decrease the research productivity, increase costs and administrative problems, degrade the ability of the laboratories to respond to changing military requirements or emergencies, deprive the DOD of valuable recruitment, retention, and training incentives, and incur unfavorable host-country reactions.

The quality of the consultants and the cogency of their statements made a compelling case for the DOD position. One of the most comprehensive statements was made by Dr. John R. Seal, formerly commander of NAMRUS 3 and 4. Seal, NIAID deputy director, knew the NIH's ICMRT program well and compared the effectiveness of the overseas military laboratories with that of the ICMRT laboratories. In his view few universities had the capacity to conduct multidisciplinary research programs in infectious diseases abroad and none could mount as broad a program as carried out by the largest DOD laboratories overseas, in Cairo and Bangkok. Nor did he think contractors could be found with staff or experience to conduct an program acceptable to meet military needs.

The president of one prominent pharmaceutical company and the research director of another argued in effect that contracting out to private industry would not provide a satisfactory substitute for the military laboratories abroad. The reasons pertained mostly to skill shortages and career patterns. There was no surplus of qualified scientists and clinicians who could be engaged to conduct the work of the laboratories abroad. Competent scientists who might have been available would risk career disadvantages by taking an assignment abroad for a year or two. The military services would be deprived of the pool of trained and experienced tropical disease specialists that the system produced.

Among unsolicited comments cited in the Winter Report is one from Professor Thomas Weller, Nobel laureate and head of the Department of Tropical Public Health at Harvard University from 1954 to 1983. Weller, too, concentrated on the shortage of skilled manpower. He noted a global shortage of tropical disease specialists, particularly epidemiologists, pathologists, medical entomologists, and medical malacologists. Few academic institutions, he said, have faculty qualified in the scientific disciplines basic to the study of tropical diseases, and no U.S. academic institution could from its ranks provide the equivalent of the scientific staff of the Navy laboratory in Cairo. Even an academic consortium, if one were formed to take over a laboratory, would be faced with providing dual salaries, to cover the discipline in the parent institution while the alternate was abroad; salary guarantees upon return home for those who accepted service overseas; and staffing complications from family factors and academic pressures for publication.

Scope

The military laboratories, and the research and development commands of which they are a part, are responsible for a very broad range of actions. They conduct biomedical research on the nature of disease organisms, clinical research on the effects of a disease on people, epidemiological research, and drug and vaccine development and testing. Their mission is not completed until they find the means to protect members of the U.S. armed services from the deleterious effects of diseases.

In pursuing their mission, the military laboratories generate a great deal of knowledge useful to host-country scientists and health practitioners, and this knowledge is freely shared. This range of action and responsibility, broad as it is, does not fully cover the spectrum. The military laboratories are not charged with concern for local community health problems and for the development of very-low-cost preventions and remedies.

Collaboration

The nature and extent of collaboration with local scientists and institutions by each military laboratory abroad varies from country to country:

USAMRU-Brasilia is fully integrated into the Nucleo de Medicina Tropical of the University of Brasilia. A small number of USAMRU researchers work under the direction of Prof. Aluzia Prata, head of the Nucleo de Medicina Tropical.

USAMRU-Kenya has strong ties with the Kenya Institute for Medical Research, where it conducts collaborative research on visceral leishmaniasis. It is also linked with the Kenya Trypanosomiasis Research Institute at Mugugu.

USAMRU-Malaysia conducts collaborative research with the Malaysian Institute of Medical Research on the immunology and epidemiology of scrub typhus and vector chiggers.

AFRIMS-Bangkok is really a two-country laboratory. The Thai military component shares the same quarters as the U.S. component, but each tends to conduct its own research. Vaccine trials have been conducted in cooperation with the Thai military medical staff. Additional collaboration, on Japanese encephalitis, occurs with Mahidol University and with the children's hospital across the street from AFRIMS.

NAMRU-2 in Manila has collaborative relationships with the San Lazaro Hospital, the Bureau of Research and Laboratories, the Schistosomiasis Control Council, provincial and city health departments, the University of the Philippines Medical School and Institute of Public Health Veterans Hospital, the Santo Thomas University Hospital, the Subic Naval Hospital, and the Clark Air Force Base Hospital.

The NAMRU-2 Detachment in Jakarta maintains working relationships with and uses laboratory space provided by the Ministry of Health in the compound of the National Institutes of Health, Research and Development, and the Communicable Disease Center. The detachment works also with provincial and city health departments, the Indonesian navy, the University of Indonesia Medical School and Hospital, the Sumber Waras Hospital, and the University of Gadjah Mada Department of Microbiology. Program content is subject to approval by a joint U.S.-Indonesia coordinating committee.

NAMRU-3 was considered by Egyptian officials interviewed by the Winter team to be one of Egypt's major health assets, the leading local institution for training in medical research. Since 1945, most of Egypt's best medical researchers have trained or worked at NAMRU-3 at some time in their careers.

NAMRU-3 collaborates closely with Ain Shams University, the Egyptian Vaccine Institute, and the Abbassia Fever Hospital. Outside of Egypt, NAMRU-3 cooperates with the ministries of health and agriculture in both Sudan and Somalia.

Impact on Disease

The most famous contribution overseas of the military to the control of disease was of course made by Walter Reed in Cuba at the Turn of the Century. His work helped Col. William Crawford Gorgas to control yellow fever and malaria and made possible the construction of the Panama Canal.

Less dramatic but perhaps even larger scale results flowed from the work of the U.S. Typhus Commission laboratory in Cairo. In World War I, six million deaths were attributed to typhus fever. To forestall a similar tragedy, President Franklin D. Roosevelt set up the commission in 1942 with members from the Army, Navy and the Public Health Service. The Cairo laboratory was instrumental in curtailing a typhus outbreak in Egypt and a serious epidemic in Naples. In addition, the laboratory

isolated various strains of typhus organisms from Africa, Asia, and Europe and sent them to the United States for testing against vaccines. The laboratory first field-tested DDT as an insecticide against lice, the vector of typhus.

NAMRU-2 contributions include work on effective cholera therapies, including oral rehydration, and major advances in understanding of the etiology, diagnosis, treatment and prevention of chloroquine-resistant malaria, several major viral diseases including dengue and Rift Valley fever, cerebrospinal fluid meningitis, hemorrhagic fever, schistosomiasis, and leishmaniasis.

Impressive as these contributions are, the Winter report assigned yet greater value to the ability of the laboratories to develop medical personnel with experience and understanding of tropical disease and to monitor disease status in strategic areas of the world.

Capacity Building

The military laboratories contribute to strengthening local capacity in a variety of ways. The smaller laboratories function within or in direct association with local institutions, which benefits the latter through collaborative association, provision of equipment, and training. AFRIMS strengthens the medical research capabilities of the Royal Thai Army, although it has less of an impact on the university-based research community. NAMRU-3 in Cairo performs a valuable training function and maintains the best medical library in Egypt.

The requirement that the overseas laboratories study only diseases of potential military importance is a constraint; for example it limits the amount of attention that can be paid to childhood diseases. However, in general, it is not an onerous restriction in terms of the selection of maladies for investigation. The priority assigned to military matters is probably a greater constraint on the amount of effort the laboratories make to strengthen local capacities for work on tropical diseases.

It is to this area of strengthening local capacities, however, that most suggestions for strengthening the work of the overseas military laboratories are frequently directed. More medical personnel from the less-developed countries could be trained in these facilities. With additional resources, the functions of the laboratories could be augmented by a clinical role. One proposal is that one or more laboratories test the expanded role of becoming a regional center for clinical tropical medicine, research, and training. The trust and good will that DOD has built up with these laboratories abroad can further foster the humanitarian goals of the United States.

Conclusion

The balance sheet on the overseas military laboratories is strongly positive. They operate across a broad range of activities concerning

tropical diseases, from monitoring their occurrence to biomedical and clinical studies, epidemiology, and the development of preventive and therapeutic measures to protect members of the armed forces. They create a career corps of active specialists in tropical medicine within the military and are able to dispatch trained teams on short notice to remote areas of the world. They are generally welcome additions to the U.S. presence abroad in the countries where they are located. The chief reservations concerning the system seem to be that because of limitations of funds and narrowness of mandates the potential benefits of these overseas installations may not be currently realized. It is possible, too, that the military nature of the facilities could become a liability, particularly if efforts were made to expand their functions.

GORGAS MEMORIAL LABORATORY, PANAMA

The Gorgas Memorial Laboratory for the study of tropical diseases was founded in 1928 by the Gorgas Memorial Institute, a private, nonprofit U.S. organization, in memory of Maj. Gen. William Crawford Gorgas. The land and original buildings were donated by the government of Panama, and the U.S. Congress authorized an annual contribution for operating funds. This contribution continues, in amounts up to \$2 million. Panama contributes a modest research fund and grants tax advantages. Additional contracts and grants for research are received from U.S. agencies and international programs for specific projects.

Originally, core support for operating expenses passed through the U.S. Department of State. In the mid-1950s, NIAID administered the award, and this responsibility was passed to the Fogarty International Center of NIH in 1971. Administration of the grant does not carry with it the power to govern or control the laboratory, which remains private, governed by a 47-member board of directors based in Washington, D.C.

In 1983, NIH responded to pressures on its budget by including no funds for the laboratory in its budget request. NIH said funds provided to the laboratory were not subject to the same peer review process as other NIH programs and the savings would be used to fund additional investigator-initiated research.

There can be no doubt that NIH does not welcome the role of conduit for funds over which it can exercise no control for quality or process, but the decision to omit funds for the laboratory altogether from the budget may have reflected an awareness that neither the Congress nor the Department of State was likely to permit the laboratory to founder at a time of heightened political tension in Central America.

A U.S. Senate request led to a General Accounting Office (GAO) study of the scientific review procedures applied to work at the laboratory, the similarity of research at Gorgas to other Federally funded research, and the extent of efforts to broaden the base of financial support for the laboratory. At the same time, the Senate requested the Office of Technology Assessment (OTA) to examine the quality and relevance of research at Gorgas.

The Gorgas Laboratory began, and achieved distinction, as a research institute concentrating on malaria, trypanosomiasis, and leishmaniasis. It has always played a role in surveillance of yellow fever. More recently, increased attention has been given to other insect-borne diseases as well, and their vectors. In addition, current projects concern sexually-transmitted diseases, specific cancers, and ecological studies. Some projects involve clinical work; about 1,000 patients per year are treated as a service to the community and a source of learning about the natural history and treatment of disease invasions of the isthmus from South America. The laboratory also offers access to a supply of Aotus monkeys, an animal useful for malaria studies. A six-week tropical medicine course, sponsored by the U.S. Navy, is the principal training activity. The laboratory also hosts predoctoral and postdoctoral students and scientists.

The laboratory's scientific staff in 1983 consisted of six U.S. scientists, nine Panamanians and one Peruvian, all under the direction of Raymond H. Watten, Phillip's colleague in Bangkok and later commander of NAMRU-3 in Cairo.

The laboratory's annual budget over the last several years has run about \$2.5 million, of which about \$1.8 million has been core support. In Fiscal 1985 the budget was over \$3 million, with \$2 million in core support.

The OTA review of the scientific facility and relevance of work at Gorgas gave the laboratory high marks. OTA noted the special value to U.S. science of a laboratory located in the tropics and found over-all scientific quality at the laboratory to be high, if a bit uneven. With exceptions almost entirely in the core-funded activities, OTA found the research relevant to the various parties at interest. OTA made several suggestions for improvement, including the proposal that Gorgas seek more association with universities and collaboration with groups from other countries and international organizations. The report also recommended that better use be made of its Advisory Scientific Board in planning research and as part of an improved peer review process. Also, the laboratory should plan to move more fully into modern scientific technologies, such as use of monoclonal antibodies and other immunological diagnostics and biotechnology for vaccine research and development. The over-all conclusion of OTA was that the positive attributes of the Gorgas Laboratory far outweighed its costs, and that defunding would be a mistake.

The GAO study was somewhat more critical but found no evidence that the laboratory's research was unneeded, duplicative, or of poor quality.

GAO was particularly critical of Gorgas for little effort to expand its financial base. In recent years, only Panama has made financial contributions, in amounts under 4 percent of total cost, in addition to those of U.S. agencies. The institute contacted 150 foundations and other private funding organizations without encouraging results. Other countries in Central America were not solicited because they were thought to be too poor to contribute. WHO and the Pan American Health Organization, contacted by GAO, indicated they could not provide additional funding.

Among the alternatives for funding the laboratory suggested to GAO was the internationalization or regionalization of Gorgas. Internationalization on the model of ICDDR,B is one possibility. Regionalization along the lines of INCAP, the model for the original SEATO cholera laboratory in Dacca, is another.

The Panamanian Minister of Health formally proposed internationalization in 1982, suggesting that his country and other states of the region would be more willing to contribute if invited to participate more actively in laboratory decisions and if they would greater benefits from the research. The minister later had reservations about his own idea, because the laboratory could end up like INCAP, with some member countries far in arrears in their payments but still participating in laboratory decisions. A U.S. Department of State official noted that internationalization would not well serve some of the laboratory's purposes, including improving environmental and health quality in Panama, training military physicians, and serving diplomatic interests in dealing with the government of Panama.

Another set of critical GAO findings concerned the processes of planning and administering research at the laboratory. GAO could identify no formal long-range program plan or planning process for the work of the laboratory. The recruitment process is said to set the shape of the program. Scientists appointed to staff positions are free to determine their own research directions, subject to an internal review. The review process is informal, and, given the small number of scientists at the institution and the diversity of their interests, cannot approximate the quality of the internal review process at NIH. External reviews are conducted approximately every three years by the Fogarty Center. The 24-member Advisory Scientific Board has been rarely utilized and has never met as an entity.

All this does not necessarily reflect adversely on the quality or productivity of the laboratory. Both OTA and GAO found the publication record of Gorgas scientists to be good, and the Fogarty external review team in 1980 concluded that the laboratory's studies were of scientific importance to the United States, Panama, and the region. Over-all research quality was high, and the scientific value and benefits derived from the laboratory were deemed a worthwhile return on U.S. investment.

The OTA and GAO reports offered ample grounds for the Congress to insist that funding be restored to the endangered laboratory, and within the Executive Branch, the Secretary of State urged in a letter to the Secretary of Health and Human Services that the matter be reconsidered because defunding would be inconsistent with U.S. posture in the region. This episode demonstrated the practical lack of a mechanism other than agency-head intervention for the consideration of diverse elements of the national interest in assigning budgetary priority to such projects. Each agency typically defines its priorities under its own terms of reference and authorizations, taking no formal notice of the multiple benefits that an activity may produce.

Scope

Gorgas is an unusual resource, able to conduct basic and applied research in a tropical setting with extraordinary diversity of endemic problems. Its range of activities, including some clinical research and drug and vaccine testing, is very broad. However, it is not focused, as was the Pakistan-SEATO lab, on a single family of diseases, nor is it part of a coherent, targeted effort against a disease, as are the military laboratories, except for those parts of its work which are contracted for by the U.S. armed forces or other agencies. The result is not a wide range of activities along a single spectrum but a wide variety of activities along disjointed segments of different disease spectra.

This may be a problem of insufficient numbers of scientists working together on particular problems. If Gorgas had a single disease concentration, or if it were an integral part of the research program of a major laboratory such as NIAID or WRAIR, it might have more impact on one or more diseases.

At one time, Gorgas appears to have had a somewhat greater concentration on a single disease--malaria. Investigators have worked on vector biology, vector control, response of the parasites to drugs, drug resistance, epidemiology, monkey hosts, and other aspects of malaria.

Collaboration

Gorgas has good working relationships with Panamanian Ministry of Health and hospital authorities, without whose cooperation field and clinical studies could not be conducted. Informal ties are also maintained with the Smithsonian Tropical Research Institute (STRI), another U.S. biological institution operating in Panama. At various times Gorgas scientists have collaborated with STRI scientists in specific research projects. Relationships outside Panama have occurred with the Medical Entomology Research and Training Unit in Guatemala, the Centers for Disease Control, NIH, Louisiana State University, the University of Alabama at Birmingham, Johns Hopkins University, and other academic and scientific institutions. It has undertaken a number of activities, such as conducting environmental assessments of major project proposals, which are of service to the government of Panama. It has not, in general, sought to establish collaborative relationships with other institutions in the region or to expand its training programs to accommodate very many scientists from the region.

Impact on Disease

OTA reported favorably on the value of the Gorgas research to U.S., Panamanian, and regional health concerns and to biomedical research generally.

Capacity Building

One observer familiar with the scientific program at Gorgas noted that the laboratory has done relatively little clinical investigation, with the exception of some work on cutaneous leishmaniasis. In general, opportunities for collaborative clinical studies with Panamanian hospitals have not been fully exploited.

The laboratory contributes to expanding U.S. capacity for research and disease control through its training course and its facilities, which offer access to a useful primate population and to areas in which many insect-borne diseases are endemic. Several Panamanian researchers are trained and employed at Gorgas, frequently moving on to university or public health positions in which their Gorgas experience is invaluable.

Gorgas has not had as part of its mission history the building of local and regional research capacities. This appears to be a major shortcoming of the present operation, one that could probably not be remedied without additional resources.

Conclusion

NIH has no express mandate to initiate medical activities for diplomatic purposes. The State Department lacks the expertise and the specific mandate. None of the U.S. Government's mission agencies is in a position to define the optimal use of U.S. resources for medical research in the Caribbean in light of scientific, diplomatic, military, developmental and humanitarian considerations, all of which are elements of the national interest.

The U.S. Government's supply of 75-80 percent of the core funding and most of the grant and contract funding of a private institution, Gorgas, is atypical. Some sources mentioned in the OTA report thought that the Board of the institute was and remains an obstacle to its internationalization. However, two official U.S. laboratory facilities--the NIH Middle America Research Unit and a USAMRU--were established in Panama since the Gorgas Laboratory was set up and both have had to close for budgetary or personnel reasons. Gorgas has survived, perhaps because it is not a part of the Federal system.

A third--not strictly comparable--entity, STRI, has been operating in Panama since 1962, is a bureau of the Smithsonian Institution, and has not had to face obstacles similar to those faced by Gorgas in ensuring its funding. As a custodian of Barro Colorado, a natural preserve established by the governor of the Canal Zone and subsequently recognized in the Carter-Torijos treaty, STRI is accepted in Panama as a conservation organization. Like Gorgas, STRI has to present its budget (through the Smithsonian) for approval by Congress each year. STRI presently operates in Panama under a contract with the ministry of health.

STRI has secured funds from the Exxon Foundation for scholarships and assistantships to Latin American students and from the Tinker Foundation for sabbatical visits to STRI by prominent Latin American

researchers. A similar fund-raising effort by Gorgas could pay dividends in the training of (and interactions with) Latin American scientists and in good will generated in Panama and elsewhere in the region.

INTERNATIONAL CENTERS FOR MEDICAL RESEARCH AND TRAINING,
INTERNATIONAL CENTERS FOR MEDICAL RESEARCH,
AND INTERNATIONAL COLLABORATION IN INFECTIOUS DISEASE RESEARCH

In the late 1950s, NIH health strategists were aware that, although greatly expanded during World War II, the capacity of the U.S. medical establishment to deal with tropical diseases was atrophying. They deemed it important to maintain at least a modest level of interest and competence in tropical medicine among U.S. biomedical scientists and made plans to establish several training centers in port cities in the United States.

The passage of the International Health Research Act in 1960, Public Law 86-610, allowed NIH to expand its concept and include overseas activities. The authorization provided for international cooperation in health research, research training, and research planning in order to advance the status of the health of people of the United States. Authority to engage in international cooperation to advance the health sciences internationally was accorded to the President. Delegation of that authority has been enjoyed recently only in the U.S.-Japan cooperative medical research program.

Congressional hearings in 1962 suggested that NIH was precluded from participating in overseas programs for the benefit of non-Americans. Congress did not want the confusion and duplication that could arise if the foreign assistance program were fragmented.

Consequently, the language establishing the International Centers for Medical Research and Training (ICMRT) program refers to benefits that will accrue to U.S. citizens. The program's principal purposes were to provide stable, long-term overseas sites for research and research training on environmental, ethnic, and biomedical conditions of scientific interest that could not be studied directly within the United States. This extramural program would increase the number of U.S. scientists competent in biomedical research and familiar with health problems in other countries. Underlying these objectives in the minds of NIH and NIAID directors was an intent to strengthen research capabilities of developing country universities by twinning them with U.S. counterpart institutions. Thus research efforts were to be broadly based, not narrowly targeted to a few tropical diseases. At the same time, they took steps to promote and strengthen international collaborative research within NIH's own laboratories.

Four grants were made to universities in 1960 and one the following year for the establishment of overseas centers at cooperating universities abroad:

- o University of California in San Francisco, with its overseas center at the Institute for Medical Research in Kuala Lumpur.

Units were also located in the Faculty of Medicine, University of Singapore, in the 1960s, and in the faculty of Medicine, University of Malaya from the mid-1960s on.

- o Tulane University School of Medicine, with its overseas center at the Universidad del Valle in Cali, Colombia.
- o Johns Hopkins University School of Medicine and School of Public Health and Hygiene, with their center at the Calcutta School of Tropical Medicine and the All-India Institute of Hygiene in Calcutta, India.
- o University of Maryland School of Medicine, with its center at the Institute of Hygiene and the Medical Institute College at Lahore, Pakistan.
- o Louisiana State University School of Medicine, with its center at the University of Costa Rica School of Medicine in San Jose, Costa Rica.

The grants were for 5 years, averaging \$500,000 per year, which stayed fairly constant as its value declined through inflation. One of the express purposes of the program was to provide stable bases for work in tropical medicine on which people could plan their careers with confidence in continuing employment opportunities. The program was never re-advertised, but the grants to a participating institutions were renewed after periodic reviews. The original four universities each remained active for the full 20-year span of the program. Louisiana State University was dropped from the program in 1970, when a reduction in funding made it necessary to reduce the number of centers. The total cost of the program was about \$45 million. Successful institutions used their grants as core funding and were able to attract personnel paid from other sources. Thus the total expenditure was always much greater than the total of the NIH grant.

The grant conditions allowed the universities broad latitude in designing their programs, depending upon the interests of faculty members and the medical priorities in the area in which their centers were located. Although most of the work would deal with infectious diseases, other subjects, such as malnutrition, genetic diseases, and population dynamics, were eligible for inclusion. Interdisciplinary approaches were to be employed, including the social sciences.

The California-Malaysia center conducted research on arboviruses, especially dengue, because of its prevalence in Malaysia. Scientists at the center demonstrated that, although usually an urban disease, dengue infection occurs in monkeys in the forest canopy and that a previously unknown mosquito is a probable vector.

Another important segment of the Malaysia program was parasitology, especially host-parasite interaction, with special attention to natural or acquired resistance of vector snails to the larval stage of human parasites. The long-range objective was to develop biological methods to control snails, the vector for schistosomiasis and other parasitic diseases.

U.S. social scientists and epidemiologists collaborated with Malaysian scientists in studies of Malaysian community health, ethnomedicine, demography, traditional Malaysian medical care, and sociomedical determinants of disease. The variety of peoples in the country provided opportunities for the study of abnormal hemoglobin occurrence and other genetic conditions, such as thalassemia. This work was closely coordinated with similar studies in San Francisco.

Some of the center's offices and laboratories were located in the same building as USAMRU-Malaysia. The pattern of association was quite different. USAMRU research generally was quite self-contained, its own personnel working in its own laboratories. The center's people were dispersed throughout the institute, working as staff members of its research divisions. Extensive collaboration resulted in many fields over the years from this arrangement. Only a few of the center's researchers collaborated with USAMRU scientists, possibly because having come halfway round the world they were eager to work with Malaysians rather than Americans.

The Tulane-Colombia group conducted a vigorous program on malnutrition, including clinical research on hospitalized adults and children, experimental animal studies, and field surveys. This was possible because of excellent Colombian investigators who were interested in a range of nutrition issues.

The second largest effort by Tulane was on infectious parasitic diseases, including Chagas' disease (American trypanosomiasis), intestinal parasites in school-age children, and the ecology of insect vectors of parasites of man and animals. Epidemiological investigations of diarrheal disease and fungal infections were also conducted.

Encouraged by the ICMRT Advisory Committee, the Tulane-Colombia center added program elements in behavioral sciences and social epidemiology, including social psychiatry, health systems, anthropology, health service utilization, and psychiatric origins of criminal behavior.

In 1975, Tulane changed its institutional affiliation from Universidad del Valle to COLCIENCIAS, the Colombian national research council.

The Johns Hopkins-Calcutta group did not concentrate exclusively or primarily on diarrheal diseases. Their research efforts included hepatitis, malnutrition and anemia, filariasis, and the ecology of certain insects and mammals in India.

After the move in 1972 to Dacca, the work focused primarily on diarrheal diseases, nutrition, and population dynamics. The last two years of the project found the ICMRT in collaborative research on diarrheal diseases with the Gorgas Memorial Laboratory in Panama.

The Maryland-Lahore center's most active studies were of genetic variations in mosquito species. These studies were for the purpose of devising methods for biological control of vectors of malaria and arbovirus infections. Another project dealt with the treatment of drug-resistant malaria found in Pakistan, and additional work was done on scrub typhus.

The Louisiana State University-Costa Rica group focused primarily on parasitic infections, working also on viral infections including hepatitis.

In 1973, the training element was dropped. The ICMRT program became International Centers for Medical Research (ICMR). NIH felt strong pressures from OMB and the Congress to reduce training at NIH. The word training in the name of any program could jeopardize its existence, so it was dropped. The training intended in this program was only meant to benefit U.S. scholars, so the change in titles may have been expected to have produced little change in practice. However, in the opinion of Frederick Dunn who spent seven years in Malaysia under this program, the consequences of the change were enormous. In his view, the strength of the program was in the training and experience it provided for hundreds of U.S. health science professionals in the developing countries. Dropping the training was one step on the road that led to the demise of the program.

An earlier step on the same path was transfer of its funding to the budget of NIAID in 1968. Previously, ICMRT had been insulated from the research focus of any single NIH institute by being administered by the Office of International Research. Transferring the program to NIAID led to increasing pressures for emphasis on infectious diseases research and on research as such rather than research training. According to Dunn, work by hematologists, geneticists, social scientists, cancer epidemiologists, psychiatrists, and heart-disease epidemiologists was increasingly viewed as inappropriate. The program gradually became a tropical disease research program instead of a medical research and research training program in the tropics, as it had begun. Another reason for refocusing the program was underfinancing. The funds made available to the program in its last 10 years were insufficient to support a broad mission.

Despite program's size and significance, it received no formal evaluation when it ended in 1980. An evaluation plan was drawn up and discussed with the Institute of Medicine of the National Academy of Sciences, but in the end NIAID decided not to follow through with it. There is no comprehensive document on which to rely for judgments of the outcome of this relatively large investment of research funds.

A rather formal mid-course study of the Tulane program was conducted by Shirley B. Laska of Tulane in 1974.

Each of the grantee institutions negotiated its own arrangements with its hosts. All found it necessary to make some accommodation to the professional needs and interests of the host institution, but there was a good deal of variety in the result. Some centers were in effect U.S. laboratories housed abroad for convenience. This was consistent with the terms of the award but sometimes made it difficult to demonstrate program benefits to host-country institutions. In other cases, such as California-Malaysia, the center was a highly collaborative association of U.S. and Malaysian scientists working in laboratories and in the field.

Tulane was on the collaborative end of the spectrum. A project advisory committee governed field activities. Colombians were represented on it beginning in 1965 and for a time were a majority of

the committee's members. In 1969, the committee was reorganized, with three members appointed from Tulane and three from Valle. All members had equal voting power. Valle members could veto any research proposal made by someone from Valle, Tulane, or some other institution. The Tulane members could veto any proposal approved by Valle members. This arrangement assured that all proposals were deemed appropriate and important by the host institution and that Tulane could remain responsible to NIH for the pertinence and quality of the proposals accepted.

Tulane recognized that facilitating Colombian research and training Colombians was of major importance, not only to ensure their own welcome but also because of the dearth of other research opportunities for their colleagues. This goal was not formally acknowledged, however, because of the terms of the grant. It would not do to be perceived as offering foreign assistance.

Even while enjoying a share in the governance of the project, and access to research funds, some of the Colombians complained that they did not have equal access to facilities and funds. Some of the U.S. scientists complained that the selection process was subject to personal biases and that they were somewhat isolated professionally while in Colombia.

In general, the project appears to have been successful, popular, and productive: 25 theses and dissertations were produced in its first 13 years, and 244 publications, 22 percent of which first appeared in Spanish.

Laska commented that the Valle scientists considered one of the project's principal values to be the opportunity to gain a better understanding of the medical problems of their country, but this was "not of special concern" to the U.S. participants, "who as researchers have a greater concern for the advancement of scientific knowledge." This may represent only the author's personal judgment, but it may also reveals a common attitude in the medical research community. It could account for the fact that nowhere in the examination of participants' feelings about personal advantages gained from the program is there mention of the possible impact of the research on the disease burden of Colombians. That was not the purpose of the program, nor apparently was it the result.

In addition to the Laska study, evaluative comments on the ICMR program are found in John Seal's letter of support for the military overseas laboratories. This letter was written in 1980, when the ICMR program was already at an end, and the military laboratories were endangered, so Seal's remarks may tilt somewhat in favor of the military model in the interests of maintaining national capacity for field research abroad. Also, Seal had had a Naval career. Nonetheless, his points are instructive. He wrote that there is no career available in U.S. academic institutions for individuals whose primary interest is international medical research and that lasting competence cannot be established through grant and contract programs that do not produce tenured positions.

As evidence, he said, 20 years of stable ICMRT-ICMR support for 4 of the better U.S. medical schools failed to build a continuing U.S. capacity for international work on infectious diseases. Capacity seemed instead to have declined, as indicated by the failure of three of the four schools to compete successfully for the grant program that followed--International Collaboration in Infectious Disease Research (ICIDR). This point is a bit unfair, because many in the universities saw the ICMRT-ICMR program primarily as a training vehicle to prepare people for careers in other institutions, not their own. The ICIDR competition was different. Many of the participants in the preceding program were interested in medical issues in tropical countries but not specifically in problems of infectious diseases.

Seal also pointed out that schools of medicine offered few opportunities for entomologists, veterinarians, sanitary engineers, and other specialists often needed in overseas research. Nor did physicians with valuable international research experience tend to stay in the field. NIH had another program, from 1963 to 1969, aimed at giving overseas research experience to young physicians. By 1979, of the 23 physicians assigned through the program to military overseas laboratories, ICMRs, or the Cholera Research Laboratory in Dacca, 1 remained in the U.S. Government and 8 in academic medicine; of the 8, only 3 had a current relationship to overseas research. These figures were challenged by one participant, who personally knew of 8 still very active in tropical medicine. Perhaps some left the field immediately after their initial experience and later returned.

In 1974, in anticipation of a full scale review of ICMR program accomplishments before the fourth round of funding, Howard Minners, a Public Health Service officer charged with administering the program at NIAID, wrote an article in which he broached a number of issues concerning operations of the program. Among them were the following:

- o How could ICMR achievements be evaluated quantitatively for their contributions to scientific programs and to individual careers?
- o Were participating universities able to maintain a sustained level of high quality research in the field?
- o How sharp a focus is appropriate? Should each center select a single theme?
- o How relevant are the center's research programs to NIAID objectives?
- o What concentration of specialists, what critical mass, is needed for centers abroad?
- o Should the centers be located to cover a broad geographic range?

The anticipated review did not take place. Instead, in 1976, a decision was made to redefine, restructure, and re-advertise

international research grants, with the ICMR allowed to terminate in 1980. The new NIAID director felt strongly that the original broad mission envisioned for the ICMRT program should be supported by more than one NIH institute or by central funds. Therefore the new program was designed to reflect NIAID's mission, and the intent was to stimulate fresh approaches for research on tropical diseases.

The new program, ICIDR, is more narrowly confined--to research in immunology and infectious diseases. It emphasizes work on the diarrheal diseases plus the six diseases targeted by the international Special Programme for Research and Training in Tropical Diseases (TDR)--malaria, schistosomiasis, filariasis, the typanosomiasis, the leishmaniasis, and leprosy. The importance of building the research capacity of the host-country institution is explicit, and 70-80 percent of the funds are to be spent abroad on problems relevant to health status of the local people.

The ICIDR program was announced in 1975. Of the 14 proposals received, 6 were rated average or better, and 5 were awarded 5-year grants. Tulane was the sole survivor from among ICMR institutions. The University of Maryland project failed the competition but received continued NIH funding for two years because of State Department pressure to avoid closing the program in the midst of a period of diplomatic tension.

The successful applicants and their host institutions were the Harvard School of Public Health, with the Federal University of Bahia, Brazil; Cornell School of Medicine, with the Federal University, Bahia, Brazil; and the University of Brasilia; Bahia, Brazil; Michigan State School of Medicine, with the Central Laboratory of the Ministry of Health, Khartoum, Sudan; the University of Illinois School of Medicine, with Chiang Mai University, Thailand; and Tulane University School of Public Health and Tropical Medicine, with COLCIENCIAS, Cali, Colombia, and Institute Francais d'Haiti, Port-au-Prince, Haiti.

The first cycle of ICIDR awards ended in September 1984. Tulane, Harvard, Michigan State, and Cornell competed successfully for the second round. Three new projects were also funded: Yale University, in Bogota, Colombia; Johns Hopkins University, in Lima, Peru; and Wayne State University, in Addis Ababa, Ethiopia.

ICIDR also provides exploratory grants to individual scientists. Grants totaling \$277,000 were made in 1980 for projects in Mexico, India, Nigeria, and Brazil. In the second round, grants were made for work in Indonesia, Venezuela, Kenya, and Brazil.

Total funding for ICIDR is about \$2.8 million, around the same level as earlier expenditure for ICMR. Each institutional project receives only about half the amount annually that went to the ICMRs.

U.S. ICIDR investigators do not usually reside abroad; generally, they visit overseas for four to six months at a time. ICMR investigators were often abroad for two or more years. Training is not a primary objective of the ICIDR program, nor was it of ICMR in the later years. Foreign investigators are allowed travel funds now but were not under ICMR.

An informal report to NIH from the Michigan State group in October 1984 describes a vigorous collaborative program, thriving under conditions of political uncertainty.

Ten Sudanese scientists are full participants in research in the field and frequent visitors for varying periods to Michigan State. Eight senior Michigan State scientists and six graduate students and research associates have participated. A number of clinically trained students plan to pursue careers in tropical medicine and infectious diseases, one of whom hopes to do so in the military.

Research underway includes investigations of genetic and other sources of immunity to malaria, monitoring pathologic changes in schistosomiasis, the epidemiology of onchocerciasis, which can cause blindness, and testing of various therapeutics. Research funding supplementary to the ICIDR has been received from various departments of Michigan State and from several pharmaceutical companies.

Scope

The ICMR program seems to have extended further along the problem-solving spectrum of international health than the ICIDR program because it included a broader range of investigators, such as social scientists. This may be an illusion. The social scientists in Cali, for example, followed their own research interests, not necessarily relevant to the diseases of concern to their medical colleagues. Similarly, in Malaysia, the center avoided interdisciplinary research. The California group sought to support people with outstanding research ideas and plenty of enthusiasm rather than to find people to fit predetermined slots in existing research projects.

Investigator freedom to define the research task is the hallmark of the sponsoring agency, NIH. The annual site visits to the ICMRs arranged by NIH were considered by staff to be unusual, made necessary perhaps by the breadth and complexity of the enterprises. They were also a major factor in helping the individual field directors to maintain quality and phase out programs and individuals who were unproductive. The stronger the program the more the visits were appreciated. The ICMR committee was remarkably stable, competent, and dedicated, and the annual site visits and meetings in the U.S. with host institution principal investigators were a major factor in the relative success and longevity of the program.

It would be unfair to criticize the ICMR program for not being a tightly knit, targeted attack on tropical diseases when that was not its stated purpose. It is legitimate to question, however, whether the approach favored by NIH and the university community would be the most effective way to use limited funds if the purpose were to reduce the disease burden for people who live in the tropics. Perhaps the optimal pattern of organization for stimulating new discoveries and for training outstanding researchers is not ideal for carrying the scientific process to the point where people directly benefit from it.

Collaboration

Close collaboration with host-country scientists was possible, under the ICMR, as in Cali and Kuala Lumpur, but it was not universally achieved nor was it required under the terms of the grants. In some circumstances, such as Lahore, it may not have been possible, given the level of local medical institutions. The ICIDR program, reflecting changes in the international climate perhaps, or heightened NIH sensitivity, is meant to be highly collaborative.

Curiously, the two ICMRTs that achieved the closest collaboration with host-country institutions, Cali and Kuala Lumpur, were both led in their early years by British expatriates.

Impact on Disease

In the absence of an evaluation of the ICMR program, determining its contribution to understanding and controlling tropical disease is difficult. The Johns Hopkins group in Calcutta made significant contributions to understanding cholera and diagnosing E. coli and shigella, and it contributed to development of ORT. Other ICMRs may have made similarly vital contributions.

In general, however, as Laska put it, the programs were designed to advance scientific knowledge and train researchers rather than to have an impact on the course of a disease.

Capacity Building

The ICMR program was explicitly designed to provide in U.S. medicine a small core of competence in exotic diseases. Seal argued that the increase in capacity of U.S. institutions sought through the program did not occur, largely because tenured positions could not be offered. It's an important point, if valid, but the evidence is not available to confirm or refute it. Dunn mentioned a dozen former participants in the program who continued their involvement in international health at the University of California at San Francisco and nearby institutions. Tropical medicine is very strong there because of the ICMR program. The reasons the university did not compete successfully for the ICIDR program have more to do with lack of researchers' interests in infectious diseases, with interests in other parts of the world, and with the jungle dengue project's having reached a logical stopping point by 1980.

Despite this explanation, the lack of success of three of the four universities with ICMRs in competing for ICIDR grants is perplexing, given their advantages in field experience. Possibly it is difficult to sustain an interest in tropical diseases in a university setting.

One indication that this was so is that the universities often had to reach outside their faculty ranks in order to staff their overseas centers. Even those scientists with long term interest in tropical diseases did not wish to stay abroad for many of the 20 years of the

program. It was professionally costly to be out of the mainstream of U.S. science for too long, often working in poorly equipped laboratories. It was also disruptive of the teaching programs for senior people to spend too much time away, even on university business.

The results of the ICMR program in terms of institutional capacity building seem therefore to be disappointing. In manpower terms, the ICMRs may well have been a success. They provided abundant opportunities for relatively large numbers of scientists to gain experience in tropical disease research, but they didn't provide career inducements to keep them engaged for the balance of their careers.

International Center for Diarrheal Disease Research, Bangladesh

The Bangladesh center's contributions to development of oral rehydration methods as therapy for cholera have helped humanity to deal with, if not defeat, one of humanity's most terrifying afflictions. What directions has ICDDR,B research taken recently, and what does the center's experience suggest about the value of creating an international center as a device for concentrating research on a tropical disease problem?

There are superficial similarities between two recent triumphs of modern science in Asia: ORT for diarrheal diseases, and the short-strawed rice varieties that doubled or tripled yields per acre. Both involved work by Western and Asian scientists in internationally controlled laboratories in tropical areas where the plants and diseases of their interest thrive. Both international endeavors continue to enjoy a diversity of funding sources and widespread attention from the development community. The creation of an international center as a device for ensuring research continuity, applicability, and excellence, largely insulated from political or parochial concerns of any country, has been replicated a dozen times or more in agriculture. In medicine, however, the ICDDR,B remains the sole model.

An extensive analysis of the parallels and divergences of the two fields would be rewarding but would have to go too far into the realm of agricultural research to be pursued here. Still, because the international center model is one serious alternative open to the United States if it decided to make a major commitment to attacking tropical diseases, the experience of the ICDDR,B deserves special scrutiny.

As a model international center, ICDDR,B is inappropriate. After losing its SEATO affiliation at the time of Bangladesh's independence, the cholera laboratory for several years existed as practically a bilateral institution, with its future status in doubt. Many in the new government favored turning CRL into a national institution dealing as it did and does with some of the most serious health problems of the country. This alternative was found not to be feasible if a high level of international participation, particularly by NIH, was desired. The result was a compromise--an internationalized institution with continued responsibility for treating diarrheal diseases in Bangladesh. It is international and national at the same time.

The center's role as a health-care provider is a boon to the country and probably has some scientific advantages in terms of access to a large patient population. However, the center's presence may have inhibited the growth of a national capacity to deal with diarrheal diseases and may have distorted the pattern of development of the local medical profession through the lure of international salaries.

The center's bilateral origins account also for a much higher ratio of local to scientific foreign staff, 40:18 in 1983, than would be the case for an international research institution begun from scratch. Marginal local scientists have been employed, with no solid research training program to improve their performance. Apart from distorting local career patterns, a heavy reliance on local appointments can have a stultifying effect on a center because such people tend to remain in their positions longer than staff members drawn from abroad.

The center's board has decided to follow WHO policies and establish a geographical distribution system for recruiting international staff. These positions will be filled by contracts of up to three years, with tenure ordinarily not to exceed six years. These measures will lead to a more balanced distribution of nationalities among the staff although they do not of themselves guarantee improved quality.

Another perceived disadvantage, which may account for its being less emulated than its agricultural counterparts, is that it was the child, rather than the parent, of success. When the International Rice Research Institute (IRRI) was set up in the Philippines, its scientists were aware that they could achieve major gains by dwarfing the rice plant so that it could use increasing amounts of fertilizer to produce a bigger head without toppling over. The trick had already been done for wheat, so it was only a matter of time for rice. Within three years IR-8 was heralding the high-yield Green Revolution.

ICDDR,B is unlikely to produce a revolutionary product to rival what was already accomplished before the center was internationalized, but its research program could still be at the frontiers of knowledge if quality were assured: research on invasive diarrheas not alleviated by ORT; efforts to elucidate the interactions of diarrheal diseases, nutrition and fertility; and vaccine trials. All are of major potential significance. Top-quality research is less easy to ensure, however, now that the organic links enjoyed by the CRL with CDC and NIH are severed.

The World Bank has asserted that until 1975 the international agricultural research centers produced very high return on investment. No such figures are available or calculable for curing or preventing human diseases. The Bangladesh laboratory's dealing with human diseases evidently was a financial liability. Feeling persists that funds for research on a disease that affects chickens are notoriously easier to obtain than are funds for research on a disease that afflicts millions of people who live in the tropics.

The ICDDR,B record in its first five years is strongly positive. In a remarkably short time the center has attracted a broad range of financial contributors. Initially, a core grant from AID of \$1.9 million per year for five years represented over 95 percent of the center's revenues. Within 5 years, the number of contributors grew to

22, and the core grant was only 25 percent of the \$7.1 million budget for 1984. The budget for 1985 was \$9.1 million, including \$1 million for extensive field trials of a new oral vaccine for cholera. AID has been in the process of determining whether its commitment of core funds for the next quinquennium will remain at the same or a higher level.

Ability to raise large sums is not, unfortunately, an unmitigated blessing. Some veterans of the CRL days believe the quality of research at ICDDR,B has suffered, in part because the size of the institution makes it difficult to turn down large programs for which funding is available. Also, availability of funds may permit initiation of certain activities ahead of higher-priority programs. Nevertheless, the ability of ICDDR,B to diversify its sources of funding was an important objective of AID.

When AID sought to internationalize the center in the late 1970s, it cited four general goals: To achieve permanence, to develop scientific potential, to attract high-quality staff, and to obtain broad-based support for operating and capital costs from multiple donors. The first and fourth of these objectives have been met, and progress has been made on the second and third. The center continues to enjoy unique advantages in having the capacity to conduct high-quality research; to learn about the technical, managerial, and sociocultural problems of conducting health programs; and to adapt and field-test new products as they become available. No other institution can match the center's ability to conduct interdisciplinary research on the complex and important biological and social interrelationships of diarrheal diseases, human reproduction and nutrition.

Recognition of the research value of the Matlab Demographic Surveillance System led to its designation by the United Nations Population Division and WHO as one of five regions for extensive studies of mortality.

Despite its unusual importance, the institution has scientific shortcomings and rising costs that its trustees and staff seek to remedy. In 1982 an AID review of scientific work at the center found several weaknesses although the research was of excellent quality and great significance. The review found the program to be generally balanced but detected some lack of expertise in epidemiology and immunology. Training was deemed overly structured rather than concentrated on field-based and laboratory bench experience. Equipment was not up to standard, the quality of publications less than first rate, and the dissemination of information limited by travel funds.

Subsequent external reviews found shortcomings in laboratory equipment and in the research objectives being pursued in some fields. The issue of rising costs stems in part from continuing pressures to increase salaries and the number of international posts. Adoption of United Nations pay scales for 42 staffers has added over \$1 million to the budget, and 13 additional posts have been proposed for international status.

Scope

This is one of the strongest characteristics of an international center organization model as it assumes vertical responsibility for work on a disease from the laboratory to the village, generally on a worldwide basis. ICDDR,B village research includes interrelated work on nutrition and fertility in addition to diarrhea.

The center's geographical reach is more limited than what might be expected of an international center. The conditions with which it deals require control programs too varied to be replicated readily. Also, the WHO Special Programme for Control of Diarrheal Diseases (CDD) performs much of the international monitoring and liaison required for keeping track of research developments concerning these diseases. CDD was organized by WHO in about six months, just before CRL was internationalized. The two cooperate, as in recent testing of the oral cholera vaccine at Matlab, but relations have not been particularly close. This situation may improve with the CDD director's appointment to the ICDDR,B board.

The center undertakes the important task of helping to keep scientists and health professionals aware of pertinent research developments. With support from the International Development Research Centre of Canada, in 1982, ICDDR,B established the International Diarrheal Disease Information Service and Documentation Centre. Among its activities is quarterly publication of the Journal of Diarrheal Diseases Research, containing original papers and a comprehensive bibliography of available research papers.

Collaboration

For an international center, collaboration must include relationships both with national research institutions and health care providers and with basic biomedical laboratories in the advanced countries. In biomedical research, scientists in international centers in the tropics can become isolated. Internationalization of the CRL ruptured some long-established ties with NIH, CDC, and Johns Hopkins, and it jeopardized its ability to draw from reliable sources of talent.

Impact on Disease

The center's role in development of oral rehydration is well known. Over the next five years, the two major foci of the ICDDR,B will be expanded research and training on oral rehydration solutions and field testing and research on vaccines. The first vaccine trial was to begin recently in collaboration with the WHO and the government of Bangladesh. Both points of emphasis are controversial. Some feel strongly that research on ORT has gone beyond the point of diminishing returns. Others believe the candidate vaccines now available are not sufficiently promising to warrant elaborate field trials.

Capacity Building

Through extension activities, ICDDR,B has helped Maldives, Indonesia, China, Saudi Arabia, the Philippines, Sri Lanka, and Pakistan to build up their personnel resources for research and training to control diarrheal diseases. Definition of the center's training role remains somewhat controversial. One observer said the center's international efforts weakened its ability to meet priority research and service goals in Bangladesh and almost broke the bank. Simply put, they are not trainers and have exhibited no interest in becoming trainers. Capacity building for a research laboratory should have focused on high-powered, postdoctoral, or graduate-level training of laboratory and clinical investigators. Community-service aspects of the eclectic ICDDR,B program commanded a great deal of attention of the training group.

In Bangladesh, the center is assisting the government to strengthen a comprehensive system for disease prevention, detection, surveillance, and control and to introduce proven maternal-and-child-health and family-planning methods into delivery of health services. The center's contribution to Bangladesh is mainly in strengthening the disease control program rather than the research capacity of the government, except insofar as the center functions as a national institution itself.

This differs from the IRRI experience. IRRI made a special effort to cooperate with and strengthen national research systems. Almost every government recognizes the need for its own agricultural research system; few apparently find it necessary to establish a medical research system. Medical research is likely to be in the universities but not in the ministries of health. Governments seem to be lagging in defining their medical research requirements. This appears to accentuate need for international medical research centers.

Conclusion

ICDDR,B has succeeded in establishing itself as an international institution and in expanding its program and breadth of support. Its origins as a bilateral institution and its continuing role as an integral part of the government's health care delivery system have affected its quality and perhaps its ability to respond to needs of other countries. Opposition within WHO to the concept of an international center added to its difficulties, and its costs can be viewed with concern if contrasted to the level of expenditures for the TDR program, for example. Although the experience of the ICDDR,B to date is not likely to raise a demand for more international disease-oriented research centers, the center has made solid progress on complex biological and social problems. It remains an important resource for research on diarrheal diseases, for research on diarrhea-fertility-nutrition interaction, and for the adaptation and field-testing of new products.

FOUNDATION-SUPPORTED AND INTERNATIONAL RESEARCH GRANT PROGRAMS

The distinction between programs designed to create centers for research and those that simply fund research is important. Grant programs provide money intended to move institutional capacity toward a goal, but they don't lay the same continuing claim to resources that institutional programs do. Grant programs can be terminated, truncated, or redirected with less bureaucratic turmoil than can institution-building programs.

Foundations are socially accountable, to their trustees and to the public, but they need not produce a quick profit or win a vote. They can afford the long view and can identify and work on problems not yet high on the public agenda.

The disadvantage to funding from foundations is that it is likely to be short-lived. Foundations cannot afford to be locked into expenditures that might endanger their innovative character. Consequently, they tend to look for program initiatives that when well underway will continue with financial support from other sources, public or private.

Probably the most successful example of foundation innovation in an area pertinent to our subject is in the field of tropical agriculture. The Ford and Rockefeller foundations established four international agricultural research centers that demonstrated the value of high-quality research in raising tropical food production potential. These centers were the nucleus of the system of 13 institutions now funded through the Consultative Group for International Agricultural Research at an annual cost of about \$170 million. Almost none of that cost is currently borne by the foundations. This is an example of using foundation funds as seed to attract or lever larger funds to work on a problem. It is measure of effectiveness of foundation programs.

Rockefeller Foundation: Great Neglected Diseases of Mankind

The Rockefeller Foundation, since its founding in 1913, has had the longest and most productive record of any U.S. foundation in dealing with tropical diseases. Its objective was to enhance "the well-being of mankind throughout the world," and among its first efforts was a program to promote public sanitation and the spread of knowledge of scientific medicine. The foundation's early work on yellow fever and hookworm was pathbreaking, much of it by staff scientists associated with research institutes around the world.

The foundation's announced goal was the eradication of yellow fever, an aim that had to be revised in the early 1930s. Forest mammals maintained a reservoir of the disease long after human population seemed forever rid of it. Before abandoning the field in the late 1930s, the foundation demonstrated that with vector control and a new vaccine any government interested in controlling yellow fever within its boundaries could do so. In Brazil, the foundation's successful campaign to eradicate A. aegypti, a vector for both malaria and yellow fever, was led by Soper, who later established INCAP and was first director of the PSCL.

In 1951, the foundation launched a major program to explore the field of arthropod-borne viruses. This coincided with expanded virus programs in the Army laboratories (directed by Smadel), NAMRUs 2 and 3, and NIH. The ensuing 20 years were a period of vast advances in identifying and categorizing viruses and in understanding the part played by the arthropod vectors in transmitting them.

The organizational model was effective but has not been copied. The foundation sent its own staff researchers abroad on long-term assignment. The program's success may be attributable in large part to: Selection of highly trained foundation scientists from the United States and other countries; joint support of each overseas laboratory by a national government agency and the foundation; integration of foundation scientists with scientist-nationals of the host country, including joint publication of research findings, resulting in truly balanced collaboration; and planned phase-out of foundation support and staffing in a 10- to 15-year period coinciding with continued funding by the national governments.

The foundation created its own central laboratory at the Rockefeller Institute, now Rockefeller University. This was moved in 1964 to New Haven where it became the Yale University Arbovirus Research Unit and is now the designated WHO reference center for arboviruses. It no longer has direct Rockefeller support.

The foundation almost dropped out of the tropical diseases field in the early 1970s. Its medical program centered on population issues. The balance was redressed with the inauguration in 1977 of the Great Neglected Diseases of Mankind (GND) program, "devoted to bringing the power of the finest scientific institutions of the world to the development of new and better tools" (vaccines and drugs) "and methods of control" (diagnostic tests, appropriate targeting of therapy) "for these vast scourges of mankind, such as malaria, schistosomiasis, and diarrheal diseases."

The program refers to "neglected" diseases because, a report to the foundation's trustees said, for the previous 40 years the medical science focused little on diseases of the mostly rural, poor people of the less developed countries.

The decision to embark on the GND program was prompted by several factors, including increased awareness both of the destructive impact of the diseases upon tropical societies and of the gains that recent biomedical advances might make possible. Because of funding constraints, new research technologies had not been employed extensively against tropical diseases.

The GND program set out not to create facilities but to build on existing centers of excellence, making it possible for the neglected diseases to bid for the attention of the most able scientists. Scientific interest of the diseases is high now in part because the previous neglect may be followed by fairly dramatic gains through the application of advanced research techniques.

Grantees in the program's first two years were six general medical units, four units devoted to research in biochemistry and pharmacology, and four immunology units. Seven were in U.S. institutions; the others were at Oxford, Cairo, Tel Aviv, Stockholm, Mexico City, and Bangkok.

Each received assured funding for eight years of from \$50,000 to \$100,000 per year.

Although currently only two units are in less-developed countries, collaborative efforts in 22 different countries bring research expenditures in the less-developed countries to 35 percent of the program. In the first six years of the program, \$12 million went to institutional grants. In addition, eight career development fellowships were awarded, covering research and travel costs as well as salary.

In five years, the GND program involved 200 scientists and 200 trainees who together produced 736 publications, many in the most prestigious journals of the medical field. A report by external reviewers found the program to be of high quality, innovative, timely and productive. They recommended continuation of core funding for the major units and suggested that the annual meetings of scientists, an integral and important part of the program to date, be continued at their present size and scope.

Edna McConnell Clark Foundation: Schistosomiasis Research

Worms are among the most prevalent infective agents of mankind. Ascariasis and trichuriasis infections each strike a billion persons; hookworm, 600 million; filariasis, 300 million; and schistosomiasis, up to 200 million. The estimates are inevitably crude. Schistosomiasis estimates range from 100 million up. The margin of error is immense in part because a microscope is required for accurate diagnosis.

Schistosomiasis, one of the oldest diseases known, probably has been on the rise since World War II. As irrigation brings economic benefits to many areas, it also may enlarge the habitats of the snails that are indispensable intermediate hosts to the schistosome. It is a cruel disease, hitting most the children who play in the water and the farmers, fishermen, and launderers who work in it.

When the Edna McConnell Clark Foundation decided to focus on the disease in the early 1970s, probably less than \$1.5 million was spent in the world each year on investigating the malady. Clark put in \$2 million per year, galvanizing the field. The international TDR program has selected schistosomiasis as one of its six priority diseases and has added \$2 million per year. With the additional work on schistosomiasis under Rockefeller's GND program, expenditures now run at about \$8 million annually, a very healthy increase well rewarded by advancing knowledge. (Even so, this amount is far less than the incidence and effect of this disease warrant.)

The Clark Foundation took a novel approach; it started its program by devising, with the help of a broad range of scientific experts, a Strategic Plan for Schistosomiasis Research. The foundation sought to ensure that the program focused on developing the means to control schistosomiasis and that the fruits of research were put into practical use as soon as possible.

The foundation mapped out four areas of activity with target dates for anticipated accomplishments. Hope centered on the development of a

successful vaccine, which some thought would be possible within five years, although the plan more prudently set 1986 as the target date. Drug development was a second line of action, beginning with further research on compounds with known activity in man or animals and, in the longer run, working on more specific drugs based on the expanding knowledge of the biochemistry and physiology of schistosomes. The third line of action was to improve the tools for controlling the snail vector, and the fourth was to improve the awareness of those in a position to organize and fund control programs of the impact of schistosomiasis on society. The Clark strategy was to fund research along these lines, to offer coherence and direction to dispersed efforts in the field, and to facilitate the communication of findings by sponsoring symposia, publishing progress reports, and supplying bibliographical materials to investigators at no charge.

The goals listed in the strategic plan are revised annually, with the help of an expert advisory committee. Early optimism concerning immunization has tempered; unanticipated benefits have come from drug development, although not exclusively that supported by the foundation.

After 10 years of program effort and expenditures of about \$22 million, the Clark Foundation has begun to reduce its commitment to schistosomiasis and to explore other tropical diseases, particularly those causing blindness. Again, a strategic plan is under preparation to guide program expenditures. The device of a strategic plan was not adopted by the Rockefeller or MacArthur foundations in mounting later research programs in the tropical disease field, but the Clark staff and trustees believe it offers useful coherence and focus.

In the past 10 years, a great deal has been learned about schistosomiasis and how to deal with it. Attribution of these advances to particular programs is difficult. No single development has had the drama of the NAMRU-2 discovery of the therapeutic potential of the sodium transporter for oral rehydration in cholera. The incremental gains against the burden of schistosomiasis are more typical of scientific process.

The general trend of incidence of schistosomiasis is not known. Surveillance techniques have improved since 1973, and the program played a key role in making progress possible, but data are still poor for a disease, such as this, which is not generally fatal.

Control measures have improved to the point where the severe clinical effects of the disease can be reduced substantially. New antischistosomal drugs can be administered in a single oral dose, or several doses in one day, with only minor side effects. This is a great advance over the recent past, when the only drugs available for this disease were highly toxic and had to be administered in doses several weeks apart. The advantage of treating the disease in infected persons with drugs is that it causes an immediate, sharp reduction in the intensity and prevalence of infection, ameliorating the impact of the disease on the victim and at the same time decreasing egg output into the environment and the infection rate in snails. The natural history of schistosomiasis requires both the human being and the appropriate snail. Knowledge of the disease cycle makes possible the targeting of control programs for greater efficiency.

Other control techniques include the use of snail-killing chemicals (molluscicides), provision of fresh water, and improved sanitation. These measures may be too expensive or, with molluscicides, ineffective, if used alone. But they can be important adjuncts to drug treatment in controlling the disease. Health education is important.

Transmission of schistosomiasis will only be halted when an effective, affordable vaccine is available, and that is still years away. New techniques of molecular biology offer great promise. Only candidate antigens have been identified, not fully protective in experimental animals. After adequate answers are found in the laboratory, a considerable period of further development and testing will be required before a vaccine becomes generally available.

Much remains to be done in immunology, biochemistry and drug development, and epidemiology and control before we are able to deal with schistosomiasis satisfactorily. The catalytic value of the foundation's entry into the field has been realized.

MacArthur Foundation: Molecular Biology

In October 1984, the MacArthur Foundation announced its commitment of \$20 million over five years to establish a consortium of research groups using molecular biology and other advanced disciplines and techniques in the study of parasitic diseases.

Jonas Salk, a foundation trustee, explained:

"In focusing this new initiative on basic research, the MacArthur Foundation demonstrates its conviction that intensive application of modern cellular and molecular biology, genetics, and immunology to the study of the biological bases of parasitic diseases will produce the most significant progress in finding effective means of reducing the worldwide suffering caused by parasites.

"The field of parasitology has been slow to assimilate and apply the astounding advances in our knowledge of the molecular and genetic bases of biological processes and the sophisticated new techniques for increasing that knowledge."

United Nations Development Programme, World Bank, and World Health Organization: Special Programme for Research and Training in Tropical Diseases

The Special Programme for Research and Training in Tropical Diseases is the largest single effort in tropical disease research. The TDR program began in 1976, and by the end of 1984 more than 3,700 scientists, from 125 countries, had participated in it. By 1984, the program had spent over \$150 million, and it continues to raise an annual operating budget of \$25 million from over 30 donors. Denmark, at \$25.5 million, was the largest contributor in that period, followed by the United States, at \$20 million, and Sweden, at \$16 million. Each of its three sponsoring agencies--the United Nations Development Programme, World Bank, and World Health Organization--are major contributors,

with the World Bank now contributing \$2.5 million per year, 12 percent of the total. TDR represents 25-30 percent of the world's identifiable research effort on tropical diseases.

TDR represents one important alternative potential means of increasing U.S. commitment to controlling tropical diseases--just by increasing the U.S. contribution.

TDR's scientific impact has not received comprehensive evaluation, but the management of the effort, its goals, scope and balance, and its financing, were studied extensively by an external review committee, reporting in April 1982. That committee was chaired by David Bell, of Harvard University, who subsequently chaired the National Research Council study for which this paper was commissioned. Most of the information about TDR here comes from that 1962 review. A major scientific review of TDR was scheduled in 1985.

TDR's organization deserves special attention because of the scope and complexity of program tasks. The program concentrates on six specific diseases: malaria, schistosomiasis, filariasis (including onchocerciasis or river blindness), trypanosomiasis (African sleeping sickness and Chagas' disease), leprosy, and leishmaniasis. The programme has two principal, distinct, and sometimes competing, objectives:

- o Research and development of improved tools for dealing with the six diseases, and
- o Strengthening research capacity in the countries whose populations are affected by these diseases.

An elaborate structure is required to mount so extensive an effort. Its elements include:

- o A Joint Coordinating Board, on which contributors and developing countries participate in directing the program;
- o A Standing Committee, of representatives of the three sponsoring agencies, which serves as an executive committee for the board;
- o Scientific working groups and steering committees, made up of scientists who guide the research program;
- o A Research Strengthening Group, made up of scientists (from all over the world) who advise on efforts to strengthen research institutions in affected countries;
- o A Scientific and Technical Advisory Committee, made up of persons with extensive experience in scientific research and research management from both industrialized and developing countries who function as an independent review body, providing continuing evaluation of the scientific and technical aspects of the program and recommending priorities and budget allocations; and

- o A program coordinator, a program director, and a secretariat that together provide a strong focus of responsibility and authority for carrying out the work of the TDR.

The 1982 review suggested improvements in the workings of this structure, but it was strongly positive about the achievement of the sponsoring agencies in setting up a framework that provides simultaneously for the responsible participation of those directly concerned, the mobilization of scientific talent worldwide, independent scientific and technical evaluation and priority-setting, a clear and strong focus of operational responsibility and authority, and effective collaboration with the regular elements of WHO. The review committee found the entire program to be well targeted, well launched, and of major significance.

The committee also praised the networking concept chosen by the program as its *modus operandi*. Instead of channeling research funds to a few established or new centers, the program from the beginning built on WHO's extensive experience and contacts to develop a network of involved scientists throughout the world. Although the review committee recognized that a more concentrated approach, such as the centers program for international agricultural research, may be more efficient for the resolution of specific problems, the network concept offers the ability to mobilize scientific expertise worldwide towards common objectives and has a widespread impact on strengthening research capacity in countries where these diseases are endemic. The network approach also requires less capital expenditures, and it facilitates the assumption of responsibilities by local authorities.

A danger inherent in the network approach is the risk of dissipating efforts through a multiplicity of committees and meetings of various kinds. In 1980, the committee noted, 69 meetings were organized by TDR, primarily for managing the program's scientific elements, and in 1981 TDR held 80 such meetings. The review recommended streamlining the operation, reducing the number of steering committees, merging the working groups into the steering committees, and producing fewer reports.

The review committee looked at the work of the secretariat, at the functions of TDR staff assigned to the WHO regional offices, and at the workings of the various working groups and committees and made suggestions for simplifying procedures and curtailing bureaucratic sprawl. It reinforced particular accomplishments, such as the introduction of peer review in making research grants, and it noted subjects that warranted attention.

Among such subjects is the process of strengthening research capacity in institutions of countries in which these diseases are endemic. This includes training scientific personnel, providing supplies, and building up research facilities to enable research institutions to carry out not only biomedical research but also epidemiological and operational research and the evaluation of new drugs, vaccines, and tests, all of which by their nature must be done in tropical countries.

Strengthening research capacity is a long, difficult, critically important task, because eventually these countries must be responsible for their applications of new and improved technology. Success depends on careful selection of recipients, efficient execution of activities, and on the commitment of recipient countries to continue support of the established research programs after TDR phases out.

Promotion of linkages between developing country institutions and research laboratories in advanced countries can be one of the most effective means of transferring scientific standards and techniques. Matching institutions and arranging exchange visits can be a demanding task, requiring sensitivity to personal, political, and cultural factors as well as scientific considerations.

The review committee recommended that greater efforts be made to interrelate research capability strengthening and research and development activities so that they reinforce each other. Increasing numbers of institutions in developing countries that have received grants for research strengthening have competed successfully for grants awarded by TDR scientific working groups.

The review committee found the allocations between research and capacity building and between expenditures in developed and developing countries to be about right. The original target was for at least 20 percent of the funds to be devoted to capacity building, leaving 80 percent for research and development. This target was exceeded, and by 1980 slightly over 25 percent of the program was going to institution building. In addition, half the research funds were obligated for expenditures in developing countries, so 62.3 percent of TDR funds was being spent in countries directly concerned with these diseases.

Mainly because of shortages of trained personnel in the tropical countries, too few field projects were funded to meet scientific objectives. More epidemiological and socioeconomic studies are needed to assess the effectiveness of new methods and to provide information on field conditions. Such information is essential for program administration and research and development strategy. Dr. A.O. Lucas, TDR director, cited the lag in field research as the most serious problem encountered. The value of combining research with control activities is still not appreciated by many governments in endemic countries.

Not surprising for the early years, no new drugs or vaccines emerged from TDR efforts.

Intermediate results, as distinct from final cures or preventive measures, have been promising. Lucas noted that TDR's effort to induce scientists from many disciplines to take a fresh look at these diseases produced a response exceeding expectations. Major scientific advances occurring outside TDR in molecular biology, immunology, and in techniques for in-vitro culture of parasites have added momentum to the TDR.

One example of the benefits of international cooperation and the networking concept is found in the production and sharing of leprosy bacilli. U.S. scientists discovered that the injection of leprosy bacilli into the nine-banded armadillo could produce massive infection after two years. This made it possible to harvest large amounts of the

bacilli for research purposes, the first step in the development of a vaccine. Each participating laboratory does not have to keep a supply of armadillos; laboratories in Louisiana, Georgia, Florida, and Washington have been contracted to produce the bacilli. A laboratory in England purifies and stores the bacilli, and antigenic analyses take place in various parts of the world including Norway, Sweden, and the United States. Skin tests and vaccine tests have been carried out in Venezuela, and epidemiological studies in Africa. The review committee said that only through a mechanism such as TDR, working through WHO, could such cooperation occur.

Comparison

Several general observations can be made about the efficacy of the tropical disease research grant programs of the private foundations and the TDR.

Scope

TDR endeavors to act along the full spectrum of research needed to understand and deal with a disease, in locations from advanced microbiology laboratories to villages. TDR is not uniformly successful in sponsoring activities at all levels needed. It lags in field research, which is often most difficult to organize, and it suffers from scarcity of institutional resources and trained personnel. TDR committees view their tasks in the whole, dealing with whatever research problems command priority in learning to deal with a disease, and the long-run mission of building competence in institutions in disease-endemic areas is accepted. Some of the scientific working groups responsible for setting research directions and monitoring progress have placed special emphasis on development and testing of new disease-control products and technologies that emerge from TDR-supported research.

Foundation programs tend to favor laboratory research, basic and applied. This emphasis utilizes the strengths of foundations in stressing research quality with a minimum of bureaucratic constraint. Laboratories can be selected for participation without regard for regional balance or political factors that sometimes intrude on the workings of international programs. Field programs usually are more expensive than foundations prefer and require more staff for program development and management. Yet foundations, notably Rockefeller, have supported field programs on a large scale.

Both Rockefeller and Clark attended to the processes by which scientists keep informed of the advancing frontier. The GND annual conferences have proved invaluable for that purpose, and the annual revision of the strategic plan for schistosomiasis research is a useful communications device. Extending as it does from laboratory research to field research and control activities, the strategic plan has an impact across a broader spectrum than the GND program.

The success of foundation work in agriculture has not been matched. The leveraging of funds accomplished by the formation of the Consultative Group for International Agricultural Research has no parallel in international medical research.

Collaboration

TDR is striving to be a collaborative program. The 1982 review found an unnecessary, undesirable gap between two main TDR thrusts--capacity building and research. The second tends to be centered on advanced laboratories, while the former is concentrated in developing countries. Some pairing of laboratories has occurred but not as much as the review committee thought would be desirable. This situation appears to have improved over the last several years. Some awards include support for travel and/or training visits to laboratories in industrialized countries. TDR training awards have fostered collaborative relationships, which continue as part of research carried out upon the trainee's return to an institution in the tropics.

The foundations fund collaborative work.

A third of GND funds is spent in developing countries, although only 3 of the 14 participating laboratories are located there. Funding collaborative research through the more advanced partner has advantages in terms of efficiency and administrative convenience but can leave the other feeling like less than a partner. This has not happened with the three laboratories in Cairo, Bangkok, and Mexico City. There the project directors have retained their control while reaching out to collaborate with laboratories in the United States and Europe. Egypt, Thailand, and Mexico are countries where, as one Rockefeller reviewer noted, "the importance of medical research has dawned and thus support from national sources will be forthcoming." Vesting scientific and financial control of a project in poorer, less developed countries, where the tropical disease burden is often greater than in the middle-tier countries, could prove much more difficult administratively.

Neither TDR nor the foundations have found an ideal formula for promoting collaborative research.

Impact on Disease

The TDR external review committee found the program results inconclusive. Although some immediately usable results were noted, such as improved diagnostic tests, most of results needed further development for disease control.

Rockefeller Foundation staff gave their GND program similarly mixed interim reviews. They noted that the research programs are of very high quality, and the achievements are cost-effective, but there is concern about the problem of translating the outcomes of the biomedical research into products and practices to improve the health in the developing countries.

The Clark Foundation staff, reporting to its trustees, noted an explosion of knowledge about schistosomiasis in the 10 years of its program; it did not attempt to suggest which credited to Clark and which to other programs. Advances were noted particularly in understanding of the human immune response, in drug development, in understanding of the worm's metabolism so new drugs can be designed, and in understanding of the public health impact and epidemiology of schistosomiasis, with resulting improvement in control strategies.

Capacity Building

Research capacity strengthening is built into TDR. The external review committee commended the program's allocation of 25-30 percent of its funds to upgrading the research capacity of developing countries, a higher allotment than originally targeted but still a second priority to the urgency of making scientific progress through research. The review urged greater efforts to pair institutions in developing countries with advanced laboratories abroad and special efforts to identify promising talent.

GND is essentially a capacity-building program, mostly by funding work on tropical diseases in already successful laboratories. The patterns of funding, local control, and international collaboration seem ideal. The strategy is to increase the quality and quality of tropical disease research by building on existing centers of research excellence. The Rockefeller Foundation is not sure of the long-range outcome, however, due to its limited resources. Young researchers, attracted to GND by the quality of its scientific work, may shift their attention when resources are no longer available.

The Clark approach may be less effective in building research capacity. The device of the strategic plan, so useful in maintaining the focus of expenditure on the advancing frontier of knowledge, may inhibit expenditures for long-range building of research capacity in the absence of an explicit program objective for doing so.

Conclusion

Each of these programs has genuine strengths, and each appears to be excellent use of private and international funds. But however well run, the grant programs don't seem able to do the job alone. Solid support structures seem to be missing. For all its shortcomings, a center like ICDDR,B, anchoring research on a particular disease, is reassuring. IRRI, in agriculture, demonstrates the utility of a center as a base from which to strengthen a nation's research capacity. There seems to be no reason why similar success could not be achieved in research on schistosomiasis and other tropical diseases. Careful study should be made to determine the pros and cons of these models for health research in the tropics.

TDR's scientific working groups perform some of the functions of an international center, keeping track of priority needs and reviewing

progress. They involve some of the world's best scientists. WHO scientific staff based in Geneva with administrative responsibilities for TDR prepare impressive documentation and disseminate them freely to scientists all over the world. The reports serve an important communications function and identify research priorities.

SMALLPOX ERADICATION CAMPAIGN

Thomas Jefferson in 1808 wrote to Jenner, discoverer of the smallpox vaccine, that because of his discovery "in the future the peoples of the world will learn about this disgusting smallpox disease only from ancient traditions." Jefferson was right, but his prediction took 170 years to come true.

The smallpox campaign was not primarily a research effort, although applied research was essential to its success, nor was it a U.S. accomplishment, although D.A. Henderson and the CDC played pivotal roles. It was primarily a triumph of management, the use of scarce resources through international collaboration to accomplish an historic task. It is an example of effective use of U.S. scientific, technological, and leadership capabilities.

The eradication campaign is not put forward as a model approach to all, or even many, disease problems. Several characteristics of smallpox made it an unusually vulnerable target for eradication. It is easily diagnosed and relatively slow to spread. Protection can be conferred with a single application of an easily administered, highly stable vaccine. There are no vectors to worry about and no animal reservoirs of the virus.

Eradication of most other diseases for which there is no natural reservoir other than man is unlikely for several reasons: Lack of a vaccine offering long-term protection with one or two injections; clinical features that make detection and diagnosis difficult; and epidemiological characteristics such as the rapidity with which measles can spread. Political commitment to eradication can be difficult to obtain when the disease in question is a seemingly minor health problem in a poor country.

A few other diseases may be susceptible to eradication efforts, according to William Foege, former head of CDC and an active participant in the smallpox campaign. Guinea worm could be gone in 10 years, and human transmission of yaws may be stoppable by the end of the century. The technology to get rid of polio seems to be available but not the necessary determination.

The biggest, most costly eradication campaign on a global scale was launched by WHO in 1955 against malaria. The discovery of DDT late in World War II gave rise to hopes that the Anopheles mosquito, the main malaria vector, could be eliminated because of its tendency to rest on a vertical wall after taking a blood meal. If the walls of houses could be coated with DDT, the mosquitoes would die, and interrupting transmission of the disease. Dramatic reductions in the disease were observed in Sardinia, in Venezuela, and in other areas where DDT campaigns were mounted. In 1950 the Pan American Sanitary Bureau

decided, at Soper's urging, to undertake a regional malaria eradication program.

The WHO campaign followed because the first scattered reports of mosquito resistance to DDT began to filter in. The threat of widespread vector resistance was a goad to action, although many remained unconvinced that eradication was possible. The campaign could not have achieved its stated objectives. WHO made no serious efforts to eradicate malaria south of the Sahara. Nevertheless, its program went on for nearly 20 years, mostly with U.S. financing.

WHO adopted a standard approach for the malaria-endemic countries. It created a separate, distinct malaria eradication service with higher quality and better paid staff than others in the health services. They were to perform no duties unrelated to malaria and so were of very little help in the smallpox campaign. Funds for malaria eradication were often taken from malaria control programs, professional efforts of long standing. Research on alternative strategies was neglected.

The malaria eradication campaign set the scene for the smallpox eradication campaign. Malaria drained the reservoirs of funds and enthusiasm before they could be tapped by the smallpox effort. The United Nations Children's Fund, for example, contributed handsomely to the malaria campaign but very little to smallpox. Senior officials including those at WHO were skeptical of the smallpox campaign and concerned about another failure. Particularly after the malaria embarrassment, WHO generally opposed vertical campaigns, those shaping action around a specific disease.

The smallpox eradication campaign got off to a slow start after it was adopted at the 1958 World Health Assembly. It was a Soviet initiative. The United States had backed the malaria effort and provided 95 percent of its voluntary contributions. The Soviets, having just returned to WHO in 1957, were not involved in the malaria effort. They had reported no cases of smallpox since 1938, having rid their country of the disease by making vaccination compulsory beginning in 1919. Sharing long borders with smallpox-endemic countries such as China, Afghanistan, and Iran, they were understably interested in eradicating the disease. In addition to proposing the resolution for WHO commitment to eradication, they pledged to release 25 million doses of freeze-dried vaccine for the campaign.

The assembly adopted the Soviet resolution, which called for the vaccination or revaccination of 80 percent of the population within five years. Primary responsibility was to rest with the individual countries. WHO budgeted for one full-time medical officer and 18 months consultant time, an international conference, two training courses, and the distribution of donated vaccines.

Five years later, the campaign appeared to have achieved very little. Many countries lacked the administrative structure for massive vaccination. Some found smallpox a low priority in terms of the health status of their populations and refused to devote resources to it. There were shortages of reliable vaccine supplies, and WHO itself was not pushing the campaign.

Individual countries had achieved more than was recognized, especially China, where the last case of smallpox occurred in 1960 (a

record not known or properly documented until 1978, five years after China joined WHO). Vaccination campaigns halted smallpox transmission in Vietnam, Cambodia, Laos, Iraq, Saudi Arabia, Democratic Yemen, and Iran during this period, but pilgrims and laborers from southern Asia repeatedly reintroduced smallpox to the Middle East. In the Western Hemisphere, Ecuador and Bolivia succeeded in interrupting transmission, but the disease became endemic again in Peru after its spread from the Amazon area of Brazil. Brazil itself made little effort to eradicate the disease, in part because the disease there took a milder form, with a death rate of no more than 1 percent.

Despite progress, national information systems were so unreliable that not more than 5 percent of all cases were being reported, according to later estimates. In Africa, in the midst of independence movement, health problems got little attention, and smallpox was seldom a priority.

By 1965, pressure was building within the World Health Assembly for WHO to take a more active role in smallpox eradication. The Soviet Union was impatient with the lack of progress, and two other developments added to U.S. interest in the idea. These were the development of a jet injector for smallpox vaccinations and the commitment by AID to support a smallpox eradication program in 18 countries in West and Central Africa.

The jet injector as originally conceived would not serve a smallpox vaccination campaign in the field, because it was electrically powered and it delivered inoculations subcutaneously rather than intradermally as required. In 1962, Aaron Ismach, of the U.S. Army, developed a special nozzle that permitted intradermal inoculation and a hydraulic power system operated by a foot pedal. CDC demonstrated the efficacy of the modified device, which could vaccinate as many as 1,000 persons per hour at one-third of the cost of conventional methods.

The African smallpox program grew out of a faltering AID measles vaccination program in Upper Volta and neighboring countries in 1961. Logistical and technical problems arose, and AID requested CDC to assist by providing medical officers to 10 countries for 6 months. CDC doubted the long-term value of the measles program, because the vaccine cost more than \$1.00 per dose and the host governments would not have the resources to continue the program after the anticipated four years of AID support. Measles spreads rapidly in western Africa, and 3 years after the vaccination program ceased 90 percent of children there under 3 years of age probably would experience the disease. CDC proposed smallpox vaccination along with measles vaccination, because the smallpox vaccination could have permanent results. Eventually 20 countries participated in the program.

With the support of the United States, the Soviet Union, and many developing countries, the World Health Assembly decided in 1966 on an intensified global eradication program to be supported, in part, by an allocation of \$2.4 million from the regular budget of WHO.

The campaign plan differed from that of malaria eradication in three ways. The campaign in each country would be adapted to take account of available resources, local conditions, and the epidemiological situation in each country rather than follow a set format. The reporting system

would record cases at the inception of a campaign as well as after the attack phase. The plan would encourage research. The plan retained the basic strategy of reliance on mass vaccination using freeze-dried vaccine but was augmented by the concept of surveillance.

Surveillance techniques developed and refined by Alexander Langmuir at CDC had been applied domestically but rarely internationally. As applied to smallpox, they involved a systematic attempt to detect possible cases and to investigate the source and site of acquisition of the disease. Discovery of the means of transmission was to be followed by an intensive vaccination program in the immediate area. In countries of high incidence of the disease, surveillance might have to be deferred until a vaccination campaign in the areas most infected was completed but could not be delayed until the country-wide vaccination campaign was complete. This strategy, which emerged from experience, proved important to the success of the campaign.

The need for continuing research in epidemiology and virology was seen as unnecessary by most health officials, including many at WHO. They insisted that the disease and how to combat it were well known and all that were needed were the mobilization of resources and administration of the program. Eventually agreement was reached to leave research in the plan, but less than \$50,000 was allocated for this purpose.

An over-all expenditure of \$180 million was foreseen; \$48.5 million would be from international sources. The estimates were rough and did not take inflation into account but were not far off. Between 1967 and 1980, international support in the amount of \$120 million was required.

The timing of the initiation of the AID-CDC western Africa program was fortuitous. By the end of 1966, agreements had been signed with most of the 18 countries, a staff of 50 had been recruited and trained at CDC, operations manuals had been developed, and supplies and equipment ordered. The draft manuals for field operations and for the operation and maintenance of the jet injectors were a boost to the WHO campaign. They were soon revised to meet WHO needs and were translated into French and Portuguese.

The eradication campaign, larger than a Cecil B. DeMille epic, involved 150,000 people working in 50 countries, a WHO headquarters unit of 6 professionals, and 5-10 professional staff in the participating regional offices, and up to 4 professional international staff in each of the participating countries. At any one time, however, there were never more than 100 international staff working in the program. The story deserves detailed telling, and fortunately it will have it. Much of this information is taken from draft chapters of a book by D.A. Henderson.

Here we can attend only to some of the organizational and informational elements of the campaign and to the role of research. Why were many public health officials, including some senior WHO staff, unenthusiastic about the campaign? They believed the objective to be unattainable and that, as a WHO expert committee said in 1964, eradication required the vaccination of everyone. Smallpox was then endemic in many of the most primitive and remote areas of the world, and eradication seemed unrealistic.

Also, the malaria eradication campaign was already in trouble in 1966, and was resented deeply by the regular health services. Proponents of the malaria campaign had argued that it would contribute to the development of the basic health services, but in most countries it remained an autonomous authority. There seemed no reason to believe the smallpox enthusiasts would have different results despite their intention to rely on current health service personnel to conduct the campaign. WHO officials perceived that international resources could become subject to faddish campaigns against particular diseases, one after another, with the result that the basic health infrastructure in many countries would never satisfactorily develop.

Not all governments wanted to participate. Before the intensified campaign got underway in 1967 such reluctance on the part of governments could be explained by local priorities for the use of scarce resources. After that, the availability of funds in the WHO budget meant that for most countries, particularly in Africa, participation in the eradication campaign cost no more than control programs. WHO was able to supply vaccine, vaccination instruments, supplies and technical assistance, and a limited number of vehicles.

Staff quality is key to the success of any venture. At the outset of the intensified campaign, the international staff consisted of 15 in WHO and the 50 CDC personnel in western Africa. Gradually the international cadre grew in size and quality. Emphasis was on youth, vigor, and technical competence; duties frequently involved travel into the interior on foot or by mule. The number of international staff never exceeded 100 at any one time, but nearly 700 took part at one time or another. The esprit de corps that developed still opens doors when veterans of the eradication campaign encounter one another.

The sources of able staff were varied and sometimes surprising. A Soviet vice minister of health identified a group of able epidemiologists from his ministry and permitted Henderson to interview and select five to join the program. Able contingents also came from the High Institute for Public Health in Alexandria and from Oxfam, a British voluntary organization. The CDC offered five full-time staff when an unexpected smallpox outbreak occurred in Bangladesh and was ready on short notice to meet specialized staffing needs. National programs themselves were valuable reservoirs of experienced staff who could be tapped for international service. Outstanding people were recruited from Afghanistan, Bangladesh, Brazil, India, Indonesia, Nepal, Sudan, and Togo. The smallpox group came to be known as among the best and most dedicated of any in international service. They were kept that way by careful selection and the easing out of those who wearied of extensive travel and heavy responsibilities.

The headquarters unit in Geneva had responsibility for global strategy and coordination, mobilizing international resources, and stimulating needed research. They traveled at least a third of the time and sometimes spent 50-70 percent of their time outside Geneva. Although four additional medical officers were later authorized, conditions in Ethiopia and Pakistan at the time required their full-time assignment there.

Rapid, effective communication is essential to a global scientific enterprise such as this. Campaign workers in all participating countries had to be kept aware of progress, not only for morale purposes but also in order to learn of field observations elsewhere, successful innovations and failures, and useful research results. The surveillance system, new to international practice, was founded on the notion of rapid and accurate communication of knowledge about the origins and incidence of the disease. National policy-makers, World Health Assembly delegates, and the public needed to know about the campaign and its prospects in order to generate the necessary support. The energy and ingenuity required to generate these information flows in an international agency are exceptional.

In late 1967 the unit began issuing quarterly surveillance reports, mimeographed documents sent to all international staff and national program directors dealing with smallpox. After 1968 it was agreed that a brief report might be inserted periodically into the Weekly Epidemiological Record a publication in which all quarantinable diseases are to be listed based on telegraphic reports from national authorities. This was a boon for the smallpox unit; the record is printed rather than mimeographed and is distributed to 5000 health officials and others throughout the world.

Information in the record was limited to epidemiological data, and the campaign needed access to such additional information as research results and conclusions of expert committees. So the Geneva unit packaged and mailed this kind of information on biweekly basis to 150 persons in the campaign.

The smallpox unit cultivated the mass communications media. Reasoning that voluntary donors, governments, and policy-makers in directly concerned countries were more likely to be responsive if the program were widely known, the unit took every opportunity to interest the media in the campaign. They arranged trans-Atlantic press conferences with correspondents in New York, Washington, London, Geneva, and Delhi interviewing Henderson in Geneva. Correspondents from the Soviet news agency Tass, Japan, and the United Kingdom covered the program closely.

Organizational communication was advanced, too, by frequent staff travel from headquarters and some regional offices and by annual conferences. The conferences began as sessions where national reports on progress were read, but soon the format was changed to focus on specific findings and strategies employed in particular national programs. The events were important means for sharing experience and building the program's momentum.

Keys to success included imaginative management, improved technology, and applied research. Managerial improvisation characterized the program. As an example of the campaign's flexibility, the operations manual never got beyond the draft stage. Changes were made as conditions required, but nothing was cast in concrete. Flexibility does not mean carelessness. Accurate reporting, rigorous surveillance, and prompt response to outbreaks were essential to ensuring that the disease was actually eradicated and not just temporarily set back. Over the years, the campaign solved many

logistical and resource problems (it was generally short of funds and vaccines). But this program characterized by a high level of resourcefulness, imagination, and a certain irreverence concerning standard operating procedures.

One of campaign's principles was that no country where the disease was endemic should be constrained by shortages of vaccine or of vaccination devices. This was a difficult rule to live up to because of another principle that no vaccine should be purchased by the program: The 25 million doses annually donated by the USSR, plus vaccine supplied bilaterally as in western Africa, were originally thought to be sufficient.

Investigation in 1967 and 1968 of the source and quality of vaccine available revealed that few laboratories were producing vaccine of acceptable standards, most did not test their vaccine for stability, and some assessed potency simply by vaccinating a group of young children.

To ensure the availability of adequate supplies of effective vaccines, the programs assisted production laboratories in smallpox-endemic countries, developed vaccination devices requiring less vaccine than conventional devices, and actively solicited contributions from producer countries.

The conventional scarification technique of vaccination, which left dime-sized indentations on the upper arm, used a whole drop of vaccine. A vial of 0.25 milliliter contained enough vaccine for 20-25 persons. The jet injectors used only a third of that amount. Jet injectors proved to be of limited value outside of western Africa, Zaire, and Brazil, however, because of problems of maintenance and repair. In Asia, where vaccination house to house was common, jet injectors were impractical. A new bifurcated needle, which could hold a tiny amount of vaccine by capillary action between its tines, was becoming available in the United States. Field trials in Kenya, Egypt, and Bangladesh demonstrated that it could be used effectively to vaccinate 100 or more persons with a single 0.25 milliliter vial.

The research dimensions of the campaign are of particular interest. In 1966, many in WHO and outside it did not believe further research was necessary. Henderson says without doubt that the campaign would not have succeeded without the strategic adaptations that research made possible.

In 1967 the research agenda was by no means clear except for the critically important problem of ensuring that there was no animal reservoir of the variola virus. Research on this problem continued for many years, revealing that smallpox needed a human host and also discovering and characterizing monkeypox, a disease that could be sustained by human transmission alone.

Other research accomplishments included the refinement of the epidemiology of smallpox and consequent changes in campaign strategy. The disease was not usually so widely disseminated or virulent as had been supposed. The University of Maryland ICMR in Lahore conducted elegant, comprehensive epidemiological studies in 1965 and 1966. The findings, soon confirmed by others in Africa and Latin America, were vital to the strategy adopted for the eradication campaign.

Other accomplishments included improved techniques for sample survey assessment, better vaccine production and testing procedures, the adaptation of vaccination technology, and genetic mapping of variola and vaccinia viruses, providing new insights into the relationship of different viruses. The vaccination of newborn children was demonstrated to be effective, and concepts of the efficacy and duration of vaccinal immunity were altered.

Most of the research was operational--learning and adapting procedures and technology while pursuing the campaign. Improved procedures originated from the national programs as well as from laboratories. Important contributions were made by CDC; the Institute for Virus Preparations, Moscow; the National Institute of Health in Japan; the Department of Virology, St. Mary's Hospital School of Medicine, London; the Rijks Institute, Netherlands; Wyeth Laboratories, in the United States; the Public Health Institute, Bangladesh; the Pakistan Medical Research Center, Lahore, home of the Maryland ICMR, and others. Most of these contributions were funded from sources other than WHO but frequently were in response to problems posed by the campaign.

Conclusions

The framework of discussion of other programs for research on tropical diseases is of limited utility here. The smallpox program, being global in nature and achieving total eradication of a disease, is of course the ultimate in collaborative effort and in results.

The results of the campaign in terms of capacity building for dealing with smallpox is not an issue. However, a related question is central to a continuing debate on international health assistance strategies. Is the mobilization of a national health service to carry out a campaign against one or several diseases an effective way to improve the over-all competence of the system? Designation of measurable health objectives for well-designed campaigns may be a valuable tool for capacity building.

The history of the smallpox campaign offers some insight on the usefulness and limitations of WHO as a channel for U.S. funds to combat tropical diseases. Henderson and his colleagues sometimes seemed successful despite rather than because of WHO, but the campaign would not have been possible without WHO.

The annual World Health Assemblies were invaluable for developing consensus on the need for a global campaign. Standards set by WHO for vaccine became universally accepted. The movement of biological and other materials across national borders is greatly facilitated by WHO procedures. Multilateral pressures on governments to participate in a global effort may be more acceptable than bilateral pressures. WHO involvement seems to represent a necessary, but not sufficient condition, for the success of a global campaign.

The campaign was a rare example of Soviet-U.S. cooperation. U.S. scientists and institutions played key, probably indispensable roles. Henderson's independent base as a CDC employee on loan to WHO gave him

more leverage there than he might have had otherwise. To the U.S. reader, the success of the effort may seem more than anything else to be due to a "can-do" attitude which we like to think of as our own.

ISSUES

Scope

Only the international programs, ICDDR,B and TDR, and the schistosomiasis program of the Clark Foundation seem to accept responsibility for research across the spectrum (basic to applied). TDR and the Clark Foundation have mechanisms for establishing and amending strategic research plans--agendas of timely, promising, or otherwise appropriate research.

Of the U.S. Government-supported programs, the Department of Defense laboratories operate along the widest bands of the spectrum, from seeking to understand the biological nature of the pathogen to devising methods of human protection from the disease. The military laboratories fall short of the international programs and the Clark approach by having a limited concern for epidemiology, the economics of protection, and village society and environment. In devising protective strategies, the military scientists can assume standards of sanitation, disciplined conduct, and financial resource availability that do not prevail widely.

For the U.S. Government as a whole, there is no agency or office specifically responsible for monitoring the status, defining the research frontier and devising research strategies, or formulating comprehensive policies for dealing with tropical diseases, except the subject comes within the mandates of individual agencies.

The path of scientific discovery cannot be charted; it is difficult to know what line of research will produce knowledge of value in understanding or protecting against a disease. Hence, it may be unwise to attempt to formulate strategic plans for attacking diseases. But the science to bring most tropical diseases under control is not always lacking. A hundred years ago, morbidity and mortality rates were as high or higher in Europe and the United States as they are today in developing countries. The technologies and human behavioral changes needed to reduce disease incidence are frequently known; the question is of investing in sanitary facilities, clean water, and education. From this point of view, research expenditures on trypanosomiasis are justifiable in order to advance our understanding of the immune system, without implying commitment to the pursuit of substances protective against the disease. Many scientists in basic research believe that science should go where the best scientific investigators want it to go, irrespective of other considerations.

Collaboration

Scientifically, the most productive institutional collaboration of those noted here probably occurred between the Cholera Research

Laboratory, in Dacca, and NIH and CDC in the United States. They were all U.S. institutions, basically, but the relationship was productive because the quality of the work was outstanding, the substance of the work was at the advancing research frontier, and each institution brought something of value to the process. CRL gained from access to first-class staff, and CDC gained valuable epidemiological field experience for a generation of young workers. NIH also gained field experience for its staff.

Currently, the GND program of the Rockefeller Foundation and the ICIDR program of NIH include good models of collaboration on a limited scale and on an abbreviated segment of the research spectrum.

Only three laboratories in (relatively advanced) developing countries were selected as GND grantees. Collaborative relationships with institutions in the poorer countries are much more difficult to sustain, as recent national political struggles that may jeopardize the work of the Sudan-Michigan State ICIDR illustrate.

TDR is attuned to the interests of developing countries and their scientists and is intended to build their research capacity but falls short of the collaborative ideal. Mechanisms for supporting long-term relationships between laboratories in advanced countries and those in disease-endemic countries have not been established. However, TDR training and grants have facilitated much collaborative work resulting in joint publications.

Investigator-initiated, peer-reviewed, competitive grants programs, which constitute the bulk of the funding for medical research, are unlikely to spawn many collaborative projects. Communications problems, language factors, and differing research traditions are likely to complicate efforts to win highly competitive awards. Programs such as ICIDR, requiring collaborative relationships, should be expanded if the collaborative process is to be encouraged.

Impact on Disease

U.S. medical research seems to operate on the laissez-faire assumption that the combined effect of each investigator's pursuit of his or her individual research interests will maximize in social terms the value of the research funds available. In the search for unique research topics, the theory might go, proposals will emerge to bridge every perceivable gap. Overly structured or narrowly targeted research designs would distort the allocation of brainpower by directing research along beaten paths into the unknown while leaving large wilderness areas in between.

The quality and productivity of the U.S. medical research establishment are indisputable. Perhaps the system depends for success on a large number of active investigators. Where resources are scarce and investigators few, the targeted approach may be more efficient..

Some types of experiments that may be vital in linking different segments of the research spectrum don't fit well into the existing array of programs and institutions. For example, Rockefeller Foundation work in St. Lucia sought to determine costs of different approaches to

reducing the island's schistosomiasis infection rate. From these experiments came valuable information that can help policymakers to choose among various disease-control strategies, taking environmental factors and resource availability into account.

That type of experiment would be unlikely to be funded in military laboratories, where marginal costs of control alternatives are of minor significance, or in Gorgas, which concentrates mainly on the diseases of Panama. Nor, because of biomedical orientation, would an ICIDR grantee be likely to undertake such an experiment. AID might fund such a program, although no parallel example comes to mind.

Today's Federal programs and institutions are not designed to track a tropical disease problem from its biomedical origins through to the point of choosing among alternative protective measures. There are gaps, and no agency has explicit responsibility to identify or bridge them.

Capacity Building

Building U.S. capacity for tropical disease research is not synonymous with building such capacity in the developing countries. The military medical research system has been successful in building and retaining U.S. capacity for work on tropical diseases. The ability to offer extended field laboratory experience to career employees permits the Army and Navy to develop and deploy trained personnel within the limits of resources available.

The Cholera Research Laboratory was remarkably successful in offering field experience to many people who remained in tropical medicine, possibly because of the organic links among CRL, NIH, and CDC, and possibly because research there was recognized as important. The laboratory contributed to U.S. and foreign international health capacity.

The ICMR, ICIDR, and GND programs all offer or offered excellent field experience for U.S. researchers, although in limited numbers and without strong career opportunities.

Gorgas, situated in a tropical area, itself represents an institutional capacity for work on tropical diseases; its value could be substantially advanced had it an assured supply of bright young researchers for residencies. This might be accomplished through links with more U.S. universities, although Gorgas would require additional funding.

CRL is the most notable example of U.S. efforts to build such capacity in the developing countries. CRL was built largely with foreign assistance funds, with a hefty assist from blocked local currency under Public Law 480. The experience is unlikely to be repeated. Blocked currencies are nearly exhausted, and long-range institution-building efforts at AID have largely given way to activities that seem to promise more immediate, direct payoff.

The GND program does not attempt to build new institutional capacity as such, but in Bangkok it is benefiting a research institution built years earlier with assistance from a previous Rockefeller Foundation

program designed to strengthen medical faculties in selected universities of developing countries. That same program helped shape the medical faculty at Universidad del Valle, in Cali, where the Tulane ICMR was based initially. Institution-building programs like the earlier Rockefeller effort are very-long-range, expensive undertakings, no longer popular in foundation or government circles. Whether there are shorter, cheaper ways to build the same level of local competence is not clear.

The ICMRs in Cali and Kuala Lumpur seem to have left lasting legacies in the institutions where they were based. The ICIDR grants may have similar results, although it is too early to tell.

Gorgas has not seen local or regional capacity building as a major part of its mission, although that could in future be a valuable role for it to play. Again, additional funding and a new outlook would be required.

The U.S. record in developing institutional and individual capacities for tropical disease research thus seems sporadic. No Federal agency has a clear mandate to build health research capacity in the developing countries. There may not be agreement that building research capacity should have priority over other activities, such as conducting research programs or carrying out disease control projects.

Even if a pool of funds is earmarked for building tropical disease research capacity, it is not clear that there is an agreed course of action to follow.

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