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SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES

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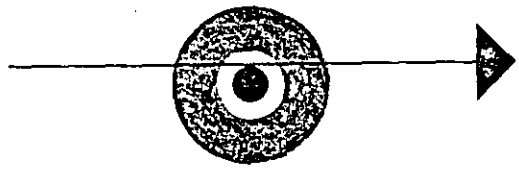
Tropical Disease Research:

A Global Partnership

Eighth Programme Report:

The First Ten Years,
with Highlights of the 1985-86 Biennium



UNDP/WORLD BANK/WHO Special Programme
for Research and Training in Tropical Diseases

TDR

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World Health Organization
Geneva
1987

1 Overview

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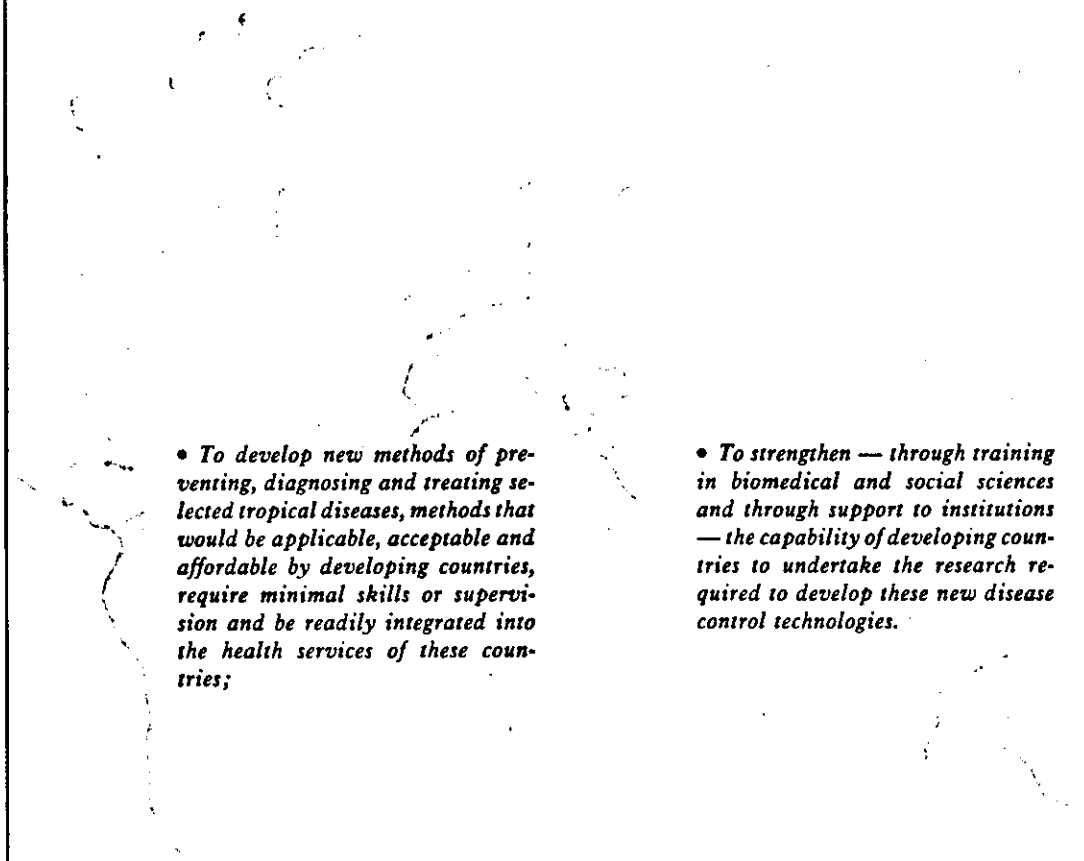


- *To develop new methods of preventing, diagnosing and treating selected tropical diseases, methods that would be applicable, acceptable and affordable by developing countries, require minimal skills or supervision and be readily integrated into the health services of these countries;*

- *To strengthen — through training in biomedical and social sciences and through support to institutions — the capability of developing countries to undertake the research required to develop these new disease control technologies.*

The Special Programme for Research and Training in Tropical Diseases (TDR) is a globally coordinated effort to bring the resources of modern science to bear on the control of major tropical diseases. TDR provides a mechanism for international scientific collaboration and plays a unique role as coordinator and facilitator among the growing number of national and international tropical disease research programmes. In its first ten years, the Programme has demonstrated that its *modus operandi* is a formula for success: TDR has recruited into its worldwide network scientists of the highest calibre, whose work is beginning to bear fruit in the form of vaccines, drugs, diagnostic tests and other disease control tools, and more and more scientists in tropical countries are being trained, through TDR-supported activities, to participate in this international research effort.

TDR's activities are targeted towards six disease groups — malaria, schistosomiasis, the filarial diseases (including onchocerciasis), the trypanosomiases (both African sleeping sickness and the American form, Chagas' disease), the leishmaniases and leprosy. These diseases were chosen because of their major impact on public health, the inadequacy of methods of controlling them and the likelihood that research could lead to better disease control methods.

Why only six disease groups? First, the six groups actually comprise over 20 different disease entities. Second, the complexity of their pathogenesis and transmission mechanics and the correspondingly difficult control problems they pose already strain a small research programme like TDR up to and often beyond its resources. And third, a global research programme like TDR could only work efficiently within the limits of a selected number of targets.

To make TDR workable, choices had to be made that sometimes implied drawing the line between the desirable and the achievable. Whether or not the original choices are still applicable is a question that will be addressed during the second five-year review of the Programme to be completed by an External Review Committee in 1988. Meanwhile, some of the research goals originally set for the Programme are actually being, or are well on the way to being, achieved.

1 Overview

Introduction

The creation of TDR ten years ago was attended by hopes and doubts. The hopes stemmed from the assumption that modern science could offer some means of alleviating the enormous suffering caused by tropical diseases. Among the doubts: Could a large international organization, with its inherent constraints, set up and operate a productive research programme? To what extent could tropical countries themselves be involved in a global research effort?

This Eighth Programme Report takes stock of the position ten years later. Over the decade, not only has TDR expanded its own activities but many other agencies, foundations and research councils, as well as industry, have increased their support of tropical disease research. Much of this renewed research effort has gained impetus from new technology, from the growing number of competent scientists engaged in tropical disease research and, most encouragingly, from the increasing involvement of the tropical countries themselves in research and disease control activities (Fig. 1.1).

A moving target

TDR's targets (see Box 1.1) — the diseases themselves, the infectious agents that cause them, the vectors that carry these agents and the animal reservoirs that harbour them — are constantly changing in response not only to natural evolution but also to human attempts to control them.

The diseases

It is difficult to obtain precise figures for diseases affecting vast numbers of people, many of whom live in remote areas without health services. In 1976, the protozoan parasite *Trypanosoma cruzi*, which causes Chagas' disease, was thought to infect around ten million people: TDR-supported studies have shown that just under 16 million are now infected. Malaria is increasing in frequency in Latin America and in African cities. In recent years, India has been experiencing a resurgence of visceral leishmaniasis (kala azar), which has also been reported for the first time in Afghanistan and Bolivia. Filariasis is spreading into new areas of Sri Lanka, and a major outbreak of sleeping sickness has occurred in Uganda.

Infectious agents, vectors and animal reservoirs

The infectious agents themselves also show capacity for change. Drug-resistant organisms have become a severe problem for the treatment and control of malaria and leprosy. In many ways drug resistance can be looked upon as a new disease, requiring new diagnostic tests (see Box 1.4), new methods of treatment and control, and training in the use of control tools. Chloroquine-resistant malaria, for example, is now spreading rapidly in Africa and was reported for the first time in 1983 in several West African countries. Other than drug selection pressure, the reasons for this spread have not been identified nor is it yet possible to curtail it.

Parasites differ even within what appears to be a single species. There are significant strain differences in the parasites which cause onchocerciasis, the African trypanosomiases, Chagas' disease, the leishmaniases and schistosomiasis. Different strains of the same parasite species may have different degrees of pathogenicity to humans or may cause different diseases. Previously, strains were

identified by morphological criteria. Now new techniques, such as protein and isoenzyme analyses, monoclonal antibody-based assays and DNA probes, are disclosing heterogeneities which may have practical implications for disease control.

These new techniques are also being applied to vectors and are revealing new species complexes with behavioural and other characteristics associated with disease-transmitting potential. Such information permits more precise targeting of vector control measures.

Animal reservoirs can be a major source of human disease. The *gambiense* form of African trypanosomiasis, for example, which was formerly thought to be an exclusively human infection, has been found in pigs, and the rat has been shown to be an important reservoir for leishmaniasis in Peru.

Human behaviour

There is an increasing awareness that tropical diseases can be occupational hazards. For example, large-scale forest clearance in Latin America, notably the Amazon basin, and in South-East Asia carries a high risk for leishmaniasis and malaria, respectively; gem mining in Asia and gold mining in Brazil both carry a risk for malaria, as does tin mining in Zaire for schistosomiasis.

Box 1.2 Vaccine development

Protective immune responses can be mediated by antibodies or by T cells. Antibodies protect by neutralizing the toxins of infecting agents, blocking penetration of microbes into cells, promoting inflammation and phagocytosis, inhibiting biochemical pathways of parasites or directly destroying parasites. T cells mediate protection by destroying infected cells, promoting inflammation, activating the interferon system and stimulating macrophage killing mechanisms. They also play a key role in promoting antibody production.

The multifaceted role of T cells in regulating immunity has important implications for vaccine design. BCG, one of the safest and most widely used vaccines (it has been administered to more than one and a half billion people), is known to induce strong T-cell responses. If the genes coding for protective antigens of human pathogens could be introduced into the BCG genome, this bacillus could become a useful recombinant ("expression") vector for future vaccines. Research towards this objective is being supported by TDR in collaboration with WHO's Programme for Vaccine Development, the National Institutes of Health, Bethesda, MD, USA, and the Rockefeller Foundation in New York, NY, USA.

Among the parasitic diseases of concern to TDR, malaria has witnessed the most rapid development towards vaccines, particularly vaccines that induce host antibodies capable of blocking cell penetration by the parasite and/or further parasite development. Most of the target molecules of such blocking antibodies have been identified. A major challenge now is to identify the target molecules for T cells involved in antibody production and in the destruction of malaria-infected cells in the body.

A vaccine has to circumvent or overcome the strategies developed by parasites to evade the host's immune response. Antigens of the parasites of malaria and Chagas' disease, for example, consist of repetitive sequences of a few amino acids. The role of these sequences is unclear but they are believed to facilitate gene shuffling, thereby increasing an organism's biosynthetic versatility or otherwise enhancing its ability to cope with the host's immune defences.

The rapid progress in malaria vaccine development has highlighted the enormous potential of modern biochemical research. The stage is set to attack even more complex, multicellular and mainly extracellular parasites, like those of schistosomiasis and filariasis. Biochemical pathways specific to life-cycle stages of these parasites may offer a fruitful avenue of research.

Leprosy and leishmaniasis present challenges of a different type. The causative organisms of these diseases thrive inside the host's "professional" phagocytes (macrophages), which have an array of mechanisms for dealing with the invaders. Other vaccine strategies may have to be used, such as those based largely on T-cell mechanisms. Conventional "whole-cell" vaccines can be used to identify appropriate target mechanisms of potential second-generation "subunit" (e.g., epitope-based) vaccines.

Despite the possibilities now offered by the sophisticated new techniques of molecular biology, the development of a vaccine is still a painstaking process, spanning many stages, each culminating in a breakthrough that carries the research to the next stage. Although to those waiting for a vaccine this process is frustratingly slow, to those working on vaccine development the pace is excitingly fast and accelerating with every new discovery.

Knowledge: a foundation for progress

One of TDR's main tasks is to support the development of new tools for disease control (see Boxes 1.2, 1.3 and 1.4), and most reports of progress focus on this objective. However, in an environment of increasing financial constraints, setting priorities between applied and more fundamental research has become a major challenge for TDR. Results of research efforts — including many TDR products (Table 1.1) — are increasingly based on advances in basic biomedical research and in fundamental knowledge about parasites and parasite-host interactions. Antigens suitable for malaria vaccines, for example, are not sought on a hit-or-miss basis: candidate molecules are selected for their accessibility to host immune mechanisms and for the importance of their biological roles in the parasite life cycle. Research on schistosomiasis vaccines, both within and outside TDR, has been guided by the findings of basic studies on parasite and host mechanisms, particularly parasite biochemistry and host immunity (see Box 1.2).

Applying biomedical technology to tropical disease research

More than ever before, investment in basic research is providing a starting point for the development of new disease control tools. Advances in molecular biology, genetics and immunology are beginning to change the face of health care technology in developed countries. Their application to research on the diseases of tropical developing countries could be a turning point in the struggle against these diseases. Gene cloning is now in progress for the agents of all six groups of diseases of concern to TDR and should help to elucidate their molecular composition and provide a potentially inexhaustible supply of macromolecules for immunological, biochemical and functional studies. Many of the parasites themselves can now be cloned from single organisms and cultivated *in vitro* to provide genetically uniform populations for the study of antigenic variation, strain heterogeneity, drug resistance and other topics related to disease control.

The African trypanosome has emerged as a leading organism for research on gene expression and antigenic variation. Whether or not it will be possible to interfere directly with these processes for therapeutic benefit remains to be seen. Meanwhile, research has led to a greater understanding of the immunology and epidemiology of sleeping sickness. It has provided evidence, for example, suggesting that antitrypanosomal vaccines based on variant antigens would not work and that priority should be given to the development of other tools for controlling this disease.

Research where it is needed

To achieve its second major objective — enabling tropical countries to acquire the capability to conduct the research needed to control the diseases directly affecting them — TDR has adopted a policy of strengthening selected research institutions in tropical countries.

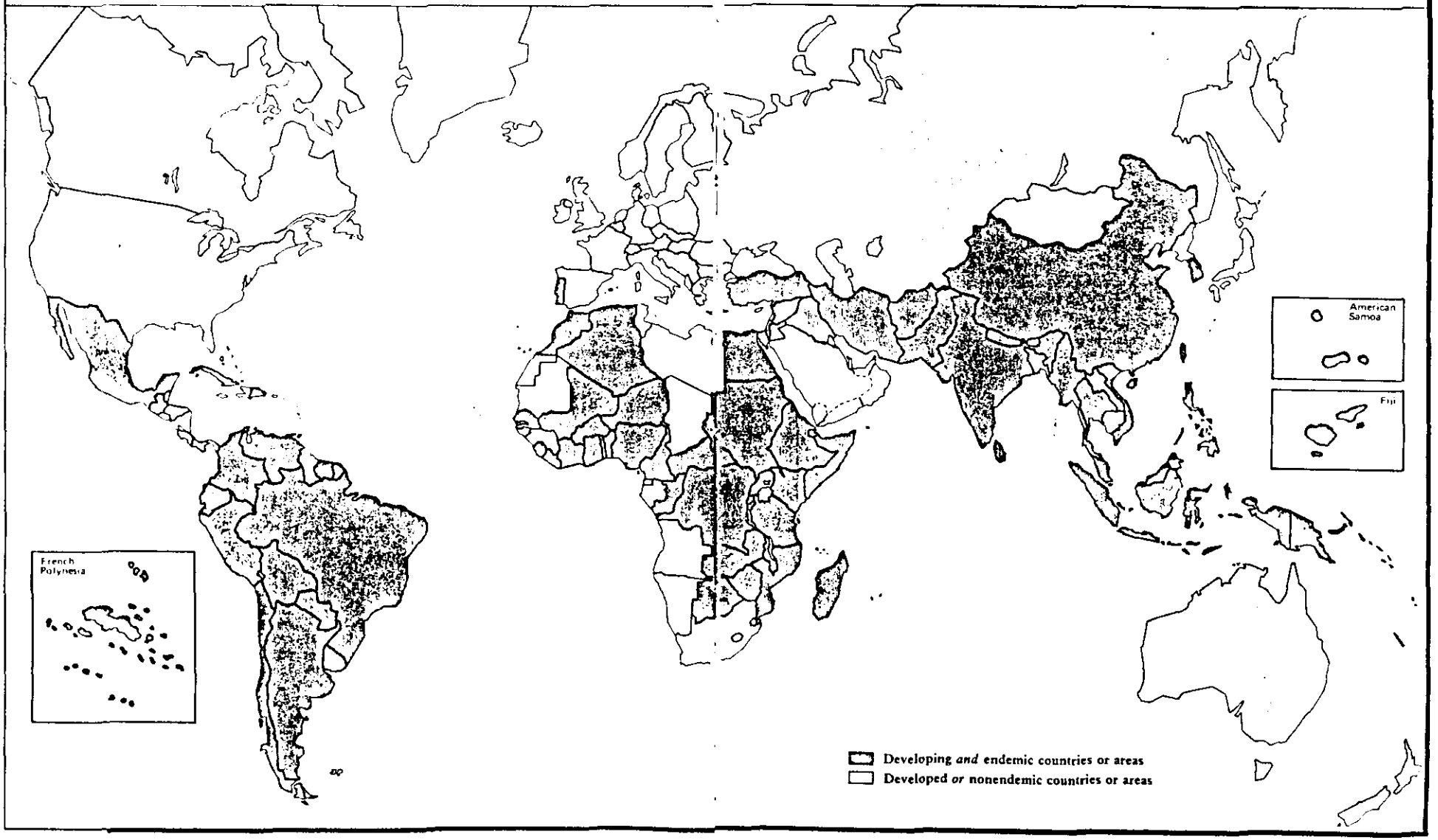
Since this policy was first put into effect in 1976, many institutions have benefited from TDR support. On completing the five-year period of a long-term grant, some may require further support to maintain the momentum of the research-strengthening process.

Areas of research that have received priority for strengthening and training in recent years include medical entomology, epidemiology and social and economic research. Modern biomedical technology has also been promoted by TDR in institutions in Brazil, India and Thailand, and will continue to receive support in the future.

The importance of scientific leadership in fostering a productive research environment, especially in countries with limited economic resources, is generally recognized. But progress in science will depend increasingly on the input of young scientists. In some countries traditions favouring the hierarchical entrenchment of older scientists may need to be broken for competent young scientists to become more directly involved in research planning and evaluation.

Inevitably, TDR's institution-strengthening activities have pursued a somewhat separate course from its research and development activities. Now, as laboratory research is making drugs, vaccines and tests available for field-testing in tropical countries and as institutions are acquiring greater research capability, more opportunities exist for drawing together the two areas of activity, institution strengthening and research and development, in a partnership between scientists of developed and developing countries.

Fig. 1.1 A global operation: countries and areas where TDR has supported research and development and research-strengthening activities over the decade



Box 1.3 Drug development

TDR-supported research on drug development has two main objectives: to improve the use of existing drugs and to develop new drugs.

Improving the use of existing drugs

• A good example of work under the first objective is in leprosy, where TDR has played a leading role in devising chemotherapy regimens based on combinations of existing drugs. The need for such regimens was first appreciated when resistance to the most widely used drug, dapsone, was shown through TDR research in the late 1970s to be a worldwide phenomenon. Regimens of two years' duration or less were developed using different combinations of antileprosy drugs in an attempt to forestall or circumvent resistance of leprosy bacilli to a single drug. The urgent need for combined chemotherapy has speeded its introduction into control programmes throughout the world, with the result that very large numbers of patients are now being released from lifelong dapsone therapy. At the same time, more patients than ever — about 50% more, in some control programmes — are seeking treatment.

New drugs

New drugs are developed through one of four main strategies: "blind" screening of potentially interesting compounds; chemical manipulation of compounds active against the disease of interest; identification of compounds, including registered drugs, active against a disease other than the disease of interest; and identification of potential drug targets in parasite biology and biochemistry.

Drug screening

A crucial step in drug development — and one to which TDR has devoted much effort and funding — has been the establishment of facilities for screening compounds against the different parasites in various animal models. Over the decade, tens of thousands of drugs have been passed through these screens.

The three other strategies, however, are proving more fruitful in TDR's search for new drugs.

Chemical manipulation of compounds active against the disease of interest

This strategy is well illustrated by the story of artemisinin or "qinghaosu", a completely new type of antimalarial compound isolated by Chinese scientists from the herb "qinghao" (*Artemisia annua*).

• Since artemisinin is very insoluble in both water and oils, chemically modified, more soluble and more effective derivatives are now undergoing preclinical testing and should enter clinical testing early in 1988. Several simple synthetic compounds based on the trioxane-ring structure of artemisinin have exhibited *in vitro* antimalarial activity ten- to twentyfold that of artemisinin itself. Studies *in vitro* suggest that the artemisinin class of compounds may be effective against "multidrug-resistant" malaria parasites.

Testing of compounds and registered drugs active against a disease other than the disease of interest

Several antifilarial compounds illustrate this strategy:

• Ivermectin was developed by the pharmaceutical firm Merck, Sharp and Dohme (MSD), Rahway, NJ, USA, initially as an antiparasitic drug for veterinary use, and was found to be active against *Onchocerca cervicalis* in horses; its anti-onchocercal activity was confirmed in TDR's onchocerciasis cattle screen. It has given excellent results in trials involving to date 1300 onchocerciasis patients, and larger community studies are planned.

• The compounds CGP 6140 and CGP 20376, discovered by the firm Ciba-Geigy S.A. of Basle, Switzerland, are derivatives of a compound (amoscanate) that, although very active against schistosomes and hookworms, was found to be toxic. The two derivatives are being developed in collaborative toxicological and clinical research involving Ciba-Geigy, the Onchocerciasis Chemotherapy Project (OCT) and TDR and are now undergoing initial clinical trials in filariasis (including onchocerciasis) patients.

Drugs targeted against biological and biochemical parasite mechanisms

TDR-supported research has disclosed aspects of parasite biochemistry that offer potential targets for new drugs.

• One example is DL-α-difluoromethylornithine (DFMO), which was initially developed as an anticancer agent by Merrell Dow Pharmaceuticals, Cincinnati, OH, USA, and was found to interfere with the ornithine metabolism of African trypanosomes: DFMO has been called a "resurrection drug" because of its remarkable clinical effects in late-stage African trypanosomiasis. Another example is allopurinol riboside, whose antileishmanial action is based on the dependence of *Leishmania* on the human host for its nucleic acid synthesis.

Managing the science

TDR is founded on the active participation of scientists in determining its policy and planning its activities. Scientists in TDR's Scientific and Technical Advisory Committee (STAC) set the Programme's overall research priorities and goals in the form of recommendations to the Joint Coordinating Board (JCB), TDR's top management body. Scientists in Steering Committees guide the activities of TDR's specialized Scientific Working Groups (SWGs) and select research projects for funding. And scientists in TDR's Research Strengthening Group (RSG) review the progress of institution-strengthening and training activities and assess proposals for future funding. Through this peer-review system, which provides TDR with flexibility and authority, scientists worldwide receive support for, and training in, laboratory and field research.

TDR arose through the World Health Organization's concern with tropical diseases. WHO's Malaria Action Programme, Parasitic Diseases Programme, Division of Vector Biology and Control, and Leprosy Programme (within the Division of Communicable Diseases) all aim at the prevention and control of tropical diseases. Coordination of TDR activities with those of other WHO programmes is ensured by the participation of the WHO Secretariat in TDR's Scientific Working Groups and Steering Committees. TDR also welcomes the opportunity of collaborating with other special programmes administered by WHO, such as the Onchocerciasis Control Programme in West Africa (OCP), the Programme for Vaccine Development (PVD), the Diarrhoeal Diseases Control Programme (CDD), the Special Programme of Research, Development and Research Training in Human Reproduction (HRP), the Expanded Programme on Immunization (EPI) and the Special Programme on AIDS (SPA). Co-sponsorship of TDR by the United Nations Development Programme (UNDP) and The World Bank ensures, moreover, that TDR's activities are closely linked to broad development issues.

Flexibility is a major feature of the scientific management of TDR. As diseases change and research progresses, priorities change. The increasing threat of drug-resistant malaria, for example, prompted increased TDR funding for research on malaria chemotherapy and vaccines. Early research on a leprosy vaccine was devoted mainly to the production and isolation of the causative organism, *Mycobacterium leprae*, in armadillos: today, vaccine field trials are in progress and genetic engineering is being explored for large-scale production of suitable "protective" antigens.

Box 1.4 Tools for diagnosis

Diagnostic tests can be useful in four main areas of tropical disease control: identifying disease with a view to providing suitable treatment; detecting infection and identifying the infectious agent with a view to acquiring the epidemiological data needed for control interventions; determining the sensitivity (or vulnerability) of disease-causing or disease-transmitting organisms to control tools (drugs, insecticides, biocontrol agents); and measuring drug levels in the blood of patients in order not only to establish optimum dosage levels but also to check for patient compliance with prescribed treatment.

A wide range of tests designed to detect and/or identify parasites or telltale fragments of parasites present in human, animal or insect fluids or tissues are being explored by TDR-supported researchers. These tests rely on a variety of techniques, including: microscopic examination of parasites in tissue or fluid specimens; DNA probes based on the affinity of a single strand of genetic material from a known parasite species or strain for the corresponding second strand from the same species or strain; monoclonal antibodies that recognize structures unique to specific parasites; and biochemical analysis of products, particularly metabolic products, of parasite physiology that can be detected in human fluids.

Tests are also required to determine the presence in serum of antibodies to a suspected infecting agent. The finding of such antibodies indicates present or past infection. Methods are also needed to discriminate between parasites resistant and those sensitive to drugs.

In addition, TDR is playing a particularly active role in the development of simple kits for testing malaria parasites for drug sensitivity (one such kit is already being produced in the Philippines).

TABLE 1.1

Products of research in which TDR has participated

Product	*In clinical trial*	*In field trial*	*In disease control use*
Malaria			
Drugs			
Mefloquine hydrochloride	x	x	
Mefloquine/sulfadoxine/pyrimethamine combination	x	x	x
Halofantrine	x		
Diagnostic/surveillance tools			
Microtest kit for *Plasmodium falciparum* sensitivity to antimalarial drugs		x	x
Portable, low-cost, battery-operated field incubator for use with microtest kit		x	
Field kit for measuring blood levels of several antimalarial drugs		x	
DNA probes for detection of *P. falciparum* and *P. vivax* in blood		x	
Cloning and characterization of *P. falciparum* parasites for epidemiological studies on drug resistance		x	
Synthetic *P. falciparum* sporozoite surface antigens for antibody detection in epidemiological studies	x		
Vaccines			
Anti-*P. falciparum* sporozoite peptide vaccine	x		
Vector control tools			
Diagnostic monoclonal antibody-based (Zavala) test for species-specific detection of sporozoites in mosquitos		x	
Cytogenetic methods for mosquito identification		x	x
Isoenzyme analysis	x	x	
Cuticular hydrocarbon analysis		x	
Selective insecticide spraying		x	x
Electrostatic sprayer		x	
Schistosomiasis			
Diagnostic/surveillance tools			
Diagnostic urine filtration technique		x	x
CF6 diagnostic antigen	x	x	
Indium-slide assay	x		
Vector control tools			
Selective use of plant molluscicides	x		
Filariasis			
Drugs			
Ivermectin for onchocerciasis	x		
Ivermectin for lymphatic filariasis	x		
CGP 6140 for onchocerciasis	x		
CGP 20376 for lymphatic filariasis	x		
Diagnostic/surveillance tools			
A monoclonal antibody probe for *Brugia malayi* infective larvae		x	
DNA probes for *B. malayi* infective larvae		x	
Preventive tools			
Guinea-worm water filter		x	
African trypanosomiases			
Drugs			
DL-α-difluoromethylornithine (DFMO)	x		

TABLE 1.1 (cont.)

Product	*In clinical trial*	*In field trial*	*In disease control use*
Diagnostic/surveillance tools			
Card agglutination test for trypanosomiasis (CATT)			x
Miniature anion-exchange centrifugation technique (MAECT) kit			x
Vector control tools			
Monoconical tsetse fly trap			x
Pyramidal tsetse fly trap		x	
Insecticide-impregnated screens		x	
Chagas' disease			
Diagnostic/surveillance tools			
Two serological tests (GP-25 and MAB-5)		x	
Monoclonal antibody-based antigen test	x		
Agglutination blood-screening test for *Trypanosoma cruzi* antibodies in transfusion blood		x	x
DNA probes for *T. cruzi* detection	x		
Vector control tools			
Insecticidal paints		x	
Insecticide fumigant canister		x	x
Triatomine detection box		x	x
The leishmaniases			
Drugs			
Allopurinol riboside	x		
Allopurinol + antimony compounds	x		
Paromomycin ointment	x		
New regimens of antimony compounds	x	x	x
Diagnostic/surveillance tools			
Dot-ELISA (enzyme-linked immunosorbent assay) test	x		
Indium-slide test	x		
Direct agglutination test	x	x	
Standardized counting technique for quantifying parasite load in spleen biopsies			x
Leprosy			
Drugs			
Multidrug therapy regimens			x
Long-acting sulfone drug formulation	x		
Pefloxacin	x		
Ofloxacin	x		
Diagnostic/surveillance tools			
Mycobacterium leprae-specific monoclonal antibodies		x	
Vaccines			
Heat-killed *M. leprae* vaccine		x	
Biological control of vectors			
Bacillus thuringiensis H-14		x	x
B. sphaericus		x	
Larvivorous fish (several species)		x	x
Social and economic research			
Adult education materials with information on tropical diseases		x	
Community-based health education materials on tropical diseases		x	x
Computer program for monitoring cost-performance of a malaria control programme		x	

Changing circumstances also call for adjustments to the balance of expertise among the scientists overseeing, as well as those conducting, TDR-supported research. In its early days, TDR's Scientific Working Group on Biomedical Sciences (BIOS), for example, was formed to take advantage of rapid progress in basic biology. Over time, however, the disease-oriented SWGs began vigorously exploiting the biomedical sciences and by 1986 a separate "trans-disease" SWG like BIOS was no longer required. Again, although Steering Committees with expertise in, say, epidemiology, chemotherapy or immunology, may tend to concentrate on their own disciplines, experience has sometimes shown the advantages of amalgamating Steering Committees to achieve a more integrated perspective.

The willingness of eminent scientists to take part in the planning and review of TDR-related research and to conduct research projects themselves has enabled TDR to play an active role in the global coordination of such research activities. In malaria vaccine development, for example, TDR, although not a major funding agency, takes a worldwide lead in planning research and promoting scientific collaboration.

TDR's support of research has stimulated a wide range of scientific activities, many of which are described in this Report. Financial and technical restraints, however, have prevented the Programme from following all the promising new avenues for research and development that have opened up over the past decade. Indeed, because of inadequate funding, TDR may find itself unable to effectively pursue major research topics, especially in the African trypanosomiases, Chagas' disease and the leishmaniases.

Reaping the rewards

No doubt the new disease control agents stemming from research will meet the needs of affluent groups in tropical countries and of travellers from

Box 1.5 "Banking" for science

Among the services TDR provides to researchers worldwide to facilitate their studies on the six major groups of tropical diseases of concern to the Programme, "banking" is growing in importance. In several centres throughout the world, TDR has set up banks that stock scientifically precious materials, reference materials or information, which are available to scientists everywhere:

***Precious materials**, such as:*

- a few microcuries of ^{14}C-labelled suramin for filariasis research;
- trypanosome strains for sleeping sickness research;
- *Leishmania* reference strains, leishmanin skin-test antigen and control solutions for use in immunological studies on the leishmaniases;
- *Mycobacterium leprae*-infected armadillo tissues, purified *M. leprae*, natural and synthetic phenolic glycolipid-I antigen, *M. leprae* gene clones and anti-*M. leprae* monoclonal antibodies for leprosy research;
- different formulations of bacterial control agents for research on biological control of vectors.

***Reference materials**, such as:*

- reference antibodies to asexual *Plasmodium falciparum* blood stages and standard clones of malaria parasites (particularly *P. falciparum*) for studies on the immunology and chemotherapy of malaria;
- lyophilized adult worms and lyophilized soluble egg antigens of *Schistosoma mansoni* and *S. japonicum*, and anti-*S. japonicum* antisera, for use in research on schistosomiasis;
- serum samples from patients infected with *Wuchereria bancrofti*, *Onchocerca volvulus* and *Brugia malayi* for immunodiagnostic studies on filarial infections;
- standard *Trypanosoma cruzi* strains and antisera for research on Chagas' disease.

***Information**, such as:*

- data on trypanosome stocks and lines for studies on the African trypanosomiases;
- *M. leprae* nucleotide and amino acid sequences, including those of T- and B-cell epitopes, for leprosy research.

developed countries visiting the tropics. But how can TDR help to ensure that these new tools will be brought to bear on disease control where they are most needed, i.e., among the poor of the developing countries? This question is answered by TDR's policy of seeking both to protect public sector interests in products developed with TDR support and to stimulate the field evaluation of such products, including their epidemiological validation and social and economic assessment (Table 1.1).

Acceptability and affordability

New control tools must be acceptable to local populations and suitable for delivery where they are most needed, especially at the primary health care level. Vaccines, for example, should ideally be effective in single doses and not require continuous refrigerated storage.

Affordability will always be a major concern, especially for countries with a total annual health budget equivalent to less than US $1.00 per person. TDR collaborates, coordinates and negotiates with industry to ensure that the final products of its research efforts are made available to developing countries at the lowest possible price. Approximately half of the products stemming from TDR-supported research and now in operational use (see Table 1.1) are being produced exclusively in developing countries. Of the remainder, some are partly produced in developing countries, some are purchased directly by developing countries, while some are competing effectively for financing through bilateral and international aid programmes.

Field evaluation

Determining to what extent new control agents are effective and suitable for use in poor countries may be a relatively simple task: the card agglutination test for trypanosomiasis (CATT), for example, has been experimentally assessed in the field for its value in the diagnosis of African sleeping sickness and is now being used, with WHO support, in operational control programmes in 11 countries. Then again, assessing a new tool may be complex, expensive and time-consuming, as is the case for the leprosy vaccine, for which trials have started only recently.

Epidemiological, social and economic evaluation

Before new tools can be effectively applied to disease control, information is needed on the prevalence and geographic distribution of disease, as well as on the many factors which increase the risk of disease or hamper disease control. These factors, which include malnutrition, multiple infections, inadequate housing, ecological circumstances, human beliefs and practices, and economic conditions, are the object of epidemiological and of social and economic investigations supported by TDR. Epidemiological studies seek not only to determine disease incidence and prevalence but also to identify and evaluate risk factors for infection and disease and the mechanisms of transmission most susceptible to control efforts. Sociological studies explore how people can best avoid or treat diseases through their own actions and how disease control programmes can best be conducted from the perspective of those directly affected by control measures.

Estimating the overall economic cost of a disease and its control involves several possible yardsticks, such as loss of cash earnings and productivity, and diminished quality of life. Individuals, families and communities, for example, have developed coping mechanisms that can mask — and add to the difficulty of estimating — the direct effects of a disease. The cost of control includes monetary resources, trained technicians and scientists, and, no less importantly, the time and energy supplied by the community or by individuals.

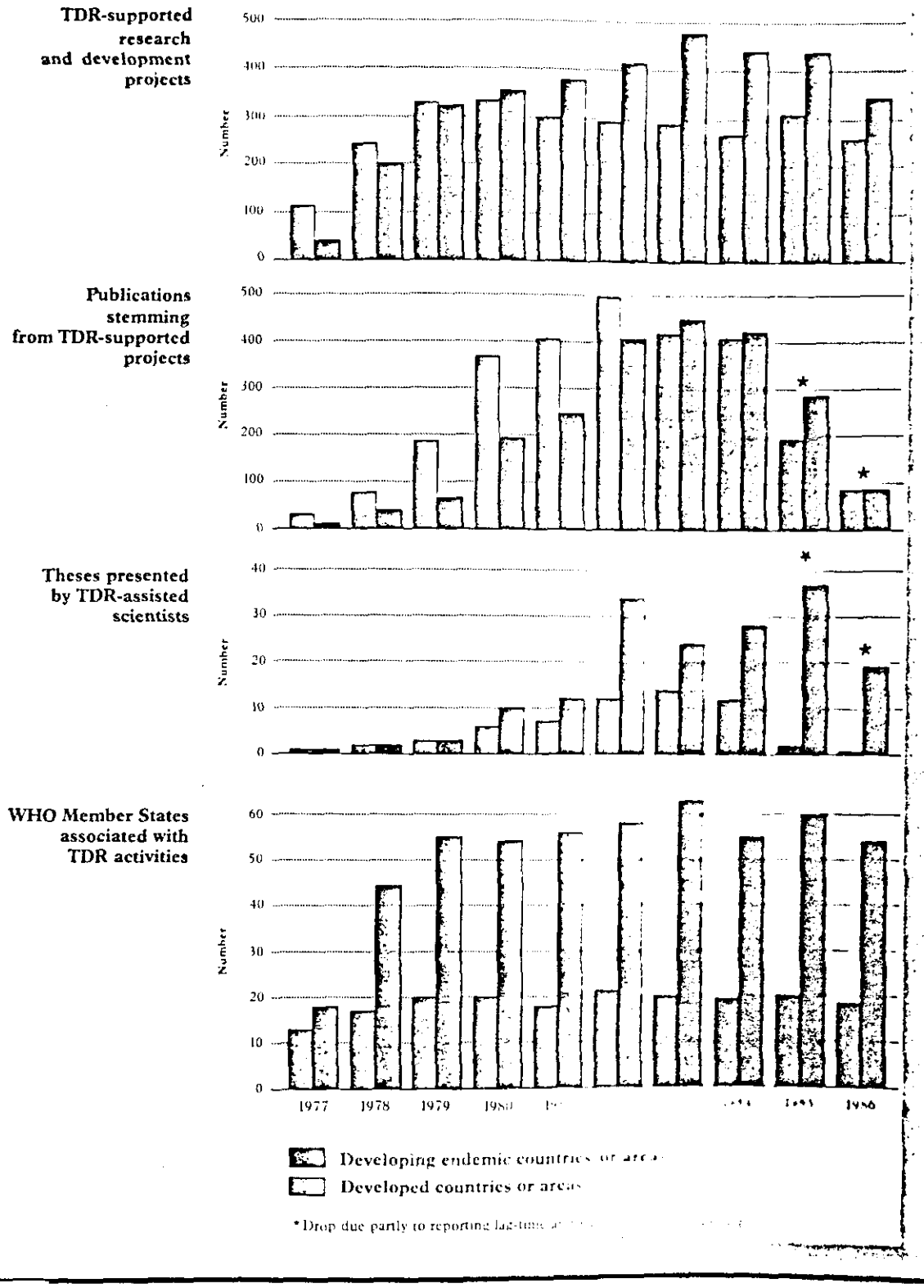
The future

Where does TDR go from here?

The Programme's greatest single asset has been the willingness of experienced and talented scientists to contribute to all aspects of its work, from the preparation of broad strategies for research and institution strengthening to the carrying out of laboratory and field projects.

TDR's first decade has been a time of planning and of creating a basic structure — a workable management system, global networks of participating scientists and institutions (see Figs. 1.1 and 1.2), and mechanisms for reviewing and planning scientific research. The last few years have also witnessed the emergence of the first products whose development was facilitated by TDR: more than 40 such products are ready for or are now undergoing field-testing (see Table 1.1). In the time-scale required to produce such disease control tools ten years is not long — 20 years is generally thought to be the average time needed to take a new drug from the laboratory into field use (see Box 1.3). Yet the

Fig. 1.2 Facts and figures



process is often a painstaking one, involving many steps.

Three examples illustrate this process:

- In the late 1960s and early 1970s, mefloquine was synthesized and subsequently developed up to the field trial stage by United States Army researchers. Since 1976 TDR has supported studies required for registration of the drug and has helped to make it available to malaria control programmes in several countries. Altogether, a 16-year development cycle — and further research is still needed to establish optimum dosage and safety in selected population groups.
- The leprosy vaccine now being tested in large-scale field trials has an even longer research history. In the early 1970s, the armadillo was discovered as a source of parasite material and a correlation was found between cell-mediated immunity and clinical outcome of *M. leprae* infection. These developments led to the first *M. leprae*-based vaccine, which was submitted, with TDR support, to early Phase I trials in Norway in 1983, and immunoprophylactic trials in Venezuela in 1984 and Malawi in 1985. Current trials in Malawi and Venezuela are expected to produce the first analysable results by the early 1990s. Altogether, a 20-year time-frame.
- Ivermectin, a new antifilarial drug that could help to make river blindness a disease of the past in many endemic areas, has a somewhat shorter history. After initial studies in 1975 at the research laboratories of the pharmaceutical firm Merck, Sharp and Dohme (MSD) in Rahway, NJ, USA, it was launched in 1981 as an antiparasitic drug for veterinary use. Following the discovery of its potential against human filarial worm species, human trials began in 1981, followed by full-scale double-blind trials in 1983. Finally, extensive trials were undertaken in 1985. Altogether, a ten-year research cycle to bring this product to the stage of field-testing.

Not only do these three examples illustrate the time-frame needed to make such tools available for field use — and hence the importance of sustained financial support for research towards their development — they also highlight the role of TDR in exploiting and supporting the further development of tools that have already been brought to the stage of potentially usable products through the conceptual and investigative spadework of others.

Already, the past activities of TDR are creating needs for the future. As more and more disease control tools emerge from research laboratories and scientific "think-tanks", they need to be put to the test of reality in the field. Over the coming years, TDR will clearly have to give greater emphasis to strengthening field research capabilities in developing countries. This new thrust will in turn call for greater crosslinking and crossfertilization among TDR's different Research and Development Components (or Scientific Working Groups), as well as between the Scientific Working Groups and the Research Strengthening Group.

Advances in biomedical research can be expected to accelerate over the next decade. Increasingly, drugs, vaccines, diagnostic tests and vector control agents will be designed on the basis of insights into the intimate molecular biological processes of the disease-causing organisms. A continuing investment will be needed to ensure that tropical disease research is not left out of these advances, for the diseases and the parasites responsible for them are fitting objects not only of a global control effort but also, in their complexity and durability, of scientific enquiry and of simple human wonder.
