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COUNTRY AND INTERCOUNTRY PROGRAMMES AND PROJECTS

Assistance for a global project

Special Programme for Research and Training in Tropical  
Diseases (Phase III) (GLO/86/005)\*

Recommendation of the Administrator

Estimated UNDP contribution: \$7,500,000 requested now 1/  
Duration: Three years requested now  
Executing Agency: The World Bank will act as fiscal agent and the  
World Health Organization (WHO) will be responsible  
for the implementation of project activities

I. BACKGROUND

1. At its January 1978 meeting (E/1978/53/Rev.1, annex II, para. 6), the Governing Council approved a contribution of \$5.5 million for the Special Programme for Research and Training in Tropical Diseases (TDR), of which the United Nations Development Programme (UNDP) is a co-sponsor together with WHO and the World Bank (DP/PROJECTS/R.9/Add.4). This contribution followed preparatory assistance (DP/PROJECTS/R.6/Add.1) in the amount of \$107,500 which the Council approved at its twenty-second session in June 1976 (E/5846/Rev.1, para. 298), bringing the total amount contributed by UNDP to the programme to \$5,607,500. At its twenty-eighth session in June 1981 the Governing Council approved a further \$7,567,300 (DP/PROJECTS/R.14/Add.1), bringing the total amount so far contributed to the programme to \$13,174,800. At present, TDR has an annual budget of about \$25 million and is active in over 100 countries.

\* A financial summary and organizational chart are available on request.

#### A. Summary

2. Ten years ago, WHO, UNDP and the World Bank joined forces in a unique venture in international technical co-operation: the Special Programme for Research and Training in Tropical Diseases. The objectives of the programme are twofold:

(a) to develop new methods, and to improve those already existing, for the prevention, diagnosis, treatment and control of six major tropical diseases: malaria, schistosomiasis, the filariases (including onchocerciasis and dracunculiasis), the trypanosomiasis (African sleeping sickness and the American form called Chagas' disease), the leishmaniasis and leprosy; and (b) to strengthen the research capabilities of tropical countries affected by these diseases.

3. TDR has played a major role in developing a number of products that have now been integrated into the repertoire of tools and methods used in disease control programmes. Just a few highlights of these products include: the new antimalarial drug mefloquine; a test for parasite susceptibility to antimalarial drugs; a simple diagnostic test for African trypanosomiasis; an effective combined chemotherapy regimen for treating leprosy; biological control agents and larvivorous fish to control insect vectors.

4. In addition, more than 20 products are now undergoing field testing before being made available for use in disease control programmes. Fifteen other products have reached the stage of clinical testing, including a malaria vaccine developed with recombinant DNA technology and new drugs for malaria, filariasis, African trypanosomiasis, leishmaniasis and leprosy. A leprosy vaccine is now at an advanced stage of field trials in Venezuela and Malawi.

#### B. Objectives of the special programme

5. The objectives of the Special TDR Programme are:

(a) To develop new methods of prevention, diagnosis, treatment and vector control specifically suited to selected tropical diseases and to the countries most affected by them. The cost of the new methods must be within the resources of developing countries, require minimal skills and supervision, and be capable of integration into the health services, especially the primary health care systems, of developing countries.

(b) To strengthen, through training in biomedical and social sciences and through various forms of institutional support, research capabilities in countries most affected by tropical diseases. The biomedical research capability of these countries must be strengthened to enable them to conduct research relevant to the control of indigenous diseases. Research on the specifications, development and testing of new tools must increasingly take place in countries where the diseases are endemic, to ensure that the tools are appropriate and effective in the circumstances in which the diseases occur.

### C. The diseases

#### Malaria

6. Malaria is still the most important parasitic disease in the tropics. In 1984, malaria was indigenous in about 100 countries: one twelfth of the world's population, or about 400 million people, are currently exposed to malaria in areas where no specific antimalaria measures are being applied. After the strong resurgence of malaria in India in the mid-1970s, the latest figures reported to WHO indicate a continuation of the decline in the number of cases observed since that time, mainly due to a downward trend in China and India. Elsewhere, on average, the prevalence is slowly growing, and the pattern is marked by local resurgences of the disease. In tropical Africa, urban malaria is an increasing problem. Probably the most important threat to effective control of the disease is resistance of the causative organism, Plasmodium falciparum, to drugs, and in particular, the continuing spread of resistance to chloroquine, the mainstay of malaria treatment for many decades. Chloroquine-resistant malaria has now been confirmed in 53 countries, 24 of which are in Africa.

#### Schistosomiasis

7. Schistosomiasis is still on the increase world-wide, affecting communities in more and more parts of Africa. It is estimated that about 200 million people are actually infected and over 600 million exposed to the risk of infection.

#### Filariasis

8. Filariasis comprises several diseases, most of which are caused by filarial worms and transmitted by bloodsucking flies. Onchocerciasis or river blindness is probably the most serious of the filarial diseases. It affects about 40 million people, mainly in tropical Africa. The other main filarial infection, lymphatic filariasis, is found in Africa, South America and Asia and the Pacific islands. About 90 million people are infected and an estimated 905 million are at direct risk of becoming infected.

#### Trypanosomiasis

9. African trypanosomiasis, or sleeping sickness, is a severe, often fatal, disease that occurs widely in sub-Saharan Africa. About 50 million people are at risk of developing the disease. The incidence of reported cases is currently about 20,000 a year, but it is on the increase in several countries, and severe outbreaks have occurred over the last ten years. Chagas' disease, the American form of trypanosomiasis, is a chronic illness that is confined to the American continent. About 90 million people, roughly a quarter of the total population of Latin America, are directly exposed to the risk of T. cruzi infection, and between 16 and 18 million people are actually infected. Of infected individuals, approximately 10 per cent develop chronic Chagas' cardiopathy.

#### Leishmaniases

10. The leishmaniases comprise a group of diseases that occur in Africa, Latin America, Asia, the Mediterranean Basin and parts of the Soviet Union. The total

number of leishmaniasis cases has been estimated to be in the order of 10 million, with about 400,000 new cases each year. Notably, there has been a major resurgence in recent years in India of the most severe form, "kala-azar".

### Leprosy

11. About 1.4 billion people, nearly a third of the world's population, live in leprosy-endemic areas, mostly in Asia, Africa and Latin America. More than a third of the estimated 10.6 million leprosy patients in the world face the threat of permanent, progressive physical disability, often with the concomitant of social rejection. A major problem in leprosy treatment has been the growing resistance of Mycobacterium leprae to dapsone, the only cheap, safe and effective antileprosy drug, which has been used widely for almost 40 years. Dapsone resistance, which has been confirmed in surveys carried out in all parts of the world, is now widespread and increasing.

#### D. Research capability in the endemic countries

12. Enhancing the research capability of institutions in endemic countries is an essential element in the TDR strategy for improving disease control in tropical countries. When the programme was launched a decade ago, there was only a handful of institutions in the developing endemic countries engaged in research on the TDR target diseases. Although a number of teaching and research institutions had previously been established in these countries, they often focused their research priorities on clinical research and on non-communicable diseases. Field research received negligible support and most of these institutions had only minimal operational links even with ministries of health or national health care systems, much less with institutions abroad. In addition, opportunities were limited for training scientists, especially at the doctoral level, in disciplines relevant to the control of tropical diseases. The second main TDR objective is to strengthen research capability in countries most affected by tropical diseases. A task of such magnitude can succeed only with the initiative and long-term responsibility of the national authorities of tropical countries, without their commitment nothing of significant and lasting value can be achieved. TDR assists national authorities in carrying out the training and research they need for disease control and provides support to institutions for research related to one or more of the six diseases in a way that is in keeping with national capabilities and resources. More specifically, TDR strengthens the infrastructures of selected national institutions and trains key personnel, but always in the context of national health development plans and existing programmes of research and disease control.

#### E. TDR management and review processes

13. Research and development under the programme is overseen by scientific working groups (SWGs), which are extensive networks of scientists in institutions both in developing and developed countries. SWG activities are co-ordinated and managed by steering committees, which are usually composed of eight to twelve leading experts in their fields. Steering committees plan activities and review research projects, and they provide TDR with a horizontal and flexible structure for research

management. An analogous body, the Research Strengthening Group (RSG), similarly oversees the institution-strengthening and training activities of the programme. An elaborate peer review system is applied at all levels of the programme, from peer review of projects by individual scientists to policy decisions taken by the Joint Co-ordinating Board (JCB), the top management body of the programme. All proposals submitted to TDR are subject to peer review by the appropriate steering committee or the RSG. The activities of SWGs and their steering committees and RSG are in turn subject to review by the Scientific and Technical Advisory Committee (STAC), an independent body, which makes recommendations to JCB. Finally, the entire programme is subject to in-depth external review and evaluation; the first such review took place in 1981-1982 and the next will be carried out in 1987-1988.

14. The unique role of TDR is to co-ordinate, through international collaboration, the activities carried out within its world-wide network. The programme works together with a number of non-governmental organizations, such as the Wellcome Trust, the International Federation of Anti-Leprosy Associations, the MacArthur Foundation, The Rockefeller Foundation and the Edna McConnell Clark Foundation, and with other international organizations, such as the Food and Agriculture Organization of the United Nations (FAO) and the United Nations Environment Programme (UNEP). Close co-operation is maintained with the Onchocerciasis Control Programme in West Africa and other WHO programmes and divisions such as the Parasitic Diseases Programme, the Malaria Action Programme, the Division of Communicable Diseases, The Division of Vector Biology and Control, the Programme for Vaccine Development, the Diarrhoeal Diseases Control Programme and the Control Programme on AIDS. In addition, TDR is collaborating with industry, which plays an increasingly active role as TDR products approach the stages of final development and application. The fundamental policy of TDR is to protect the public sector rights by making products available to the developing countries at the lowest possible reasonable price; to this end, the programme enters into detailed discussions and agreements with companies to safeguard the interests of developing countries to the maximum extent. TDR has provided a demonstrably efficient mechanism whereby academic institutions, Government ministries and agencies, industrial concerns from many countries and international agencies collaborate and work together effectively towards well-defined common goals. Today, TDR provides an international recognized forum where scientists of widely differing disciplines and cultures can pool their experience and skills in pursuit of these goals.

15. The programme operates on a biennial budgeting system and its funds are allocated to different programme components as recommended by STAC and approved by JCB. JCB members include: (a) representatives of 12 Governments selected by the financial contributors to the programme; (b) representatives of 12 Governments selected by WHO regional committees from among those countries directly affected by TDR target diseases or providing scientific or technical support to the programme; (c) representatives of three Governments or agencies selected by the JCB itself; and (d) representatives of the three co-sponsoring agencies: UNDP, the World Bank and WHO. Over 40 multilateral, bilateral and other agencies are currently contributing to the TDR budget, which is about \$25 million a year, 72 per cent of which is spent on research and development and 28 per cent on strengthening research capability.

## II. THE PROJECT

16. The programme is achieving tangible results in pursuit of its two overall objectives and is carrying out scientific work the highlights of which are summarized below.

Malaria

17. Mefloquine was first registered in 1984 and is now being used alone and in combination for operational research in several countries. Other antimalarial drugs active against multiresistant P. falciparum are being developed. In 1986, one such compound, halofantrine, entered clinical trials under the auspices of TDR and may become available for use in control programmes within the next five years.

18. In addition, a new group of structurally new antimalarial compounds are being developed. Artemisinin, the active principle of the Chinese medicinal herb Artemisia annua, used against malaria for centuries in China has been shown to be one of the fastest acting antimalarials; it is also effective against multiresistant malaria. The parent compound was isolated by Chinese scientists and found to be only sparingly soluble in oils and water. Subsequent studies have led to more soluble compounds, and structure/activity analyses of related compounds are underway. TDR is currently developing an artemisinin derivative which has potential as a fast-acting and effective compound against severe, complicated malaria. This derivative may be available for experimental treatment of severe malaria within the next two years.

19. One of the key strategies for malaria prevention is the development of malaria vaccines. Two vaccines, one of which is being developed with TDR support, entered clinical trials in 1986; both are based on a major surface antigen of the sporozoite (the parasite form injected by the mosquito into the human). Other vaccines, acting against the blood stage of the parasite (merozoite) and against the sexual forms of the parasite that develop in the mosquito mid-gut (gamete, ookinete, zygote), are being developed experimentally. The first results of malaria vaccine field trials are expected within the next five years. Meanwhile, other methods of malaria control, including residual insecticides, impregnated bednets and fish that feed on larvae, are being assessed in field trials. Some species of larvivorous fish also provide an important dietary source.

Schistosomiasis

20. A realistic, demonstrably effective control strategy, recently endorsed by a WHO expert committee has been established for schistosomiasis. It is based on quantitative epidemiological evaluation, chemotherapy, supplemental mollusciciding, follow-up of patients at pre-determined intervals, community education and integration of control operations into health care delivery systems. The success of this strategy depends on the resolve of the endemic countries to adapt it to local needs and to mobilize the political and administrative resources required for its implementation. TDR has collaborated in the development of this strategy, primarily through support of large-scale field projects on schistosomiasis associated with the Volta Lake project in Ghana. The development of vaccines against schistosomiasis is now gaining momentum. Several leads have been made in

experimental systems and potential protective antigens have been identified and the genes cloned. Vaccines against schistosomiasis are expected to reach the stage of clinical testing within five years.

### Filariasis

21. About 10,000 compounds have been screened in animals for activity against filariasis. Ivermectin, derived from a naturally occurring antibiotic substance, was developed by Merck, Sharp and Dohme in the United States and it has now been shown in more than 1,200 patients that a single dose is capable of clearing patients of Onchocerca microfilariae without causing serious side effects. Two other compounds are now being clinically tested against onchocerciasis and lymphatic filariasis. These developments are taking place in close collaboration with the Onchocerciasis Chemotherapy Project (OCT), funded by the Onchocerciasis Control Programme in West Africa. Ivermectin appears to block transmission of onchocerciasis and it may therefore be a very interesting compound for the control of onchocerciasis. Large-scale field studies are expected to begin in 1987 or 1988 and the results of such studies should be available within five years. Experimental studies have indicated that it may be possible to develop vaccines against filariasis. Development of candidate vaccines at the experimental level is expected to take place during the coming years.

### African trypanosomiasis

22. Basic metabolic research on the parasite has led to the discovery that DL-alpha-difluoromethylornithine (DFMO) is effective against the late stage of African trypanosomiasis. After screening in animals, the drug has now been tested in more than 120 patients, many of whom had relapsed after conventional treatment. The results are so promising that DFMO has been labelled the "resurrection" drug. It is the first new drug effective against the late stage of sleeping sickness since melarsoprol was developed in the early 1940s. The Card Agglutination Test for Trypanosomiasis (CATT), a simple, sensitive diagnostic test for field use, is now integrated into sleeping sickness control programmes in a number of countries. Simple, effective insecticides, impregnated insect traps and screens developed for use by rural communities have reduced tsetse populations by over 90 per cent in some areas. Impregnated traps and screens are now in a final stage of field testing and expected to go into control programmes soon. In collaboration with FAO, the screens and traps will also be assessed in terms of their impact on trypanosomiasis in domestic animals and on cattle breeding.

### Chagas' disease

23. Slow-release insecticidal paint formulations have been field-tested and found effective for up to nine months against the triatomine bugs which convey the parasite of Chagas' disease. Such new paints can be easily applied and are well accepted by the community. The paints are now undergoing further large-scale field testing. Another new vector control method, a simple, fumigant insecticide canister, is also undergoing field testing. Chagas' disease can also be transmitted by blood transfusion. A number of compounds for sterilizing blood have been identified in in vitro screens and one has been selected for further study. The disease shows different clinical patterns in different geographical areas, and

several methods (monoclonal antibodies, DNA probes and biochemical methods) for identifying variant strains have been developed. The recent cloning of a surface antigen which appears to be involved in parasite penetration into the host cell represents an important breakthrough in research on Chagas' disease and a stepping stone towards the development of vaccines against the disease. Such vaccines are expected to reach an advanced stage of experimental testing within the next five years.

### The leishmaniases

24. Studies of parasite biology have led to the identification of a new group of compounds for treating the leishmaniases. The most studied of these, allopurinol riboside, has recently reached the stage of clinical testing. Another drug, paromomycin, is undergoing clinical testing as an ointment for topical treatment of ulcers. Leishmania comprise about 15 different parasite species. Several methods for precise diagnosis of parasites are now undergoing clinical testing. Both experimental studies and earlier clinical studies suggest that protective immunity can be induced against leishmania. Vaccines against leishmaniasis could reach clinical testing within five years. Simple diagnostic tests developed in different laboratories are now being compared, and a test suited for field conditions should be ready for trials within five years.

### Leprosy

25. TDR organized world-wide surveillance of dapsone resistance and promoted the development of multidrug therapy in leprosy, which has now been integrated into leprosy control programmes. Short-term regimens have given promising results. The introduction of multidrug therapy in leprosy has changed the focus of research because treatment is stopped after a fixed duration; current research emphasis is therefore on duration of therapy. Determination of relapse using serological tests based on detection of specific antigen now has high priority and several such tests are being developed. Vaccine development in leprosy has reached an advanced stage. Human trials using killed M. leprae vaccine have been undertaken in Norway, where studies were carried out on toxicity and optimum dosage for sensitization. Field trials are now underway in Venezuela and Malawi. The first results of such trials are expected to be available during the next five-year period. Second generation leprosy vaccines are being contemplated now that the whole genome of M. leprae has been cloned in Escherichia coli. A new drug against leprosy, pefloxacin, has reached the stage of clinical testing, and another, ofloxacin, will soon undergo clinical trials.

### Vector biology control

26. This TDR component has identified Bacillus sphaericus as a particularly promising biological agent against the mosquito vectors of filariasis. The agent is presently undergoing advanced field testing and could be integrated into control programmes within the next five years. B. thuringiensis, another larvicidal bacterium, has been thoroughly integrated into the Onchocerciasis Control Programme in West Africa as a vector control method against blackflies, which are becoming resistant to other agents. Local production in endemic countries may be possible for both these agents.



### Trans-disease components

27. In addition to work on the target diseases, TDR has three trans-disease components - vector biology and control, epidemiology, and social and economic research - which focus on research areas applicable to most or all of the diseases. The epidemiology component places major emphasis on training because of the world-wide shortage of epidemiologists, particularly in developing countries. The social and economic research component is designed to address the cost-effectiveness of various disease-control approaches and the role of behaviour, attitudes and other social and economic factors related to disease control. A striking feature that many of these projects have revealed is the lack of knowledge about relationships between disease and disease transmission and the control methods introduced for use in their communities. This component also focuses on cost analysis studies of control methods.

### Research capability strengthening

28. Strengthening research capability in developing countries is a long-term process. Even at this relatively early stage, there are encouraging signs that significant progress has been made. The number of projects originating from scientists in developing countries has grown steadily, as has the volume of scientific publications resulting from projects supported in developing countries. Of the more than 600 scientists who have received training grants during the first TDR decade, more than 95 per cent of the trainees who completed their training returned to their home country. Many institutions in developing countries have played an important role in TDR activities. For example, institutions in Brazil, Thailand and Zambia have carried out 18 clinical trials of the antimalarial drug mefloquine. These trials provided the clinical information required to obtain registration of the drug.

29. The Onchocerciasis Chemotherapy Research Centre in Tamale, Ghana, plays an essential role in the development of drugs for the treatment of onchocerciasis. The Clinical Research Centre in Nairobi, Kenya, has produced evidence which has led to the revision of traditional drug regimens using allopurinol riboside combined with antimonials in the treatment of leishmaniases. The Institute of Tropical Medicine at the University of Sao Paulo, Brazil, is the co-ordinating centre for a network of 14 institutions collaborating on the standardization of serodiagnosis in Chagas' disease. The Malaria Eradication Service in the Philippines, in collaboration with the WHO Regional Office for the Western Pacific and TDR, has organized the production of microkits for the field testing of P. falciparum sensitivity to 4-amino-quinolines and mefloquine. At the Faculty of Tropical Medicine of Mahidol University in Bangkok, Thailand, a multidisciplinary group of epidemiologists, behavioural scientists, clinicians and parasitologists has contributed substantially to the development of strategies for malaria control. At the Oswaldo Cruz Foundation in Rio de Janeiro, Brazil, molecular biologists are using DNA restriction enzyme analysis to classify Trypanosoma cruzi and Leishmania species. A new classification method is now being applied to epidemiological research in Chagas' disease.

## III. TDR AND THE FUTURE

30. The development of new drugs and vaccines is a time-consuming process: it often takes 20 years or more before they can be integrated into control activities. Long-term endeavours require long-term support. At each stage of development, new problems may arise which necessitate recycling back to previous stages of development. At the close of the first decade, however, new products are coming out of TDR at a faster rate than predicted by even the most optimistic forecasts made when the programme was launched. In the coming years, TDR will face the particular challenge of strengthening field research so that new products and methods can be assessed in the field as soon as they become available. Another important task for TDR is to ensure collaboration with disease control programmes and authorities to ensure that the new disease control technologies are brought into use as expeditiously as possible. More emphasis will be placed on research in developing countries and even stronger links will be established between research capability strengthening and the research and development activities of the programme. TDR will have a crucial role to play over the next 10 years: it is the only programme that has the full capacity to link advanced laboratory research in developed parts of the world with field research and applications to disease control in developing countries. The co-sponsors of the programme and co-operating Governments and agencies understand and accept these facts. It is recognized that the achievement of the objectives established for the programme, although costly, will contribute substantially to human well-being and the possibility of health for all by the end of the century. The Administrator attaches the highest importance to the attainment of that goal, and considers that UNDP should continue to support the Special Programme during the fourth programming cycle. UNDP support will continue to be provided to the programme as a whole, without being earmarked for any particular component.

31. The components of the proposed UNDP inputs are as follows: 2/

	\$
Subcontracts	7 485 000
Mission travel	<u>15 000</u>
	7 500 000

## IV. RECOMMENDATION

32. The Administrator recommends that the Governing Council:

(a) Approve UNDP assistance to this project; and

(b) Authorize the Administrator to make the appropriate arrangements with the executing agencies for the execution of this project.

Notes

1/ The programme will be considered for continuation following the results of an external evaluation to be held in 1987-1988. At that time, additional funds of \$5 million will be requested for a further two years.

2/ Since UNDP is a co-sponsor of the TDR programme, no agency overhead costs will be charged to this project, which forms part of the UNDP/WHO/World Bank Special Programme for Research and Training in Tropical Diseases.

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