Tropical Disease Research

TDR

Seventh Programme Report
1 January 1983 - 31 December 1984

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

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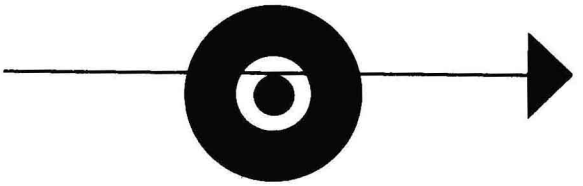

UNDP / WORLD BANK / WHO
Special Programme for Research and Training
in Tropical Diseases

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Preface

The UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) is a goal-oriented research and training programme with two interdependent objectives:

- research and development to obtain new and improved tools for the control of major tropical diseases;
- strengthening of the research capabilities of the tropical countries.

The research is conducted on a global basis by multidisciplinary Scientific Working Groups; the training and institution-strengthening activities are limited to the tropical countries where the diseases are endemic.

The six diseases initially selected for attack are malaria, schistosomiasis, filariasis (including onchocerciasis), the trypanosomiases (both African sleeping sickness and the American form called Chagas' disease), the leishmaniases and leprosy. Scientific Working Groups are also active in "trans-disease" areas: biological control of vectors, epidemiology, and social and economic research.

The Seventh Programme Report describes work during 1983 and 1984. It provides a more descriptive and analytical account than previous Programme Reports and also shows how the great variety of TDR research topics and training activities — from gene splicing to geographical surveys and from individual training to international workshops and institutional networks — all interrelate to achieve the common goal of improving disease control and human welfare in tropical countries.

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1 Overview

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1 Overview

The Special Programme for Research and Training in Tropical Diseases (TDR) is now in its third stage of development. ***Planning*** dominated the first stage: goals were defined and plans drawn up. The second stage focused on ***implementing plans***: research projects were funded and scientists throughout the world, working in many disciplines but often separately, were brought into a network through which they could channel their expertise into the achievement of common goals. At the same time, through grants to institutions and support for training and other activities, TDR began helping developing countries strengthen their research resources. The present, third stage in TDR's development is marked by ***results***: usable products and technologies are emerging from work supported by the Programme.

Looking back, these stages can be viewed not as discrete entities but as parts of an interacting system: advances in research permit the definition of new goals; strengthened research facilities in tropical countries generate new resources; experience gained in developing one product can be used to develop others. The system has been shown to work and to be capable of transforming plans into products.

This report, which covers the two-year period 1983-84, presents tangible examples of progress made, through TDR support, in developing the tools needed to control the six major tropical diseases within the Programme's mandate—malaria, schistosomiasis, filariasis, the trypanosomiases, the leishmaniases and leprosy.

These tools, the result of TDR's efforts in mobilizing, stimulating and coordinating the activities of national academic institutions and the pharmaceutical industry throughout the world, have from the outset been designed to meet strict specifications. They must be: ***effective***, in preventing and/or curing infection and disease in endemic areas; ***safe***, so that they can be used without special skills or supervision; ***simple***, so that they can be used under a wide variety of field conditions, particularly in a primary health care context; ***practicable***, within the limits—economic, social and cultural—of local communities.

Some of the tools developed through TDR support are ready for use or are actually being used for disease control and treatment. Others are at an advanced stage of development: they have been shown to be effective but require refinement before they can be used. Yet others are still only promising leads derived from TDR-supported research.

Four main types of tools are being developed for the control of the six "target" diseases: ***drugs***, to treat individual patients and help control diseases within a community; ***vaccines***, for primary prevention and sometimes as adjuncts to chemotherapy; highly specific, sensitive ***diagnostic methods***; and ***new vector control techniques***, especially those based on innovative approaches.

Not all the developments described in this report stem originally from TDR-supported work. Nor have they all been supported exclusively by the Programme. But in many cases where original discoveries were made outside the Programme, their subsequent development—including the many stages of laboratory and field testing—has benefited from TDR support.

Chemotherapy and drug development

Drugs ready for or in use

Drug combinations for leprosy

For decades, monotherapy with dapsone had been the mainstay of leprosy treatment and control, until resistance developed to the drug. To assess the magnitude of the problem, the Programme has sponsored surveys on the prevalence of primary and secondary dapsone resistance.

Controlled clinical trials sponsored by the Programme have led to the formulation, by a WHO Study Group, of recommendations on new multidrug treatment schedules comprising rifampicin, dapsone and clofazimine. These schedules render patients noninfectious in a relatively short time, substantially reduce the duration of treatment and diminish the risk of drug-resistant strains emerging. Although rifampicin is relatively expensive, the operational efficacy conferred on multidrug regimens

by this powerful bactericidal agent makes them highly cost-effective.

Mefloquine and mefloquine combinations

In collaboration with the Walter Reed Army Institute of Research (WRAIR) in the United States and with the Swiss pharmaceutical firm, Hoffmann-La Roche and Company, a new antimalarial drug, mefloquine, has been developed to the stage of registration for human use, initially only in adult males and nonpregnant females and in children over two years of age. Clinical trials conducted in Africa, Asia and Latin America have confirmed that the drug is not only well tolerated but also effective against strains of *Plasmodium falciparum* resistant to chloroquine and other drugs.

To reduce the risk of mefloquine-resistant parasite strains appearing and spreading, mefloquine will normally be used in combination with other drugs. TDR-supported projects have shown that the fixed combination of mefloquine with sulfadoxine and pyrimethamine is effective and well tolerated. Where this fixed combination is contraindicated, mefloquine should be given alone, followed by a dose of primaquine to prevent transmission of chloroquine-resistant strains. This approach has been successfully field tested by TDR and WHO's South-East Asia Regional Office.

In agreement with the drug company, mefloquine will only be sold in accordance with guidelines established by TDR and WHO experts. It will be available for sale in nonendemic countries for the use of short-term visitors to endemic areas. In endemic countries it will not be sold over the counter nor promoted publicly, but offered for sale through governments in areas where the parasite does not respond adequately to chloroquine.

Drugs at an advanced stage of development

Malaria

Several antimalarial compounds are now at an advanced stage of development, i.e. their antimalarial activity has been demonstrated in experimental animals and there is evidence that they would be effective in man. TDR is cooperating with Chinese scientists in the development of artemisinine and its derivatives. This compound, which was originally extracted from the traditional herbal remedy *Artemisia annua*, is effective against chloroquine-resistant parasite strains. Unrelated in chemical structure to any existing antimalarial compound, it will probably lead to the development of a new generation of drugs with a novel mode of action and therefore less risk of parasite crossresistance to other drugs.

Several other antimalarial compounds are now ready for trial in man and will be developed in collaboration with industry. One, halofantrine, will be developed in collaboration with WRAIR and a pharmaceutical company.

Within the next five years, at least three antimalarial drugs with novel chemical structures will probably become available for use. Malaria control programmes now relying on chloroquine and related compounds will have a variety of drugs available for prevention, treatment and control.

The leishmaniases

Treatment of the leishmaniases, especially of systemic forms, remains a challenge, since no satisfactory drug exists. Trials of allopurinol in patients with visceral leishmaniasis have shown promising results. Interest is currently focused on allopurinol riboside, the metabolite which seems to be the active principle of the compound and which is currently under trial in the treatment of the mucocutaneous form of the disease.

African trypanosomiases

Studies of *Trypanosoma brucei* metabolism have highlighted the key role of polyamine synthesis and, in particular, the enzyme ornithine decarboxylase. DL-α-difluoromethylornithine (DFMO), known to be a specific inhibitor of this enzyme, has proved effective in experimental infections and is currently being evaluated clinically, both alone and in combination with bleomycin.

Filariasis

In collaboration with the Onchocerciasis Chemotherapy Project, TDR has accorded highest priority to the development of new drugs, especially for the treatment of onchocerciasis. Currently available drugs are of limited efficacy: they have unpleasant side-effects and unless used under the careful supervision of an ophthalmologist, may cause permanent eye damage. In collaboration with industry, major advances have been made in the search for safe and effective drugs.

The most promising compound is ivermectin, a drug originally developed by industry for veterinary purposes and now undergoing clinical trials for the treatment of human onchocerciasis. WHO is collaborating with the manufacturer in the evaluation of this compound. Early results are encouraging: a single dose has an apparently strong microfilaricidal effect, and the limited evidence so far available suggests that ivermectin is better tolerated than existing drugs. If preliminary safety and efficacy findings are confirmed, ivermectin would represent a major

advance in the treatment of river blindness.

Other anti-onchocerciasis drugs are in the pipeline. One which would kill or permanently sterilize the adult onchocercal worm is still needed. In a study carried out in Mexico (in an institution receiving a TDR long-term support grant), parenteral flubendazole produced a marked, sustained fall in microfilarial counts in onchocerciasis patients, but the injection was painful. The drug is currently being reformulated before being further evaluated in man.

Two experimental compounds, CGP 6140 and CGP 20376, have been found to kill filarial worms in animal experiments. They are now ready to be submitted to Phase I clinical trials: CGP 6140 will first be tested against onchocerciasis and CGP 20376, against lymphatic filariasis.

Sterilization of Trypanosoma cruzi-*infected blood*

In some areas endemic for Chagas' disease, blood transfusion carries a relatively high risk of *T. cruzi* infection. Although stored blood can be sterilized with gentian violet, the resulting deep purple staining is often unacceptable. Moreover, gentian violet may have other, as yet unknown, effects on blood or on the transfusion recipient. A new screening technique developed by the Programme has led to the identification of 21 promising compounds for sterilizing blood. The list is being narrowed down to two compounds, one of which may turn out to be safe and effective.

Promising leads for new drugs

Screening

TDR gives support for the screening of compounds for activity against malaria, the trypanosomiases, the leishmaniases, filariasis and leprosy (Fig. 1.1). The pharmaceutical industry and academia submit to these screens compounds which in many cases are selected on the basis of structure-activity relationships and other leads.

Rational drug development

Comparative biochemistry is providing useful leads for the development of new drugs. Studies on the purine metabolism of *Leishmania*, for example, have led to the identification of allopurinol as a potentially useful drug for the treatment of leishmaniasis. Attempts are being made to identify and exploit other metabolic differences between the parasite and the host.

Re-examination of existing drugs

The Programme has systematically re-examined drugs being used in the treatment of the six tropical diseases. Findings from these studies are leading to more effective, safer drug use and providing leads for the development of new drugs. New data on drug distribution and metabolism are enabling empirically established drug dosage schedules to be designed on a rational basis. New regimens, for example, have been devised for pentavalent antimony compounds in the treatment of visceral leishmaniasis and new formulations and dose schedules are being developed for organic arsenic compounds in the treatment of African trypanosomiases. Although chloroquine's mode of action and the mechanism of the malaria parasite's resistance to chloroquine remain perplexing problems, significant progress has been made in the study of primaquine metabolism.

Vaccines and immunotherapy

Rapid progress has been made in the development of vaccines against leprosy and malaria.

Vaccines at an advanced stage of development

Leprosy vaccine

A candidate vaccine against leprosy, based on killed armadillo-derived *Mycobacterium leprae*, induced cell-mediated immunity and was well tolerated in a Phase I trial in volunteers from a nonendemic area. Phase II clinical trials are now in progress in endemic areas. Significant advances have also been made in cloning *M. leprae* genes and should lead to the development of second-generation leprosy vaccines based on well-defined antigens produced by genetic engineering techniques.

Malaria vaccines

Work towards malaria vaccines has advanced on several fronts. Well-defined candidate antigens have been tested in experimental animals and are showing promising results. Research is most advanced on a sporozoite vaccine. Studies conducted within and outside the Programme have led to the chemical characterization of the circumsporozoite antigen, and the biologically active sites of the molecule are being identified. A sporozoite vaccine will in all probability be tested in man within the next few years. In collaboration with the United States Agency for International Development (USAID) and other agencies, the Programme has stimulated the interest of the pharmaceutical industry in the next phases of malaria vaccine development. One company is committed to developing, in collaboration with TDR, a polyvalent vaccine (directed against sporozoites, merozoites and gametes).

Promising leads

The leishmaniases

Significant progress has been made in probing, with a view to future vaccine development, the immune mechanisms involved in leishmanial infections. Further work will focus on the identification of candidate antigens that might be capable of conferring protective immunity.

Other diseases

Host-parasite relationships are now better understood for African trypanosomiases, Chagas' disease, schistosomiasis and filariasis, but more work needs to be done before the feasibility of developing vaccines against these infections can be assessed.

Diagnostic tests

Simple, sensitive, highly specific tests are being developed for clinical and epidemiological use.

Tests ready for or in use

P. falciparum *drug-sensitivity kits*

The Programme has developed *in vitro* test kits, based on a method discovered outside the Programme, to determine the sensitivity of *P. falciparum* to drugs. "Macro" kits, requiring a relatively large quantity of blood (10 ml), have now been replaced by "micro" kits, which require only a few drops of blood (0.1 ml) obtainable by finger-prick. Kits are now available for testing *P. falciparum* sensitivity to chloroquine, amodiaquine, mefloquine, quinine and pyrimethamine, as well as to the sulfadoxine/pyrimethamine combination.

The trypanosomiases

A simple card agglutination test for the diagnosis of African trypanosomiases has been submitted for

FIG. 1.1

GLOBAL NETWORK OF DRUG SCREENS*

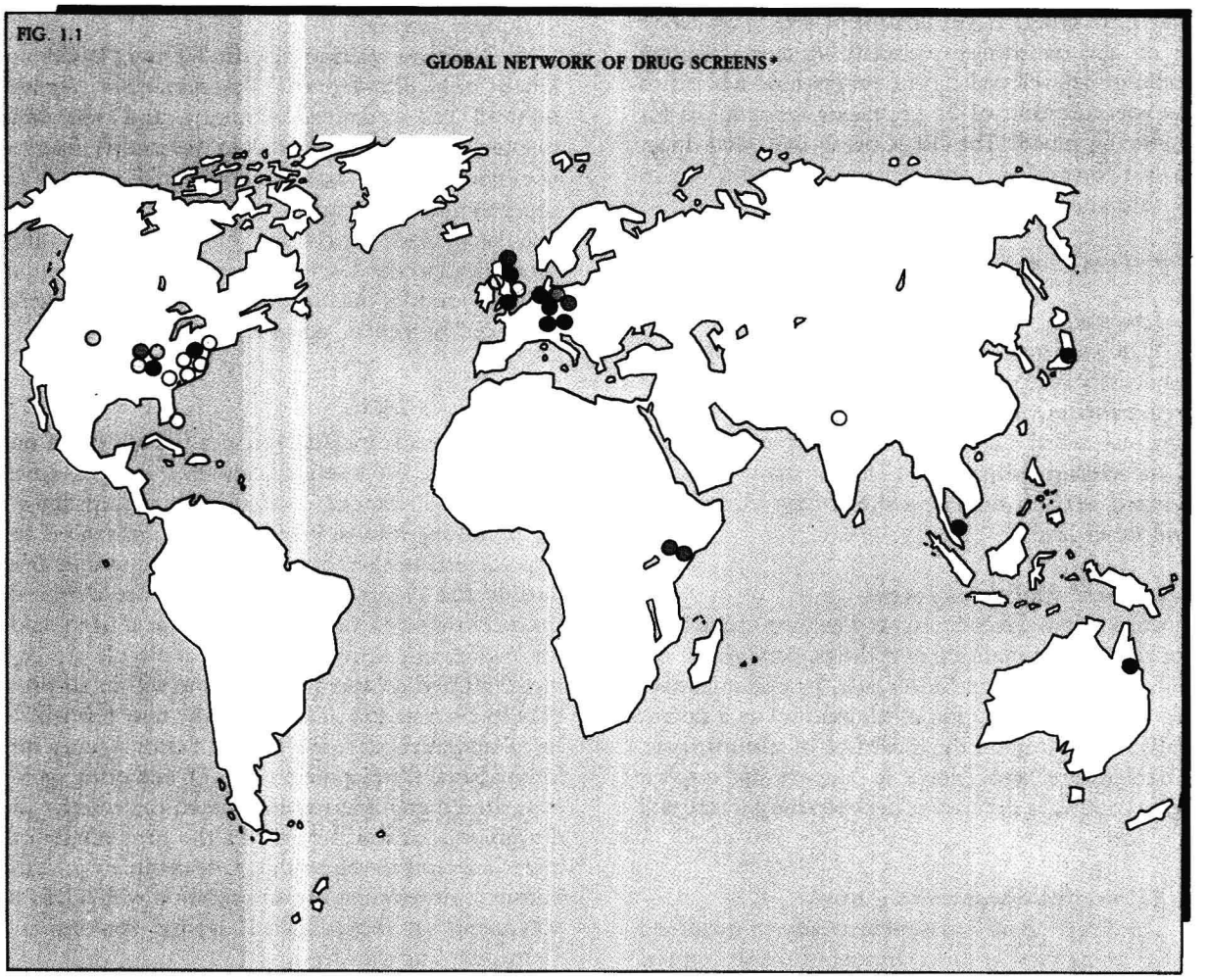


FIG. 1.1

GLOBAL NETWORK OF DRUG SCREENS*

Malaria:

- ○ *In vitro* screen against cloned *P. falciparum* isolates (Washington, DC, USA)
- ○ Long-acting blood schizontocidal activity (Miami, FA, USA)
- ○ *In vitro* gametocidal activity against *P. falciparum* (New York, NY, USA)
- ○ Exoerythrocytic activity against *P. berghei in vitro* (Rockville, MD, USA)
- ○ ** Causal prophylactic and tissue schizontocidal activity *in vivo*, including *P. cynomolgi* screen (Lucknow, India)
- ○ ** Causal prophylactic and blood schizontocidal activity *in vivo* (London, England)
- ○ *In vitro* screen against cloned *P. falciparum* isolates (Chapel Hill, NC, USA)
- ○ ** Blood schizontocidal activity *in vivo* (Washington, DC, USA)

Filariasis:

- ● * *In vivo* filaricidal screen using *D. immitis* in ferrets and dogs (Rahway, NJ, USA)
- ● *In vivo* screen using *Onchocerca* infection of cattle (Townsville, Queensland, Australia)
- ● *In vivo* screen using *B. pahangi* in jirds (London, England)
- ● *In vivo* screen using *B. pahangi, B. malayi, D. viteae* and *L. carinii* in multimammate rats (Giessen, Federal Republic of Germany)
- ● ** *In vivo* screen using *L. carinii* and *D. viteae* in rats and jirds (Frankfurt/Main, Federal Republic of Germany)
- ● ** *In vivo* screen using *B. pahangi* in jirds (Beckenham, England)
- ● *In vivo* screen using *B. malayi* or *B. pahangi* in *Presbytis* monkeys (Kuala Lumpur, Malaysia)
- ● *In vivo* screen using *L. carinii* and *B. pahangi* in jirds (Athens, GA, USA)
- ● ***In vivo* screen using *L. carinii* in cotton rats (Basel, Switzerland)
- ● ***In vivo* screen using *L. carinii, D. viteae* and *B. malayi* in jirds and mice (Basel, Switzerland)
- ● *In vivo* screen using *L. carinii* in cotton rats (Tokyo, Japan)

African trypanosomiases:

- ● *In vivo* trypanocidal activity in mice (Nairobi, Kenya)
- ● *In vivo* activity in vervet monkeys (Nairobi, Kenya)
- ● Activity against cerebral infection in mice (Glasgow, Scotland)
- ● ** *In vivo* activity in mice (Berlin [West])

Chagas' disease:

- ○ *In vivo* primary screen (Athens, GA, USA)
- ○ *In vitro* screen using compounds registered for use in man (Beckenham, England)

Leishmaniases:

- ○ Primary screen against *L. donovani* in hamsters (Athens, GA, USA)
- ○ *In vitro* screen against *Leishmania* promastigotes and amastigotes (Denver, CO, USA)

Leprosy:

- ○ *In vivo* screen of new compounds (Atlanta, GA, USA)
- ○ *In vitro* screen using *"M. lufu"* (Borstel, Federal Republic of Germany)

* Primary, secondary and tertiary screens refer to a progressive series of tests which use a variety of *in vitro* and *in vivo* models to select compounds effective enough to be tested in man.

** Not TDR-funded

further field evaluation and is now commercially available.

The miniature anion exchange column test (MAECT), developed outside the Programme, has been evaluated with TDR support for the diagnosis of African trypanosomiases and is now available for operational use. Techniques for the serodiagnosis of Chagas' disease have been standardized, and sera from known infected and uninfected individuals are being provided by a TDR-supported central Reference Laboratory in Brazil to a network of 12 laboratories, of which 11 are in Latin America.

Tests at an advanced stage of development

Chagas' disease

A simple immunodiagnostic test has been developed for the rapid screening of stored blood for Chagas' infection and is now undergoing further evaluation before being made available for use.

Sporozoite infection in mosquitoes

The test devised at New York University by Fidel P. Zavala and associates for the identification of sporozoite species in mosquitoes, using monoclonal antibodies in a sensitive assay system, is now being developed into a field kit and should provide epidemiologically important information about malaria vectors in endemic areas, which could help malaria control personnel identify the precise roles of individual vectors in malaria transmission and target antivector measures more selectively.

Monoclonal antibodies in research on the leishmaniases and leprosy

Monoclonal antibodies are being widely used in research on all six diseases within TDR's mandate. They have been found particularly useful in the identification of *Leishmania* species and subspecies. Monoclonal antibodies recognizing epitopes present on *Mycobacterium leprae* but not on related organisms are now being exploited for possible leprosy-specific diagnostic tests.

DNA probes

DNA probes are being used to identify *Plasmodia, Leishmania*, trypanosomes (both *T. brucei* and *T. cruzi*) and other parasites, and suitable field methods are being developed.

Vector control

Biological control has greatly advanced during the past few years and some new agents are already being used in the field.

Vector control agents ready for or in use

Sporogenic bacteria

Discovered outside the Programme, *Bacillus thuringiensis* was developed in collaboration with industry and is now being used by WHO's Onchocerciasis Control Programme (OCP) to control *Simulium* vectors in the Volta River Basin area in West Africa. New formulations are also being tested for use in mosquito control.

Mechanical traps

Simple tsetse fly traps, originally designed in work conducted outside the Programme, have been further developed with Programme support and evaluated in different ecological settings. TDR has stimulated collaboration among scientists hitherto working separately; traps of greater efficacy have been designed and in some areas are now being used for sleeping sickness control.

Vector control agents at an advanced stage of development

Bacillus sphaericus

Three strains of *Bacillus sphaericus*—1593, 2297 and 2362—are currently being investigated. There is particular interest in the use of *B. sphaericus* for mosquito larvae control, as it is effective in polluted streams, and in some situations significant antilarval activity is maintained for several weeks after a single application.

Lagenidium giganteum

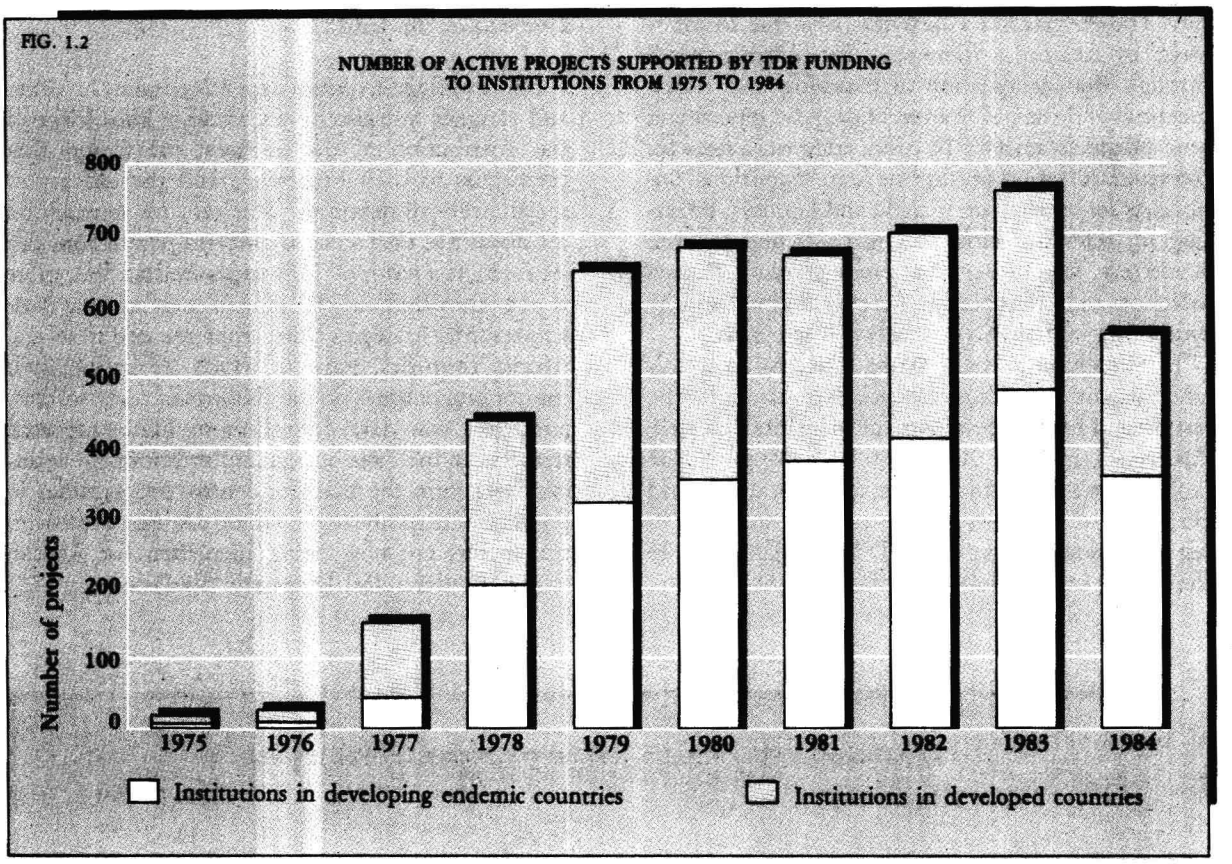
The development of another promising agent, *Lagenidium giganteum*, had previously been limited by the difficulty of cultivating the organism in the laboratory. This problem has been solved, and *L. giganteum* is being evaluated and developed into a usable tool.

Promising leads

An asporogenic strain of *B. thuringiensis*, offering certain advantages over the original sporebearing strains, is being investigated, as are other promising agents, according to the WHO five-stage testing procedure.

Basic research

The advances so far described represent intermediate or final stages in research and development. The Programme also supports the more fundamental studies which provide the groundwork for future



advances. Some examples:

- The cloning of *P. falciparum* opens the way to a variety of genetic and biochemical studies, including research on drug resistance.
- A method has been discovered of cultivating *in vitro* the infective larvae of two *Brugia* filarial species and it is now being exploited to obtain filarial antigens for diagnostic studies.
- DNA analysis, using restriction enzymes and probes, is being used to identify parasites and study the relationships between parasites and disease.
- Monoclonal antibodies are being used to improve diagnostic tests, to identify parasite antigens and to serve as reagents for antigen preparation and assessment of immunity following passive transfer.
- Genetic engineering technology is being used to obtain antigens suitable for tests and vaccines.

These and other new concepts and techniques are moving research forward in ways unthinkable a few years ago, and are already having a profound impact on the development of new tools. Malaria vaccines, for example, could never have been developed to such an advanced stage were it not for these advances in biological sciences.

TDR's changing role in research and development

Initially, the role of TDR was to stimulate and support research on the six target diseases. From 1975 to the end of 1984, the Programme supported a total of 2290 projects, of which 1331 were in developing endemic countries (Fig. 1.2). One measure of the output of this research is the number of reports of TDR-supported work published in the scientific literature (Fig. 1.3), which had reached 3817 (plus a further 421 in press) by the end of 1984, compared with 2798 at the end of 1983 and 1800 at the end of 1982. Of these 3817, nearly half appeared in 1983-84, with a fairly even distribution between developing and developed countries.

In many cases, Programme support has been seminal, providing encouragement and often enabling scientists to obtain additional resources. Most of the scientists working on malaria vaccines, for example, received their first grants from WHO and TDR, and now obtain more extensive funding from other sources.

TDR is increasingly called upon to coordinate efforts now supported by a variety of funding agen-

cies. The Programme fulfils this new role in many ways: by creating a framework for future research through the organization of planning and review meetings and the publication of progress reports and state-of-the-art reviews; by conducting workshops for the standardization of reagents (e.g. monoclonal antibodies for research on malaria and leprosy); by setting up reference biological reagents and parasite strains (e.g. reference sera for serodiagnosis of *T. cruzi* infection and reference *Leishmania* strains); and by promoting exchange visits between scientists.

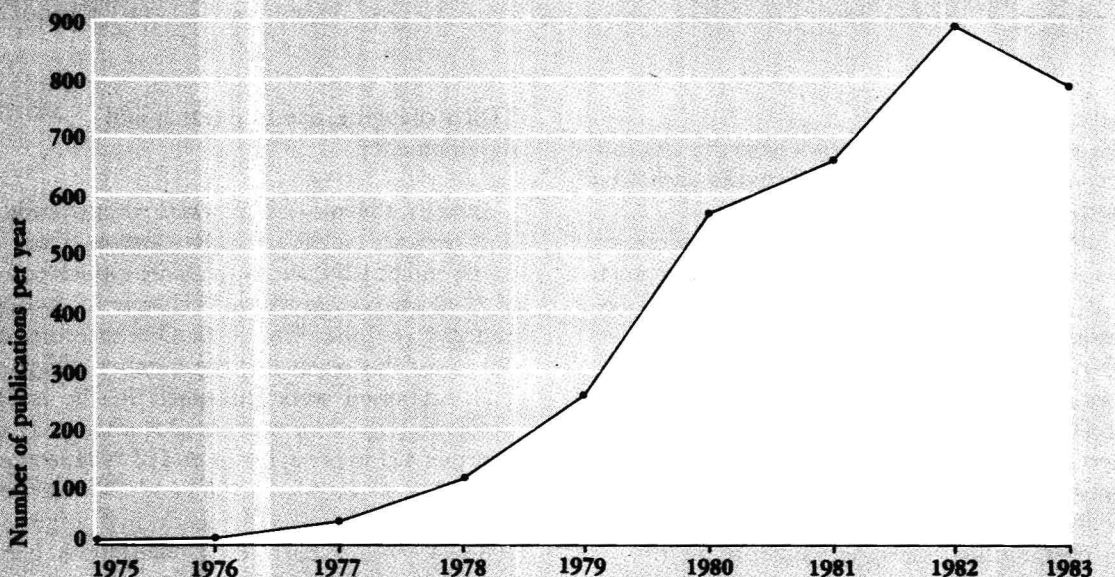
The Programme is also being called upon to collaborate with the pharmaceutical industry in the testing and further development of agents that were discovered, in some cases, with TDR support. The Programme's ability to organize the clinical and field evaluation of new products in endemic areas is being increasingly recognized (TDR is working with 20 companies on a variety of projects [Table 1.1]).

Research in the field

Effective disease control depends not only on drugs and vaccines but also on an accurate knowledge of the distribution of the diseases, the factors that predispose to their occurrence and the efficacy of specific control measures. This calls for research on the diseases as they occur in different populations and settings. As a result of TDR-supported studies, more is now known about the effectiveness of new anti-schistosomal strategies being implemented in several African countries, some of which are basing their control programmes on the findings of these studies. Similarly, new data derived from TDR-supported research on the distribution and extent of the leishmaniases form the basis for control programmes in several countries affected by these diseases. Moreover, risk factors are now being identified for African trypanosomiases and lymphatic filariasis.

FIG. 1.3

PUBLICATIONS (REPORTED TO TDR) FROM PROJECTS SUPPORTED BY TDR FUNDING TO INSTITUTIONS FROM 1975 TO 1983*



Year	1975	1976	1977	1978	1979	1980	1981	1982	1983	Cumulative Total 1975-1983
Institutions in developing endemic countries	2	1	8	39	62	190	245	396	408	1351
Institutions in other countries	1	5	30	78	188	371	411	498	379	1961

= 3312

* 1983 data incomplete

TABLE 1.1

TDR's collaboration with industry: Number of TDR projects contracted between 1975 and 1984

Country	*No. of firms*	*No. of projects*	*TDR Component*								*TDR support (US$)*
			MAL	*SCH*	*FIL*	*TRY*	*CHA*	*LEI*	*LEP*	*BIO*	
Belgium	1	1	—	1	—	—	—	—	—	—	35 000
China	1	2	2	—	—	—	—	—	—	—	72 610
Germany, Federal Republic of	3	4	—	1	2	1	—	—	—	—	262 500
India	1	2	1	—	1	—	—	—	—	—	54 850
Switzerland	1	2	—	1	1	—	—	—	—	—	53 782
United Kingdom	1	4	—	—	2	—	1	—	1	—	476 652
United States of America	12	22	6	4	3	—	2	1	5	1	1 735 417
Total	20	37	9	7	9	1	3	1	6	1	2 690 811

MAL = Malaria
SCH = Schistosomiasis
FIL = Filariasis
TRY = Trypanosomiases
CHA = Chagas' disease
LEI = Leishmaniases
LEP = Leprosy
BIO = Biomedical sciences

Ultimately, to have some chance of success, disease control measures must be understood and accepted by the populations involved, as well as being affordable, in terms of money and effort, by these populations. TDR-supported research relating to malaria, filariasis and leprosy has shown how important a community's perception of disease is in determining whether people's behaviour will help or hinder disease control. Application of such findings to control programmes is now under study.

Methods of assessing the cost-effectiveness of control programmes are also the subject of several studies supported by the Programme, and ministries of health in a number of endemic countries are showing increasing interest in using the findings of these studies to improve their disease control services.

Strengthening research capabilities in developing countries

During 1983-84, a total of 25 institutions received grants, through TDR's Research Strengthening Group (RSG), in support of research activities, and 139 scientists and other research personnel received training grants. Institutions are also being strengthened through their participation in the research and development activities of the Programme, formal training courses have been supported by the Programme for Master of Science degrees in medical entomology, epidemiology and malacology, and short courses and workshops have been organized to promote the rapid transfer of technology to developing countries. Scientists and institutions in developing countries have made major contributions to the development of tools for the treatment and control of the six target diseases, notably in activities best carried out in the endemic areas—epidemiological surveys, clinical trials, social and economic research. These activities have resulted in important scientific achievements: the discovery of *T. cruzi* schizodemes, test kits for malaria parasite sensitivity to drugs and the worldwide mapping of chloroquine sensitivity to drugs, to mention only a few. Strengthened institutions are providing training for scientists from other institutions in the same or different countries.

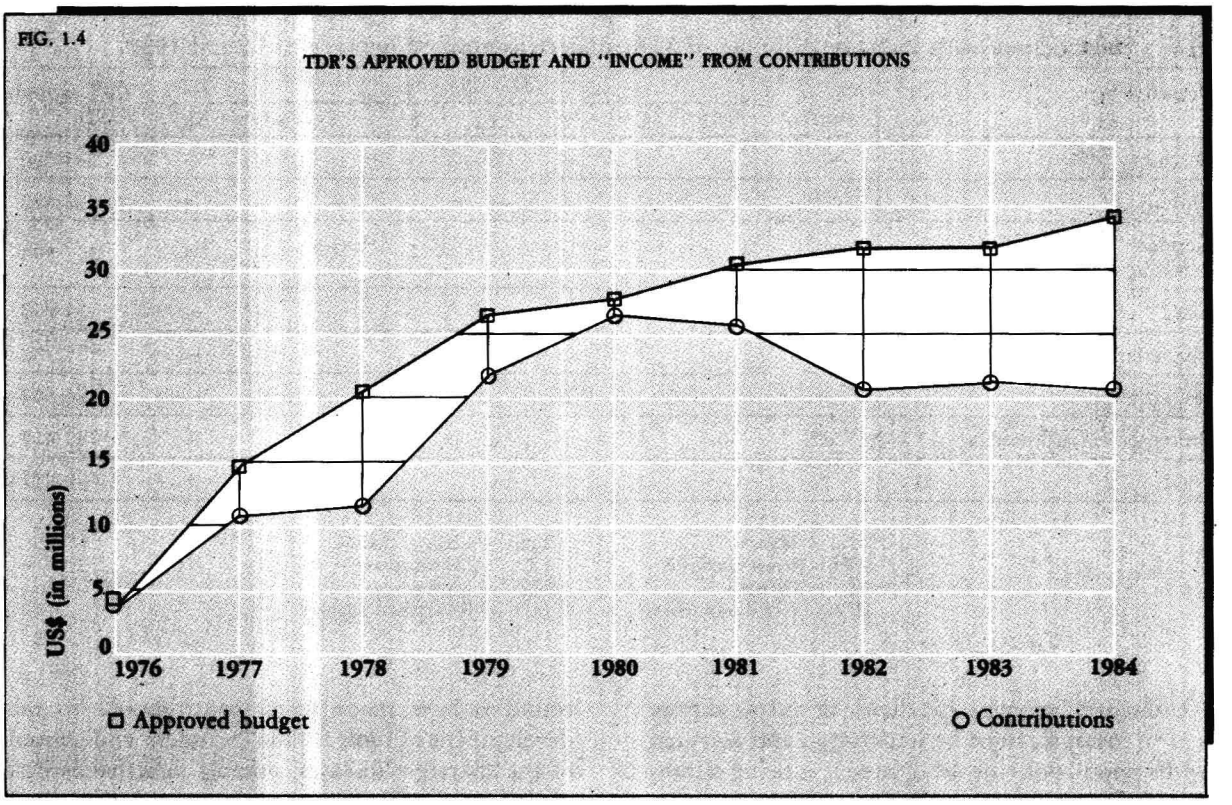
At the national level, institutions being strengthened by TDR are providing ministries of health with technical support for disease control activities, and data generated from field studies are being used to plan, modify and evaluate control programmes. Over the next two years, the RSG will focus on strengthening capabilities in field research and basic biomedical sciences.

Maintaining the momentum

The mechanisms established by TDR to promote research and carry research findings through to the point where they become practical tools for disease control do seem to work. But if the initial investment in creating these mechanisms is to reap its full benefits, the effort must be sustained: promising scientific leads take time to develop into useful disease control tools—time and, of course, money.

Clouding TDR's horizon is the widening gap between the Programme's budget and the financial

FIG. 1.4



resources being made available to it through voluntary contributions from government agencies, philanthropic foundations and other sources (Fig. 1.4). Because of this gap, planned activities cannot be completed nor hoped-for results achieved as quickly as they might be, and the promise of some exciting leads cannot be fulfilled as urgently as it should be.

On the other hand, parasitic diseases are coming more and more to exert their own fascination as subjects of scientific scrutiny. More scientists than ever before are aware of the human problems related to tropical diseases. And the interest and concern of research funding agencies and of industry have been aroused.

TDR's efforts are beginning to bear fruit and to justify the hope that lasting improvements can be made in the health of tropical peoples. It is now critical that adequate, sustained financial support be forthcoming so that these early results can be elaborated into a unique, powerful and realistic offensive against the diseases that have kept these peoples for so long under so heavy a burden of suffering.