NATIONAL INSTITUTES OF HEALTH (USA): ROLE IN TROPICAL MEDICINE RESEARCH

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The National Institutes of Health (NIH) can trace its origin to the National Hygienic Laboratory established on Staten Island, New York in 1887. The modern NIH, however, is the result of two historic events. The first was the decision in 1934 by Franklin Roosevelt to bring all US Government health laboratories together in a rural area of Bethesda, Maryland to create a National Institute of Health. The second, following World War II, was to provide the NIH with the authority to make external research awards. Today, the NIH is the research and research training arm of the domestic US Public Health Service (USPHS). NIH consists of 24 Institutes, Centers, and Divisions (ICDs) which carry out research through their own intramural laboratories and extramural research awards. In Fiscal Year (FY) 1997, the NIH budget approached US$ 12.2 billion, the bulk of it (84%) being extramural and the rest intramural (12%). While NIH conducted international research from its beginning, the formal authority to do so (1963) provided that international activities should be relevant to the health and safety of US populations. In 1988, that authority was extended in HIV/AIDS and related diseases to include training, technology transfer, and institutional strengthening.

The National Institute of Allergy and Infectious Diseases (NIAID) is the third largest NIH ICD. In FY 1997, its budget of US$ 1.25 billion accounted for about 10% of the total NIH effort. The NIAID budget is equally divided between AIDS (US$ 647 million) and Non-AIDS (US$ 610 million). NIAID is organized into four research divisions: 1) Intramural Research (12%); 2) Microbiology and Infectious Diseases (32%); 3) Allergy, Immunology and Transplantation (21%); and HIV/AIDS (40%). Traditionally, the HIAID Research Mission has included:

- Bacteria, Viruses, Parasites, Fungi, and Rickettsiae
- Immune Systems and Host Response
- Vaccine Development and Evaluation
- Anti-Viral Agents
- Sexually Transmitted Diseases
- Vaccine Development and Evaluation
- Anti-Viral Agents

In recent years, this Mission has been expanded to include new priority areas, such as:

- HIV/AIDS and Related Conditions (1984)
- Tuberculosis (1992)
- Tropical Medicine and Medical Entomology (1993)
- Emerging and Re-Emerging Infectious Diseases (1995)

NIAID relies heavily on the investigator-initiated research grant (66%) mechanism to carry out its research. Under this policy, NIH invites researchers to submit their most exciting proposals in the form of grant applications which will be subjected to rigorous peer review. NIAID funds the best research proposals large from a unallocated grants pool of over US$ 700 million. About 13% of NIAID research is funded through contracts, which SUPPORT applied research to carry out research which NIAID wants done. Contacts are used to support reagent repositories, prospective epidemiology research, and most clinical trials. Intramural research (12%), the third largest category, is also investigator-driven, but carried out by NIAID's own intramural scientists. Individual and institutional research training awards comprise another 2% of the budget. The remaining 2% consists of taps on NIAID for NIH-wide initiatives or transfer of funds to other ICDs or agencies.

Just as NIH conducted international research before it had formal authority to do so, NIAID was the primary source of NIH funding for Tropical Medicine Research for many years without a specific mandate to do so. In 1993, however, Congress formally expanded NIAID's mission to include Tropical Medicine. NIAID defines tropical medicine as the study of those conditions which pose a public health threat to US citizens and/or which disproportionately affect populations in tropical or resource poor settings. The NIAID definition, there-

fore, is broader than the six diseases included in the WHO/World Bank/UNDP Special Program for Research and Training in Tropical Diseases Research (TDR). The NIAID definition is also narrower than the health priorities of international development agencies such as USAID or WHO which have defined international health priorities in terms of preventable deaths and disease due to acute respiratory infections, including tuberculosis; diarrheal diseases; viral infections, and parasitic diseases, particularly malaria.

The NIAID definition of what diseases are tropical is also flexible and is reviewed periodically in the light of changing disease patterns. This is necessary because of the diverse populations, economic disparity, and environmental conditions across the USA. Tropical diseases such as malaria, dengue fever, yellow fever, and cholera were endemic in the USA at the turn of the century. Some, such as sylvatic plague and rabies, persist. Efficient vectors of malaria and dengue fever are widespread. Ecological changes and/or deficiencies in public health programs result in the recognition of new problems such as Lyme disease or multiple-drug resistant (MDR) tuberculosis. Improved surveillance and diagnostic tests permit the detection of other new or previously unrecognized conditions such as ehrlichiosis, and Sin Nombre hantavirus.

As a result, conditions such as tuberculosis, which were on our Tropical Medicine list ten years ago, are currently considered domestic research priorities. Opportunistic parasitic and fungal diseases associated with HIV/AIDs have also resulted in a distinction between domestic and tropical conditions. Were dengue fever to reappear in Texas or Florida, it would probably also move into the domestic area.

In order to fulfill its domestic and international mission in Tropical Medicine, NIAID has developed several special emphasis programs in: 1) Tropical Medicine; 2) HIV/AID; 3) Sexually Transmitted Diseases; 4) Tuberculosis; 5) Emerging Viral Diseases; 6) Vaccine Dicovery and Evaluation Units (AIDS and Non-AIDS); and most recently; 7) the Malaria in Africa Multilateral Initiative.

Special initiatives in Tropical Medicine are the oldest and most highly developed. The NIAID International Centers for Tropical Diseases Research (ICTDR) Network consists of: 1) NIAID intramural laboratories; 2) Tropical Disease Research Units (TDRUs); 3) International Centers for Infectious Disease Research (ICIDR) Program; 4) Tropical Medicine Research Centers (TMRCs); and 5) Middle Eastern Regional Cooperative (MERC) Centers.

- TDRUS (Table 1) presently consists of five domestic centers of excellence in tropical medicine research concerned with the vector control, drug discovery, or vaccine evaluation.

- ICIDRs (Table 2) are eleven awards to US institutions to pursue truly collaborative research with counterparts in a developing country.

- TMRcs (Table 3) provide direct NIAID funding to three tropical medicine centers in the tropics; and

- MERCs (Table 4) are eight NIAID-USAID research contracts in leishmaniasis or echinococcosis to institutions in Israel, Jordan, Lebanon, Morocco, and Tunisia.

The Sexually Transmitted Disease (STD) Cooperative Research Centers Network are similar to the TDRUs. They are seven awards to US domestic centers of excellence which are required to have one international project.

The International HIVENT Program is modeled after the ICIDR Program. It provides nine awards to US institutions to collaborate in the development of a defined population in which HIV vaccine and other preventive research could be carried out. Prevention studies have involved reduction of maternal-infant HIV transmission; sexually transmitted disease (STD) diagnosis and treatment to reduce HIV; topical microbicides; tuberculosis diagnosis and treatment; and behavior modification. Overseas HIVNET awards are Brazil, Haiti, India, Kenya, Malawi, Senegal, Thailand, Uganda, and Zimbabwe. In the HIVNET re-competition, foreign investigators were eligible to apply directly. The results of the re-competition will be announced in September 1997.

The Tuberculosis Research Center (TRC) is an NIAID master contract to Case Western Reserve University to coordinate a network of tuberculosis research groups with expertise in basic, clinical, and epidemiological research. Overseas subcontracts are in Brazil, India, and Uganda.

Last year, NIAID funded three new Emerging

Viral Diseases Centers and four Hepatitis C Centers in US institution. NIAID has also taken a leadership role in the Malaria in Africa Multilateral Initiative which has solicited letters of interest from African investigators which will be reviewed by TDR for further development. The NIAID Vaccine Discovery and Evaluation Units are US based and are concerned with both AIDS and Non-AIDS vaccines. Vaccine candidates which progress to Phase III trials in the USA may be suitable for Phase II-III trials outside the USA. A recent example is the successful evaluation of acellular pertussis vaccines against whole cell pertussis vaccine in Italy and Sweden.

NIAID supports Tropical Medicine and International Research through six different funding mechanisms. They are: 1) Collaboration with intramural scientists, including the Visiting Scientists Program; 2) Foreign awards; 3) Bilateral (country-to-country) agreements; 4) International Organizations (USAID, WHO); 5) Fogarty International Center (FIC/NIH); and 6) Domestic research awards with a foreign component.

Collaboration with intramural scientists is simple and direct. Scientists communicate with each other and collaboration develops with the resources available at the NIAID intramural laboratory. The Visiting Scientist Program is a longer-term investment which offers research training to young post-doctoral, mid-career, and senior foreign scientists in an intramural laboratory. The host NIH laboratory usually provides the stipend and travel expenses.

Foreign scientists are eligible to apply for NIH grants and, under special circumstances, for research contracts. Foreign applications are usually not encouraged because of the intense competition for NIH grants. The TMRCs and the acellular pertussis field trials, however, are examples of NIAID foreign grant and contract awards.

Bilateral agreements may occur at the Head of State, USPHS, NIH, or ICD level. NIAID participates in a number of Head of State Programs, including the US-India Vaccine Action Program and the US-South Africa (Gore-Mbeki) Health Committee, and a more limited number of ICD level scientific exchanges with counterpart institutions.

NIAID has had serveral interagency agreements with USAID in malaria, HIV/AIDS, and tropical medicine. The MERC Program is the largest example of NIAID-USAID cooperation. NIAID-WHO cooperation consists primarily of encouragement of NIAID staff and awardees to participate in WHO programs on an individual basis.

The NIH Fogarty International Center (FIC/NIH) has the responsibility of coordinating NIH international activities and providing support for international research fellowships, biodiversity research; and international training in tropical medicine, HIV/AIDS, and emerging and re-emerging infectious diseases. FIC/NIH has accomplished this by supplementing NIAID grant awards in these areas and/or building an international component on NIAID domestic research and training wards.

The largest portion of NIAID international research is carried out through domestic research awards with a foreign component. Much of this occurs in the regular investigator-initiated grant process. The ICIDR and international HIVNET Programs are examples in special emphasis areas.