

NIAID Tropical Disease Research: Priorities and Future Directions

Karl A. WESTERN

*National Institute of Allergy and Infectious Diseases,
National Institutes of Health*

Let me start by defining "tropical diseases" for the purpose of this presentation. At the National Institute of Allergy and Infectious Diseases (NIAID), we define "tropical diseases" as those infectious conditions which affect the citizens of tropical or developing countries more severely than their counterparts in economically advanced countries. The NIAID approach, therefore, is broader than the six diseases (e. g. filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis) of the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases (TDR/WHO). It also is more restricted than the health priorities of development agencies (e. g. USAID, WHO) which have defined international health priorities in terms of conditions which produce preventable death and disease in vulnerable populations (e. g. acute respiratory infections, diarrheal diseases, viral infections, and parasitic diseases).

This audience will also appreciate that the U. S. A. with its diverse populations and economic disparities is still in many respects a developing country with health indices worse than some developing countries. Furthermore, large areas of the U. S. A. are semi-tropical while Southern Florida, Puerto Rico, the Virgin Islands, and the Pacific Trust Territories are truly tropical. Tropical diseases, therefore, which 19th Century Europe considered dangers to expatriots and expeditionary forces were endemic diseases in much of the U. S. A. Foggy Bottom where our State Department now stands was once notorious for its malarial fevers. Thousands of workers died of malaria, cholera, and yellow fever constructing the Chesapeake and Ohio Canal which starts near Foggy Bottom and runs through Georgetown to the interior in West Virginia. In Abraham Lincoln's day, you could tell a Mississippi Valley settler from the ravages of relapsing malaria and our Southern populations were notorious for their torpor brought on from poor nutrition, malaria, and hookworm infections. Indeed, at the same time that the Nagasaki Institute of Tropical Medicine was established, the U. S. Government found it necessary to set up what is now our Centers for Disease Control in Atlanta to control malaria in civilian and military populations.

To this day, tropical diseases persist in the U. S. A. to a degree not seen in Europe or Japan. Even where they have disappeared, the potential for reintroduction continues through persistence of efficient vectors and/or poor sanitary practices. The U. S. A., for example, has persistent foci of malaria in the San Diego area, cholera in the Gulf of Mexico, leishmaniasis in south Texas, and schistosomiasis in Puerto Rico. Sylvatic plague is well established west of the Mississippi and zoonotic rabies (foxes, skunks, bats, raccoons) exists in most areas.

Several years after my graduation from the London School of Hygiene and Tropical Medicine (LSHTM) the late Professor Bruce-Chwatt was disappointed to learn that CDC had assigned me to be State Epidemiologist for Virginia. He was pleased when I told them that LSHTM had been excellent training for my new assignment.

Because many tropical diseases still persist or pose a threat to U. S. citizens, several U. S. Government agencies share responsibilities in tropical medicine. The major players are the National Institutes of Health (NIH), the Centers for Disease Control (CDC), the U. S. Army, the U. S. Navy, and the U. S. Agency for International Development (USAID), NIH is a civilian agency heavily committed to basic research, prevention research (e. g. vaccine development), and clinical research. CDC, as its name indicates, is responsible for surveillance and prevention of control programs. The Army and the Navy are both concerned with the prevention or treatment of tropical diseases in active duty military and dependents. USAID is responsible for international technical assistance and economic development.

My further remarks will concentrate on NIH research in general and NIAID tropical medicine research in particular. While NIH can trace its history to the founding of the Bacteriology Laboratory at the Marine Hospital on Staten Island, New York in 1888, the modern NIH began only in 1935 when President Franklin Roosevelt decided to put the scattered Government laboratories doing health research on one site to reach what we now call a "critical mass". The new NIH was placed on "Tree Tops", a 19 hectare estate in rural Bethesda, Maryland. "Tree Tops" had recently been donated to the Government by Mr. Luke Wilson, a New Dealer and Roosevelt admirer. The second most significant event in creating NIH was the U. S. Government's decision following World War II to transfer the grants program of the War Department's Office of Scientific Research and Development extramural programs to the NIH. Before this decision, NIH was not a significant funding source for U. S. universities. Tropical medicine and infectious diseases comprised a significant portion of this war-related research portfolio. NIH, therefore, inherited an ongoing research effort which among its many accomplishments had developed chloroquine and penicillin.

From 1946-1967, the NIH Office of International Research managed most externally funded tropical disease research. In 1968, however, the Fogarty International Center was established to coordinate NIH international activities. The NIH Office of International Research disbanded and international research awards were transferred to the appropriate line institute at NIH. Tropical medicine research awards, including the International Centers for Medical Research and Training (ICMRT) came to NIAID. NIAID continues to support over 95% of NIH's tropical disease effort.

In FY 1991, NIAID Tropical Medicine Research (Handout 1) consisted of 435 research grants, four research contracts and 41 intramural research projects with a total budget of \$88.8 million or 9.8% of NIAID research. The fact that over 90% is carried out through competitive extramural research awards is consistent with the 9:1 overall extramural/intramural ratio at NIH. An important point to make is that most of this research is done by U. S. investigators in the U. S. A. NIAID support for tropical medicine has grown at the same pace

as non-tropical infectious diseases. This is a reflection of research opportunities in these diseases and the high quality of the investigator-initiated research proposals submitted to NIH, not priority treatment for tropical medicine.

NIAID is a domestic research agency which does not have an international budget. Our mandate to conduct international research is based on the Public Health Service (PHS) Act of 1963 which authorized NIH to conduct international research relevant to the health and safety of U. S. populations wherever they might be. This authorization did not permit NIH or CDC to provide technical assistance, transfer technology or strengthen institutions outside the U. S. A. In the U. S. Government, these activities have been the responsibility of the USAID. The PHS Act of 1988 (often referred to as the "AIDS" Act), however, modified our mandate to conduct international research for the first time in 25 years. It authorized NIH and CDC to carry out "USAID-type" activities internationally in AIDS—especially in Africa and the Caribbean. As is frequently the case, however, we were given this authority but no additional funds to carry it out.

Despite its domestic mandate, NIAID has a low-profile, but extensive international health research effort. The mechanisms we use with illustrative examples are summarized in Handout 2. Briefly, the mechanisms are; 1) intramural collaborative research and research training; 2) foreign research awards; 3) domestic research awards with a foreign component; 4) official bilateral programs; and 5) international agencies and organizations.

Let me illustrate these mechanisms with respect to Japan. Intramurally, 34 (13.5%) of the foreign scientists at NIAID last year were from Japan. While we have made awards directly to Japanese investigators in the past, we currently have no active foreign awards in Japan. The major portion of NIAID international activities are supported through grant application from U. S. scientists to fund research that has an international component. We have found, however, that research applications involving collaboration with scientists in developing countries on tropical diseases do not compete successfully in the NIH peer review process. NIAID, therefore, has created three special extramural and one intramural programs to fulfill our research mission in tropical diseases. They are:

- NIAID Intramural Tropical Disease Research Center (INCIDR), INCIDR consists primarily of the Laboratory of Parasitic Diseases (LPD/NIAID) and the recently established Laboratory of Malaria Research (LMR/NIAID).
- Tropical Disease Research Units (TDRU). TDRUs support domestic U. S. multidisciplinary centers of excellence in tropical medicine. About 25% of TDRU research involves international collaboration.
- International Collaboration for Infectious Disease Research (ICIDR) Awards. An ICIDR is a linkage award to a U. S. institution to conduct collaborative research with counterparts in a developing country. Approximately 70% of the research is in the host country.
- Tropical Medicine Research Centers (TMRC). TMRCs are research centers of excellence which receive NIAID directly. All the research is done in the tropics.

Special mention should be made of the U. S.-Japan Cooperative Medical Sciences Program (CMSP). Established in 1965, this Program is unique among U. S. bilateral programs in two respects: 1) it is managed by working scientists rather than administrators; and 2) it is concerned with the health problems of Asia rather than just Japan or the U. S. A. NIAID provides the U. S. Secretariat for overall U. S.-Japan CMSP and seven of the nine U. S. Panels and one Board in the CMSP. The U. S.-Japan Panels on Parasitic Diseases, Viral Diseases, AIDS, Cholera, Hepatitis, Leprosy, and Tuberculosis are particularly relevant to the tropical medicine research activities of both countries. NIAID values the U. S.-Japan CMSP for the opportunity it provides not only to interact with the Japanese scientific community, but to access industry and policy makers through scientific rather than foreign policy or political channels.

During World War II, U. S. tropical medicine research policy was directed by the military with scientific guidance and advice from the Armed Forces Epidemiology Board (AFEB)—on which the U. S.-Japan CMSP is modeled. After the War, interest in international research became more prominent as the U. S. Government committed itself to assisting with the reconstruction of institutions, training of scientists, and support for research in war-ravaged Europe countries and Japan. A similar effort to build biomedical research capability in newly independent countries of Africa and Asia, however, did not emerge as a major feature of U. S. research policy. The rationale for this was complex and beyond the scope of this presentation. Tropical medicine research needs, resources, and policy were, however, re-examined periodically from 1946–1962 through Conferences sponsored by the U. S. Army, NIH, and the Rockefeller Foundation and attended by eminent scientists—not just in tropical medicine, but in biomedical sciences. One of the many casualties of the Vietnam War was the break-up of this military-scientific-private sector alliance.

By 1982, interest in and support in the U. S. A. for tropical disease research had flagged. Ironically, this decline was occurring at a time when scientific advances in immunology and molecular biology were revolutionizing microbiological research and providing the scientific basis for the development of immunodiagnostic tests, drugs, and vaccines. Furthermore, the division of tropical disease among the several agencies raised obvious doubts in the Executive Branch and Congress regarding duplication of effort and waste of tax dollars on diseases which were not major problems in the U. S. A. External events such as a Department of Defense (DoD) decision to shut-down the overseas laboratories of the U. S. Army (Brazil, Kenya, Thailand) and Navy (Egypt, Indonesia, Peru, and Philippines), a Congressional study of the activities of the Gorgas Memorial Laboratory (Panama), and an effort by the new Thatcher administration to close the LSHTM prompted the American Society of Tropical Medicine and Hygiene (ASTMH) to approach Congress and the National Academy of Science (NAS) to study the state of Tropical Medicine in the U. S. A.

This concern led to a Congressional directive that its Office of Technology Assessment (OTA) examine the status of biomedical research and technologies for controlling tropical infectious diseases. The OTA report Status of Biomedical Research and Related Technology for Tropical Diseases appeared in 1985. Building on the OTA findings, the U. S. Army

Research and Development Command (USARDC), NIAID, CDC, USAID, and the Rockefeller Foundation funded the Board on Science for Technology and International Development, National Research Council (BOSTID/NRC) and the Institute of Medicine, National Academy of Sciences (IOM/NAS) to conduct an external evaluation entitled *The U. S. Capacity to Address Tropical Disease Problems* (1987). Among the major findings of this BOSTID/NRC-IOM/NAS Report were:

- A need for stronger collaborative research and training relationships with scientists and public health officials in less-developed countries;
- A need for U. S. investigators to become familiar with tropical diseases and health conditions in developing countries through residence overseas at a formative stage of their careers;
- An unstable career structure in tropical medicine—particularly for U. S. tropical health professionals who are broadly trained in science, medicine, public health; and disease control and field experience in the tropics;
- A need for more U. S. contributions to the training and development of foreign competence, particularly in research and disease monitoring.

The Report made both general and specific recommendations to the sponsoring agencies on how to address these problems. Subsequent relevant IOM/NAS external reports have dealt with *Malaria: Obstacles and Opportunities* (1991) and *Emerging Infections: Microbial Threats to Health in the United States* (1992).

NIAID has dealt with the recommendations of these reports in the context of the NIH Strategic Plan being developed under the leadership of Dr. Bernadine Healy and our own program planning process which includes recommendations from the National Advisory Allergic and Infectious Disease Council (NAAIDC) and two policy retreats each year by the NIAID leadership and senior staff. NIAID priorities and future directions in tropical infectious diseases are outlined in the Report of the Task Force on Microbiology and Infectious Diseases (January, 1992). Major Task Force Recommendations included:

- NIAID basic research in infectious diseases should focus on the following four areas: 1) genetics, molecular biology, and structural biology; 2) pathogenesis; 3) epidemiology; and 4) immunology;
- Efforts should be made to stimulate more multi-disciplinary research and training in infectious diseases—including cell biology, immunology, molecular genetics, vaccine development, epidemiology, biostatistics, and behavioral research.
- Every effort should be made to facilitate information and technology exchange among scientists within Government, industry, and academia. This exchange is critical for the continued development of antimicrobial drugs and vaccines.
- NIAID should continue its longstanding efforts to foster support, and expand (where possible) broad-based international studies of infectious diseases, including clinical research, epidemiology, and field trials of promising vaccines and antimicrobial drugs.

In an effort to implement these policy recommendations in tropical medicine during the present economic climate, NIAID has established a new program we call the International Centers for Tropical Disease Research (ICTDR) Program. ICTDR brings together the existing TDRC, TDRUs, ICIDRs, TMRCs, the Office of Tropical Medicine Research in the NIAID Director's Office (OTMIR/NIAID), the NIAID Division of AIDS (DAIDS/NIAID), and NIAID-supported Cooperation Groups. DAIDS/NIAID currently supports the International Cooperation in AIDS Research (ICAR) Program—which is a linkage program similar to the ICIDR and the new Preparing for AIDS/HIV Vaccine Evaluations (PAVE) Program which will support U. S. groups to assist institutions in Africa (Kenya, Malawi, Rwanda, Uganda, and Zimbabwe), Asia (India and Thailand), and the Caribbean (Haiti) get ready to evaluate promising AIDS vaccine candidates. Cooperating Groups are U. S. universities or research institutions which may not have a TDRU or ICIDR award, but receive substantial NIAID research support in parasitic diseases or vector biology.

The ICTDR will serve as a network to promote multidisciplinary research and facilitate information exchange and cooperation among NIAID scientists and NIAID-funded tropical medicine investigators. At present, the major ICTDR activity will be a networking meeting each Spring at NIH. The inaugural ICTDR meeting (Washington, DC: 30 April–1 May, 1992) was preceded by a NIAID–TDR/WHO Forum on “Tropical Diseases” (Bethesda, MD: 29 April, 1992). The meetings produced a policy document *Current Approaches to Ancient Problems. Report of the First Annual Meeting of the NIAID International Centers for Tropical Disease Research*. NIAID has also conducted an inventory of the activities and resources available at ICTDR participating institutions. This information is contained in the NIAID document *International Centers for Tropical Disease Research: Training and Research Resources*.

In this presentation, I have provided a snapshot of current NIAID tropical infectious disease priorities and trends. The Second ICTDR Network Meeting will be held in Bethesda from April 28–30, 1993. It will be an open scientific meeting in which all interested scientists and institutions are invited to participate. I would like to take this opportunity to extend an invitation from Dr. Anthony S. Fauci, NIAID Director to all of you and to the Nagasaki Institute of Tropical Medicine in particular to come to Bethesda next April to join with NIAID in tropical disease priority setting and program planning at the national and global levels.

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