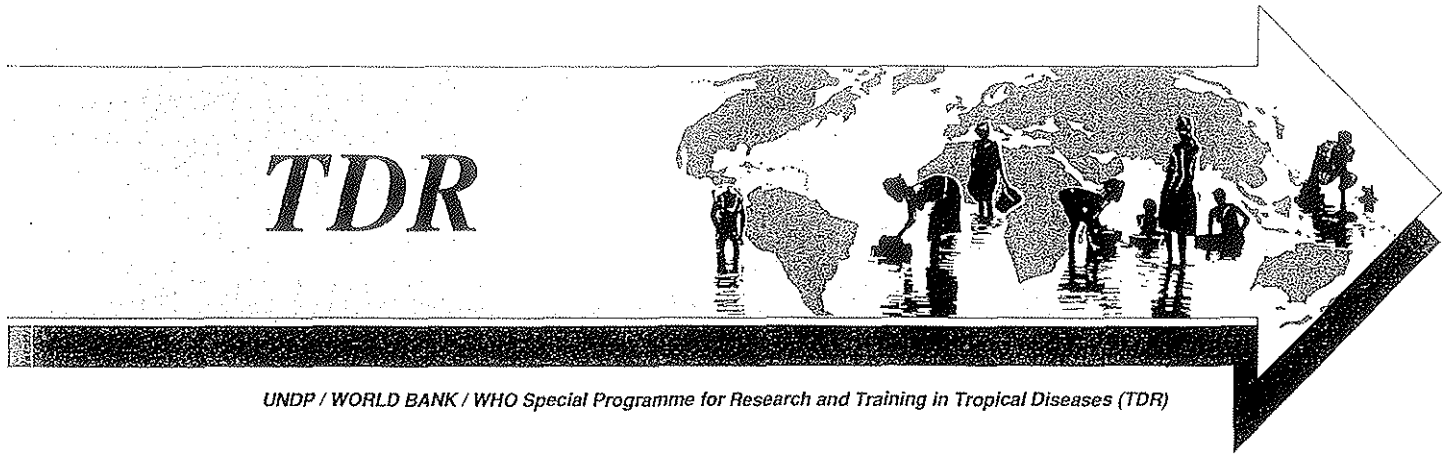
Report of the Second External Review Committee

Special Programme for Research and Training in Tropical Diseases



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

WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

Report of the Second External Review Committee

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

Eleventh Session of the Joint Coordinating Board
Geneva, 27 - 29 June 1988

Second External Review Committee

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TDR/JCB(11)/88.6 Rev.1

The geographical designations used in this report do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Contents

Glossary of Acronyms and Abbreviations

AIDS	acquired immune deficiency syndrome
BCG	Bacillus Calmette-Guerin (vaccine)
BCV	Biological Control of Vectors (Component)
CATT	Card Agglutination Test for Trypanosomiasis
CHEMAL	Chemotherapy of Malaria (Component)
DEC	Developing endemic country
DFMO	DL-α-difluoromethylornithine
DNA	deoxyribonucleic acid
EPD	Epidemiology (Component)
ERC	External Review Committee
FIELDMAL	Applied Field Research in Malaria (Component)
HIV	human immunodeficiency virus
IMMAL	Immunology of Malaria (Component)
IMMLEP	Immunology of Leprosy (Component)
JCB	Joint Coordinating Board
OCP	Onchocerciasis Control Programme in West Africa
OCT	Onchocerciasis Chemotherapy Project
R&D	research and development
RCS	research capability strengthening
RSG	Research Strengthening Group
SC	Steering Committee
SER	Social and Economic Research (Component)
STAC	Scientific and Technical Advisory Committee
STRC	Scientific and Technical Review Committee
SWG	Scientific Working Group
TDR	Special Programme for Research and Training in Tropical Diseases
THELEP	Chemotherapy of Leprosy (Component)
UNDP	United Nations Development Programme
USAID	United States Agency for International Development
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

1. Overview and Summary

The second external review and evaluation of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was conducted by an External Review Committee (ERC) during the period November 1986 to December 1987. The terms of reference for the review (see Section 2 and Annex 1) included assessment of the contributions and scientific accomplishments of the Programme, the fundamental bases for its existence, its approaches, and its future role and development. In the light of its resources and time, the ERC chose to focus upon those aspects of its very broad and detailed terms of reference that it felt most fundamental to the specific mission of the Programme.

The summary below represents the findings, conclusions, judgements and recommendations of the External Review Committee.

1.1 Mission of the Programme: The Scope and Evolution of its Activities

The enormous health and economic burden of tropical diseases, especially the TDR target diseases, compellingly justifies the continued existence of the Programme. The fundamental mission of the Programme should continue to be the development of new and improved tools for the control of major tropical diseases. A necessary part of the development process is the demonstration of the utility of the tools in their intended setting of use (i.e., countries where the target diseases are endemic) and the initial exploration of the most appropriate means of their application. These are legitimate aspects of TDR's mandate and the evolution of the Programme must reflect greater emphasis on them in the coming decade; this will entail expansion of field testing which will necessarily need to be conducted in developing countries where the target diseases are endemic.

Strengthening the research capability for tropical disease control in developing endemic countries is essential in fulfilling the Programme's mission. Research capability strengthening (RCS) was therefore rightly regarded as a necessary activity for TDR. Institution strengthening is a high-cost, long-term venture for which predictors of success are presently not entirely reliable. In recent years TDR has been the major funder of such efforts (both institution strengthening and tropical disease research training). The Research Strengthening Group (RSG) has developed a sound set of operational criteria for research capability strengthening efforts. Progress to date has been encouraging; further efforts will be needed to evaluate the long-term impact of investments to date. Research capability strengthening is a legitimate second formal objective of the Programme but its assignment to a separate Programme Area has led to less than the desirable level of integration with Research and Development (R&D) activities. This was inevitable at first, but now the two Programme Areas -- RCS and R&D -- must be fully integrated. The ERC believes that research capability strengthening should remain a major feature of TDR efforts but should be much more strongly linked with overall Programme needs, especially those of the R&D Components, than was the case in the first decade of the Programme's existence. Action taken by Director, TDR, to achieve this aim is commended.

The proportion of the total budget presently devoted to research capability strengthening (25 per cent) is judged by the ERC to be reasonable, but staffing for this Programme Area needs to be increased in the light of the anticipated increased workload due to new funding activities, e.g., programme-based grants.

Owing to the anticipated expansion of field testing activities in the next decade, there is likely to be a greater need for epidemiological expertise, already scarce, in developing endemic countries; hence, RCS activities should emphasize training in epidemiology in the

next few years. Field testing will require increased emphasis on epidemiology in the disease-specific components.

The ERC approves of recent actions taken to integrate more closely epidemiological activities into overall R&D and RCS activities, including the participation of a member of the Epidemiology Steering Committee (SC) in each disease-specific SC. It favours development of a strategy to achieve stronger involvement of individuals with social and economic research expertise in selected R&D Steering Committees, but believes the SC on Social and Economic Research (SER) should continue to exist and fund projects in order to preserve a focus for its efforts.

The time frame for the development of new disease control tools -- from identifying and understanding the etiological agent through field testing and initial application -- is 15 to 30 years. Even the more targeted later phases can take a decade. After reviewing the current status of progress towards development of disease control tools for the TDR target diseases, the ERC judges that there is a clear need for the Programme to continue for at least 10 years. The situation should be reviewed again at that time.

Having weighed many factors which influence decisions on the selection of target diseases, the ERC considers that there is no strong case to drop any of the diseases presently included in TDR's activities, nor are resources currently adequate to add any diseases. The ERC recommends no change in the content of the Programme at this time. The worldwide epidemic of acquired immune deficiency syndrome (AIDS) resulting from infection with the human immunodeficiency virus (HIV) will, however, require that TDR addresses interactions between HIV infection and TDR target diseases, in collaboration with the WHO Global Programme on AIDS.

Further development of the Programme will need to take place in the following areas: (1) expansion of efforts in field testing; (2) rational drug development; (3) social and economic research, including health economics and development policy; and (4) greater integration of the RCS and R&D Programme Areas. Pursuit of these efforts should not be at the expense of biomedical research and development since a strong base will be needed to underpin the development of new disease control tools.

1.2 Accomplishments and Contributions

TDR already has a considerable record of accomplishments. In its first decade of existence it has fulfilled its mission laudably by identifying rational objectives and pursuing them through appropriate, well-managed mechanisms. It is now a central and indispensable feature of global research and development efforts to find new and better tools for tropical disease control.

The Programme has made many broad contributions to the development of control tools for tropical diseases in addition to the impressive accumulation of scientific results from research it has supported. These include raising awareness of the need for tropical disease control R&D; recruiting and enabling an expanded cadre of investigators to enter tropical disease R&D; providing a source of funds and intellectual peer support for good but previously underfunded investigators (e.g., in developing countries and in social and economic research); improving communication among disparate relevant disciplines; establishing effective collaboration with industry in a fashion that has been sensitive to public health needs in developing disease-endemic countries (DECs); providing a model for the 'management' of targeted research by scientists; and providing proven strategies and criteria whereby research capability strengthening can be effectively pursued.

The list of 'products' stemming from research in which TDR has participated is impressive (see the TDR *Eighth Programme Report**, which should be regarded as an essential companion to this review). Some 60 products are now in use or in advanced stages of development (in clinical or field trials). Important R&D contributions of the Programme include:

- organizing transnational drug trials of new therapeutic agents for malaria;
- supporting a broad range of work critical to malaria vaccine development;
- sustaining field research in malaria;
- supporting work to lay a basis for possible development of a schistosomal vaccine;
- promoting, in collaboration with industry, the clinical development of ivermectin for the treatment of onchocerciasis, along with other drugs for this and other filarial diseases.
- providing virtually unique support for a comprehensive spectrum of activities in African trypanosomiasis control R&D, including work on drugs (DL-α-difluoromethyl-ornithine and analogues) and the Card Agglutination Test for Trypanosomiasis (discovered outside the Programme but developed for field use with TDR resources) and developmental work on tsetse-fly traps;
- catalysing the development of a network of first-rate research and development centres on Chagas' disease in DECs, which have contributed to understanding of the pathogen, its antigens and pathogenicity, the social aspects of the disease and improved vector control;
- organizing very important trials on multidrug therapy for leprosy;
- facilitating the development of a first-generation leprosy vaccine candidate by creating a global network of investigators and providing organizational and financial support for their activities up to the stage of clinical trials;
- increasing understanding of many aspects of the leishmaniases and uncovering their widespread global distribution;
- developing a new regimen for antimonial drugs, which has been established as the recommended treatment of visceral leishmaniasis;
- supporting the development of *Bacillus thuringiensis* as a biological vector control agent, which is now used extensively in onchocerciasis control;
- enhancing the epidemiological quality of field studies on control of the target diseases.

These practical contributions -- many of which are now actually being put into use in developing countries -- attest not only to the scientific productivity of TDR but also to the fact that the Programme is developing tools truly appropriate for the settings in which their use is intended.

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* *Tropical Disease Research: A Global Partnership. Eighth Programme Report: The First Ten Years, with Highlights of the 1985-86 Biennium.* (J. Maurice & A.M. Pearce, eds.) Geneva, World Health Organization, 1987, 191 pp.

The focus of the Programme's R&D contributions is evolving from the generation of scientific research results towards the development of actual products, in no small measure as a consequence of research it has promoted.

The contribution of the Programme's research capability strengthening activities include: principles and guidelines by which research capability strengthening can be effectively pursued; a significant number of successfully strengthened institutions in developing countries; and a total (by 1986) of over 500 new researchers trained in various aspects of tropical diseases. These are significant accomplishments for a total expenditure for the decade 1976-1986 of only approximately US $44.5 million.

TDR's chosen *modus operandi* as a catalyst, convener and leader is appropriate and cost-effective. Overall, the ERC finds the Programme to be effective and productive.

1.3 Social and Economic Research

During the last decade, social and economic research on tropical diseases was either non-existent in many DECs or it arose mainly through the stimulus provided by TDR. The most significant achievement of TDR's Social and Economic Research (SER) Component is the initial research 'infrastructure' it has established by creating essentially the first cadre of trained social scientists and supporting the first social and economic research projects on tropical diseases conducted in endemic countries by local social scientists. This is SER's unique contribution not only to TDR but to the scientific community of developing countries.

In asking the questions of who does what, where, when and why, SER projects have contributed to the identification of populations and individuals at risk at the community and household levels. Answers to these questions have also helped establish the basic building blocks for disease control efforts through increasing understanding of the social, economic and cultural aspects of tropical diseases, such as: patterns of occupational and household activity; seasonal dimensions of these activities; man-vector-parasite connections (including knowledge, perceptions, attitudes and practices vis-à-vis specific diseases); patterns of coping with disease; mobility and settlement patterns; response to treatment and control measures, etc. With respect to the latter, some good cost-effectiveness studies have been supported by the SER SC.

However, study of the economics of tropical diseases and research on community participation and on the integration of tropical disease control in primary health care have proven to be more intractable. These clearly represent areas which will require considerable work well into the future.

In the shorter term, other indicators of progress must be investigated, including factors such as changes in knowledge, perceptions, attitudes and practices; changes in health-related human behaviour; and changes in disease incidence and prevalence.

The ERC firmly believes that social and economic research will be critical to the eventual control of tropical diseases, and the Committee has made a number of specific recommendations which are described in Section 5. Much greater emphasis needs to be placed on social and economic research within Programme Area III (RCS), and social science disciplines should be strengthened in the membership of the Scientific and Technical Advisory Committee (STAC), the Research Strengthening Group (RSG), the Scientific Working Groups (SWGs) and relevant disease-specific Steering Committees. Given the magnitude of the tasks, the ERC is convinced that the budget of the SER Component should be doubled over the next five years and that an additional staff member is needed to support SER SC activities.

1.4 Research Capability Strengthening and Research and Development

The ERC affirms its conviction that research capability strengthening is an essential activity in fulfilling the Programme's mission.

Establishment of Programme Area III, Research Capability Strengthening, in addition to that of Programme Area II, Research and Development, has been beneficial in emphasizing the importance of research capability strengthening. Since the beginning of the Programme, there has periodically been debate about the relative balance between RCS and R&D. It seems to the ERC that there is agreement, within the Joint Coordinating Board (JCB), STAC and TDR as a whole, as well as within much of the community familiar with its efforts, that the present balance between RCS and R&D is appropriate and acceptable. However, the ERC is concerned that, while approximately 25 per cent of TDR resources are devoted to RCS, there are proportionally far fewer staff in this Area than in research and development, although RCS requires considerable resources in terms of proposal development and project management.

The ERC concurs with the overall strategy adopted by the RSG in institution strengthening, namely supporting the development of existing national institutions in relevant subject areas in preference to creating new, specialized international institutes or centres. The ERC recognized that some institutions in which strengthening was attempted would not achieve success for reasons beyond their control or that of TDR. The adopted strategy avoids potential problems of isolation from national government efforts and, importantly, enables research training to be undertaken on a broader basis. In addition, it makes possible investments (albeit smaller) in a larger number of institutions, thereby reducing the risks of losing investments in an area where there are no clear predictors of success.

To help TDR-strengthened and other institutions in developing endemic countries expand their activities in research and development, cooperation between Programme Areas II and III needs to be intensified to lead to greater integration of their activities. Ideally, Steering Committee members and Secretaries need to have input into all phases of the research strengthening process. The ERC approves of the directions being pursued by Director, TDR, in this regard, whereby research capability strengthening is viewed as a phased process, beginning with training, followed with a phase similar to that covered by the present five-year institution-strengthening grant, then with programme-based grants for research activities, and resulting finally in support from R&D Components.

Geographic needs for institution strengthening are becoming more focused and, in the future, activities should increasingly emphasize RCS activities tied more closely to Programme needs (e.g., field testing). The proposed programme-based grant, an intermediate grant between institution strengthening and research grants, is a very suitable mechanism for achieving progress in this direction. Therefore, it appears to the ERC that there should be a smaller number of institution-strengthening awards in the second than the first decade.

In the area of research and development, the ERC supports expanded efforts by Steering Committees and SC Secretaries to stimulate individuals (or groups) to develop R&D proposals in line with the SC short- and long-range work plans.

1.5 Programme Execution

Although complex, the management structure of TDR is appropriate to the activities undertaken and the chosen *modus operandi*. Steering Committees amd Scientific Working Groups create a network of scientists committed to work on tropical diseases. The ERC wishes to stress the fact that strategy setting by scientists and peer review form an integral part of Programme execution.

The ERC proposes no change in the present arrangements whereby WHO technical unit staff serve as Secretaries of the Scientific Working Groups of corresponding TDR Steering Committees. This arrangement can usefully consolidate and formalize ties between TDR and WHO regular budget programmes.

The ERC recommends a review of Steering Committees and of the staffing needs for SC operations. Further, the ERC recommends that mechanisms be developed to improve the grant-making operation of SCs; suggestions are made for streamlining such procedures and making more uniform use of SC members and external reviewers (see Section 7). The ERC considers it possible to increase staffing within Programme Area III and the SER Component at the expense of staffing within Programme Area II. It should also be possible within the staffing pattern to increase input into Programme Area III by staff primarily engaged in Programme Area II activities. The ERC proposes that an in-depth analysis of staffing needs for the coming years be made by TDR management in collaboration with a consultant experienced in science administration.

After assessing the management of TDR, the ERC feels that the present term of office of the JCB Chairman is too short to allow development of the desirable level of familiarity with the Programme. The need for such familiarity will increase with the envisaged JCB involvement in fundraising described below (see also Section 10). Accordingly, the ERC recommends that a term of office of three years be considered for the JCB Chairman.

The Programme's goals can only be pursued effectively by a group that can maintain a truly global and objective perspective and promote linkages irrespective of regional boundaries. The ERC therefore believes that the present structure and administrative arrangements of the Programme are appropriate to meet the challenges before TDR in the coming decade.

The ERC reviewed the roles and responsibilities of the Special Programme Coordinator and the Programme Director and their relationship. It believes that the existing arrangements have worked successfully and recommends that these not be changed. The Programme's co-sponsors should be actively involved in the selections and appointments of the Programme Director and the Special Programme Coordinator.

The ERC is impressed with the Programme's achievements in its Management Information System (MISTR) and proposes no changes in the manner in which it is organized. If the recommendations under 'Communications' (see Section 9) are implemented, MISTR could well play an expanded role in developing information for Programme promotion.

1.6 Responsibilities in the Development and Application of Disease Control Tools

The field testing of prototype disease control tools will require active communication and collaboration between TDR Components (disease-specific Steering Committees; the Components on Biological Control of Vectors, Social and Economic Research, and Epidemiology; and the RSG); WHO technical units; national governments (ministries of health, disease control programmes, primary health care systems); research institutions in developing and, possibly, industrialized countries; TDR regional representatives; and probably industry. Collaboration will be most effective in a situation in which respective roles are understood by all participants and in which each has the resources to contribute according to its appropriate responsibilities. The ERC has therefore formulated guidelines for TDR responsibilities, which include the following:

- The Programme should participate in and fund field research necessary to demonstrate the utility of new disease control tools in DECs and to identify the optimal initial approaches for application of these tools. TDR involvement in such field research should focus on model studies with new classes of disease control tools to demonstrate how such testing should be conducted. The responsibility for application of new

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The ERC hopes that its efforts and suggestions will assist the JCB and TDR Secretariat in pursuing TDR's important mission. With regard to implementation, these bodies should view the spirit of the recommendations as being more important than the specific options suggested. The ERC believes that contributors to the Programme should recognize that TDR has an important mission and has adopted appropriate strategies to fulfill it (including direction and management by leading scientists, which truly makes it a 'Special Programme'), and that it is well managed, has a considerable record of accomplishments and contributions to date, and is already developing appropriately to meet the challenges of the coming decade. Substantial changes have been made during 1987 and these meet many of the needs to which we have drawn attention.

2. The Committee's Assignment and Approach

The Joint Coordinating Board, at its Eighth Session on 26-27 June 1985, decided that a second external review and evaluation of the Programme should be carried out. The first External Review Committee [ERC(1)] judged in 1982 "that because the first three years of the Programme was a building up period, the scientific results available now are not extensive" and that a further review of such achievements in approximately five years was desirable. In concurrence with the recommendation of ERC(1) approved by JCB(5), the second review initiated by JCB(8) was intended to include evaluation of the scientific accomplishments of the Programme. JCB(8) also recommended that the impact of the Programme should be studied and the experience gained in the past should be assessed to determine the future role and development of the Programme.

2.1 Objectives and Terms of Reference

Objectives and terms of reference for the second external review and evaluation of the Programme were set out by JCB(8) and JCB(9) as follows:

(a) to review the Special Programme in terms of its objectives and its achievements;

(b) to examine the fundamental basis of the Special Programme and its future role based on achievements and experiences both inside and outside TDR over the last ten years; and

(c) to make recommendations on the objectives and terms of reference and other related matters examined in the course of the review.

The JCB decided that the review would be carried out by an independent External Review Committee, which would be guided by the Standing Committee. The ERC would report to the JCB at its Eleventh Session in June 1988. The specific terms of reference, objectives, mechanisms and operation of the review are contained in document TDR/JCB(9)/86.6 Rev.4, a copy of which is attached as Annex I. Membership of the Committee is listed in that document. An Executive Secretary (Dr R. Widdus, Director of the Division of International Health, Institute of Medicine, US National Academy of Sciences) was appointed to assist and support the Committee in its work.

2.2 Context of the Review

The second external review and evaluation of TDR was initiated shortly after a new Director had been appointed and the occupants of a number of senior Secretariat positions had changed. Additionally, an assessment of an important Programme Area, Research Capability Strengthening, was nearly complete. These events, irrespective of the establishment of the ERC, had led to an environment in which the Secretariat had begun evaluating future Programme directions and making those managerial changes which were considered desirable.

In its progress report to JCB(10), the ERC recognized the need for Director, TDR, to be able to implement those changes he considered desirable without unnecessary delay. The Committee had several extremely useful discussions with Director, TDR, about changes he was considering to improve Programme management, and the ERC hopes its comments were useful. The ERC believes that all recent initiatives will be beneficial, especially the closer integration of Programme Areas II (Research and Development) and III (Research Capability Strengthening), as outlined in Annex II of the report of the twelfth meeting of the Research Strengthening Group (document TDR/RSG(12)/87.3). As a result of discussions with Director, TDR, action has already been taken or may be under way on some of the concerns identified below. The ERC judged that by providing timely interim assessments of issues, it would maximize the utility of its deliberations to the Programme.

The ERC judged the terms of reference for its review to be extremely comprehensive and detailed. The Committee decided, given the available resources, to focus in its report upon those aspects of its mandate which it considered most fundamental to the specific mission of the Programme (Sections 3 and 8).

2.3 Activities

The Committee held four meetings, at the first of which Mr W.W. Furth, Assistant Director-General of WHO and Special Programme Coordinator, welcomed the members and reviewed the Committee's mandate. Also at the first meeting, Dr T. Godal, Director of TDR, provided an overview of the Programme. The Committee held interviews with many persons closely associated with the Programme, including both present and previous members of the Secretariat, many persons from related WHO programmes, including technical units responsible for supporting tropical disease control (see Section 8), and external scientists and policy makers. Dr A.O. Lucas, previous Director of TDR, spent a day with the Committee during its second meeting.

The Committee met twice with Dr H. Mahler, Director-General of WHO, at the outset and towards the end of its activities, to review some issues of concern the Committee had identified.

Members of the Committee conducted site visits to TDR-supported institutions in Argentina, Brazil, Colombia, Kenya, Nigeria, the Philippines and Zambia.

Interviews were conducted by individual Committee members with a wide range of researchers and policy makers in developed and developing countries, both those actively involved in the Programme and those not involved but knowledgeable about tropical diseases. Meetings of this nature were held in Brazil, Colombia, India, Nigeria, the Philippines, the United Kingdom and the United States of America.

A list of persons consulted is included as Annex II. Letters soliciting comments on issues of key concern to the ERC were sent to members of the JCB and STAC, and to other individuals or institutions with interests related to those of the Programme. The substantive text of this letter is included as Annex III.

The ERC reviewed extensive documentation on TDR. This included the *Seventh Programme Report* and *Eighth Programme Report*; JCB, STAC, STRC, Standing Committee and RSG reports; SWG work plans; SC minutes and other documents; "Facts and Figures" documents; management and budget reports; lists of publications from TDR-supported activities; selected country profiles; project files and various materials prepared for specific purposes or meetings. Additionally, a number of analyses and documents were prepared specifically for ERC use by the Programme's Management Information System.

The ERC members individually reviewed the overall body of work undertaken and the award-making procedures in the various Programme Components and Areas. They also reviewed in detail material relating to a selection of five projects, chosen by Steering Committee Secretaries, in each of three categories: (a) successful; (b) unsuccessful; and (c) meritorious but not funded because of resource constraints.

On the basis of these activities and its collective experience in the management of scientific and development endeavours, the Committee reports in the following sections its findings, conclusions, judgements and recommendations. It hopes that its efforts and suggestions will assist the JCB and the Secretariat in pursuing the Programme's important mission.

The Committee wishes to express its gratitude to all those who assisted it in carrying out the review. Particular thanks are extended to the Secretariat, which provided documentation and comments efficiently and willingly. Ms A.M. Pearce provided helpful and greatly appreciated editorial suggestions. Finally, the Committee wishes to express its appreciation to Mrs P. Lynch and Miss S. Block for their assistance in preparing the report and their management of logistic support for the Committee's activities.

3. The Mission of the Programme and Evolution of Its Activities

3.1 Background

The origins of TDR have been described concisely in the booklet "Science at Work":

"In May 1974, the World Health Assembly of the World Health Organization (WHO) passed Resolution WHA27.52, which included the following statement:

'Recognizing that tropical parasitic diseases are one of the main obstacles to improving the level of health and socioeconomic development in countries of the tropical and subtropical zones;

Bearing in mind the need to develop research on matters connected with the most important tropical parasitic diseases;

Realizing that national, regional or global programmes of tropical parasitic disease control can be implemented only if scientifically-based methods and effective means for their control are available;

Requests the Director-General:

- to intensify WHO activities in the field of research on the major tropical parasitic diseases (malaria, onchocerciasis, schistosomiasis, the trypanosomiases, etc.) taking into consideration that such activities be carried out in endemic areas whenever possible and feasible;
- to define the priorities in research on the problem of tropical parasitic diseases in the various regions of the world, bearing in mind the primary needs of the developing countries;
- and to extend cooperation with national institutions and other governmental and nongovernmental organizations in regard to the coordination of research in this field.'

This resolution forms the mandate and broad terms of reference for the Special Programme for Research and Training in Tropical Diseases (TDR). Behind its formal language lay recognition of the importance of research as an integral part of efforts to improve control of major tropical diseases and concern over the inadequacy of research activities being conducted at the time. There was also an underlying premise that much of this research should be internationally based. The first step was to develop the resolution into a programme of well-defined scope and structure. TDR was then formally established in February 1978, although many activities began before that date. From its beginning, TDR was seen as likely to continue for 20 years or more. Recognizing that TDR's objectives and activities relate to the economic potential of tropical disease-endemic countries, the United Nations Development Programme (UNDP) and The World Bank joined the World Health Organization as co-sponsors of the Programme, with WHO as the Executing Agency."

The objectives of the Special Programme are usually stated as follows:

- 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 six diseases selected for inclusion in the Programme are malaria, schistosomiasis, filariasis (including onchocerciasis), the trypanosomiases (both African sleeping sickness and the American form, Chagas' disease), the leishmaniases and leprosy. The criteria on which these diseases were selected are discussed below.

The terms of reference of the ERC included consideration of fundamental questions about the Programme's existence, activities and time frame.

3.2 The Need for a Programme on Tropical Diseases

The burden that tropical diseases, and particularly the TDR target diseases, impose on developing countries is still enormous. Information on estimated incidence or prevalence has recently been reviewed in the TDR *Eighth Programme Report*.

- The worldwide incidence of malaria is in the order of 100 million cases a year, with an enormous consequent mortality and morbidity, including fetal death and low birth weight. Annual mortality from malaria is probably in the range of 1.5 to 2 million, most of which occurs in infants and children.

- More than 200 million people are estimated to be infected with the schistosomiasis parasite. Consequences of the disease include liver and kidney damage and, not uncommonly, bladder cancer in advanced disease.

- Filariasis appears to be spreading and now just over 108 million people are believed to be infected with one of the four filarial parasites that cause human disease. One of the major consequences of infection with lymphatic filariasis is elephantiasis, while onchocerciasis causes blindness.

- African trypanosomiasis is also on the upsurge but reliable estimates of incidence and

prevalence are difficult to generate. Fifty million people live in areas of transmission, and prevalence rates have in the last two decades risen to an average of 1 to 2 per cent. They reach 18 per cent in some foci. The disease is invariably fatal if untreated, and current treatments of advanced disease have unacceptable side-effects.

- The parasite causing Chagas' disease *(Trypanosoma cruzi)* is now estimated to infect 16 to 18 million people in Central and South America. This is an increase over the estimate of 10 million in 1976. Acute Chagas' disease is relatively mild, except in young children in whom myocarditis or meningitis may occur. Chronic Chagas' disease can entail heart disease and/or severe digestive tract problems.

- The worldwide prevalence and incidence of the leishmaniases are believed to be in the order of 12 million and well over 400 000 cases per annum, respectively, but these estimates may not be reliable because of the difficulty inherent in tracking these diseases. Only the visceral form is fatal but overall estimates of mortality have not been made; epidemics cause thousands of deaths, e.g., in 1977-1978 India suffered 20 000 fatalities. Cutaneous and mucocutaneous forms result in severe skin or nasopharyngeal tissue destruction.

- Leprosy is estimated to afflict 10 to 12 million people worldwide. In some areas in Africa and Asia, incidence rates of 10 per 1000 may occur.

- Additionally, with some exceptions, vectors of tropical diseases have been little affected by control programmes: where insecticides have been used, resistance to them has emerged. They will continue to represent constantly moving targets.

The present situation is difficult to compare with that at the Programme's inception. At that time, precise global data were not available. Although much more is now known, in large part as a result of TDR's efforts, estimates still have considerable uncertainty. It is clear, however, that in the last ten years awareness of tropical diseases has increased in developing endemic countries, that progress is being made in some areas (e.g., in reducing infant malaria mortality), and that the increasing knowledge of the epidemiology of the diseases is in itself a powerful tool in the fight against them. It is better understood that the infectious agents, their vectors and animal reservoirs are 'moving targets', all showing a capacity for change, which necessitates continued vigilance. Additionally, the implications of human migration for the control of tropical diseases can now be better assessed.

The Committee concluded that the continuing enormous health and economic burden of tropical diseases, especially the TDR target diseases, compellingly justified the continued existence of the Programme. (The scope of the Programme, in terms of the diseases included within its mandate, is discussed below.)

3.3 Objectives and Activities of the Programme: The Necessity for Both Research and Development and Research Capability Strengthening

The formulation of the Programme was considered by the Committee. The ERC sees the fundamental mission of the Programme as the development of new and improved disease control tools appropriate for use against the six diseases in the countries where they are endemic. An integral part of the development process is the demonstration of the utility of the tools and exploration of the most appropriate means of application and delivery in the setting of intended use. The cost of the new methods must be within the resources of developing countries, require minimal skills or supervision, and be capable of integration into the health services, especially the primary health care systems, of developing countries. Because the target diseases only occur extensively in developing endemic countries (DECs), research on

the utility of new tools 'in the field' and on their application must occur in such countries. Insights for improvement of tools may also largely be expected to arise in situations where they are in use.

It therefore follows that much of the development process will need to be conducted through research in DECs and, equally important, by those who are familiar with the cultural, social and economic milieux in which the tools will be used, to ensure that they are appropriate and effective in the circumstances in which the diseases occur. At the outset of the Programme, most DECs did not have a sufficient base of researchers or facilities to conduct the work required. It was obvious that biomedical research capability in tropical countries needed be strengthened to enable these countries to undertake research relevant to the control of indigenous diseases, specifically, research on the specifications, development and testing of new tools. Ensuring that there was adequate research capability in DECs to undertake such work was therefore a necessary task for carrying out the Programme's mission. It is the impression of the Committee that there has been a significant increase in the capacity of DECs to undertake research directed towards tropical disease control since the Programme was established. This includes developing strength in social and economic research capability in relation to the target diseases. The ERC's impression is based upon the quantity and quality of research publications and on familiarity over time with institutions in DECs. As the major provider of support for institution strengthening in tropical disease control research, the Special Programme deserves substantial credit for this improvement. In the coming decade there will be a continuing need for further strengthening of research capabilities in DECs, particularly in some geographic areas, e.g., Africa, where the original institutional base that could be fostered was more limited. The ERC emphasizes its view that research capability strengthening is an activity requiring long-term commitment.

While the TDR effort can and should be pursued through a global network, it is a sensible aim that DECs ultimately be self-reliant in the conduct of research and development activities -- from the laboratory to the field -- necessary to control their indigenous diseases; such self-reliance is essential in forming true partnerships. The Committee therefore stresses that research capability strengthening (towards the goal of tropical disease control) must be viewed as an essential, integral part of the TDR effort to develop new ways of controlling diseases that occur in the tropical zones. The ERC wishes also to emphasize its belief that, irrespective of the case that can be made for research capability strengthening in tropical diseases as a necessary part of TDR's role, broad strengthening of institutions in DECs towards self-reliance is a valid and useful developmental activity in its own right. However, institution strengthening in areas not closely related to TDR's mission and activities must be regarded as outside its responsibility.

3.4 The Scope of Research and Development Activities

3.4.1 Pursuit of Research and Development Activities

The development of control tools for the target diseases has been pursued within the Programme through Scientific Working Groups and Steering Committees largely organized around the target diseases. For some diseases, there now exist (or have existed) separate bodies for chemotherapy, immunology (mostly vaccine development), field research or epidemiology. Consolidation of Steering Committees in some areas (e.g., African trypanosomiasis, the leishmaniases, Chagas' disease) has occurred in the last few years. In addition, there exist (or have existed) what are termed 'trans-disease' Components. The Biomedical Sciences (BIOS) Component was disestablished in 1985 and the Epidemiology Component was moved from Programme Area II (Research and Development) to Programme Area III (Research Capability Strengthening) in 1987. Thus, Social and Economic Research and Biological Control of Vectors are the only trans-disease Components now under Programme Area II.

The R&D Components in operation in 1987 were:

Chemotherapy of Malaria
Immunology of Malaria
Applied Field Research in Malaria
Schistosomiasis
Filariasis
African Trypanosomiases
Chagas' Disease
The Leishmaniases
Immunology of Leprosy
Chemotherapy of Leprosy
Biological Control of Vectors
Social and Economic Research
Epidemiology

Scientific Working Groups (SWGs) are assigned the responsibility for planning, implementing and evaluating progress in research. Objectives, priorities and strategies are formulated into work plans for each area. SWGs are somewhat amorphous bodies, including all scientists involved in any aspect of the SWG's work. SWGs meet at irregular intervals to consider the overall programme in their area, or some facets of it, when it is considered necessary.

SWG work plans are in reality executed, and generally formulated, by the Steering Committees (SCs). The composition of SCs is more rigorously defined. The major activity of SCs has tended to be the review of proposals submitted for funding, but they have over time also assumed a number of the functions of SWGs. The ERC has some concerns about the operations of SWGs and SCs, which are discussed under Section 7.

In its deliberations the Committee found that the largely disease-specific orientation of the main operational entities, SCs, has some disadvantages as well as advantages. The main disadvantage of a disease-specific management structure is the tendency for groups to work in isolation. It is, of course, desirable that some groups have an overview of the entire spectrum, from basic research to field investigations, for each disease. However, there are commonalities between diseases in the research, development and field testing progression. Similar approaches -- e.g., molecular biology applied to the study of important parasite genes, drug screening, clinical trials and field work -- may be needed for different diseases. A management structure based on phases in the innovation process has certain obvious disadvantages, such as potential discontinuities. On balance, the ERC favours continuation of the present disease-oriented approach. However, the Committee felt it desirable that greater steps be taken to ensure communication among disease-specific Components in the R&D Programme Area. Experience gained in one Component should be shared more effectively. The Committee recognizes that some steps have already been taken by the new Director of TDR, e.g., Programme-wide seminars and coordinators for certain aspects of Programme activities, such as drug development. However, the ERC encourages consideration by the Secretariat of additional methods to enhance this communication. This issue could be considered in connection with the suggestion that it may be possible to achieve some economies of staffing in the R&D Area (see Section 7). One possible option is making staff members responsible for more than one Steering Committee. Decisions in this regard should take into account the likely evolution of the activities of various SCs over the next few years. If resources can be saved in Programme Area II, they should be directed to Programme Area III.

3.4.2 Content of the Research and Development Effort: The Target Diseases

The criteria used at the outset of the Programme for the selection of the target diseases were:

- public health impact;
- absence of satisfactory methods of control under circumstances prevailing in tropical endemic countries; and
- the existence of research leads towards improved methods of control.

At the Programme's inception there were many other diseases (e.g., diarrhoeal diseases, tuberculosis and other severe respiratory infections) with a significant public health impact in the tropics for which arguments could be made for increased attention. Another factor influencing the initial selection of diseases was undoubtedly the extent of research activity at that time in WHO on the candidate diseases. The number of diseases selected as targets was also influenced by the assessment that inclusion of too many diseases would have been unwise as it would have lessened the likely impact of a targeted programme which, to be successful, needed to have a manageable scope.

As noted in the *Eighth Programme Report*, there was insufficient epidemiological information available in 1976 to judge whether the leishmaniases presented a severe public health problem of comparable magnitude to the other diseases. The decisive argument for inclusion was the potential value of study of *Leishmania* infection in laboratory animals and cultured cells as a model for parasitism in general. However, by 1981 TDR-sponsored epidemiological investigations had shown the leishmaniases to have a major public health impact in large areas of the world.

A number of factors motivated the Programme's founders and the timing of their effort:

- the heavy health burden imposed by the diseases on affected countries;
- the declining attention to tropical diseases by governments and the pharmaceutical industry following World War II;
- the inefficiency of available tools and, in some cases, the decline in their usefulness owing to pathogen or vector resistance;
- the increase in disease incidence as a result of social development (schistosomiasis) or failure of eradication attempts (malaria); and
- the promise of emerging 'technologies' for application to tropical disease control.

The first External Review Committee concluded that broadening the number of diseases after only five years of Programme operations would result in an unwise dilution of funds available for each disease. Conversely, "reducing the number of diseases . . . would run counter to the need for long-term commitment and support" necessary for the Programme to bear fruit. The second External Review Committee was charged with re-examining this aspect of the scope of the Programme, now somewhat over a decade into its existence.

Since the Programme was established, there have been significant changes in the environment in which it exists and operates. In 1982 ERC(1) noted that the WHO Diarrhoeal Diseases Control Programme (CDD) had been significantly expanded in the late 1970s and early 1980s; this expansion has been consolidated, and the Committee is pleased to note that a highly effective mechanism is in place to pursue the necessary research and development, as well as control measures, for this group of important diseases.

Control and prevention of acute respiratory infections in children are covered by the WHO Acute Respiratory Infections Programme (ARI) and a vaccine development steering committee in the Microbiology and Immunology Support Unit (MIM) of the Division of Communicable Diseases. The US Agency for International Development provides support to the US National Academy of Sciences Board on Science and Technology for International Development for a research

programme in developing countries on acute respiratory infections in children. In the last decade, development of activities within WHO on acute respiratory infections has moved more slowly than was desirable. However, the ERC does not see that closer association of TDR and ARI efforts would assist either programme.

As far as the ERC was able to determine, relatively little activity is being devoted to research and development for better therapy or prevention of tuberculosis. Prevention through the use of the currently available BCG vaccine is promoted by the WHO Expanded Programme on Immunization. However, only limited research and development for new control tools is being pursued under the auspices of the WHO Tuberculosis Unit and a steering committee on tuberculosis immunology within MIM. Expansion of activity is desirable.

The ERC could conceive of benefits from combining leprosy and tuberculosis in that their research needs are moving progressively closer in terms of vaccines, chemotherapy and operational issues of control which involve long-term chemotherapy. However, any proposal of this sort raises major problems which would have to be considered in great detail before feasibility could be assessed.

Under the auspices of MIM, a programme of vaccine research and development was launched in 1984 for a number of diseases. This covers encapsulated bacteria (e.g., *Streptococcus pneumoniae*) and viral haemorrhagic fevers (Dengue and Japanese Encephalitis virus) and acute respiratory infections. This programme is complemented by one on applied vaccinology, which will develop needed tools applicable to the delivery of vaccines in general, including those of interest to TDR.

Among tropical, and particularly parasitic, diseases not at present well covered are infections caused by the intestinal protozoa (especially *Entamoeba* and *Giardia*) and the intestinal helminths (particularly the hookworms, *Ascaris* and *Strongyloides*, as well as *Trichuris* and some other species). The tapeworm zoonoses and the trematode infections other than schistosomiasis are also of importance, but are rather local in distribution. The intestinal protozoa fall technically into the province of the Diarrhoeal Diseases Control Programme (CDD), and, unlike most TDR target diseases, they are not vector-borne. The intestinal helminths fall outside the CDD Programme; they also are not vector-borne and some would argue that because drug treatment is available and the means of control by hygienic methods so well understood that major funding for a vaccine programme is less of a priority. The Committee believes, as described above, that the amount of attention presently being paid to tuberculosis is less than desirable. However, the Committee's position is that it is at present more important to utilize all increased funding to achieve TDR's goals for the present target diseases than it is to extend the Programme into additional diseases.

Finally, increasing implementation of the primary health care concept and attention to water and sanitation (e.g., in the International Drinking Water Supply and Sanitation Decade) should lead to better delivery of tools already available for the control of some parasitic diseases and prevention of water-borne infections. [There is a need, however, to ensure that resources devoted to these activities are adequate (see Section 8.1)].

Shifts in disease burden might influence decisions on which diseases should be covered within the Programme's mandate. Dramatic shifts, such as the increase in paralytic poliomyelitis that occurred in industrialized societies in the 1940s and 1950s, might argue for inclusion of a new disease. The ERC, after reviewing available information (albeit not precise), judged that there were not sufficient shifts in disease burden to justify adding any disease to the Programme. Conversely, the burden of the target diseases had not significantly lessened; hence, with regard to this criterion, no justification was found for dropping any of the target diseases from the Programme's mandate.

An apparently new human disease will, however, require attention by the Programme. Infection with the human immunodeficiency virus (HIV), the cause of acquired immune deficiency syndrome (AIDS), may well alter the presentation of tropical diseases or the best approach to their therapy, and infections with other pathogens may modify the natural history of HIV infection. Such interactions are already suspected for some of the TDR target diseases and this is therefore a legitimate area of expanded investigations by the Programme. The ERC is pleased to note that a meeting was held in Nairobi, Kenya, in December 1987, under the joint auspices of TDR and the WHO Global Programme on AIDS, to assess the status of knowledge of interactions between HIV infection and tropical diseases. Protocols for investigation of potential interactions were developed and priorities identified. Procedures have been agreed upon for the funding of high-ranking proposals. Exploration of interactions between HIV infection and tropical diseases and means for their amelioration should be pursued in the future through such collaborative efforts.

The Committee also considered whether progress towards control (or in the development of control tools) for any of the target diseases was such that there was diminished reason for its continued inclusion in the Programme. Notwithstanding significant progress towards control tools for all of the target diseases, and in some cases the availability of useful agents (usually drugs), there are still important contributions outlined in the previous section that the Programme could make to all target diseases. The range of drugs, vaccines, diagnostics or other control tools is not sufficiently deep or broad for any disease. It is thus the conclusion of the ERC that although progress has been significant, it is not yet time to drop work on control tools for any target disease on these grounds. The conclusion was that each should be maintained, for the following reasons:

TDR funding for work on filariasis and the trypanosomiases forms a substantial part of that available for research on these subjects. TDR support is involved in a substantial proportion of publications on these two diseases (Annex IV). Each comprises two rather separate disease groups: Filariasis comprises onchocerciasis [the Onchocerciasis Control Programme in West Africa (OCP) has also been funding some work] and lymphatic filariasis. In the latter case, TDR has been responsible for extracting this important disease and growing problem from great apathy. Progress is good. In work on the trypanosomiases, TDR plays a basic funding role, especially in areas endemic for African trypanosomiases, and has catalysed the creation of a unique network of researchers working on Chagas' disease in endemic countries in Latin America. The role of TDR is crucial in relation to these two diseases.

In the case of leprosy and malaria, TDR has played a crucial innovative and coordinating role, and progress in both subjects is moving rapidly. It would be foolish for TDR to withdraw its support of these subjects in the middle of important advances, especially on the vaccine front. Both diseases continue to be major problems -- malaria having the greatest impact of all parasitic diseases -- and to require all the funds that can be made available.

In the case of schistosomiasis and the leishmaniases, both also comprise large public health problems and progress is rapid in each case. Alternative funding for the leishmaniases is hard to obtain from other sources, and the productivity of the funds invested in the Programme is high (especially in terms of publications relative to funding). In the case of schistosomiasis, where much progress in chemotherapy has already taken place and the rate of progress in immunology and vaccine research is great, alternative major sources of funding are decreasing; the disease, however, remains highly prevalent and is increasing in areas of water-resource development.

On the basis of the considerations discussed above, no case was found to cease or significantly decrease funding of work on any of the present target diseases. The gains from redistribution to any recipient Component would not equal the damage done to an abandoned target disease.

The ERC considered under what circumstances additions of other tropical diseases to the Programme's portfolio might be envisioned. It judged that the original criteria for selection of target disease were still valid, but that if any disease met the initial criteria, additional ones would then come into play. The additional issues which might influence the decision would be:

- whether the addition(s) would entail the establishment of new administrative structures (SWGs, SCs and staff) that might dilute available funding;
- the potential benefit of addressing the new disease(s) versus expanding activities on an existing target disease;
- whether the addition would be likely to attract additional funds to the Programme;
- the extent to which new funds could be usefully employed to expand efforts on current target diseases, i.e., are good proposals not being funded?

To ascertain whether the present target disease SCs could productively expand their activities, the ERC examined the proportion of applications funded in each Component and a selection of proposals from each Component that had not been funded, although considered meritorious by Steering Committee Secretaries. The ERC notes, however, that the realism of applicants tends to reduce items in this category as research workers will not direct proposals to places where they are not likely to be funded.

The extent to which meritorious proposals will go unfunded depends somewhat on efforts by the Secretariat to solicit applications to the Programme. The present proportion of R&D applications funded (approximately 60 per cent with relatively little difference between SCs) is considered by the ERC to be relatively high but must be viewed in the light of efforts to encourage applications. The ERC understands that such efforts decreased in the early to mid-1980s when the Programme was experiencing financial difficulties. The Committee believes that a prominent feature of the overall effort at targeted research should be Secretariat activity to encourage proposals in line with work plans. Thus, it recommends that Steering Committee Secretaries and members resume more active encouragement of applications based on SC work plans.

3.4.3 Conclusions on the Target Diseases

3.4.3.1 The Target Diseases

After reviewing currently available information on disease incidence and prevalence, the Committee concluded that the TDR target diseases are still in the first rank of importance in developing endemic countries.

Any question of the Programme expanding into new areas would be entirely contingent upon the availability of extra funding. The present needs of the Programme are substantial, and the ERC elsewhere recommends substantial expansion in three areas: field studies (which are very expensive), rational drug development, and social and economic research.

Other important diseases requiring R&D for better control tools are by and large being effectively addressed by other divisions of WHO or other groups. In this connection, we would judge respiratory infections, diarrhoeal diseases and AIDS as clearly overwhelmingly large problem areas and rightly the subject of separate programmes.

The Committee therefore recommends no change in the diseases included in the Programme at this time. The work proposed on the present target diseases already necessitates substantially increased expenditures. This work can be pursued and productively expanded without adding a new supporting infrastructure and should have priority over research on additional target diseases for the next five years.

3.4.3.2 Balance of Funding among the Disease-specific Components

The ERC reviewed the recent trends in funding within the disease-specific Components of Programme Area II. It noted that changes had taken place both as a result of Secretariat suggestions and of STAC recommendations. In the course of its review of specific R&D Components (see especially Section 3.6), the ERC identified many topics or areas which deserve additional funding. However, the Committee does not feel it has a sufficiently strong basis to make quantitative recommendations for the reallocation of resources between R&D Components or for the selective targeting of future resources. The ERC believes that the present process of Secretariat/STAC budget development has been reasonably responsive to needs and opportunities. Therefore, the ERC suggests that its comments regarding funding for specific areas be evaluated within these general procedures.

3.5 The Time Frame for TDR Activities

The ERC was directed by its terms of reference to pay particular attention to the time frame which should be envisaged for the Programme in the light of progress, needs and prospects. To understand the necessary time frame, the development process for disease control tools must first be reviewed. This process has a number of phases:

- identification of the etiological agent of the disease;
- improving understanding of the epidemiology and natural history/pathogenesis of the disease;
- conceptualisation of control tools;
- development of prototypes;
- laboratory and/or clinical testing;
- field testing for utility and optimal approaches for introduction in target setting; and
- application refinement

While these phases may overlap to some extent, the sequence is generally that listed above. The length of time necessary to complete each phase may vary considerably; progress in research and development is not always directly proportional to expenditure. Not all leads will prove successful. For example, understanding the surface structure or metabolism of the pathogen, often necessary to formulate strategies for disease control tools, may be stalled until new techniques are developed.

In the opinion of the Committee and those experienced in pharmaceutical development, the full sequence of phases listed above typically requires 15 to 30 years. The more targeted, later development phases often alone require 10 to 15 years for any one product. Additionally, the development processes for different control tools for the same disease do not necessarily coincide in time. For example, the conceptual basis for vaccine prevention of schistosomiasis only recently emerged, a number of years after drugs were available.

At the outset of TDR activities, knowledge of the six diseases varied as did the apparent prospects for new disease control agents. Progress has been made towards better control tools for all of the TDR target diseases, but there remains much of importance to be done where the Programme could contribute significantly. For example, for some diseases work towards vaccines is in its earliest stages.

The Committee recognizes that developments in disease control may ultimately be such that the need for the Programme, in some disease areas, hopefully all, may be markedly reduced. At that time, the incremental benefits of alternative investments will need to be assessed. However, even very significant laboratory discoveries are often applied, adopted and adapted slowly. Consideration of dismantling TDR is therefore clearly premature. The Committee concludes that the Programme is clearly needed for at least another ten years. The need for continuation should be reviewed at that time.

3.6 The Need for Evolution of Programme Activities

3.6.1 Field Studies

The sequence of stages in the development process for disease control tools can roughly be grouped as (1) targeted basic research, (2) early 'prototype' development and (3) 'utility' testing, including both research on efficacy and strategies for application in actual control situations. The first two phases are predominantly laboratory-based, while the third is conducted predominantly in the field.

At the outset of the Programme, for almost all the target diseases, there were few potential control agents in the pipeline and very few agents were available for testing. The main focus of early TDR R&D activities was to generate, through laboratory research, insights from which prototype control agents could be developed. This was done to a considerable extent by recruiting investigators involved in the forefront of advances in basic biomedical science disciplines to tropical disease research. Often these workers were in laboratories in industrialized countries. A considerable effort was also made via research capability strengthening to promote this laboratory-based type of activity in DECs.

Attempts to develop research capability in field work have been much less successful because of fundamental problems with career structures and other difficulties.

As discussed in Section 4, the Programme has contributed significantly to the present situation in which there are good prospects for many candidate diagnostics, drugs and vaccines which will require utility testing over the next few years. In the coming decade, it will be necessary for the Programme to devote more of its resources to 'field' activities in developing endemic countries, in both the R&D and RCS Programme Areas. Some principles to guide these activities are discussed in Section 8. This recommendation for a shift to place greater emphasis on field activities should be regarded as a natural part of the development of the Programme; however, it will not be an easy process. Such research is perceived as lacking elegance, scientific status, financial reward and personal comfort. Yet this is the crucial step, without which the rest of TDR remains academic.

Support for field studies undertaken by the disease-specific Components will need to be provided by the Epidemiology Component, now part of Programme Area III. The ERC stresses the importance of this need and is pleased that steps have recently been taken to increase the capacity of the Epidemiology Component to meet this need, namely inclusion of members of the Epidemiology SC on disease-specific SCs and the provision of a second staff member in Epidemiology. The latter action especially should allow for the needed expansion of epidemiological activities within the overall Programme.

The greater level of field activity will necessitate some changes in the composition of disease-specific Steering Committees. Historically, the membership of disease-specific SCs has most commonly reflected their usual previous focus on laboratory-based biomedical research. Because most centres of strength in this area were in industrialized countries,

members were mostly from such countries. The composition of disease-specific SCs will need to shift to include greater representation of disciplines relevant to the conduct of field studies. The ERC commends this issue to SC Secretaries and Director, TDR, as SC members are periodically reappointed. Director, TDR, should also bear in mind the likely expansion of field activities when considering future staff appointments.

3.6.2 Rational Drug Development

In the last decade progress in scientific understanding of the physiology of the target pathogens has been considerable. Similarly, techniques for producing and studying the structure of proteins (e.g., enzymes) essential to the life cycles of target pathogens have improved substantially. Such proteins are potential targets for drugs as many have no counterpart in the human host (permitting selective action on the pathogen). Exploiting such knowledge and capabilities in a systematic fashion -- the process becoming known as rational drug development -- is an area of great promise for the next decade. TDR is particularly well placed to promote rational drug design for its target pathogens. Unfortunately, rational drug design for tropical disease control is not likely to be high among the priorities of pharmaceutical companies because applications of the techniques to other diseases, more common in industrialized countries, are likely to be more commercially attractive. Thus rational drug development for TDR target diseases is an area where the Programme should seriously consider playing a catalytic role, in addition to pursuing drugs through more traditional 'screening' strategies.

3.6.3 Policy Implications of Health Economics

The ERC also wishes to raise the possibility of the Programme ameliorating a problem discussed more fully in Section 8. Regrettably, the resources devoted to tropical disease control in DECs are less than necessary or desirable. The new disease control tools likely to emerge from TDR activities in the next decade may be underutilized if this situation continues. Expansion of SER SC support for studies on (and training to investigate) the true household, community and financial burden of the target diseases may contribute to raising political awareness of tropical diseases and mobilizing the necessary resources for dealing with them. Such an expanded role in health economics and development policy should be given serious consideration.

3.6.4 General Remarks

These areas of needed Programme evolution are additional to the need for greater integration of the R&D and RCS Programme Areas and for expansion of SER activities, which are discussed elsewhere in this report. Pursuit of these efforts should not be at the expense of biomedical research and development since a strong base will continue to be needed to underpin the development of new disease control tools.

4. Accomplishments of the Special Programme, Status of Progress towards Control of the Target Diseases and Future Directions

The first External Review Committee recommended that the second such review include assessment of the scientific accomplishments of the Programme. Accordingly, this task was included in the terms of reference of the second External Review Committee.

This section addresses this aspect of the Committee's mandate; the broader contributions of the Programme are addressed first, then the accomplishments and directions in special areas are discussed. [Because of the significance of social and economic research, the Committee chose to devote a separate section to it (Section 5).]

An assessment of the contributions of the Programme towards control of the target diseases entails much more than a review of the scientific results and productivity of funded research. It requires: a full understanding of the role which the Programme set out to assume and the approaches by which it chose to pursue that role; an attempt to develop criteria for assessing difficult questions (such as research quality); and a judicious effort to apportion relative merit in situations where achievements have resulted from interactive and collaborative efforts.

4.1 The Programme's Approaches

At the time of the Programme's establishment, research on tropical disease control tools was at a low ebb. However, it was never envisaged that the Programme would be the major funder of such research. A number of strategic choices were made early in the Programme's existence: (1) to aim for a catalytic, facilitating role, rather than operating in isolation; (2) to institute direction of the Programme by scientists through Scientific Working Groups, Steering Committees and peer review; (3) to promote 'networks' of scientists involved in research on particular diseases; (4) to strengthen existing national institutions in developing endemic countries (rather than to create 'free-standing' tropical disease centres); and (5) to use training as the other main approach in research capability strengthening.

The first External Review Committee endorsed these choices and the second External Review Committee concurs with that endorsement. As practical approaches, the choices have stood the test of time and have led to recognition of the Programme as an indispensable part of the global effort in research and development for tropical disease control (as discussed below).

4.2 Breadth of Programme Contributions to Tropical Disease Control Research and Development

In addition to the scientific results of research studies and the contributions to development of specific disease control tools, the beneficial impact of the Programme is multifaceted:

- It has raised awareness of research and development needs among scientists and philanthropic foundations and, to an increasing degree, policy makers and industry. New foundations have launched major efforts on tropical diseases, and by commitment to institution strengthening, many governments in developing endemic countries have signalled their recognition of the importance of the target diseases. The European Economic Community has launched a major programme of funding in tropical diseases. The increased awareness and activity has been manifest not only among traditional contributors to the Programme but in a much broader community. The ERC believes that TDR can claim at least some credit for these positive developments.

- By stimulating this attention and providing opportunities for training, the Programme has encouraged and enabled a new generation of young investigators to embark upon careers in tropical disease research.

- TDR has provided a model for the management of targeted research by scientists, showing that such a system can operate in an objective and effective manner.

- The Programme has provided a source of funds for certain important (but previously underfunded) groups of investigators (e.g., those in developing endemic countries or those trained in social and economic research) to pursue significant work on tropical diseases. Additionally, it has provided a focus for peer support and intellectual crossfertilization in these communities.

- Through its Scientific Working Groups and Steering Committees, TDR has drawn together disparate investigators (both geographically and scientifically isolated) into actively communicating and collaborating collegial networks on the target diseases.

- TDR has recruited scientists from the forefront of other rapidly advancing disciplines (such as immunology and molecular biology) to work on tropical disease research. This has been noteworthy in malaria, trypanosomiasis, schistosomiasis and mycobacterial genetics.

- The Programme has recently proven to be exceptionally effective at collaborating with pharmaceutical companies and stimulating their increased involvement in R&D efforts on tools for tropical disease control, such as drugs and vaccines.

- By no means least, TDR has developed clear, effective criteria and strategies whereby institutional and general research capability strengthening could be pursued by others.

The ERC concluded that the Programme now plays a key leadership role in R&D efforts on tropical diseases by convening the major funders of tropical disease research and other participants, providing a forum for setting strategies and priorities, and facilitating international collaboration. (The fact that other groups with traditional roles in tropical disease research, e.g., the Rockefeller Foundation, wish to undertake joint ventures with TDR attests to its influence.)

An attempt was made in the course of the external review to estimate the level of funding devoted by industrialized countries (including the private commercial sector within these countries) to research and development for control of the TDR target diseases. The estimate, very crude and subject to considerable sources of omission and error, is US $100-120 million annually. This figure is somewhat greater than the estimate made by the first External Review Committee. TDR funding (totalling approximately US $25 million per year) thus comprises about 25 per cent of expenditures by industrialized countries; this percentage is smaller if one counts only TDR funds allocated to R&D (about two thirds of the total budget).

TDR's ability to play a catalytic, leadership role is partly due to the fact that WHO is the Executing Agency of the Programme; this facilitates *inter alia* working with governments. Another essential factor is its ability to fund important research. The formulation of the Programme as an extrabudgetary entity operating under WHO's 'wing' provides a unique capacity to deal with governments, institutions and individuals in a fashion relatively free of bureaucracy.

The Programme's goals can only effectively be pursued by a group that can maintain a truly global perspective and promote linkages irrespective of regional boundaries. The ERC therefore believes that decentralization or regionalization of the Programme's central strategy-setting and administrative responsibilities would be damaging.

Often the needed work will be of an exploratory or 'gap-filling' nature. Only a group like TDR can monitor what is happening globally in order to identify strategically essential work. The inclination of other funders of tropical disease research to participate in strategic planning with the Programme would be greatly diminished if TDR were not also a significant financial supporter of work in the pertinent areas. Another key element enhancing acceptance of the Programme's leadership role is that it is 'managed' (through its Steering Committees) by recognized experts in the relevant disciplines.

The quality of the funded research and the usefulness of other TDR activities (described in detail below) in relation to the strategic plans are derived greatly from goal-setting and scientific peer review. The process entails considerable consultation and discussion among experts, but these are essential to the chosen operating mode. Resources devoted to these activities should be regarded as necessary Programme expenses. They are in large part responsible for the influence and acceptance that the Programme has achieved.

In summary, the Committee concluded that the Programme has made major 'organizational' and morale-boosting contributions to the advancement of research and development for new and better tropical disease control tools as well as to purely scientific results. It has developed and demonstrated strategies by which targeted research capability strengthening can be pursued. By increasing attention to tropical disease control R&D and by providing leadership and cohesion in these efforts, it has become an irreplaceable part of the picture.

4.2.1 Malaria

The activities of the three Steering Committees in the Malaria Component, described below, exemplify the role that TDR can play by coordinating research and development on a transnational scale, a challenge that other entities are less likely and less able to tackle.

Over the last five years there has been a large increase in the number of publications dealing with malaria (Annex IV). From a level of about 375 publications a year between the years 1975 and 1980, the number rose to about 750 in 1985. The rise started in the late 1970s just after TDR's establishment. Publications resulting from TDR-supported projects constitute a moderate share of total publications on malaria (approximately 25 per cent in the last years for which figures are complete).

It is apparent that there has been a renewed interest worldwide in research on malaria. A combination of factors may be responsible. In addition to TDR, other research-sponsoring organizations, such as the US Agency for International Development (USAID) and the Rockefeller Foundation, have given priority to such research. Furthermore, it is likely that rapid developments in molecular biology and immunology issuing from the advent of new technology, such as monoclonal antibodies and recombinant DNA and other techniques, have stimulated researchers to work on malaria parasites. It is unquestionably an intellectual challenge to study the molecular biology and biochemistry of the various stages of the malaria parasite life cycle and to develop vaccines against them.

The role of TDR in these developments is difficult to assess accurately. It may be deduced from the pattern of publications over the last ten years that TDR may have played a significant role in stimulating research on malaria. Thus, between the years 1979 and 1982 publications from TDR-supported projects represented 20 to 30 per cent of total publications. After 1982, the number of publications stemming from TDR-supported projects remained the same, whereas the total number of publications increased substantially.

4.2.1.1 Chemotherapy of Malaria

TDR has certainly played an important role in the development and testing of antimalarial drugs. Much of this work has been done in collaboration with other organizations and with the

pharmaceutical industry. In this connection, it is important to stress the fact that TDR, by being a member of the WHO family, has considerably better possibilities than other research-sponsoring agencies to overcome difficulties which may arise in connection with studies to be conducted in developing countries. The ERC wishes to emphasize that TDR's ability and willingness to cooperate with other agencies and the pharmaceutical industry in efforts to attain the Programme's goals are highly commendable.

Over the last ten years, the SC on the Chemotherapy of Malaria (CHEMAL) has supported, with a total sum of about US $13 million by the end of 1986, a number of projects on basic biochemistry and pharmacology, development of diagnostic tools, development of drugs and drug screens, and clinical trials of drugs. The drug trials conducted under the auspices of CHEMAL seem to the ERC to have been particularly important contributions. Together with the Walter Reed Army Institute of Research (WRAIR) and different pharmaceutical companies, TDR has carried out extensive clinical trials using mefloquine, mefloquine in combination with other drugs, and halofantrine. The results of these studies have provided basic information needed for the use of these drugs in malaria control programmes. TDR has been involved since 1979 in the isolation of compounds with antimalarial activity from the herb *Artemisia annua*. In recent years, various derivatives of the compound artemisinin have been prepared and are being tested. There seem to be good reasons to expect these compounds to become important tools in malaria treatment. With TDR support, a large number of compounds -- more than 2000 -- have been screened for antimalarial activity.

An important aspect of drug trials deals with the availability of methods to measure drug levels in body fluids. TDR has put considerable effort into developing suitable methods for this purpose. Tests have been devised utilizing modern techniques such as high-performance liquid chromatography and enzyme-linked immunosorbent assay. In drug trials it is also important to be able to test parasite sensitivity to various drugs in the field. TDR has developed several such tests.

In the longer perspective, detailed knowledge of parasite biochemistry is a prerequisite for advances in drug development and drug design. The CHEMAL SC gives high priority to such studies. Examples include work on metabolic pathways to detect parasite-specific enzymes and on mechanisms used to transport various compounds, including drugs, into cells. It should be mentioned that extensive additional work on parasite biochemistry is going on outside TDR.

In summary, the work conducted under the CHEMAL SC has been both important and successful, not least that involving the development and testing of drugs. Importantly, in the planning and execution of malaria drug trials TDR filled an initial gap in the existing global efforts aimed at developing chemotherapy for this major disease.

4.2.1.2 Immunology of Malaria

The work conducted under the SC on the Immunology of Malaria (IMMAL) may be considered in three parts: research directly related to vaccine production; immunodiagnostics; and the biology of the malaria parasite.

Vaccine Research

The multistage development of the malaria parasite, which confronts the host with stage-specific antigenic components, makes the vaccine problem difficult. Although many antigens are present, only a small fraction are likely to evoke a protective response. The strategy is therefore based on identifying and characterizing the antigens which stimulate a protective immune response and on employing vaccine techniques based on contemporary biotechnology.

In principle, three types of vaccines may be developed: a sporozoite vaccine, which is likely to be prophylactic and prevent infection; an asexual blood-stage vaccine, which will

reduce the severity of clinical manifestations without necessarily eliminating parasitaemia; and a gamete vaccine, which will not protect vaccinated individuals but will block transmission via the mosquito. Progress has been made in identifying antigens that might be useful for the three types of vaccine.

Sporozoite antigens: Impressive work has been done with the circumsporozoite (CS) protein, a major surface protein of the sporozoite. The antigen has been identified in a number of plasmodial species (*Plasmodium berghei, P. knowlesi, P. falciparum, P. vivax* and *P. cynomolgi)*, and the genes for the CS protein have been cloned. The immunodominant epitopes in the CS molecule consist of short sequences of amino acids which are repeated. The exact epitope sequence varies with plasmodial species (nine amino acids in *P. vivax* and two chains of four in *P. falciparum)* and between strains in some species (e.g., *P. cynomolgi* and *P. knowlesi*).

Antibodies recognizing the CS protein inhibit sporozoite invasion and entry into hepatocytes. The tandem-repeat sequence code for the 12 amino acid epitope of *P. knowlesi* has been inserted into vaccinia virus. Rabbits immunized with this virus produce antibodies reacting with the sporozoite surface. The repeat sequences of *P. falciparum* have also been used for immunization studies.

Some past TDR reports have given the impression that development of a sporozoite vaccine is very close. In the light of recent studies, the ERC feels that it will be at least five years, possibly more, before a sporozoite vaccine could be widely available. Indeed, it is not yet certain that this approach will be successful or precisely what is needed to make a useful vaccine of this type. More basic research, including other approaches described below, will be needed.

Blood-stage antigens: The blood stage of the malaria parasite is a complex stage. Some antigens occur largely intact in association with host-cell components on the cell surface. Others undergo processing during the cycle and yield lower molecular-weight products. Antigenic variation has been observed in this parasite stage. Identification of protective antigenic components, therefore, presents a long-term problem. Research supported by TDR has led to the identification of a number of antigens which might be useful.

Schizont antigens: A high-molecular-weight antigen is present in several species. In rodents, antibodies against this antigen confer protection. Lower molecular-weight fragments of the antigen are produced during schizont rupture. Analogous molecules in different species, synthesized by the mature parasite, share common features; they are glycoproteins in most but not all species. In *P. falciparum*, this antigen contains strain-specific epitopes. Another schizont-specific antigen is synthesized by trophozoites and confers protection.

Merozoite antigens: These include antigens which are involved in the penetration of erythrocytes. The receptor for merozoite attachment is glycophorin (a major surface membrane glycoprotein). Merozoite proteins binding to glycophorin are transferred to erythrocytes. Antibodies against one such molecule block invasion *in vitro*. The S-antigen (a heat-stable antigen of *P. falciparum*) has been extensively studied. A monoclonal antibody to the S-antigen blocks merozoite invasion.

Erythrocyte surface antigens: Cells infected with *P. falciparum* develop sites for attachment to capillary endothelial cells, leading to removal of erythrocytes from circulation (knob formation and sequestration). In cerebral malaria, such erythrocytes block the vessels. Knob production is associated with a histidine-rich protein (HRP). The HRP-related gene contains a highly repetitive DNA sequence; its transcription products have been identified. Antigenic variation of the erthrocyte surface in *P. falciparum* is being actively studied. Research on blood-stage antigens is rapidly advancing and in the long range

will prove extremely useful. No immediate prospects of vaccines developed through this approach have been identified. However, the ERC believes that continued work in this area should be considered because the possibilities are well grounded.

Sexual-stage parasite: Antibodies against gametes occur in patients infected with *P. vivax*. These antibodies block transmission of the parasite to the mosquito. Monoclonal antibodies against identified surface antigens on the gametocyte prevent fertilization in *P. gallinaceum*. Antibodies against zygotic surface antigens in *P. yoelii* prevent the development of the ookinete. Methods for stimulating gametocyte production *in vitro* in *P. falciparum* have been developed and target antigens have been identified. Transmission-blocking antigens of *P. vivax* are being studied. The ERC feels that work on transmission-blocking vaccines is potentially very useful and should be continued, recognizing that it will not yield benefits in the near future.

Immunodiagnosis

A second major objective of IMMAL is the production of diagnostic tools for malaria. Some work has been done on the detection of parasites in blood using immunological assays. These tests have not yet improved over conventional tests and are not ready for widespread use.

Greater success has been achieved with immunological tests to detect the parasite in mosquitos. In the Zavala test, monoclonal antibody to the CS protein is used to detect sporozoites in infected mosquitos. The test is highly sensitive and species-specific.

Yet another approach to diagnosis of malaria is DNA hybridization. Thus, cloned repetitive DNA has been used as a probe to detect *P. falciparum* and *P. vivax* infections. However, this test is still less sensitive than others presently available, but prospects for improving it now appear to be good.

So far there is no practical test for protective immunity to malaria. Several lines of research are in progress to develop such tests.

IMMAL has established a registry for monoclonal antibodies to malaria antigens to collect monoclonal antibodies against blood-stage antigens. These are being evaluated as potential immunodiagnostic reagents.

Progress in the development of immunodiagnostic tests appears overall to have been slower than expected. Attention needs to be paid to this problem by the IMMAL SC in the light of the urgent need for such methods for field research, e.g., in the forthcoming conduct of vaccine trials.

Basic Research on the Immunology and Biology of the Malaria Parasite

Some 40 per cent of the research work carried out under IMMAL involves basic research on the malaria parasite and has produced useful and important results. Successful development of methods for *in vitro* cultivation of different parasite stages has been extremely important for rapid advances in the study of malaria parasite antigens and the protective properties of corresponding antibodies.

Two areas where basic research is still at an early stage are cell-mediated immunity against malaria and factors involved in the killing of the parasite (reactive oxygen intermediate; tumour necrosis factor). Glomerulonephritis and anaemia in malaria infections are very likely antibody-mediated, and cell-mediated immunity may be important in cerebral malaria. Research on these and other problems related to the biology of the malaria parasite and its immunopathology will need to be vigorously supported by TDR.

The distribution of support in the three areas discussed above (going by the titles of the supported projects and published work) is roughly speaking: work on antigens (55 per cent); immunodiagnosis (5 per cent); and basic research (40 per cent). The IMMAL SC should periodically review whether this relative emphasis should continue or be modified.

Quality of Funded Research

Judging from the quality of published research supported by IMMAL, the selection of projects has been guided primarily by the scientific merits of the projects. The ERC believes that some of the best malaria research in the world has received support from TDR.

Geographic Distribution of Research Projects

The geographic distribution of funded IMMAL research projects was reviewed: most projects are concentrated in relatively few countries. No doubt this is a reflection of the present distribution of research capability in the world, but attention needs to be paid to encouraging applications from centres of growing research strength in DECs.

4.2.1.3 Applied Field Research in Malaria

The achievements of the SC on Applied Field Research in Malaria (FIELDMAL) to date should be measured in terms of their effect on applied malaria research as a whole rather than in terms of specific discoveries, though these are also important and diverse.

Ten years ago the need for rigorous adherence to a set plan, which was required for the execution of attempts at malaria eradication, had led to a decline in and often a disapproval of research so that the atmosphere in national control programmes combined a rigidity of mind with a demoralization resulting from the gradual collapse of malaria eradication (except in those countries where it had been successful -- and they lost interest in malaria for other reasons!). Only the military needs of some nations kept malaria research active, and that did not include field research directed at the problems of those living in areas of rapidly spreading endemicity. Young research workers had not entered malariology, anticipating that it would provide no career.

FIELDMAL thus began in a scene of immense need, with almost no other provision of resources or interest in the subject. Nor were any new tools for malaria control near to being available, so that the stimulus of basic scientific advances was absent at that time and research workers were not to be found. Nor was there a pool of expertise (unlike in vaccine development and chemotherapy) that might be diverted from other diseases, and epidemiologists were scarce in any area.

FIELDMAL first addressed the problem of spreading chloroquine resistance in *P. falciparum*. The SC was responsible for developing the *in vitro* test for chloroquine resistance, taking it from a complex assay that was difficult to interpret and developing it into a simple, standardized test kit available for use in the field. The resulting increase in reliable knowledge of the extent and spread of chloroquine resistance has been of major importance. Other important studies have clarified the operational significance of drug resistance and have extended field testing for resistance to other antimalarial drugs, including the newly introduced mefloquine. This shows a welcome shift to pre-emptive activity in relation to drug resistance.

The other major form of resistance impeding malaria control, insecticide resistance, has also been the subject of several studies of direct local applicability and wider relevance on strategies to reduce insecticide use but to achieve equal protection. FIELDMAL has supported the evaluation of impregnated bednets, a matter of great topical interest and potential importance, and revived the use of larvivorous fish in Somalia. FIELDMAL has funded work that

has differentiated species complexes in several areas of Africa and Asia. This is not yet of direct application to control but may well prove to be highly relevant.

In the last few years FIELDMAL has utilized monoclonal antibodies to define antigens of *Plasmodium* in human populations of Papua New Guinea. This is giving a much more detailed analysis of parasite-host interactions of epidemiological importance for the planning and evaluation of future vaccine trials. The Committee foresees a great increase in work of this type, where new reagents and probes to detect parasites are evaluated in the field for their epidemiological utility.

Although it does not have the funds to bear the whole cost of major community-based studies, FIELDMAL has recently supported population-based chemotherapeutic interventions aimed at reducing malaria morbidity and mortality. The ERC considered the results obtained in Kenya and in Guatemala important in themselves as examples of better control at lower costs and also as the types of population-based work that will be essential on a larger scale in the future.

The FIELDMAL Steering Committee has been limited in its activities by the shortage of epidemiologists and by the poor quality of applications. The rejection rate of research proposals has been higher than in some subject areas and standards have not been lowered. Because the scientific community is aware of the likely limitations to the size of grants from TDR, proposals for very large or complex population studies are usually not submitted to FIELDMAL.

The scarcity of good epidemiological proposals is a recurrent theme of the disease-specific Steering Committees and a major problem for the FIELDMAL and Epidemiology Steering Committees. This results from a combination of factors: the low scientific status and lack of personal comfort entailed in field epidemiology and control; the degree to which field work is contingent upon local political and economic events; and the fact that field study (unlike laboratory work) lies between university and government.

Overall, FIELDMAL has succeeded in restoring field studies of malaria to scientific respectability; able, young investigators are now entering this research area and a period of major projects is due to begin.

Because of its early work arising from operational control programmes, FIELDMAL has had closer contact with ministries of health and weaker ties with universities than other Steering Committees. This will need attention, and support to bring these two types of organization into closer contact with each other (and with specialized institutes), as is happening in Colombia, is strongly recommended.

The ERC strongly supports the closer interaction being achieved between the Steering Committees of the Malaria Component of the Programme and between TDR and the WHO Malaria Action Programme. The two Programmes are complementary and it is good to see that this is now fully recognized.

4.2.2 Schistosomiasis

During the past ten years, there have been several major advances (in some of which TDR has played a part) in knowledge of the schistosome, drug therapy and new approaches to prevention. These include:

- The demonstration in 1979, following a series of clinical trials, that praziquantel is an effective drug (with no significant side-effects) that is curative in a single dose for all forms of schistosomiasis. The drug is therefore suitable for large—scale control programmes. (The ERC recognizes that TDR had no involvement in the development of praziquantel).

- Production of monoclonal antibodies specific to schistosome surface antigens.

- Isolation of several genes coding for schistosomal surface antigens using recombinant DNA technology.

- The discovery in rats and humans of antibodies, particularly IgM antibodies, capable of blocking the host protective immune response to schistosome infection.

- The report of the successful use in animals of an anti-idiotype antibody vaccine.

- The report from Brazil of the dramatic reduction of hepatosplenic schistosomiasis through a very extensive control programme involving the widespread use of molluscicides and antischistosomal drugs in some areas.

During the past two years particularly, there has been a considerable increase in the rate at which several surface antigens of the schistosome and the schistosome egg have been cloned and characterized, and it is clear that work on the molecular biology of the parasite is progressing rapidly, particularly due to the introduction of monoclonal antibody and recombinant DNA technology. In parallel, the remarkable success of praziquantel and related drugs has made curative therapy a reality. However, there is still a need for more effective molluscicides, as the available molluscicides are not ideal in all respects. Overall, the success of the last ten years, in particular the last five years, is impressive, and it seems clear that continued support will lead to several major advances in understanding of the immunopathogenesis of schistosomiasis and in corresponding new ways of controlling the infection, while advances in the development and use of molluscicides should permit control of the parasite.

A consideration of the state of the art of schistosomiasis research reveals several areas which seem to be ripe for intensive study at the present time:

- In immunopathogenesis it is important to know whether immunity to the schistosome is mediated by IgA or IgE antibody, or whether it is exclusively cell-mediated. Techniques are now available to permit an experimental approach to this question in animal models. It is also desirable to know which antibody is most protective and whether IgM antibody actually blocks immunity mediated by other antibodies or by cellular mechanisms. The target antigen(s) of protective antibodies and protective T-cell clones need to be elucidated.

- The feasibility of using subunit or peptide vaccines (composed of the critical antigens that stimulate protective immunity) to induce only cell-mediated immunity -- and thereby heighten protection -- needs investigation.

Many of the above questions are directed at the long-term development of a simple, cheap and easy-to-use peptide or protein subunit vaccine which could be administered inexpensively in large-scale programmmes and which would confer a reasonable degree of protective immunity.

- In chemotherapy it must be recognized that while praziquantel is an excellent drug, its price is still too high to permit large-scale use in many developing countries. In addition, the potential for drug resistance developing in the near future necessitates the continued search for effective curative drugs with the same efficacy as praziquantel, but with lower cost and a different mechanism of action.

- Although a number of molluscicides are available which permit some degree of snail control, there is a need to develop cheaper and more effective molluscicides. They might well be used in a focal manner to maintain reduction in transmission in communities where the worm burden has been reduced by chemotherapy.

These considerations led the Committee to a number of conclusions with respect to work on schistosomiasis:

- The Programme should consider ways to facilitate, encourage and support the continued search for new curative drugs against schistosomiasis.
- TDR should also continue to support and encourage the search for new and better molluscicides.
- The possibility of major TDR involvement in global efforts directed towards a vaccine should be seriously considered.

Important specific activities to which additional funds could be devoted include:

- Analysis of the molecular biology of the schistosome, its surface antigens and membrane proteins, and their structure and immunogenicity.
- Analysis of the molecular and cellular immunology of the host response to schistosomal infection. In particular, what antigens elicit neutralizing antibodies of the IgA and IgE type and/or protective T-cell clones?
- Attempts to develop a peptide or protein vaccine which could confer protective immunity with relatively simple, cheap and easy administration. Such a vaccine, if it could be effectively applied, would greatly simplify the task of reducing the burden of schistosomiasis in developing countries.

Immunological laboratories should be encouraged to collaborate with laboratories working on the molecular biology of schistosomal antigens in an attempt to develop strategies to answer some of the questions raised above. (Much of this work will occur in developed countries because of the present distribution of expertise in these disciplines. However, every opportunity should be sought for expanding work on schistosomiasis in developing endemic countries.) The ability to clone a variety of cell surface and internal molecules of the parasite, to determine the DNA sequence of these molecules and to determine the specificity of protective antibodies and/or protective T-cell clones directed against these molecules indicates that the technology is at hand to determine the feasibility of producing an effective peptide or protein vaccine, which could be determined within the next three to five years and applied in the subsequent five years.

4.2.3 Filariasis

The past ten years have seen major advances in the understanding of the biochemistry and antigenicity of filarial parasites and the development of several new drugs with dramatic therapeutic potential. Major advances have been made in understanding the extent of filariasis, treatment of the disease, and new methods of immunodiagnosis. TDR has played a highly significant role in much of this progress (see the *Eighth Programme Report*). Advances include:

- The detection of a new, hitherto undescribed, human filarial parasite -- *Brugia timori*.
- Ivermectin has been shown to be safe and effective in the treatment of animal filarial parasites and more recently has undergone human trials, which demonstrated both the efficacy and safety of ivermectin in the treatment of human microfilarial infection due to onchocerciasis and bancroftian filariasis. In addition, two new experimental drugs, CGP 6140 and CGP 20376, have been introduced into Phase I and Phase II clinical trials.

- Successful transmission of *Wuchereria bancrofti* infection to monkeys has been achieved, and animal models of several filarial and onchocercial infections have been established in cattle and monkeys with successful *in vitro* cultivation of *B. malayi* and *B. pahangi*.

- Monoclonal antibodies specific to antigens of *Onchocerca gibsoni* and *B. pahangi* have been developed for use in immunodiagnosis of filarial infections.

- Initial development of both DNA and monoclonal antibody probes to detect *B. malayi* infection and of other probes to distinguish between human and animal *Onchocerca* species is under way.

A survey of the present status of research on the biochemistry, immunology and chemotherapy of the various filarial infections indicates that there are still several areas in which advances are needed to facilitate diagnosis, treatment, vector control and prevention, including the following considerations:

- While several monoclonal antibodies have been developed which can identify several different filariae, few monoclonal antibodies tested to date show complete specificity. The availability of recombinant DNA technology should permit the cloning of filarial antigens, their use in transfection into mouse cell lines, and the use of such transfected cell lines expressing particular antigens to produce highly specific monoclonal antibodies. Such monoclonal antibodies would be of great value in immunodiagnosis and would permit the use of simple blood tests to detect the presence of filarial antigens. Because of the number of different filariae, this is a somewhat complicated process, but the use of such an approach, focusing on the major forms of filariasis, should permit the development of rapid, safe and effective field tests.

- While ivermectin is a highly effective drug, research should continue to be supported on diethylcarbamazine and suramin, both of which may be effective in reducing parasite load or clearing parasites in treatment regimens in individual patients.

- The problem of vector control is complex due to the large number of insect species that carry filarial parasites. Control methods are known for some vectors, but there is a need to extend knowledge of vectors and their behavioural patterns so that vector control techniques specific for each vector can be developed if necessary.

- As with many other parasitic infections, there is clearly a complex host immune response to filarial parasites. There is thus a great need to study mechanisms of immunity and of suppression of the immune response, particularly to the major and more common filarial parasites. In particular, several questions need to be answered: Is protection mediated by antibody? Is protection cell-mediated? What are the major antigens involved in protective immunity? Additionally, every effort should be made to isolate antigens which induce either protective antibodies or protective cellular immunity.

- Continued study of the biochemistry of filarial parasites should yield information leading to the design of effective new drugs, and this research should be supported insofar as possible.

Among the areas ripe for research, listed above, several should be emphasized for continued support in the coming five years:

- The ivermectin trials should be carried out to completion so that if successful the drug can be distributed for general wide-scale use.

- Research on precise identification of vectors and development of vector control techniques for each individual vector should continue to be supported by TDR wherever and however possible.

- There is a major need to increase research support for studies designed to identify the mechanisms of the immune response to filarial parasites, to determine whether protection is mediated by antibody or cellular immunity and to elucidate the nature of the critical antigens that induce protective immunity. Because of the complexity of filarial parasites, the large number of insect vectors, and the attendant problems of attempting to prevent the disease by controlling the parasite, prevention, if it can be can be made cheaply and widely available, has obvious advantages over chemotherapy of already established infections.

- As with schistosomiasis and other parasitic infections, every attempt should be made to determine whether it might be possible to use protein or peptide vaccines to specifically induce protective cell-mediated immunity to filarial parasites. Such immunity, if induced in a manner designed to establish long-lasting cellular and/or humoral immunity, should permit a major reduction in the number of infected individuals.

4.2.4 African Trypanosomiases

In the opinion of the ERC, the TDR-sponsored research and development projects on African trypanosomiases illustrate in a convincing way the role TDR has played and is playing in combating a tropical disease. Prior to TDR, research efforts on the African trypanosomiases were rather limited, not least due to scarce funds. Yet the diseases were and are serious public health problems. Over the last ten years, the role of TDR in research on African trypanosomiases has grown steadily and now seems vital. There is no question that TDR has played a coordinating function and has also stimulated increased research on the subject outside TDR. Since its inception, TDR has allocated about US $12 million to some 160 projects, spanning disciplines from basic biochemistry to vector control. The input of TDR is apparent from an analysis of publications on the trypanosomiases (including Chagas' disease). Between 1975 and 1980, about 275 papers were published yearly. The first papers resulting from TDR-supported projects appeared in 1978. In 1981 about 120 papers resulted from TDR-supported projects and the total number of publications was approximately 425. This level has remained stable and TDR projects account for 100 to 150 of the publications appearing yearly. Of the other TDR target diseases, only filariasis shows a higher contribution from TDR projects in terms of the share of total publications. The total number of publications on filariasis is, however, much less than that on the trypanosomiases. Even though publication data are important, they do not necessarily reflect the whole role of an organization, in this case TDR, in coordinating and stimulating research. Within the field of research on African trypanosomiases, there are several examples of findings which have been made outside TDR, but which have been brought into practical use thanks to TDR. A prominent example of this is the Card Agglutination Test for Trypanosomiasis (CATT).

TDR-sponsored research on African trypanosomiases shows the importance of a broad attack on a disease. The basic biochemical research carried out to date has already been profitable. Characterization of the glycoprotein surface coat of the parasite and elucidation of the genetic mechanisms behind its variability have led to an accumulation of information that will provide the basis for new therapeutic measures. Detailed work on basic parasite biochemistry has already yielded a compound that interferes with carnitine metabolism in the parasite. Further, the characterization of glycolytic enzymes, showing marked differences in protein structure compared with the same enzymes from animals, should eventually lead to the development of drugs that interfere with glucose metabolism in the parasite. Promising leads for treatment have been developed by TDR.

Intensive clinical trials of DL-α-difluoromethylornithine have been and are being conducted, and the results are very promising. Work is also under way with a potentially better drug, monofluoromethyldehydroornithine methylester. Other potential drugs are being screened by units in Kenya and the United Kingdom with support from TDR. With respect to vector control, considerable progress has been made in developing effective tsetse-fly traps.

In summary, TDR has played a significant role in recent research on African trypanosomiases. In fact, TDR has been the only entity significantly funding a broad range of research and development aimed at sleeping sickness control. Furthermore, control measures have been developed that should now be put into use on a wide scale. This latter aspect of TDR activities points to a general problem which will become greater as new and improved tools are developed inside and outside TDR: the real possibilities for bringing new tools into wide-scale use in developing countries. This problem is discussed in Section 8.

4.2.5 Chagas' Disease

The momentum gained by Chagas' disease research is another outstanding example of the essential role TDR has played in promoting basic and applied research in developing endemic countries. This has been possible not only through financial aid (from 1982 to 1986, 73 per cent of the budget, or US $2.1 million, was allocated to Chagas' disease research projects in endemic countries) but also through the establishment of collaborating centres carrying out research under standard guidelines and covering the following aspects: (a) country-wide surveys on human infection with *Trypanosoma cruzi* and house infestation by triatomine bugs; (b) longitudinal follow-up studies; (c) a network of 14 collaborating laboratories for the standardization of Chagas' disease serodiagnosis -- now working in 11 countries; and (d) a network of collaborating centres for standardized classification, isolation and storage of *T. cruzi* strains to be used in analytical epidemiological studies.

Considerable progress has been made in the classification and study of different strains of *T. cruzi*: at least five strains have been identified and classified according to their infectivity, their aggressiveness in humans and/or laboratory animals and their possible antigenicity. However, much more profound clinical knowledge is needed, not only for detecting primary infection but also for determining the latency period between primary infection and the appearance of late clinical manifestations. Xenodiagnosis, as it continues to be practised, belongs only to a few specialized laboratories and is not generally available in endemic areas, most of which are quite remote and isolated. The development of a more precise diagnostic tool (i.e., a quick, reliable serodiagnostic method for determining the presence of active infection) could also lead to the acquisition of more reliable epidemiological data in endemic areas.

There is no question that TDR has contributed effectively to the transfer of modern biotechnologies to numerous research centres in endemic countries: most laboratories are now familiar with the use of monoclonal antibodies, immunoelectrophoresis, immunosorbent assays -- both radioactive and nonradioactive -- and gene sequencing of parasites. This has been achieved not only through grant funding but also through research strengthening and training activities, and the SCs on Chagas' disease are to be commended for their success in obtaining active collaboration and interaction between different groups of basic scientists.

Also, as regards clinical aspects, good cooperation has been established among parasitologists, internists, cardiologists, pathologists and laboratory workers in dealing with the late complications of the disease (mainly cardiopathy and, to a lesser extent, megacolon) and different disease manifestations. However, these aspects can only be studied in well-equipped university hospitals that are usually distant from endemic areas, and in many cases it is difficult to establish a link with the endemic area or with the time of the primary infection. It remains unknown whether treating parasitaemia would influence the

course of cardiopathy or other late manifestations, or whether the effects on smooth muscle fibers are due to the interaction of the parasite with other factors (autoimmune or genetic factors) which may be prevalent long after the parasite has disappeared from the host. Treatment schemes and protocols might differ radically depending upon whatever is the actual situation. In any case, Chagas' disease chemotherapy continues to rely heavily on nifurtimox (a nitrofuran derivative) and benznidazole (nitroimidazole), although research continues on the screening of new drugs with possible trypanocidal activity.

New approaches to vector control have also been developed with the help of the Programme: insecticidal paints have been effective in controlling insect vector infestation in up to 96 per cent of houses in some endemic areas. Canister or cartridge for fumigation has also been field-tested with good results. The ERC feels that more SER activities should be dedicated to Chagas' disease, particularly to studies on the implications and cost of using new building materials to replace the mud-wall and thatched-roof construction of houses prevalent in impoverished endemic areas.

The Programme has also brought about advances that seem to indicate the possibility of both new and effective diagnostic tools and, perhaps within a decade, a vaccine. Foremost among these advances has been the cloning of a parasite gene encoding a major *T. cruzi* surface antigen involved in parasite penetration into host cells. Also, immune modulators -- through which the parasite evades the human immunological system -- have been identified. The immune response elicited by a vaccine should, of course, avoid all possible damage to smooth muscle tissue and be limited in its effects to destruction of the parasite.

In summary, TDR is looked upon as the main source of external funds for research on Chagas' disease in Latin America. TDR support has been instrumental in developing a chain of well-equipped laboratories managed by excellent, dedicated scientists who have, in recent years, increased the number of important publications on the trypanosomiases. TDR should draw more attention to the need to increase government support of field research and epidemiological studies, help in lessening the difficulties frequently encountered with local customs services for the importation of equipment and reagents, and also contribute to the development of SER activities in endemic areas.

4.2.6 The Leishmaniases

TDR-supported work on the leishmaniases has followed a rather different pattern from that of other subjects. This has stemmed from the original perception of the leishmaniases as being of lesser public health importance than the other five diseases, a very limited level of funding early in the Programme, and the lack of continuity in staffing the Steering Committee Secretary's post. In spite of these impediments, the Component on the Leishmaniases has flourished and been notably successful in several respects. It has shown that the leishmaniases are much more widespread and of greater public health importance than had been previously recognized, and it has led to a broad programmme of research leading to some 350 publications by late 1985, a significant number in the light of the sum invested.

Initially, the Steering Committee focused on the descriptive epidemiology of the leishmaniases, which are caused by the most diverse of human parasites in terms of strains, pathogenesis, vectors and reservoir hosts. The results extended the known distribution of the diseases and in several areas led to detailed subsequent studies, of which those in Bolivia were outstanding. Here a high incidence of mucocutaneous disease creates a local major public health problem. The networks for exchange of parasite reference strains and the taxonomic work supported by the Programme, together with direct support for research projects, have led to elegant analyses of the epidemiological situation. Similar findings have been made elsewhere in the Andean region.

The Programme has supported studies of the application of monoclonal antibodies, restriction enzyme schizodeme analysis, DNA probes and pulsed field gradient chromosomal separation to supplement and hopefully replace zymodeme analysis in efforts to clarify the complex taxonomy of *Leishmania* species. The Committee views this application of new methods to practical field problems as both important in itself and as an example of the TDR approach.

The ERC was also impressed by the Component's vigorous approach to chemotherapy, which has involved both re-examination of the regimens of commonly used antimonial drugs and introduction of new compounds, of which allopurinol riboside is the most impressive, both in terms of therapeutic benefit and of rational selection on the basis of host and parasite biochemical differences. Several other new compounds are also of interest.

Rapid progress in understanding the complex immunology of leishmanial infection is being made with support from TDR and elsewhere. The use in one country of virulent parasites to achieve immunization emphasizes the need for a vaccine, and the Committee noted good progress in antigen characterization for application to vaccine development.

At the level of immediate application, a very simple agglutination test had undergone a successful field trial for rapid diagnosis of visceral leishmaniasis; it is also much safer than the traditional method of diagnosis.

Successive reviews of the Leishmaniases Component have recommended social and economic studies of risk factors, but few studies have been supported thus far. The ERC also recommends more attention to this aspect, as well as to the study of leishmanial immune responses in the human host.

Inevitably, some grants have been less successful than hoped and, inevitably with hindsight, some of those had characteristics of being very high risk. However, the Committee was impressed with the number of applications that could not be funded for primarily financial reasons. Several of these would, in our view, be judged as having substantial potential.

The SC has coped with its limited funds by supporting projects at a greatly reduced budget in most cases, and by a system of 'mini-grants' of up to US $8000 to enable promising projects to get under way, especially in the tropics. This has been particularly useful in getting extensive coverage for initial studies of distribution of the diseases and their epidemiology. However, it is clearly not a very satisfactory way of funding research in the longer term, and it is clear that this Component could productively utilize a larger budget. The diseases attract particular enthusiasm from research workers, since the severity of the disability caused by mucocutaneous disease, the danger to life posed by visceral leishmaniasis, and the rapid progress being made in several areas of highly applicable research makes this a rewarding field.

4.2.7 Leprosy

4.2.7.1 Chemotherapy of Leprosy

TDR-supported research on leprosy has so far resulted in a smaller number of total publications than, for instance, that on the trypanosomiases. Also, the contribution of TDR-supported research to the total number of publications on leprosy is smaller. These facts should not be interpreted to indicate that TDR-supported research on leprosy is of minor importance. Rather, it is apparent that the type of research sponsored by TDR is such that it does not yield a large number of publications. In the case of the chemotherapy of leprosy, TDR has chosen to stimulate and support important clinical trials that are both costly and cumbersome but result in few publications. The SC on the Chemotherapy of Leprosy (THELEP),

which has allocated a total of about US $5 million to projects during the period 1976-1986, has been and is testing various combinations of existing drugs, as well as developing new drugs, especially in view of dapsone resistance. A series of comprehensive field trials with drug combinations involving dapsone, rifampicin, clofazimine, protionamide and acedapsone, have been or are being carried out. The results are very encouraging. Work on new drugs is being actively pursued. This work is difficult and hampered by the lack of simple methods for screening potential drugs. Several promising compounds are being tested, among others some quinolone derivatives. New drugs may be used to increase the efficacy of multidrug therapy for leprosy. In parallel, the SC on the Immunology of Leprosy (IMMAL) is devoting considerable resources to vaccine research. Even if a suitable vaccine were obtained, there would continue to be a need to develop better drugs to treat the millions of patients with established disease. The ERC is of the opinion that TDR could contribute very significantly to such efforts. In summary, the ERC finds that previous work supported by TDR on the chemotherapy of leprosy has been important and successful. Future plans are comprehensive and well founded. TDR's activities in the chemotherapy of leprosy exemplify the unique role TDR can play in coordinating research and development on a transnational scale in fields that other research-supporting organizations are less likely to tackle.

4.2.7.2 Immunology of Leprosy

Whereas the aims of the IMMLEP Component are very similar to those of the IMMAL Component, developments in the area of leprosy research have taken a somewhat different course than in malaria. The IMMLEP 'package' also contains vaccine development, work on immuno-diagnostic tools and basic research on the parasite as key elements. Although knowledge of mycobacterial antigens and their molecular biology lags behind that of *Plasmodia* species, the prospects of a conventional vaccine using heat-killed *Mycobacterium leprae* are strong.

Vaccine Research

The objectives set by IMMLEP include the development of a vaccine to provide protection to people at risk and the development of immunotherapy, especially in combination with chemotherapy, based on the stimulation of cell-mediated immunity.

Three types of vaccines are being pursued: a heat-killed *M. leprae* vaccine, especially for prophylaxis; a vaccine consisting of killed *M. leprae* and live BCG (to be used for immunotherapy); and a vaccine based on cultivable mycobacteria related to *M. leprae*. The IMMLEP-supported work is confined mainly to work on the first two vaccines listed above.

In 1971, infected armadillos became available as a source of *M. leprae*. IMMLEP has helped to set up a system of armadillo colonies (four in the United States and one in the United Kingdom) which supply infected tissue or purified *M. leprae* to researchers all over the world. This is a major contribution of IMMLEP and nearly half of IMMLEP funds go to support the armadillo supply.

Trials with human volunteers in Norway showed that a heat-killed *M. leprae* vaccine is acceptable. A larger study in Malawi confirmed tolerance and immunogenicity. Large-scale and long-term field trials for prophylaxis began in endemic areas (Malawi and Venezuela) in 1984 and more trials in Asia were planned. (The results of these trials were not available at the time of writing of this report.)

Work on vaccination with cultivable mycobacteria related to *M. leprae* is being carried out outside TDR (e.g., in India) and researchers have claimed promising results. Large-scale trials in India are planned. TDR should monitor this work.

Molecular Biology of M. leprae

The *M. leprae* genome has been cloned in *Eschericia coli* and the cloned genes have been expressed in more than one laboratory. A leprosy recombinant DNA bank has been set up by TDR to maintain mycobacterial libraries. Monoclonal antibodies have been used to isolate genes coding for several *M. leprae*-specific antigens. Cloned *M. leprae*-specific T cells from vaccinated human volunteers have been shown to recognize *M. leprae* antigens expressed in *E. coli*. Although the molecular biology of the surface antigens of *M. leprae* is not as advanced as in malaria research, the possibility of developing vaccines based on defined antigens would appear to be promising.

The ERC considers TDR work in this area to be highly worthwhile, well-focused basic research likely to bear fruit in the medium to long term.

Immunodiagnosis

A number of monoclonal antibodies specific to *M. leprae* epitopes have been obtained. A library of monoclonal antibodies against phenolic glycolipid-I and protein antigens of *M. leprae* has been assembled by TDR. This should be very useful for taxonomic purposes and for developing diagnostic tests.

The skin test commonly used in leprosy employs a crude extract. Attempts are being made to standardize tests for field studies.

The ERC suggests that information be gathered on the extent to which new leprosy diagnostic tests are being used in the field and for what purposes (i.e., are they truly aiding control or treatment?).

Basic Research

Understanding of the biology of *M. leprae* (life cycle, metabolism, transmissibility) and of the immunology (cell-mediated immunity and lepromatous infection, sensitization of patients with lepromatous leprosy), pathology (nerve and tissue degeneration) and epidemiology (including genetics of susceptibility) of leprosy is very limited. Basic research in these areas deserves to be vigorously supported.

Geographic Distribution of Research Projects

The ERC reviewed the geographic (by country) distribution of IMMLEP-funded projects. The ERC sees no reason for major concern in this distribution (given the present distribution of capacity in relevant disciplines) but suggests periodic review by the IMMLEP SC to ensure that applications from strengthened institutions in DECs are encouraged.

4.2.8 Biological Control of Vectors

Although some important developments have been achieved in biological control of vectors between 1977 and 1987 and a few noteworthy biological control agents have been discovered or made more effective by TDR, progress in the overall field in general has been slow due to several factors. Only two bacterial agents -- *Bacillus thuringiensis* H-14, or *B.t.* H-14, and *B. sphaericus* -- have proved clearly effective against blackfly or mosquito larvae; although *B.t.* H-14 or its toxin are quite useful as larvicides, frequent application is needed due to the lack of recycling and the organism's tendency to sink in water. This increases the costs, compared with more conventional methods.

Another important factor resides in the ecological variation of the areas where the biological control agents are to be employed, a variation that occurs within very narrow limits. Thus, even for a given agent which has been well proved in similar tropical regions, the effectiveness may vary from one area to another. Also, much more research is needed on the bionomics of vector populations in different geographic or climatic areas.

Thus, a 'trial and error' approach becomes necessary in most situations in which a biological control agent (be it a bacterium, fungus, nematode or fish) is to be employed. TDR has contributed not only to the development of new agents but also to establishing the research steps necessary for the development of such biological control programmes. The ERC strongly recommends an increasing collaboration, not only among different SCs dealing with several aspects of a given vector-borne disease, but also with social and economic researchers who could furnish more detailed information as to the conditions prevailing in a given area and the willingness and capability of its inhabitants to employ biological control methods. Also, cooperation with departments of biology, zoology and entomology of local universities, as well as with agricultural or environmental institutions and even with local private industries, should be encouraged.

While the field of biological control of vectors has progressed slowly, overall the contribution of TDR in developing *B. thuringiensis* as an effective agent for use in the field has been exceptionally important to the Onchocerciasis Control Programme in West Africa (OCP). The pesticides available to that programme in recent years had become less effective because of resistance and *B. thuringiensis* was available at the right time to fill a gap in the OCP's control methods -- a gap which could have had disastrous consequences if the situation had persisted.

4.2.9 Epidemiology

Throughout the history of the Programme, emphasis has been placed on epidemiology and on social and economic research by succeeding committees and reviews on the basis of perceived need, and we would concur with that judgement. The original stated terms of reference of the Epidemiology Component of the Programme, in addition to coordination, were concerned with multiple disease field situations and epidemiological features common to several of the six diseases. Its practical imperative was to cope with the Tropical Diseases Research Centre (TDRC) in Ndola, Zambia, a fixed project at the inception of the Programme which consumed substantial resources. The Epidemiology Component's initial mandate was therefore a peculiar mixture of coordination, management of a facility, and development of a rather loosely defined area of field research. It took a while to redefine its role in terms of real needs, which were, and still are to promote epidemiological research to help design the optimal strategies for disease control, to develop and teach appropriate epidemiological methods for tropical disease research, and to increase the supply of epidemiologically trained personnel.

The returns in terms of scientific productivity have, therefore, in the short run, been limited. The TDRC consumed most of the budget initially and has not been highly productive, but the work done at its field station in Kampumbu has been of importance in trypanosomiasis in producing a simple surveillance system which has led both to early diagnosis and better prognosis (as intended) and to reduced transmission. There has also been significant work on malaria, especially chloroquine resistance, and on schistosomiasis chemotherapy at Kampumbu.

Elsewhere, work on the microepidemiology of malaria in Papua New Guinea has been important, and the best work of its kind. It will be followed, no doubt, by comparable studies elsewhere in endemic areas, and the Programme is specifically supporting work on the use of new techniques for assessing sporozoite rates in mosquitos and antisporozoite antibody levels in individuals.

But the greater impact has been achieved by a combination of grants, workshops and TDR-assisted training to improve the epidemiological standards of work in the field and to introduce some of the methods developed for epidemiological research on chronic diseases into work on the six target diseases. In particular, the use of case-control studies to determine risk factors for both African and South American trypanosomiases has been supported, field tests have established the value of simplified immunodiagnostic methods for trypanosomiasis and leishmaniasis, and the distribution and natural history of the six diseases have been clarified.

Because the quality of epidemiological applications to all of the Steering Committees of the Programme has been relatively low, 13 workshops have been held, attended by almost 500 workers from developing countries, and these have led to better and fundable project proposals from some of the participants.

Two things are clear from the experience of the Epidemiology Component of the Programmme. The first is that the main obstacle to progress is the lack of epidemiologists worldwide, due more to a defective career structure than to lack of training, so that the Programme has been grappling with a far larger problem than can be handled by research grants alone. The situation is analogous to that being tackled by the Research Strengthening Group. In the basic biomedical sciences, where there were many research workers in the world, it was simply that they were not tackling tropical disease problems, whereas in epidemiology the research workers were and are scarce. The second issue to emerge from the Programme's experience to date has been that the need for epidemiology is greater in relation to the specific disease areas. It should be an input, along with immunology, biochemistry, etc., to the work on each disease.

A third major issue arises now as the Programme's new tools for controlling tropical diseases are appearing. Vaccines and drugs for disease control require field testing to determine both their efficacy and strategies for their use at the community level. These trials will be complex and will require well-defined study populations in which many aspects of disease transmission will need to be measured. Such population studies are expensive, complex and need a long lead-time for logistics and baseline work prior to intervention testing. This must be the primary goal of the epidemiological work of the Programme in the future, as was formulated clearly in the report of the sixth meeting of the Scientific and Technical Advisory Committee (document TDR/STAC-6/84.3), which we endorse.

The thrust of epidemiological activities within the Programme should therefore be directed in two ways. The first is towards the disease-specific Steering Committees, and we thoroughly approve of placing a member of the Epidemiology SC on each of the disease-specific Steering Committees. The second must be towards the strengthening of epidemiological work in developing countries, and we support the relocation of the Epidemiology Component within the RCS Programme Area.

Selection and development of field research areas for trials of the new tools and for training of epidemiologists will be the major epidemiological activity of the next decade. In looking at promising sites, it is of interest that the majority of these activities fall neither directly under the ministries of health nor the universities of the countries concerned. Most either come under special research institutes or are in other respects unusual. Care will need to be taken to involve universities in this work to ensure a supply of trainees and, even more important, to make certain that epidemiological work then gets built into the education of doctors and other health workers. In addition, efforts must be made to involve the ministry of health as the responsible body for the operational application of the results of the field research. Involving these organizations adds to the complexity and difficulty of what is already a demanding task and TDR support may be essential in making it work.

The costs of population-based field trials and community studies are very large and, apart from the special case of Ndola, the Programme has avoided funding the greater part of any such studies because it did not have the resources. This may need to change if TDR is to accomplish its tasks, and the costs of population-based studies, such as the Garki malaria project in Nigeria, the Malawi leprosy evaluation project, and others in Bangladesh, India and Papua New Guinea, indicate the substantially greater scale of funding that would be needed.

The Committee therefore recommends a substantial change in the mode of operation of the Epidemiology Component of the Programme and notes with satisfaction that this has already been implemented. The ERC also envisages a change upwards in the scale and nature of the epidemiological activities funded (largely through disease-specific Steering Committees) if the Programme's goals are to be met.

4.3 Evolution of the Programme's Contributions and Activities

At the outset of the Programme, the major needs in the R&D Programme Area were: (a) to generate biomedical insights which might serve to identify appropriate leads for developing drugs, vaccines, diagnostics or other disease control tools; and (b) to gather information on the epidemiology of the target diseases, which would help focus control efforts. Research in these areas was launched and after a few years an increasing flow of publications emerged. Publications in the disease-specific areas acknowledging TDR support have been tracked by the Programme's Management Information System (MISTR), and total publications in the field are recorded by the US National Laboratory of Medicine (NLM). While the NLM system includes some categories of publication not counted by the MISTR system (e.g., abstracts), the two systems provide very useful information and facilitate useful analyses.

Of publications acknowledging TDR support, the ERC is impressed by the high proportion that are published in prestigious scholarly journals (Annex V). This indicates that TDR is supporting work and individuals of high quality. The Committee noted the significant increase in the number of publications on the various target diseases which started a few years after the Programme's establishment. The ERC believes that some credit for the overall expansion of research on the diseases which this increase in publications undoubtedly reflects can be claimed by TDR (Annex IV).

Comparison of the MISTR and NLM data can be used to assess the proportion of publications which acknowledge TDR support, overall and for each disease. The proportion of publications acknowledging TDR support is much greater than the Programme's proportional funding contribution to all tropical disease R&D. Because publications sometimes acknowledge more than one source of support, it is not possible to derive any crude measure of 'productivity' (publications/funds) from these proportions. Such a measure would also lack meaning because it omits any consideration of the quality of research.

It is apparent, however, that for some diseases (e.g., filariasis, trypanosomiases, leishmaniasis) the Programme provides at least some support for a high proportion of the work published. The likely explanation is that there are very few other sources of support for research on these diseases. Programme support of these areas is therefore especially valuable.

The total body of TDR-supported research published in scholarly journals over the last six to eight years demonstrates that the Programme has consistently supported productive, high-quality investigators. There is an obvious need for the exploration of new leads in tropical disease research, and no doubt the Programme will continue to support such efforts. Continued measurement by MISTR of TDR's contribution to the research literature in the manner described above is highly desirable since it is a way of measuring one aspect of the Programme's impact.

Research publications represent an intermediate measure of progress towards the development of disease control tools. The knowledge reflected in the publications that have emerged from the Programme has provided many leads for disease control tools which have been pursued in and outside the laboratory. TDR contributions to and accomplishments in these later phases of the process are not so much measured in publications but more in terms of the number of products under development or in use.

The Programme has participated in the development of an impressive list of products. (See the *Eighth Programme Report*, particularly Table 1.1, pp. 10-11, reproduced here for the convenience of readers.) Some 60 'products' are already in actual use or advanced stages of development, i.e., in clinical or field trials. Given the accumulating body of knowledge derived from research, it is likely over the next few years that there will be even more 'prototype' products that will need clinical or field testing.

Development of products (i.e., the phases of clinical and field testing and of introduction for application) is usually done collaboratively. This makes it difficult to apportion credit and hence to provide an objective measure of productivity to the Programme's investment in these activities. Nevertheless, the ERC feels that TDR deserves recognition for a major role in certain developments in tropical disease control (these are listed below).

The contribution of the Programme, in monetary terms, to the development of some products may have been limited, but it is important to bear in mind that the Programme can in fact work most cost-effectively as a catalyst. By providing 'seed' money, convening (potential) collaborators or otherwise facilitating action by others, the Programme will ensure or accelerate progress. TDR deserves credit as a contributor to the development of products if it has played a 'catalytic' role, even if its contribution, in terms of monetary support or personnel, has been less than that of other participants.

The ERC concludes that the Programme has an impressive record of accomplishments in promoting and speeding up the development of products for tropical disease control. (As discussed more fully in Section 6, it has also demonstrated effective strategies for research capability strengthening.) It has achieved this both through major sponsorship of certain products (where no other group took the lead) and as a 'catalytic' participant in the development of others. While credit is difficult to apportion in the latter situation, this mode of operation is probably the more cost-effective of the two and should continue to be stressed.

4.4 Summary of Conclusions on Scientific Contributions

As noted above, TDR has made some broad contributions to the R&D effort in tropical disease control. It will be obvious from the foregoing discussions of specific Steering Committee activities that the Programme has made other significant specific contributions. These include:

- organizing transnational drug trials of new therapeutic agents for malaria;
- supporting a broad range of work critical to malaria vaccine development;
- sustaining field research in malaria;
- supporting work to lay a basis for possible development of a schistosomal vaccine;
- promoting, in collaboration with industry, the clinical development of ivermectin for the treatment of onchocerciasis, along with other drugs for this and other filarial diseases;

- providing virtually unique support for a comprehensive spectrum of activities in African trypanosomiasis control R&D, including work on drugs (DL-α-difluoromethyl-ornithine and analogues) and the Card Agglutination Test for Trypanosomiasis (discovered outside the Programme but developed for field use with TDR resources) and developmental work on tsetse-fly traps;

- catalysing the development of a network of first-rate research and development centres on Chagas' disease in DECs, which have contributed to understanding of the pathogen, its antigens and pathogenicity, the social aspects of the disease and improved vector control;

- organizing very important trials on multidrug therapy for leprosy;

- facilitating the development of a first-generation leprosy vaccine candidate by creating a global network of investigators and providing organizational and financial support for their activities up to the stage of clinical trials;

- increasing understanding of many aspects of the leishmaniases and uncovering their widespread global distribution;

- developing a new regimen for antimonial drugs, which has now been established as the recommended treatment for visceral leishmaniasis;

- supporting the development of *B. thuringiensis* as a biological vector control agent, which is now used extensively in onchocerciasis control;

- enhancing the epidemiological quality of field studies on control of the target diseases.

These practical contributions -- many of which are now actually being put into use in developing countries -- attest not only to the scientific productivity of TDR but also to the fact that it is developing tools truly appropriate for the settings in which their use is intended.

5. Social and Economic Research

5.1 Development of Social and Economic Research

Systematic application of social and economic research techniques to societal problems is a relatively new endeavour generally, and with tropical diseases the application has only been very recent. During the last decade, social and economic research on tropical diseases was either non-existent in many DECs or it arose mainly through the stimulus provided by TDR. It is therefore a pioneering field, particularly as one which strives to apply as well as generate knowledge. What complicates the situation is that the field involves not one but several disciplines. The most significant achievement of the Programme's Social and Economic Research (SER) Component is the initial research 'infrastructure' it has set up by training the first sizeable cadre of social scientists from developing countries and funding the first projects in social and economic research on tropical diseases conducted in endemic countries by local social scientists. This is the SER Component's unique contribution not only to TDR but also to the scientific community of developing countries. Considering that SER practically started from scratch, this is no small feat for the Secretariat and the Steering Committee. SER has legitimized its claim to 'enfranchisement' in an environment in which there had previously been infertile soil. Now, SER should concentrate on producing more operationally significant inputs that could make a difference to tropical disease control.

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	

The in-depth report of the SER Steering Committee, covering its programme of activities for the period July 1982 to May 1987, is both timely and valuable. It gives a comprehensive insight into the problems, achievements, possibilities and future prospects of social and economic research within the TDR mandate. Beyond this formal report and many other relevant documents, members of the ERC have also benefited from extensive discussions and direct personal interaction with both the Chairman and Secretary of the SER Steering Committee in the search for a feasible, viable and realistic programme of action in the years ahead.

Evolving and maintaining strong links with mainstream social science research are at once required and yet constrained by a number of key factors which are mentioned in the in-depth report of the SER Steering Committee. First is the serious shortage of good social scientists with experience in research on tropical disease problems, particularly in regions like sub-Saharan Africa where they are needed most. Second, there is the temptation and the danger of raw empiricism that may still plague some research proposals submitted in response to SER's promotional efforts. This is manifested in the collection of social and economic data without any clear theoretical foundation or coherent analytical framework. The danger is heightened sometimes by the fad of computer-focused data analysis and interpretation by younger social scientists in some developing countries. There is, thirdly, one striking conclusion which has emerged from past SER activities: that it is exceedingly difficult to measure the impact of diseases under conditions of general poverty and that research on the social and economic consequences of tropical diseases is proving to be more complex than previously thought. Finally, there is the fact that there is far more to the potential contribution of health economics than just the measurement of economic impact of diseases in terms of production-time lost and the cost-effectiveness of disease control programmes.

When social and economic research projects have deliberately and systematically pursued answers to the questions of who does what, where, when and why, it has been possible to identify populations and individuals at risk at the community and household levels. Answers to these questions help establish the basic building blocks for disease control by increasing understanding of the social, economic and cultural aspects of tropical diseases such as:

- patterns of occupational activity and the nature of the work environment;
- patterns of household activity in terms of age and sex roles;
- seasonal dimensions of the above activities in relation to seasonal characteristics of the diseases, particularly vector-borne diseases;
- man-vector-parasite connections;
- patterns of coping with the disease and its consequences;
- mobility and settlement patterns;
- patterns of social and recreational activities;
- the nature of day-to-day living conditions; and
- patterns of response to treatment and control measures.

It is only when researchers ask parallel questions of who does what, where, when, how, why and at what cost with respect to control programmes that they can begin to identify problems and assess alternatives for improvement in programme design and management.

The development of a simple framework which incorporates these questions will go a long way towards achieving greater focus and may well facilitate the generation of more cumulative research results truly within the domain of the social sciences. Such research products will be the stock-in-trade of social scientists vis-à-vis control programme personnel, the policy makers and biomedical specialists. Unless SER addresses these questions systematically, there will be little chance of a coherent body of knowledge emerging and SER's contribution to increased effectiveness of control programmes will be difficult to detect.

5.2 Achievements and Problems

SER has clearly justified its establishment within TDR. It has already demonstrated the institutional, economic and behavioural interdependence of both the propagation and the control of tropical diseases in the endemic countries, whether at the level of individuals, households, communities, larger societies, or subregional groupings. Also important is the fact that within the world's social science research community, the Programme's SER Component is the largest (and for several developing countries, the only) single source of support and stimulation for social science research in the field of tropical diseases. That pre-eminent position of intellectual leadership and primary funding is unlikely to change in the immediate years ahead.

Partly because of its late introduction in the Programme's historical development and partly because it is operating in a milieu dominated by the different research traditions and methodologies of medical science and health technology, SER was sometimes -- indeed often -- treated or regarded as a poor relation of the other disease-specific and more technologically exciting research programmes of TDR. It has also suffered in prestige from the fact that the basic methodologies developed in its primary disciplines (economics, political science, sociology, social anthropology, linguistics, management and public administration) had hitherto not been rigorously focused on their potential application to health problems, least of all to the study of tropical diseases. However, in spite of the many methodological challenges that still lie ahead, SER has established its research integrity and great operational value within the TDR mandate over the past five years.

Study of the economics of tropical diseases has proven to be more intractable than thought when it was originally conceived and enthusiastically promoted. It is more difficult than the economics of agriculture perhaps because there are many subtleties in human behavioural response to the diseases which have yet to be identified and understood. The 'outputs' of agricultural development are also easier to measure. But this does not mean that study of the economics of tropical diseases should not be attempted; it simply means that more work has to be done.

In studies supported by the SER SC, the incidence or prevalence of the diseases has unfortunately not always been established satisfactorily even to the researchers themselves. This must not be the case in the future. In other words, the epidemiological component of the studies must be done well because this is a major point of reference in determining, later on, how effective a particular control measure has been. Where the incidence of a disease is minimal, its social and economic consequences are not likely to be felt.

5.3 Strengthening Social and Economic Research in the Next Quinquennium

The sustenance and strengthening of the SER Component's achievements over the next decade depends critically on the degree to which the Component is able to maintain a strong linkage with the main stream of social science disciplines in spite of its necessarily being anchored operationally to the medical sciences. Such a linkage with mainstream social sciences is essential for at least two reasons. One, in order to attract and retain the leading individuals in the principal social science disciplines to work on tropical diseases, SER must seek to conform to the highest theoretical and analytical standards. Second is the practical problem of incentive, in terms of providing suitable and adequate professional and career outlets for social scientists who are now branching out to specialize in or make greater commitment to TDR-focused research programmes. It may well be that this problem is more serious and more urgent in some branches of the social sciences than in others; for example, it is probably more the case for economics and management than for sociology and anthropology.

The SER Steering Committee's in-depth report on its activities from 1982-1987 raised and addressed many important issues for health improvement interventions and research which provide a challenge to the social sciences. SER needs to play a wider catalytic role within the Programme as a whole. It should raise basic questions of policy and operations that cut across the various disease-specific activities. Some examples can be given here:

- The need to develop suitable strategies to ensure that the technologies currently being developed will be socially acceptable and economically feasible, given the social and economic conditions in the disease-endemic countries.

- Careful listing and analysis of the various and significant constraints on the efficient use of existing control programmes and technologies in different endemic areas.

- The need to discover and design suitable and effective incentives for the adoption of new technologies in the disease-endemic countries, including all social engineering components of disease-control programmes.

- Establishment of a continuous monitoring system on how well TDR is succeeding in strengthening research capabilities in the disease-endemic countries, differentially indicated for the biomedical sciences, epidemiology and the social sciences.

Since the SER SC and its secretariat have already established links with all TDR and TDR-related bodies and some collaborative work is under way or planned, perhaps they can now join with social and economic research efforts in the fields of agriculture, nutrition, irrigation development, family planning, farming systems and integration of women's concerns in development. There are many lessons (positive as well as negative) to be learned from the experiences in these other fields. Such links should in time yield crossfertilization in concepts, approaches, research methodology and strategies in research capability strengthening. This need for crossfertilization should also be kept in mind when choosing future Steering Committee members.

In the meantime, other indicators of progress have to be found in such things as changes in knowledge, perceptions, attitudes and practices, changes in incidence or prevalence of the target diseases, and changes in health-related human behaviour.

5.4 Recommendations

- To nurture continuously the current research projects and investigators who have shown not only much promise but also some early notable achievements and at the same time to explore new research opportunities would require the time and talent of more than one staff member in the Secretariat. An additional full-time social scientist is clearly needed by the SER Component.

- Although we concur that research capability should be developed in social science units rather than in biomedical institutions, the definition of social science units must be broadened to include those which have had experience in applied social and economic research in agriculture, population, nutrition, farming systems, irrigation, environment, women in development, etc. The inclusion of tropical diseases in their social and economic research agenda would not only expand TDR's intellectual resources but would also be strategic in moving tropical disease research problems into the mainstream of development issues.

- A postdoctoral fellowship programme which would bring researchers from either other developing countries or industrialized countries to work as colleagues of social

scientists at their own research sites in tropical disease-endemic countries might overcome professional isolation. With support from bilateral sources and foundations, postdoctoral fellows who stayed for a longer period would be a better alternative to intermittent consultants. The Rockefeller Foundation, for example, has a very notable programme for social and economic research in agricultural research.

- Given the major tasks for the next five years, the ERC is convinced that the SER budget should be doubled over the next quinquennium. It is also important to emphasize that the higher level of SER funding is in addition to the greater attention which we also recommend that the RSG should pay to SER research capability strengthening.

- To move towards the final objective of the SER strategic plan, TDR social scientists must now start getting actively involved in the formulation of health policy issues bearing on diseases in the endemic countries. The time has come to put tropical disease policies in the mainstream of national and international development.

- There should be new and adequate guidelines for the conduct of social and economic research projects on tropical diseases, including protocols for knowledge, attitudes and practices (KAP) surveys, and multivariate analyses. Informal consultations should be held to develop the new guidelines based on TDR needs and TDR/SER projects.

- Similarly, attention needs to be given to the development, transfer and use of biomedical technology, in terms of social and economic assessments.

- The SER SC should convene a series of meetings to review curriculum development for tropical disease-related social and economic training in medical sociology, medical anthropology and health economics.

- The concept and practice of community participation in relation to tropical disease control remains very elusive, and so is the integration of tropical disease control into primary health care. These are clearly major research areas which deserve much more work.

- SER disciplines should be represented and strengthened in each and all TDR management bodies, including STAC and the various scientific or disease-specific Steering Committees. It is important that most of these new SER members should be senior social scientists from tropical disease-endemic regions.

6. Research Capability Strengthening

In its review of the Programme's research capability strengthening activities the ERC had access to, and was greatly aided by, the information that was developed for the second review of the Research Capability Strengthening (RCS) Programme Area by a Scientific and Technical Review Committee (STRC) of STAC.

The ERC notes that between 1976 and 1986 a commendable range of activities related to research capability strengthening was pursued by the Programme:

- A total of 98 institutions had received some type of institution strengthening grant, 21 of which had completed long-term support by the end of 1986;

- some 649 individuals had received training grants, including 490 for research training, such as PhD or MSc, and 108 're-entry' grants;
- Thirteen MSc and several short courses had been supported in developing countries.

6.1 The Need for Research Capability Strengthening and Its Relative Importance

It was clear from the beginning of the Programme that the distribution of the six diseases did not correspond to the distribution of research expertise and capability required to carry out the studies needed. While it was feasible, though far from desirable, to carry out laboratory-based work aimed at developing new vaccines and drugs only in developed countries, it was essential that the new products be assessed, both in patients and communities, in endemic areas. Moreover, it was necessary for epidemiological and also social and economic research to be carried out in places in which the diseases under study were indigenous. In addition, if TDR were to be efficient and not to continue indefinitely, it would be essential to build up research expertise in the six diseases in the endemic areas. These considerations, together with the interest of some Programme contributors in supporting training and other research and development activities aimed at making the endemic countries self-reliant in research, provided compelling arguments for the Research Capability Strengthening Programme Area of TDR.

The balance between research capability strengthening and research and development in the Programme's funding is essentially an arbitrary decision. There is no logical method or 'formula' by which the division of funds into two categories can be decided. However, with hindsight the part of the budget allocated to RCS (which rose to and stabilized at 25 per cent) appears to be reasonable to the Committee. It has allowed a good deal to be done in support of a broad range of institutions with regard to both disease interest and geographic location. It was a relatively high-risk activity but has proven in a substantial number of institutions to have been highly successful. When the formal data on institutional support provided were supplemented by the Committee members' assessments of institutions before and after support from the Programme, it could be concluded that much had been achieved. There have been some unsuccessful ventures, and growth towards international competitiveness by a number of institutions has been slower than hoped, but many others have done extremely well.

The Committee would have had difficulty, due to the arbitrary nature of the decision, in proposing the future level of RCS support had it been intended to keep that activity as a separate Area. Indeed, the ERC would have recommended that the RCS Area be much more closely linked to the R&D Area. However, the Programme has already decided to integrate the two Programme Areas to a substantial degree. This not only meets with our strong approval but also, through the programme-based grant mechanism, builds in a flexibility between research and development and research capability strengthening that is needed to pursue efficiently the mission of the Programme. A set of rigorous, comprehensive guidelines have recently been issued for the programme-based grant mechanism. As decisions are implemented, it will become increasingly difficult to define strictly whether some funds are R&D or RCS. Hence, the significance that need be attached to the current 25 per cent proportion will diminish. However, the ERC believes the present degree of relative attention to RCS versus R&D to be acceptable.

6.2 Strategies for Implementing Research Capability Strengthening

The Committee was aware of the efforts needed to develop the RCS programme, which originally involved considerable efforts by the Research Strengthening Group (RSG) and the

Secretariat in seeking suitable institutions and encouraging them to apply for grants. The role of the Secretariat was necessarily great. Now there are many institutions being strengthened, and the Programme will need to decrease very considerably the number of new institutions being added, and to be more selective in continuing support of those already within the Programme network. However, the Committee fully supports the RSG's position of leaving the opportunity open for new institutions to approach the Programme with a letter of intent. The RSG clearly has a most difficult task in balancing needs against opportunities for rapid scientific advances, but the Committee has great confidence in the RSG, based both on discussions with its members and on the minutes of its recent meetings.

The balance of membership in the RSG between developing and developed countries (8:4) is appropriate. RSG members from developing countries have an especially strong interest in RSG deliberations, and in this context the contributions of such members are of particular value. Members in disciplines relevant but not central to TDR's activities also bring valuable perspectives.

In building up the research capability strengthening activities of the Programme, the RSG rightly adopted in the past a very positive and encouraging attitude. It tried hard to give as much help as was feasible to institutions that showed promise. This was the way to get its highly innovative work off the ground. That phase is now completed for some institutions. The Committee has been very pleased to see the number of highly critical research scientists with international reputations from developing countries who sit on the RSG. The ERC strongly applauds the way the RSG has become more rigorous and analytical, which will be needed in negotiating the next phases of the work of the RSG.

However, it is also important for the RSG to continue to recognize that research institutions in different regions of the tropics are at differing stages of development. Human resources for research are often inversely available compared with the scale of tropical disease problems in different countries. The RSG has to match its approach to the stage of development of the research capability of each country.

6.3 Research Capability Strengthening as a 'Phased' Process

As the Committee sees the problem, the development of research capability is a 'phased' process. Different countries and their key institutions are at various phases of development at present, and the increased selectivity essential for the functioning of the RSG will in part consist of supplying only that support which is appropriate to the phase a particular institution or country has reached. The most basic situation is one in which human resources are almost completely lacking. It is clear that the RSG cannot take on all countries at once simply because there is a need. Much selectivity will need to be exercised, especially as the majority of highly appropriate institutions will already have been the subject of some support.

However, for institutions selected for support at the earliest stage of development, the key form of support will be training for potential members of staff, and in view of the time this takes and the need under the circumstances for trainees to leave the country for a time, other forms of institutional support, such as equipment, will only need to be in place and functioning at the time of the trainees' return. It should also be accepted that the assessment of research potential is difficult and that not everyone sent for training from 'new' institutions may be suitable for a research career, however great an attempt the selectors make to get the appropriate people. Therefore, such trainees (from institutions at the earliest phase of development) should not have permanent posts in their institutions until they have both completed training and also demonstrated research competence. Such an approach would ensure building a core of staff truly capable of conducting research.

The next phase, largely followed by the RSG at present, involves development of facilities, training, and usually provision of time-limited support for posts, with a guarantee that salaries will later be taken over by the institution or government (usually after five years). This is good, and highly appreciated by institutions, which receive substantial but flexible help. In general, a second five-year period on this basis is to be avoided.

In the third phase, RSG funding will be closely linked to involvement in the disease-specific projects of TDR. Programme-based grants and R&D grants are available for this phase. Decisions on programme-based grants should be made in part by the relevant Steering Committees, as discussed below.

6.4 Future Development and Integration of Research Capability Strengthening and Research and Development Activities

The Committee welcomed the detailed proposals for integration of the R&D and RCS Programme Areas, as developed at the twelfth meeting of the RSG (document TDR/RSG(12)/87.3). These were rigorous and realistic. The crucial feature of these plans was the programme-based grant, designed as the logical step in the progression from a general institution-strengthening grant to the ordinary research project grant mechanism. The programme-based grant, with its permissible five components of developmental support for new disciplines, staff interchange, limited managerial assistance, core facilities and pre-career commitment positions, combines firm control with flexibility in the support needed to get a research programme, in the form of a group of related projects, under way effectively. The pre-career commitment positions are especially welcome as a means of avoiding the premature granting of tenure to as yet unproved research trainees and junior workers.

The three 'requirements for acceptance' of an institution for programme-based support are also realistic: it must provide training nationally; it must relate to national disease control programmes for the relevant disease; and it must develop a plan for field research or field application of laboratory research which will be carried out by the institution itself or by an appropriately linked institution.

The need for very good population-based epidemiological work by institutions will, in our view, increase steadily as new products -- above all vaccines and chemotherapeutic agents -- become available for field trials and particularly for assessment of their epidemiological impact at the community level. This requires, of course, that study populations be well defined and that epidemiological baseline studies be carried out before vaccine or other trials begin. Thus, there is a substantial amount of lead time during which other studies of tropical diseases in the communities can usefully, and in the interests of the inhabitants, be pursued.

In view of the difficulty often experienced in setting up epidemiological work of this type, the Committee welcomes the active measures taken by the Programme to link such work to the award of programme-based grants. The task of carrying that through in a realistic way will be complex. The much closer linking of the Epidemiology Component to RCS activities is a sound move in facilitating this.

The Committee sees great potential in the development of sites and assessment of populations for field research. In the past, population-based research has, for historical reasons, often been 'free-standing' and supported by WHO, or related to institutions other than the major universities or other teaching and research institutions. These institutions have then been underutilized for training, have not become part of the general education of medical and other health workers, and have 'disappeared' at the end of the research period. The proposed new arrangements provide for the first time a sound basis for longer term development of population-based research.

The actual process of integrating Programme Areas II and III will likely prove to be fairly difficult. The Committee most strongly supports the process but considers that adequate staff will be needed to carry it out without losing ground along the way. There has been in recent years considerable change in the RCS secretariat. Members of disease-specific Steering Committees will need to become familiar with the staff of the institutions being strengthened, with whom they will need to interact. Regrettably, some present SC members may either be uninterested in research strengthening, lack the time, or have no particular talent for it. The Secretaries of the disease-specific Steering Committees will need to become better acquainted with the staff of strengthened institutions. Disciplinary or disease specialists (such as the SC Secretaries) are by the nature of their background, interest and appointment going to proceed from a primary interest in the subject matter rather than in institutional development, and a substantial proportion do not have qualifications or experience in the fields of education, teaching or training. Their primary goals are to study and control diseases rather than to develop research capability.

We are confident that the integration of Programme Areas II and III can be made to succeed, but it will represent a considerable challenge to the staff. The integration will require strong support from Director, TDR, and the Committee expresses some concern that the present RCS staff may be insufficient in number to handle the heavy demands on them during the complex change-over period.

The Committee noted the plans of the Programme for collaboration with the Rockefeller Foundation in 'twinning' arrangements between institutions, as discussed by the RSG, and welcomed the opportunities it provides for increased activity of the Programme. The mechanisms for setting up this collaboration were not fully worked out at the time of the ERC meetings. It will be important for the selection process to be handled sensitively by both organizations, if undue pressures are to be avoided. It will also be necessary to work out how this approach will be incorporated into RSG operations in terms of greater integration with project funding and channeling through the SCs, and with the other concerns of the RSG. The Committee hopes these questions will be addressed so that the collaboration with the Rockefeller Foundation can fulfill all its potential to be of great benefit to the goals of the Programme.

In strong support of the closer interaction between, and in some respects integration of, the Programme's research strengthening and research and development activities, and in agreement that some degree of partnership between institutions and laboratories in developing and industrial countries is greatly to be encouraged, the Committee believes that several issues must be borne in mind and handled with the greatest sensitivity.

First, the Committee would wish to see preserved the conviction, affirmed by the establishment of the Research Capability Strengthening Programme Area, that there is a need to continue to build up tropical disease research capability and self-reliance in institutions in developing countries for the future and that this activity is a valid goal in its own right. It has been the practice to view institutions in developed countries in their own right. It is not accepable to view institutions in developing countries simply as a means to achieve certain defined research goals. As the process of integration of R&D and RCS support becomes more focused and restricted (to achieving TDR goals), it is greatly to be hoped that the broader goals and activities related to strengthening DEC self-reliance in research will be taken over by WHO (as a whole) or some other entity.

Secondly, in any collaborative arrangement between institutions in developing and industrialized countries, true partnership is needed. The temptation for an institution in a developing country to view the arrangement as primarily a source of scarce funding, or for a laboratory in an industrialized country to regard it as acquiring a field facility, is unacceptable. The process of establishing collaboration must be allowed to develop naturally from common interests. The Committee recalled with approval the system followed in the past

of making the supported institutions entirely responsible for the selection of their consultants from developed (or other) countries. The consultants reported to the head of the supported institution and not to TDR primarily. This safeguarded the freedom of action of the supported institution and avoided the development of a dependent relationship.

We would also draw attention to a converse problem. It is increasingly difficult for epidemiologists and other young scientists in industrialized countries to get extensive field experience in disease-endemic countries. Institutions in DECs are doing a service to future global needs by allowing younger workers from industrialized countries to live and work in their countries (at no expense to the country), and this practice has great potential for mutual benefit.

6.5 Training

The advanced training of doctoral students has been a productive activity, and many of those trained have rapidly come to play a key role in research in their home countries and regions. The Committee was particularly interested in the changing pattern of doctoral training in epidemiological and related areas, whereby the trainee spends up to one and a half years in his/her own country doing the field work before returning to the university where he/she is registered to complete the analysis of data and write up a thesis. A visit by his/her supervisor to the field midway through the data collection is included. This combines the advantages of overseas study and a firm local grounding. The possibility of providing funding for the research (as distinct from funding for the student) during the field project makes possible genuine epidemiological research, which may require field staff and be costly, and enables the trainee and supervisor to focus on real problems of tropical disease epidemiology and control.

Among the disciplines in shortest supply for the needs of the Programme in developing countries are epidemiology and the various disciplines grouped together as social sciences. The RSG has supported individual doctoral training in the social sciences. The Committee was glad to observe that the RSG is now addressing the training of social scientists in relation to present and future Programme needs. The Programme has already increased the legitimacy of social science involvement in tropical disease research and it now needs to build on that by increasing the supply of able researchers, in the areas of anthropology and economics in particular, but also in other related areas of sociology, the management sciences, public policy, etc. Courses at the master's degree level will be of value and will need to be based in social science and other departments with the relevant experience and links to other aspects of tropical medicine. Such courses should be developed only where the local capacity to sustain them, once started, exists.

7. Programme Execution

7.1 Strategy

TDR supports goal-oriented research and training. The orientation towards specific goals does not exclude support of basic research that in a long-range perspective can be foreseen to provide information relevant to attaining the Programme's goals.

In launching the Programme, the basic strategy adopted was to rely on existing structures in the form of universities and other national institutions. This was a very important decision. Two apparent options existed: building on existing structures or creating new structures in the form of specialized institutes. The latter solution has been predominant in

building up research and development within the agricultural sector. The strategy adopted by TDR is more complex and more problematic in terms of prejudging the outcome. If an institute is created with a specific task to fulfill and there is flexibility in hiring practices and salary structure, it is possible to attract highly qualified researchers. Further, an institute may reach a high volume of research in a comparatively short time. There are, however, apparent drawbacks, not the least of which may relate to the long-term perspective. The development of an institute will depend highly on its leadership. Recruitment of graduate students may be difficult or may not even be considered. An institute may also be in danger of being separated from universities and leading a life of its own. Under such circumstances, it is even more dependent on leadership if it is to be successful.

Building on existing structures, such as universities and national institutions, has the advantage of pluralism. One can afford more mistakes since the investments will be spread over a number of institutions. One can achieve a broader commitment from the scientific community, i.e., researchers not initially or primarily involved in the specific research areas pertinent to problem solving may become interested in them. It is likely to be easier to attract graduate students and also to emphasize graduate training. Drawbacks are the likelihood of some bad investments and the time it may take, even in successful cases, before scientific productivity reaches a significant level, qualitatively and quantitatively.

The ERC concurs with the strategy adopted by TDR. Behind TDR's decision must lie the conviction that in adopting this strategy the possibilities of involving many universities and national institutions in devoting increased efforts in research and development relating to the target tropical diseases are greater than if one were to use the TDR resources for creation of a small number of institutes, devoted exclusively to research and development. Further, the strategy adopted appears to be a prerequisite for implementing the important second objective of TDR, strengthening of research capabilities in the endemic countries. In the opinion of the ERC, research training is an important aspect not only of the second but also of the first objective of TDR. The strategy adopted is more likely to enable research training to take place on a broad basis than would a strategy involving creation of separate institutes.

7.2 Balance between Research and Development and Research Capability Strengthening

The two objectives of TDR are certainly interdependent. The mechanisms developed by TDR to work towards these objectives could involve a certain danger of separating the objectives. The two objectives are reflected in two Programme Areas, and the supporting structures are somewhat different. Programme Area II, Research and Development, is primarily responsible for the first objective and Programme Area III, Research Capability Strengthening, for the second objective. The ERC feels that there have been reasons in the past to separate the two Programme Areas. By separating the objectives into two Areas, better possibilities may have been created for emphasizing the importance of research strengthening. On the other hand, the difference in the number of TDR personnel involved in the two Areas is striking. Within Programme Area II there are a number of disease-specific Scientific Working Groups with their Steering Committees and supporting staff for each of them. In Programme Area III there is one Research Strengthening Group and only a few professional staff positions. The difference is perhaps even more striking, considering, on the one hand, that for a number of years about 25 per cent of TDR's total financial resources have been utilized for research strengthening and, on the other, that research strengthening requires considerable resources in terms of management, etc.

One of the long-range goals in research strengthening is that the researchers in the strengthened institutions should be able to compete for research support from Programme Area II. To accomplish this goal, input into the strengthening process from SC members and SC Secretaries may be required. Conversely, RCS staff can play a role in SC activities by

informing SC Secretaries about, for instance, young researchers that might qualify for pre- or postdoctoral positions within Programme Area II projects. Needs for intensified cooperation between Programme Areas II and III will become more apparent in the near future as more and more institutions complete their research strengthening grants. However, in earlier phases of research strengthening there may be a need for greater input of SC members and SC Secretaries.

With respect to the balance between the two Areas, a number of factors have to be taken into account. It is apparent that at the beginning of the Programme and even more so before the Programme really got started there were differing opinions. At the one extreme, it was considered best to use the resources for support of the most advanced research, predominantly carried out in the developed countries; at the other extreme, it was considered most appropriate to use the resources for research and research strengthening in the endemic countries -- possibly in part because a major part of TDR's resources came from budgets for development assistance. Even if this discussion still surfaces sometimes, it seems to the ERC that there is, within the Joint Coordinating Board, the Scientific and Technical Advisory Committee and TDR itself, general agreement that the present balance is reasonable. In the opinion of the ERC, the balance at present is adequate. It is difficult to see that it would be possible to expand research strengthening to a significant extent with the staff resources recently and presently available within the RCS Area of TDR. In addition, the last few years of budgetary uncertainties must have had the effect of limiting solicitation of proposals from institutions that might have wished to receive research strengthening grants. These factors would have dampened any trend towards expansion of RCS. Another factor that also might have mitigated against major growth in RCS activities during the last few years is the need for evaluation of previous achievements in research strengthening. A five-year evaluation was presented in the spring of 1987 by a Scientific and Technical Review Committee of STAC and included proposals for some changes in RCS activities. These factors and events have prompted a period of stabilization and assessment of RCS activities. It seems thus that the recent policy of not trying to involve many new institutions in research strengthening has been wise.

7.3 Strategic Plans and the Role of Scientific Working Groups

TDR has a comprehensive document on its work plans, which was published in TDR Newsletter No. 22. The TDR Newsletter has a wide circulation and the work plans have thus reached a number of researchers around the world. The processes behind the formulation of these work plans are not well defined. It is probable that they represent the combined efforts of SWG meetings, SC discussions and the Programme Secretariat and Director, TDR. The overall role of SWGs in TDR management is discussed in Section 7.5.1.

It is apparent that the original ideas for SWGs have not been altogether implemented during recent years. This is not necessarily a drawback. Developments have taken place that have given SCs a bigger role in planning. Since the idea of SWGs seems to be firmly anchored, the ERC sees no reason to propose a change. It seems to the ERC that SWG meetings, whether they are workshops, state-of-the-art conferences or the like, are important in Programme development. Furthermore, they contribute to the already good collaboration between TDR staff and staff on the WHO regular budget (SWG Secretaries are regular budget staff).

7.4 Encouragement of Proposals Related to Strategic Plans

The research supported by TDR is primarily 'investigator-initiated'. This holds particularly true for the research carried out within Programme Area II. Steering Committees, members of SCs or SC Secretaries may approach scientists to ask them to submit proposals on a given issue of interest and importance for the goals of the SCs. Thus, these proposals can still be considered investigator-initiated. Within Programme Area III, applicants also have to specify in their proposals the nature of the work to be undertaken. In this case, however,

considerable effort is made by the RSG, RCS personnel and other TDR staff to assist in the formulation of proposals. In view of these procedures, it is important for TDR to make its short-range and long-range plans known widely. To this end, information is distributed in various ways. There is the TDR Newsletter with its wide circulation. The WHO Regional Offices have a role in information dissemination. Through workshops, etc., knowledge is spread about TDR and its objectives. The ERC finds that the different efforts of this type are sufficient. However, the ERC thinks that more efforts could be made by TDR staff to stimulate individual researchers to apply for research grants from TDR. TDR does not have a 'research council' type of responsibility to support research but rather is a mission-oriented Programme which must ensure, through such proposal stimulation activity, that the research needed for its goals is carried out. This encouragement of proposals should be used rather extensively.

The solicitation of proposals within the Research Capability Strengthening Area is a special case. It can be assumed to be sensitive. One must foresee the likelihood that a considerable number of institutions might benefit from research strengthening grants. On the other hand, regional distribution must be taken into account. In the opinion of the ERC, an essential criterion for the selection of institutions for research strengthening must be the probability that the institution, in being strengthened, will contribute significantly towards the achievement of TDR's ultimate goals in addition to filling national needs. National support from and commitment of the government are prerequisites for institution strengthening. The RSG has formulated a number of criteria that should be met for an institution to qualify for research strengthening. The ERC supports the RSG in this matter.

7.5 Management

7.5.1 Managerial Structure of TDR

The management structure of TDR is rather complex. The top management body of TDR is the Joint Coordinating Board. The JCB has 30 members and a number of observers, and meets once a year. The Standing Committee is composed of representatives of the co-sponsoring agencies -- the UNDP, the World Bank and the Executing Agency, WHO. It meets at least twice a year, once at the end of the year and again between meetings of STAC and the JCB. The Standing Committee plays an important role by continuously monitoring the Programme, especially concerning its overall management.

The Scientific and Technical Advisory Committee is responsible for reviewing all TDR activities. STAC, which has 15 to 18 members, also meets once a year. STAC appoints special review committees, Scientific and Technical Review Committees, which analyse specific Components of the Programme. These reviews cover a five-year period of activity, and the members of an STRC are STAC members and other experts.

There are numerous Scientific Working Groups. Excluding the SWGs on Biological Control of Vectors, Epidemiology, and Social and Economic Research, SWGs are disease-specific. In the case of malaria, there are three SWGs and in that of leprosy, two. The composition of SWGs is not fixed. In principle, the scientists involved in TDR projects within the area of an SWG are members. In addition, those researchers attending TDR meetings of various types are also members. As time has passed, it seems that the original concept and description of tasks for SWGs no longer correspond to reality. Many SWG meetings in the last few years seem more to correspond to state-of-the-art conferences, workshops, etc. In several cases, full SWGs have not been convened for several years. This has partly been due to budgetary constraints. For each SWG there is a Steering Committee which meets at least once a year to review research proposals and discuss plans of action. Research capability strengthening is handled by the Research Strengthening Group. The SCs and the RSG have six to twelve members each. The

SWGs, SCs and the RSG have Secretaries with support staff. Overall Programme management is the responsibility of Director, TDR, and his office. SWG Secretaries are WHO regular budget personnel; other staff are supported from Programme funds.

7.5.2 Staffing Structure

Total personnel employed by TDR amounts to almost 80 full-time positions. In addition, contributions are given by the staff in the technical units within WHO, Geneva. The TDR-employed personnel includes ten persons stationed in the WHO Regional Offices (excluding the Regional Office for Europe) who are partly paid for by the Regions. It would be unfair and incorrect to compare the management structure and staffing of TDR with, for instance, a research council. The tasks of TDR must be considered much more difficult and personnel-consuming since so many of the activities are carried out in developing countries. At present, about 50-60 per cent of total resources go to developing countries. Further, it should be borne in mind that the activities of TDR include arranging a number of workshops, state-of-the-art conferences and the like. Also, a number of technical reports and manuals are produced. This range of activity, which the ERC considers very important, is time-consuming for the TDR Secretariat. The ERC is impressed by the dedication and motivation which TDR personnel show for the work.

In the foregoing, the ERC has pointed out the differences between Programme Areas II and III in terms of relative levels of staffing. The ERC believes firmly in the importance of research strengthening activities and considers it possible to strengthen staffing within Programme Area III at the expense of that within Programme Area II. Furthermore, the need for some expansion of social and economic research requires additional SER staff. In the opinion of the ERC, some gains in rationalizing the operation of SCs and SC activities can be made. Maybe some gains can also be made in general support services. As stated above, the ERC is fully aware of the differences between the operations of TDR and those of a research council and has not applied a framework based on that of a research council. Yet it has to be pointed out that within Programme Area II, the total volume of grant applications, which constitute the most important part of the work of SCs, amounts to about 400 per year. This must be considered a fairly small number in comparison with the number of staff persons available for the task.

In recent years, the number of SCs has decreased. This must have led to some gains through rationalization of operations. The ERC considers it important to look continuously into the possibility of a further merging of Steering Committees. In principle, both vertical integration, i.e., one SC per disease, and horizontal integration, i.e., merging of discipline-oriented SCs (e.g., on immunology), could be considered, but their merits would need careful examination on a case-by-case basis. The possibility that the same support staff handle more than one SC should be explored; this may, in fact, be preferable to the merging of SCs.

In the foregoing, the ERC has proposed increased staffing in Programme Area III and in the SER Component at the expense of staffing within Programme Area II. It also believes increased input into Programme Area III from staff primarily engaged in Programme Area II (which is discussed below) is necessary. The ERC thinks that these changes can be accomplished if the proposals made above for streamlining SC operations (as discussed below) are carried out.

The ERC wishes to go one step further in its discussion of TDR staffing. As mentioned earlier, management of TDR involves a large number of personnel. Of the total budget of about US $25 million a year, personnel costs represent about 16-18 per cent. Total professional staff represent 33 full-time posts (of which five are stationed in the WHO Regional Offices and partly paid for by them) and general support staff, 43 full-time posts (of which five are stationed in the WHO Regional Offices and partly paid for by them). In addition, WHO regular

budget staff take part in Programme activities. Conversely, TDR staff have an input into regular budget activities. The volume of personnel has been the same for a number of years. The ERC acknowledges the need for a comparatively large number of staff in the building-up phase of the Programme but is less convinced that staff needs remain the same now that the Programme has matured. The ERC proposes that an in-depth analysis of staff needs for the coming years be made by TDR management, together with an independent consultant with expertise in science administration.

7.5.3 Grant Application Review Procedures

With respect to SC operations in terms of appraisal of grant applications, there are differences between the different SCs. A major difference deals with the extent to which external reviewers are used. In some SCs many or most applications are reviewed by external experts. In others, external reviewers are used less frequently, but predominantly in cases where the applicant is a member of the SC, or associated with a member, or when there is insufficient expertise within the SC. Furthermore, the limited number of experts in a given field may preclude the use of external reviewers -- the experts are already members of the SC. SC members receive applications by mail or upon arrival in Geneva before the SC meeting. It is often the case that a lot of material has to be given to the SC members upon arrival in Geneva, even if the aim has been to send out applications beforehand. Scoring systems have been used to varying extents in the different SCs. Some SCs have used these for quite some time whereas others have introduced them fairly recently. It appears that the aim is to have a unified system. Two scores are used, one for scientific merit and one for relevance to SC goals. SC members are not requested to send in scores to the Secretariat before the meeting. The procedure is that SC members give their scores after a given application has been presented. Each application is presented by one or two members of the SC, and the presenters are informed beforehand that they are to present an application. The presenter has access to the external reviews and informs the SC about the conclusions of the external reviewers.

Several questions may be raised concerning the procedures employed. One deals with the use of external reviewers. It is difficult to form an opinion concerning the extent to which the external reviewers' reports influence decisions. Mention has been made of the fact that two reviewers may have quite different opinions concerning a given application. Secondly, it has been said that it is frequently difficult to get people to act as external reviewers.

The time given to SC members to read and form an opinion about the applications varies and is sometimes very short. The question must be asked if it is possible for all members to go through all applications. There are several reasons why applications are not always sent out to SC members. The volume of material is large and there may be problems with postal delays. Also, there is a lack of discipline on the part of some applicants who do not observe deadlines set by TDR.

7.5.4 Options for Improving Operations

The ERC would like TDR to consider procedures with respect to grant applications similar to those used by research councils and corresponding organizations. In the opinion of the ERC, a major responsibility of the SCs is a thorough analysis of grant applications. The SC members are better informed and more aware of research goals within an SC than are external reviewers and can thus see much better if the project will meet these goals. To give SC members the opportunity to go through applications, they should always be sent beforehand. In judging the applications, every member should give an evaluation in the form of priority scores including a score for relevance to SC goals. The ERC is aware of the fact that in the SCs which cover the whole field of research on a given disease not all members can be expected to be familiar with everything. Yet, in the experience of the ERC, it is likely that a person

experienced in evaluating grant applications can form a sound opinion about an application even if it is outside his/her direct field of research. In specific cases, an SC member could limit scoring to a score for relevance of the project to SC goals. One or two members should be asked to introduce an application and should be notified thereof when receiving the application. The priority scores should be sent back to TDR to be put together before the meeting. It might be argued that those SC members who are not experts in the field of a given application might wish to listen to the presentation by an expert before giving a score. To the ERC, this means an overemphasis on the importance of the specific numerical value of a score.

External reviewers should be utilized whenever necessary but not as a rule, e.g., when the SC lacks sufficient expertise, or when the application comes from a member of the SC or somebody collaborating with a member. To overcome problems with postal matters, there could be a standardized format for applications, i.e., a maximum number of pages for research proposals. Appendices in the form of manuscripts and reprints would be sent only to those presenting an application at the SC meeting; other members would receive a list of the manuscripts and reprints appended to the application.

The above options are offered as possibilities for consideration. If changes like those indicated above were made, gains could be envisaged. The ERC thinks that the involvement of all SC members in setting priorities would be strengthened since they would all be required to express their appraisal of a given application in terms of a priority score. A consequence might be a stronger focusing on SC research goals, thereby also defining more precisely research needs. It could be of value to consult people with experience in the administration of a research council or similar organization for implementing the proposed changes in procedures for grant reviews.

7.5.5 Interactions between Programme Areas and Components

Another aspect of Programme management deals with the interaction between SCs and between SC Secretaries. The ERC finds that such interaction is important for a successful Programme. From discussions with TDR personnel, the ERC has come to the conclusion that there are considerable variations in the extent of communication between SC Secretaries. Since the ERC considers TDR to be an integrated Programme, it thinks that there are reasons to stimulate further interaction. One way could be to increase the volume of seminar-type activities, and another and complementary way could be to circulate minutes of SC meetings. This brings the ERC to the question of minutes. At present, these are confidential and available only to a given SC and its Secretary. Furthermore, they vary in format. Some are needlessly voluminous (more than 50 typewritten pages). The ERC thinks that minutes of meetings can be very informative and would like to propose that all minutes of SC meetings should be circulated among TDR staff. To avoid that minutes are not read on account of their large volume, standardization entailing a brief format could be introduced.

Another type of interaction deals with the cooperation between Programme Areas II and III. The ERC thinks that there is room for additional input into Area III from staff primarily engaged in Area II activities. SC Secretaries can certainly contribute greatly through 'on-the-spot' work in institutions being strengthened. This would mean that duty travel should be increased substantially. The ERC has the impression that duty travel in recent years has been kept at a level that is lower than that in earlier phases of the Programme. Financial considerations may be behind this development. In the opinion of the ERC, duty travel to institutions in developing countries by TDR staff has very high priority.

7.5.6 Director's Initiative Fund

One aspect of budget management deals with the possibilities of allocating grants at short notice. The Programme has a Director's Initiative Fund amounting to US $262 000 per year. Grants from this Fund normally do not exceed US $15 000. The grants are to be used for start-up or 'venture' activities and the funding is separate from Component budgets. Because of the rapid pace of progress in basic aspects of research on tropical diseases, the ERC finds that there is a need to expand this Fund and to increase the amounts that may be awarded. The Fund should also be used for the purpose of increasing the budget of a Component. The ERC is well aware of the fact that revisions (not exceeding the JCB-approved level of a Programme Component's budget) may be made by Director, TDR, with the concurrence of Chairman, STAC, and the approval of the Standing Committee. However, this mechanism of funding new leads would be disruptive of morale and work already planned in the Components from which funds are moved. The ERC therefore proposes an increase of the Director's Initiative Fund to about US $1 million per year.

7.5.7 Recent Decisions Pertaining to Programme Management

Since the ERC started its work in December 1986, several changes in Programme management have occurred. In the spring of 1987, Director, TDR, proposed a restructuring of TDR involving a closer interaction between Programme Areas II and III. The proposal was endorsed by STAC and approved by the JCB in June 1987. This measure is entirely in line with the views of the ERC. Furthermore, Director, TDR, proposed the creation of a Programme Development Fund of US $1 million for the 1988-1989 biennium. This proposal was endorsed by STAC but not approved by the JCB. In the foregoing, the ERC has proposed an increase in the Director's Initiative Fund. At its session in June 1987, the JCB set up an *Ad Hoc* Committee to look into the problems of funding the Programme over the coming five to ten years. The *Ad Hoc* Committee had its first meeting in November 1987. The ERC believes a body of this type should be established on a permanent basis.

7.6 Top Programme Management

The higher levels of the management structure of TDR include STAC, the Standing Committee and the JCB. The ERC is impressed by the work of STAC. STAC reports show clearly how much insight STAC has in the operations of the Programme. Its proposals for change in emphasis in various Components and for giving priority to projects within Components are well founded and appropriate. There are examples of shifts of resources between Components. However, the general impression is that allocation to the various Components is rather stable. This should not be considered as a lack of flexibility. If and when TDR resources increase substantially, the ERC expects Programme Management and STAC to analyse in detail which Components should be given highest priority.

The Standing Committee plays a role in the overall management of TDR. The minutes of meetings of this Committee show that the Standing Committee deals with many important questions concerning the Programme, such as budget matters, fundraising, cooperation with the pharmaceutical industry, patent questions, etc.

The JCB, TDR's top management body, has in one way a less clear role in the management of the Programme than, for instance, STAC. The JCB decides on the level of the budget and budgetary components. Extensive material, including a proposed budget, is presented to the JCB in the form of reports of Director, TDR, and STAC. It is not apparent to the ERC to what extent, if any, the JCB itself has had reasons or wishes to make changes in allocations within the budget, i.e., the precise process by which budgetary levels are decided is not clear. One has to bear in mind that the JCB is a large congregation of 30 members and a number of

observers; discussion of complex scientific budgetary matters in a group of such size is difficult. Furthermore, the Chairman is elected for only one session. The ERC believes that JCB participation in budgetary matters could be enhanced as discussed below.

As the ERC sees it, the JCB has an important role as fundraiser. It is not clear to the ERC what role the JCB has played so far in this respect. The ERC would like to propose that the JCB consider the possibility that its Chairman be elected for a three-year period and that a permanent subcommittee be set up to work on various issues between sessions of the JCB. One task of this subcommittee should deal with fundraising. The proposal of a longer mandate for the Chairman should be viewed as a measure to increase the involvement of the JCB in the Programme. The possibility of the JCB Chairman being an ex-officio member of STAC might also be considered.

The ERC reviewed the roles and responsibilities of the Special Programme Coordinator and the Programme Director and their relationships. It believes that the existing arrangements have worked successfully and recommends that these not be changed. The Programme's co-sponsors should be actively involved in the selections and appointments of the Director and the Special Programme Coordinator.

7.7 Management Information System

TDR has developed a computerized information system for the Programme, the TDR Management Information System (MISTR). MISTR monitors all TDR-financed activities. It contains data on progress of TDR projects, including funding decisions, progress reports, renewals and project completion. All publications resulting from TDR projects are recorded. Through MISTR it is possible to obtain analyses of Programme structure in terms of discipline, geographic distribution and time span. A number of documents are produced through MISTR, such as TDR "Facts and Figures" (now replaced by the "TDR Management Summary Report"), TDR country profiles, etc. MISTR also contains mailing lists for the TDR Newsletter and other TDR publications. Thanks to information from MISTR, it has been possible to compare data on publications resulting from TDR-supported projects with total publications relating to the six diseases obtained from the National Library of Medicine. The ERC is impressed with TDR's achievements in the field of information systems.

7.8 Programme Review and Evaluation

TDR is reviewed extensively. The review of applications for continuation of grants by SCs and the RSG is an important mechanism for evaluation. The review includes not only scientific progress but also an analysis of pertinence to the overall goals of a Programme Component. An additional and highly important mechanism of peer review and evaluation is built into the process of publication in scholarly journals. Much of the work supported by TDR is published in international journals with referee systems. The ERC wishes to emphasize the important role that this mechanism plays in ensuring scientific quality (see Section 4.4 and Annex V).

STAC evaluates the entire Programme each year and analyses one or several Components in detail on the basis of Scientific and Technical Review Committee reports. STRCs are appointed by STAC and have the task of reviewing in detail the activities of each Component in a five-year cycle. After having gone through a number of STRC and STAC reports, the ERC has found that the evaluation of the Programme is of high quality. Sometimes it is said that TDR may be the subject of too much and too frequent evaluation. The ERC finds that the present mechanisms are certainly adequate in quantity and does not propose either less or more evaluative activities.

The JCB has an evaluative role in a broader sense. At its sessions, the reports of Director, TDR, the Standing Committee and STAC are discussed. The JCB can make changes in

the Programme Budget and emphasize or de-emphasize Components. To the knowledge of the ERC, this happens rarely.

Even if the Programme Report is not to be considered an evaluation, the ERC wishes to mention the report in this context. The report, which is now biennial, is both extensive and well written; it provides detailed information about progress in research and development concerning the six diseases, with mention of what is happening inside and outside TDR. The latest Programme Report, the *Eighth Programme Report*, is worthy of special mention. It contains an overview of the first ten years of TDR activities and is a necessary companion to this review.

8. Boundaries of Responsibility and Capabilities in the Development and Application of Disease Control Tools

8.1 Boundaries of Responsibility

The terms of reference of the second external review and evaluation of the Programme included an examination of its relationships with other programmes and institutions active in the field of tropical diseases, including those of WHO and governments in developing endemic countries. STAC(9) recommended, with the endorsement of JCB(10), that the ERC should elaborate guidelines for the responsibilities of TDR, WHO and public health services in tropical countries for the utilization of disease control tools resulting from TDR-supported activities. The Committee considered in depth this aspect of its mandate. To ensure that it fully understood the relationship with the WHO technical units concerned with tropical disease control, the ERC met with the unit chiefs or their designees from all such sections. The Committee also held discussions with current national disease control programme directors and with those concerned with supporting the implementation of primary health care in the WHO Division of Strengthening of Health Services.

The guidelines elaborated below are not a departure from the philosophy which has underpinned the Programme since its inception, but are rather a reiteration of that philosophy in somewhat more operational terms.

The guidelines discussed later in this section derive from a number of fundamental convictions on the part of the ERC, which include the following:

- The Programme's overriding mission is to support and promote the development of new disease control tools.
- The responsibility for application of disease control tools on an operational scale lies with the national disease control programmes and primary health care systems of the governments of developing endemic countries.
- The relevant WHO technical disease control units (Malaria Action Programme, Parasitic Diseases Programme, Division of Vector Biology and Control, and the Leprosy Unit) have the responsibilities of supporting national governments in control efforts and in the initial general application of new disease control tools.
- TDR resources are most cost-effectively employed in a 'catalytic' or exemplary fashion, which includes providing models for the development and testing of tools by others.
- Active communication and collaboration between TDR Components (disease-specific SCs, the Epidemiology, BCV and SER Components and the RSG), WHO technical units, personnel in WHO Regional Offices, national governments (ministries of health, control

programmes, primary health care systems, research institutions in developing and possibly developed countries), and probably industry will be essential in testing the utility of new disease control tools. Such communication and collaboration will be most effective in a situation in which respective roles are understood by all participants and in which each has the resources needed to contribute according to its appropriate role.

These considerations led the Committee to formulate the following general guidelines for TDR responsibilities:

- The Programme should fund basic research, the results of which would have clear relevance to the Programme's objectives and work plans.

- The development of basic research findings into concepts and prototypes for disease control tools clearly should be a major activity of the Programme.

- The Programme should participate in and fund field research that is necessary to demonstrate the utility of new disease control tools in the intended settings of use and to identify the optimal initial approaches to their application. TDR involvement in field research of this type should focus upon model studies with new classes of disease control tool to demonstrate how such testing should be conducted. It should not be necessary for TDR to be a major participant in all field testing, e.g., of analogues of efficacious drugs already studied. (This recommendation arises from the conviction that the Programme's resources can be used most effectively in this fashion.)

- Social and economic research conducted in collaboration with ongoing national disease control programmes will be necessary in order to gather information about knowledge, attitudes, beliefs, and other cultural, social or economic variables necessary for understanding how these factors may affect disease control efforts and the introduction of new disease control tools.

- Because application of many of the new disease control tools emerging from TDR-supported research will be channelled through primary health care services, the Programme should support research intended to identify optimal approaches to the use and introduction of such tools into such systems.

- The Programme will need to be selective in choosing which field research projects to pursue. The ERC favours giving priority to studies involving tools developed with TDR support, as the Programme will already be familiar with such products. Under selected circumstances TDR may support operational research for increasing the effectiveness of the use of disease control tools already in routine application.

- TDR efforts in research capability strengthening should always be relevant to its targeted mission and needs. Broad institution-strengthening support should only be provided in exceptional circumstances, e.g., to fill a geographic need, and should always be clearly linked to a specific Programme objective. The RSG has a responsibility to withdraw its support of institutions that are judged either to be progressing too slowly or likely to be able to compete effectively for other sources of support (e.g., programme-based grants or R&D grants).

- TDR regional representatives should be actively involved in promoting awareness of the Programme in their Regions, facilitating research efforts and providing assistance in research capability strengthening efforts.

The ERC makes these suggestions as guidelines rather than rules; the Secretariat and governing bodies should be able to deviate from them, after appropriate consultations, if exceptional circumstances arise.

8.2 Capabilities of Entities with which TDR will Need to Interact in Clinical Testing, Field Testing and Application of New Tools

As noted above and in the *Eighth Programme Report* (especially Table 1.1), in the next few years a large number of new disease control tools will probably emerge from the laboratory phase and pass through field testing to initial introduction into disease control programmes and primary health care systems. This chain of progression involves a number of interacting groups, each with primary responsibility for particular facets. All of these entities must be functioning effectively for the process of development, from initial conception to application, to occur smoothly and without delay. The Committee considered the capacities of the major entities with which the Programme will need to interact to participate in such collaborative endeavours.

8.2.1 Industry

The ERC reviewed the many instances of collaboration between the Programme and industry, predominantly multinational pharmaceutical companies. It also reviewed the current WHO guidelines on such interaction where they pertain to patents.

The Committee was encouraged by the increasing number of instances of collaboration between TDR and industry. The ERC commends the Programme and the companies involved for establishing such productive relationships. The Committee expresses the hope that the companies presently collaborating -- and new ones -- will continue to demonstrate their concerns for the welfare of those in developing endemic countries through such efforts.

While the ERC was not able to judge the resources available to pharmaceutical and other companies that might be devoted to collaboration with TDR, it believes that in cases of obvious need, the availability of technical and financial resources *per se* within such companies will not be a limiting factor. A more likely limiting factor will be the willingness of senior management in companies to apply these resources to the needs identified by TDR. In this regard, the ability to make a well-prepared case to industry regarding the importance of the problem and their involvement cannot be underestimated. Preparing materials to support arguments for expanded industry involvement will require resources.

8.2.2 National Disease Control Programmes and Primary Health Care Systems

In utility testing and in defining optimal approaches to the introduction of new tools, TDR will need to work closely with many individuals at the local and national levels in disease control programmes and/or primary health care systems in developing endemic countries. From its aggregate expertise and interviews held in connection with the review, the ERC has grave concerns about the resources that are now available and those that are likely to be available in the future for improving health, and particularly for combating the TDR target diseases in developing endemic countries. If this situation does not change, the new disease control tools likely to emerge from TDR efforts will remain underutilized.

A number of reasons can be identified for this inadequate provision of resources:

- The economic impact of the target diseases has not been well substantiated.
- The target diseases are often predominantly rural and therefore do not gain the immediate attention of largely city-based policy makers.

- The emphasis of specific disease control programmes may be set during the establishment phases of primary health care.
- Improvement of health as a necessary component of economic and social progress has not received adequate attention.
- Most of the countries severely affected by the target diseases are suffering from economic conditions that do not allow adequate expenditures in these areas.

Funding studies of the true economic and social costs of the target diseases may help raise their priority in DECs. Thus, TDR itself might indirectly contribute to raising awareness of the target diseases.

It was obviously beyond the scope of the ERC mandate to explore these issues in depth. However, the ERC does feel strongly that the problem is not one of the redistribution of available funds. The Committee urges the Executing Agency and other Programme co-sponsors to recognize that new disease control tools may not be introduced or may be underutilized if those with whom TDR needs to collaborate (e.g., WHO technical units) or those applying the tools (e.g., health systems in DECs) do not have or do not devote adequate resources needed to play their part in the development and application of disease control tools.

8.2.3 WHO Technical Units Supporting National Disease Control Programmes

Various technical units in the regular budget programme of WHO provide support to the disease control efforts of national governments. The Committee reviewed budgetary information suggesting that the level of support for the activities of these units, at headquarters and especially at the regional level, was in decline. Because accounting procedures had changed, it was not possible to derive precise comparisons over time. Nor was it possible to determine the extent to which the decline was attributable to the general shortfall in WHO regular budget revenue.

The ERC was, however, gravely concerned that such a decline might prejudice the capacity of technical units to collaborate with TDR and to fulfill their primary function of providing support to national disease control programmes, which is essential if new disease control tools are to be utilized in a timely fashion. The usefulness of TDR would be undermined by failure to provide an adequate capacity in these units to meet expanding needs. The Committee urges the senior management of WHO at headquarters and the Regional Offices to consider whether projected support to the technical units that relate to TDR is sufficient for productive collaboration and for support of national programmes to ensure timely adoption of the use of new disease control tools.

8.3 Conclusions

In summary, the ERC reiterates that the activities of the Programme should focus upon the development of new disease control tools up to the point where their utility in the field has been demonstrated. Field testing for utility and approaches to initial introduction are part of a collaborative process in which national governments must play a role if they are to be maximally useful. Responsibility for routine application of the tools is that of national governments, with support from WHO technical units. This progression from 'bench to bush' requires contributions from a variety of sources other than TDR. To the extent possible, WHO and the other co-sponsors should take steps to ensure that all participants in this progression have adequate resources to play their part.

9. Communications and Interactions

The terms of reference for the second external review and evaluation of the Programme implicitly included the evaluation of its communications policy and interactions with other entities involved in activities pertinent to tropical disease control.

9.1 Groups with which TDR Should Maintain Communication

Groups with which TDR needs to continue to communicate and interact, either directly or indirectly, include (not necessarily in rank order):

- Scientists in the biomedical, social science and economic research communities, both those undertaking work related to tropical disease control and those who could potentially be recruited for such work. This group includes scientists working in industry.
- Educators, who influence student career paths or choices.
- Senior policy makers of commercial entities in relevant fields, especially the pharmaceutical industry.
- Policy makers in or affecting major institutions conducting research in areas pertinent to tropical disease control, such as national institutes of medical research, national research councils and national development/foreign assistance agencies.
- Individual groups involved in directing resources to relevant research, such as philanthropic foundations and independently managed funding programmes, such as the US National Academy of Sciences Board on Science and Technology for International Development Research Grants Program, which is supported by USAID.
- Staff in the relevant technical units of WHO.
- Individuals at various levels of national governments, including ministries of health, planning, labour and education; national disease control programmes; primary health care programmes; and, as noted above, policy makers in national institutions concerned with tropical disease research.
- Nongovernmental organizations involved in tropical disease research or control efforts (in some countries these groups play a major role).
- Contributors and potential contributors to the Programme.
- The scientific and popular press and other media.

9.2 Purposes of Communication

The ERC identified various reasons for which an active effort in communication with these groups was desirable:

- awareness of the impact of the target diseases needs to be raised among many of the groups noted above, and the need for tropical disease control research and development articulated to them;

- the mode of operation, objectives and scope of the Programme need to be understood by potential collaborators;
- specific opportunities to participate in the Programme need to be conveyed to them regularly;
- potential users need to be alerted to the likely availability of new disease control tools (i.e., TDR's 'products') and the best methods for their utilization;
- contributors of the Programme (and potential contributors) need periodically to be informed of its productivity and usefulness.

Thus, communication is needed to 'recruit' support -- political and financial -- to tropical disease control research and development in general and the Programme in particular, to recruit scientists to conduct Programme activities, and to prepare the way for TDR products to be utilized.

The types of information needed by the different groups with whom TDR should communicate will differ, as will the manner in which it should be presented to achieve maximum influence. Researchers may need detailed scientific information in a narrow area and will usually be willing to extract this from documents not targeted to them. On the other hand, policy makers, potential users of new tools and contributors may need to be informed quickly across a broader area of the Programme's directions, forthcoming products and achievements. The balance of communications expertise and scientific knowledge necessary to prepare and transmit such information successfully are likely to be different, so that it may be necessary to have different individuals devoted to preparing materials for the different audiences.

The ERC considered what would be the most appropriate channels for communication with the various groups listed above. For those individuals or entities that are involved in conducting or supporting research and development relevant to TDR's objectives, it seems appropriate for the Programme to have direct communication. The relevant technical units of WHO have routine contacts with the various national government groups that need to be kept informed of prospects for new disease control tools. Thus, it seems appropriate and efficient for the WHO technical units to be the primary channel for information to the governmental groups involved in disease control. Responsibility for generation of the necessary informative materials should reside within TDR. However, preparation of material should obviously be done in consultation with technical units to ensure that it meets the needs of the potential recipients, their primary clientele.

9.3 The Necessary Development of TDR Communications and Activities

As noted above, there has necessarily been an evolution in the range of activities of TDR. Social and economic research was added to initial activities in biomedical research and institution strengthening. There is presently an expansion in field development and testing of new tools. The *Eighth Programme Report* (Table 1.1) clearly illustrates that this trend will continue. More new tools will become available in the next decade for field testing or actual application.

The early phases of the Programme were characterized by a need to recruit scientists to research and development for tropical disease control. Much of TDR's communications efforts focused on information necessary for the expansion and advancement of research. Opportunities were announced in the TDR Newsletter which went to scientists. Technical information was often transmitted by TDR publication of reports of meetings, symposia and workshops. This supplemented the normal publication of research results by TDR-supported investigators in scholarly journals. The need to communicate with working scientists will continue, but the need to communicate with other groups will increase.

There has obviously also been periodic communication with individuals or entities outside the scientific research community over the years. This has been achieved in a variety of ways: sometimes at the level of Steering Committee Secretaries, but more often by Director, TDR, or senior Secretariat staff. Communication with these audiences appears to have received less visible, systematic attention than have technical publications.

The ERC believes that the Programme will need to develop a more active, systematic approach to addressing the need to transmit appropriately prepared information to all the audiences listed above. This need is a consequence of the Programme's development and will be, in the view of the Committee, essential to its future success. The Committee recommends that Director, TDR, in consultation with the Secretariat, the JCB and other relevant parties, formulate, as a matter of some urgency, a more defined overall communications strategy. Implementing such a strategy will, of necessity, involve devoting more personnel to generating the needed materials for various target audiences. As noted above, the variety of audiences and types of information needed suggest that in addition to those with technical/scientific and editorial expertise, there will be a need for individuals more oriented to supporting public relations, news media and fundraising efforts. Consideration might be given to a Communications unit with personnel for (1) supporting technical publications of the Programme; (2) supporting information flow through the WHO technical units to national governments, including control programmes; and (3) providing support to Director, TDR, in contacts with the media, contributors or potential contributors, and others involved in influencing policy relating to tropical disease control research and development.

In designing a new communications strategy, consideration should be given to the role that TDR regional representatives might play in promoting awareness of the Programme and in feeding information on needs and opportunities in their Regions to the Secretariat.

9.4 Publications Policies

Discussions with members of the Secretariat responsible for communications and publications were extremely useful and raised a number of issues upon which the ERC wishes to comment.

In the last five years, the editorial burden arising from technical publications on TDR meetings, workshops, conferences, etc., has been heavier than in the early years of the Programme's existence. The ERC favours increasing the use of scholarly journals or commercial book publishers to make this material available to the scientific community (versus the early practice of TDR publications). These publishing avenues could well lead to broader awareness of the materials than might result from self-publishing and will enable Communications unit staff to devote a greater proportion of their time to editorial and other work described above.

The biennial reports of the Programme, the *Seventh Programme Report* and the *Eighth Programme Report* particularly, are beautifully presented, comprehensive overviews of the status of research and development for control tools for the target diseases. They have conveyed the needs and intellectual challenges in the field of tropical disease research in an exemplary fashion. The Programme, and particularly those connected with report production, deserve great credit for these vehicles which effectively represent the Programme. However, the burden imposed upon the small staff of the Communications unit by their production has appeared to the ERC to be a significant one.

The possibility of modifying the nature of these reports or the schedule for their production was raised with the ERC. The Committee had considerable sympathy with the need to reduce the burden of preparing such publications. However, it firmly believes that reports of the quality and breadth represented by the recent volumes do a great deal to further the goals of the Programme and its visibility. They can, for example, be put to use as required texts

in academic courses, and thus may serve to recruit a new generation of investigators to tropical disease research.

Thus, the Committee commends to the Secretariat the reconsideration of the scope and schedule of Programme Reports, with the provision that such considerations recognize the value in producing, at reasonably regular intervals (three to five years), a comprehensive state-of-the-art review of research and development for tropical disease control.

9.5 Interactions

The fact that the Programme is but one player (albeit important) in the whole arena of research and development for tropical disease control means that it must interact and collaborate extensively with other pertinent groups. This is especially true given the 'catalytic' *modus operandi* adopted by the Programme. These pertinent groups are included in the list with whom the Programme must communicate. The extent to which interaction and collaboration will be necessary will vary depending upon the extent to which the missions of the other groups coincide with that of the Programme. Even with groups that wish to retain independent 'profiles' in the overall field (e.g., foundations which have particular terms of reference), there is potential for useful communication. Rapid communication of research results to TDR and its audiences from studies funded by third parties would promote their timely incorporation into overall Programme strategies. Similarly, meritorious applications to TDR which could not be funded because of resource constraints might be brought to the attention of other potential supporters on a routine basis.

In the next few years, there will be a large number of new disease control tools that will require field testing. This will require the extensive collaboration of many groups (including TDR) in developing endemic countries. There is already extensive experience with and involvement in such efforts by certain TDR Steering Committees, and more will be gained in the near future. The ERC suggests that the experience of these SCs should be analyzed to identify predictors of success which could be used to assess proposals for future ventures. Dissemination of this information, in the form of guidelines or principles, to SCs contemplating field work could be a part of promoting greater communication and interaction across disease-specific Components of the Programme.

The ERC was generally impressed with the Programme's extensive and productive interaction with industry in recent years. Broader sharing of experiences with industry between disease-specific Components may well facilitate the process of establishing productive collaboration by those SCs not yet so involved.

An important factor in making it easier to establish useful interactions and cooperative ventures is effective communication to potential collaborators of opportunities for involvement, as well as clear information about the Programme's role. Thus, development of a broader communications strategy, as discussed above, will assist in making the Programme's operation more productive.

10. Development of Resources

Following the establishment of the Programme, contributions rose rapidly to peak around 1980 at approximately US $25 million per year. A fall in contributions to slightly over US $20 million took place in the early 1980s, due to lower contributions from some contributors and fluctuations in exchange rates. Some carryover of funds was possible, but this period caused considerable strain within the Programme. It appears that contributions are now rising again to a level closer to US $25 million.

10.1 The Need for New Funds

The apparent levelling off of contributions at US $20 to 25 million so soon after the establishment of the Programme is viewed with concern by the ERC. In the early years of the Programme, scientific activities were largely concentrated on laboratory-based R&D. The needed shift to encompass expanded field work will require a considerable influx of new funds. Likewise, the desirable expansion of social and economic research (a doubling of funds is suggested within the next 3-5 years) should not come at the expense of other areas because TDR will always need a strong biomedical research base. Additionally, there are strong reasons for the Programme to move forcefully into rational drug development for tropical disease control. Even doing this in a catalytic fashion will entail a substantial need for new funds since it is an expensive undertaking even for single targets.

These needs being apparent, the Committee believes that it is useful to assess the general magnitude of additional funds needed by the Programme. The ERC believes that in the next five years there will be a need for funding at least 25 to 30 per cent in real terms above the present budgeted levels and that the Programme could administratively handle that amount with its present structures without problems.

The ERC suggests that precise fundraising targets be set by Director, TDR, and the JCB, on the basis of specific plans in each of the areas of likely expansion noted above -- field trials, rational drug development and social and economic research -- and of ensuring adequate funding for the presently planned efforts in all disease-specific Components, as well as in the Research Capability Strengthening Area.

10.2 Mechanisms for Supporting Fundraising

Since the Programme obviously needs expanded and more stable financial income, the ERC examined the Programme's mechanisms for fundraising.

The ERC finds that a more active effort will be needed in the coming quinquennium and that a more defined fundraising strategy needs to be developed. The ERC believes that primary responsibility for this effort should rest with the top Programme management body, namely the Joint Coordinating Board. The ERC approves of the establishment of an *Ad Hoc* Committee of the JCB to examine the Programme's financial prospects; it suggests that such a committee should exist on a continuing basis. Support to Director, TDR, and the JCB in fundraising should be provided from within the Programme. This support will need to provide expertise in fundraising techniques, communications skills in the development of materials and presentations, and knowledge of the appropriate procedures for contacting current and potential contributors. An extended term of office for the Chairman of the JCB, as suggested above, would allow more effective participation in fundraising efforts for the Programme. The exact manner in which an expanded fundraising activity is established is a matter for the consideration of the JCB, the Executing Agency and Director, TDR. However, the ERC stresses its importance in the coming five years.

ANNEX I:

Second External Review and Evaluation of the Special Programme

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

DISTR.: LIMITED
DISTR.: LIMITEE

TDR/JCB(9)/86.6 Rev.4
ORIGINAL: ENGLISH

UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR
RESEARCH AND TRAINING IN TROPICAL DISEASES

NINTH SESSION OF THE JOINT COORDINATING BOARD

Geneva, 25 and 26 June 1986

SECOND EXTERNAL REVIEW AND EVALUATION OF THE SPECIAL PROGRAMME

1. INTRODUCTION AND BACKGROUND

The Special Programme for Research and Training in Tropical Diseases (TDR) was established as an international response to major health problems of developing countries in the tropics. The Programme was planned and initiated by the World Health Organization with the assistance and co-sponsorship of the United Nations Development Programme and the World Bank and operates under the guidance of, and with resources provided by, its Cooperating Parties represented by the Joint Coordinating Board (JCB). An interdisciplinary group of scientists serve in their personal capacities as the Scientific and Technical Advisory Committee to advise the JCB upon the Programme's scientific and technical activities and evaluate progress. The Programme coordinates, with members of the world's scientific community, the planning and management of goal-oriented lines of research and training and institution strengthening towards two interdependent objectives:

- Research and development towards new and improved tools to control six tropical diseases; and
- Strengthening of national institutions, including training, to increase the research capabilities of the tropical countries affected by the diseases.

The six target diseases included in the scope of the Special Programme are malaria, schistosomiasis, filariasis, trypanosomiases (both African sleeping sickness and Chagas' disease), leishmaniases and leprosy.

The Programme was established in late 1975 and began operations in 1976. Programme activities increased rapidly and up to 31 December 1985 the Programme had supported 2600 projects in 104 WHO Member States and over 4000 scientists from 129 WHO Member States had participated in the planning, implementation, operation and evaluation of the Programme.

The Programme is financed by voluntary contributions from governments, international organizations, foundations and other non-governmental sources. During the first ten years of operations (1976-1985) Programme expenditures (obligations) were over US$ 190 million. Of this amount, US$ 140 million were granted for direct support to national institutions and scientists throughout the world, with over 53% of these funds going to institutions and scientists of developing tropical countries.

The Joint Coordinating Board, together with the other governments and agencies cooperating with the Programme, decided in 1978 that a review of the Programme should be carried out following the first five years of operations (1977-1981 inclusive). The review

was to provide a guide to the planning, organization, operation and management of the Programme over the next five years (1982-1986).

The JCB established an External Review Committee to carry out the review and the Committee reported to the Fifth Session of the Board on 30 June 1982. The report of the Committee is included as Annex IV to the Report of the Fifth Session of the JCB [document TDR/JCB(5)/82.3].

In its report the Committee noted "that because the first three years of the Programme was a building up period, the scientific results available now are not extensive, but in another five years substantial results will have accumulated, and therefore recommended that another external review be carried out in five years with provision for adequate staff support to assist the review committee to carry out a thorough, in-depth review".

JCB(5), in considering the report of the Committee, in principle agreed with the suggestion that another external review of TDR be carried out in 1986-1987 for the period 1982-1986. This review was to concentrate upon an evaluation of the scientific results of the Programme.

JCB(8), meeting on 26-27 June 1985, decided that a second external review and evaluation of the Programme would be carried out, and that in addition to evaluating the scientific achievements made by TDR, the External Review Committee should consider the future development of the Programme. Accordingly, the impact of the Programme should be studied and the experience gained in the past should be assessed to determine the future role of TDR.

2. OBJECTIVES AND TERMS OF REFERENCE

The objectives and terms of reference of the second external review and evaluation of the Special Programme are as follows:

2.1 OBJECTIVE 1: TO REVIEW THE SPECIAL PROGRAMME IN TERMS OF ITS OBJECTIVES AND ITS ACHIEVEMENTS:

2.1.1 Review and assess the progress and results of TDR's activities in research and development in relation to its objective of obtaining new and improved tools for the control of the six target diseases:

- What results have been achieved in relation to the objectives of the Scientific Working Groups (SWGs)?
- What "products" developed through TDR have been communicated to health authorities and applied to the control of tropical diseases?
- How extensive is the use of these "products" and how effective have they been?
- What "products" developed through TDR should be ready for application towards disease control within the next five to ten years?
- What has been the impact of TDR's research and development activities on the public health problems of the tropical countries?
- Are TDR's research and development strategies guiding the selection of research appropriate?

2.1.2 Review and assess the progress and results of TDR in relation to its objective of strengthening the research capabilities of tropical countries where the diseases are endemic:

- What results have been achieved by TDR's activities in relation to research capability strengthening?

- What has been the effect of TDR's research capability strengthening activities on research and development investment, abilities to deal with the public health problems and career structures in tropical countries?

- Are the strategies for research capability strengthening appropriate?

- Are TDR's research capability strengthening activities appropriately balanced with respect to:

  - the needs of different countries and geographic areas?
  - the disciplines promoted?
  - short- and long-term anticipated benefits for disease control?

2.1.3 Examine TDR's activities and relationships with other institutions and programmes active in the field of tropical diseases:

- In relation to the totality of efforts to control tropical diseases, what is TDR's share and its role in the development of new control measures and in the improvement of research capacity in tropical countries?

- Is there an appropriate relationship between research and development under TDR and related activities outside TDR, in both the public and the private sectors, including other research programmes and activities of WHO?

- Is there an appropriate relationship between TDR research capability strengthening activities and those of other similar and related national and international initiatives?

- Is the interaction between TDR and the pharmaceutical and agro-chemical industries effective?

- Are scientists, research administrators and health planners adequately informed of TDR's plans and progress in the area of research and development?

- Are health authorities in endemic tropical countries adequately informed of TDR's plans and progress in the area of research capability strengthening?

- Is there appropriate coordination and collaboration between TDR and other divisions and units of WHO concerned with tropical diseases and public health in developing countries?

2.1.4 Review TDR's basic strategies and priorities:

- Are the research and development activities appropriately balanced between research likely to yield advances in disease control in the short term, and fundamental studies to ensure a continued flow of improved control measures in the longer term?

- Has TDR exploited new advances in biological sciences and novel concepts for research on disease control?

- Is there effective and appropriate balance, interaction and integration between the "disease" components and the "trans-disease" components (social and economic research, epidemiology and biological control of vectors)?

- Are there suitable linkages and interactions between the programmes and activities of SWGs and those of research capability strengthening?

2.1.5 Review and assess the efficiency of TDR's operations:

- Have TDR's results, from both its research and development activities and its research capability strengthening activities, been achieved in a cost-efficient manner?

2.2 OBJECTIVE 2: TO EXAMINE THE FUNDAMENTAL BASIS OF THE SPECIAL PROGRAMME AND ITS FUTURE ROLE BASED ON ACHIEVEMENTS AND EXPERIENCES BOTH INSIDE AND OUTSIDE TDR OVER THE LAST 10 YEARS:

2.2.1 The fundamental basis for TDR in the future:

- Are the tools available to control the six target diseases still so inadequate as to justify special measures to promote research and development?
- Are there still gaps or inadequacies in present research and development efforts which warrant continuation of the mandate of the Special Programme?
- Is there still a need for TDR's research capability strengthening activities?
- Is it possible to forecast a time by which the Special Programme can be considered to have carried out its mandate and will no longer be required?

2.2.2 The Special Programme's future objectives and priorities:

- Are TDR's objectives and the selection of diseases for inclusion in the Special Programme still the most appropriate?
- Are the objectives and strategies of the SWGs still of high relevance to the public health problems facing the tropical countries over the next five to ten years?
- Are the objective and the strategy of research capability strengthening relevant to finding solutions for the public health problems of tropical countries over the next five to ten years?
- Will the focus and balance of scientific and technical activities (research towards vaccines, new and improved drugs, new diagnostic methods, new methods of vector control, epidemiological, social and economic understanding of the diseases etc.) continue to be appropriate?
- What should be the priorities of the Special Programme over the next five to ten years?
- What criteria should be used to determine these priorities?
- Should there be changes in the priorities among the diseases and trans-disease components, in relation to research opportunities and/or the epidemiological situation?

2.2.3 The future role of TDR:

- What should the role of TDR be in relation to other international, national and industrial research and development and research capability strengthening activities concerning tropical diseases, including organizations supporting research and development and research capability strengthening in developing countries?
- What should the role of TDR be in the process of ensuring that advances in research and development are evaluated in the field, and applied as appropriate in disease control strategies and programmes?

2.2.4 TDR's resource situation and its structures and mechanisms with regard to its future development and role:

- Are the total resources available to TDR adequate to pursue effectively current and proposed objectives?
- Should the ratio and level of resources allocated to TDR's two interdependent objectives be revised?

- Should the distribution of funding among the various disease and trans-disease components be revised?
- What criteria should be used for the distribution of funding?
- Are the existing structures and mechanisms of TDR appropriate and effective?
- What changes should be made to improve the efficiency of TDR's operations?

2.3 OBJECTIVE 3: TO MAKE RECOMMENDATIONS ON THE OBJECTIVES AND TERMS OF REFERENCE STATED ABOVE AND OTHER RELATED MATTERS EXAMINED IN THE COURSE OF THE REVIEW.

3. SPONSORSHIP OF THE REVIEW

The review and evaluation of the Special Programme will be conducted under the authority of the TDR Joint Coordinating Board.

The review will be carried out by an independent External Review Committee (ERC) which will be guided in its work by the Standing Committee. The ERC will report to the JCB.

4. COMPOSITION OF THE EXTERNAL REVIEW COMMITTEE

The External Review Committee will consist of six or seven individuals with expertise in one or more of such fields as disease control, epidemiology and public health in tropical countries; scientific research and development, especially related to the scope of the Special Programme; the biological, economic and social sciences; and research management. The Committee members should not have received or be receiving financial support from the Special Programme, or have served or be serving as members of the Scientific and Technical Advisory Committee. There should be a balanced geographical distribution, with members from both developed and developing countries.

Members of the Committee will serve in their personal capacities.

The members of the External Review Committee are proposed by the Standing Committee and approved by the JCB.

The list of members of the External Review Committee and summaries of their curricula vitae are contained in the Annex to this document.

5. SUPPORT AND FUNDING OF THE REVIEW

The Standing Committee is responsible for ensuring that appropriate administrative arrangements are made for the External Review Committee. The Executing Agency (WHO) will arrange secretariat support and other services and facilities as may be required. An executive secretary to the External Review Committee will be appointed to support and assist the Committee in its work. The executive secretary will be responsible for preparing or organizing special studies, reviews and discussions for the Committee, for drafting interim and final reports for the consideration of the Committee and for organizing the work of the Committee, including meetings and site visits.

The cost of the review is included under Programme Area I of the TDR Programme Budget for the 1986-1987 biennium. The budget for the review is set at a maximum of US$ 225 000 for the biennium, but the cost of the review should be kept as low as possible, without compromising the quality of the review.

6. OPERATION OF THE REVIEW

The External Review Committee will develop its own plans for the review following the guidelines provided by the JCB and the Standing Committee and taking note of the mechanisms

employed by and the report of the first External Review Committee. The ERC will have access to records and reports of TDR, as well as to persons responsible for the implementation of all aspects of the Special Programme. The Seventh and Eighth Programme Reports (covering the period 1 January 1983 - 31 December 1986) will serve as major scientific and technical background documents for the Committee.

The ERC will begin its work as soon as convenient after the Ninth Session of the Joint Coordinating Board (25-26 June 1986). It will prepare a final report for comments by the Executing Agency, the Scientific and Technical Advisory Committee (STAC) and the Standing Committee by 31 December 1987. This report, together with the comments of the Executing Agency, STAC and the Standing Committee, will be submitted to the Eleventh Session of the Joint Coordinating Board, which is tentatively scheduled to take place at the end of June 1988. The Chairman of the ERC will be present at the Eleventh Session of the JCB. The ERC may present an interim report outlining progress to the Tenth Session of the JCB on 24-25 June 1987.

7. REVIEW PROCESS

The ERC will meet as a group or in sub-groups, as required, to:

(a) review documents of the Joint Coordinating Board, the Standing Committee, the Scientific and Technical Advisory Committee, Scientific and Technical Review Committees, the Research Strengthening Group (RSG), Steering Committees of Scientific Working Groups, the secretariat, and other relevant documents;

(b) interview representatives of the co-sponsors, JCB, STAC, Steering Committees, RSG, the secretariat, and research scientists and trainees, as well as knowledgeable scientists and other persons not directly involved with TDR;

(c) visit (as necessary) selected institutions, public health services, ministries or agencies; and

(d) carry out any other investigations or activities deemed necessary for the review by the ERC, the Standing Committee or the JCB.

SECOND EXTERNAL REVIEW AND EVALUATION OF THE SPECIAL PROGRAMME
LIST OF MEMBERS OF THE EXTERNAL REVIEW COMMITTEE

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ANNEX II:

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Dr K. Bart, US Agency for International Development, Washington, DC, USA
Dr F. Beltrán-Hernández, Medical Officer, Research Capability Strengthening, TDR, Geneva, Switzerland
Dr N.R. Bergquist, Secretary, Steering Committee on Schistosomiasis, TDR, Geneva, Switzerland

Dr J.J. Cazzulo, Fundación CAMPOMAR, Buenos Aires, Argentina
Dr W. Colli, University of Sao Paulo, Sao Paulo, Brazil
Dr J.A. Cook, The Edna McConnell Clark Foundation, New York, NY, USA
Dr J.F. Copplestone, Chief, Pesticides Development and Safe Use Unit, Division of Vector Biology and Control, and Secretary, Scientific Working Group on Biological Control of Vectors, WHO, Geneva, Switzerland

Dr R.K. Davidson, Chairman, Steering Committee on Social and Economic Research, TDR, Geneva, Switzerland
Dr A. Davis, Director, Parasitic Diseases Programme, WHO, Geneva, Switzerland
Dr E.B. Doberstyn, Secretary, Steering Committee on the Chemotherapy of Malaria, TDR, Geneva, Switzerland
Dr B. Dobrokhotov, Secretary, Steering Committee on Biological Control of Vectors, TDR, Geneva, Switzerland

Dr J.G. Else, Institute of Primate Research, Nairobi, Kenya

Dr C. Frasch, Fundación CAMPOMAR, Buenos Aires, Argentina
Mr W.W. Furth, Assistant Director-General and Special Programme Coordinator, WHO, Geneva, Switzerland

Dr E. Garcia, Oswaldo Cruz Institute, Rio de Janeiro, Brazil
Dr T. Godal, Director, TDR, Geneva, Switzerland
Dr S. Goldenberg, Oswaldo Cruz Institute, Rio de Janeiro, Brazil
Dr S. Goriup, Secretary, Steering Committee on Applied Field Research in Malaria, TDR, Geneva, Switzerland

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* This Annex does not include many persons with whom informal discussions were held by ERC members in their home countries, namely Colombia, India, Nigeria, the Philippines, Sweden, the United Kingdom and the United States of America. Other omissions may have occurred owing to oversights in record keeping, for which the Committee apologizes.

Mr F. Hartvelt, Senior Programme Officer (Health, Water and Sanitation), Division for Global and Interregional Projects, United Nations Development Programme, New York, NY, USA
Dr J.A. Hashmi, Responsible Officer, Research Capability Strengthening, TDR, Geneva, Switzerland
Dr K. Hata, Administrative Officer, Information Systems, TDR, Geneva, Switzerland
Dr D.A. Henderson, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA

Dr Ji Baohong, Secretary, Steering Committee on the Chemotherapy of Leprosy, TDR, Geneva, Switzerland
Joint Coordinating Board, TDR: Members as of June 1987

Dr D.K. Koech, Kenya Medical Research Institute, Nairobi, Kenya, and staff of KEMRI during site visit
Mr D. Kusumawidjaja, Assistant (Information), TDR, Geneva, Switzerland
Mr F.A.S. Kuzoe, Secretary, Steering Committee on African Trypanosomiases, TDR, Geneva, Switzerland

Dr P. Ladouceur, Responsible Officer, Programme Management, TDR, Geneva, Switzerland
Dr B. Liese, Senior Public Health Specialist, Population, Health and Nutrition Department, The World Bank, Washington, DC, USA
Dr A.O. Lucas, former Director, TDR, Geneva, Switzerland (now with the Carnegie Corporation of New York, New York, NY, USA)

Dr H. Mahler, Director-General, WHO, Geneva, Switzerland
Dr L. Martinez, Secretary, Steering Committee on the Immunology of Malaria, TDR, Geneva, Switzerland
Dr F. Modabber, Secretary, Steering Committee on the Leishmaniases, TDR, Geneva, Switzerland
Dr L. Molineaux, Officer-in-Charge, Epidemiological Methodology and Evaluation, Malaria Action Programme, and Secretary, Scientific Working Group on Applied Field Research in Malaria, WHO, Geneva, Switzerland
Dr A. Moncayo, Secretary, Steering Committee on Chagas' Disease, TDR, Geneva, Switzerland
Dr R.H. Morrow, Secretary, Steering Committee on Epidemiology, TDR, Geneva, Switzerland
Dr C.M. Morel, Oswaldo Cruz Institute, Rio de Janeiro, Brazil
Dr M. Mukuyandela, Tropical Diseases Research Centre, Ndola, Zambia, and staff of the TDRC during site visit
Dr M.J. Mutinga, International Centre for Insect Physiology and Ecology, Nairobi, Kenya, and staff of ICIPE during site visit

Dr F. Neva, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
Dr S.K. Noordeen, Chief, Leprosy Unit, and Secretary, Scientific Working Groups on the Chemotherapy and on the Immunology of Leprosy, WHO, Geneva, Switzerland
Mr J. North, Director, Population, Health and Nutrition Department, The World Bank, Washington, DC, USA
Dr T.C. Nchinda, Medical Officer, Research Capability Strengthening, TDR, Geneva, Switzerland

Dr A. Parodi, Fundación CAMPOMAR, Buenos Aires, Argentina
Ms A.M. Pearce, Acting Communications Officer, TDR, Geneva, Switzerland
Dr A.L. Perez, Instituto Nacional de Diagnóstico e Investigación de la Enfermedad de Chagas "Dr Mario Fatala Chaben", Buenos Aires, Argentina

Dr P. de Raadt, Chief, Trypanosomiases and Leishmaniases, Parasitic Diseases Programme, and Secretary, Scientific Working Groups on African Trypanosomiases, Chagas' Disease and the Leishmaniases, WHO, Geneva, Switzerland
Dr C.P. Ramachandran, Scientist, Research Capability Strengthening (now Secretary, Steering Committee on Filariasis), TDR, Geneva, Switzerland
Research Strengthening Group, TDR: Members as of July 1987
Dr N. Rose, Johns Hopkins University, Baltimore, MD, USA
Dr P. Rosenfield, former Secretary, Steering Committee on Social and Economic Research, TDR, Geneva, Switzerland (now with the Carnegie Corporation of New York, New York, NY, USA)
Dr D.S. Rowe, previously Responsible Officer, Research and Development, TDR, Geneva, Switzerland
Dr T. Rothermel, Director, Division for Global and Interregional Projects, United Nations Development Programme, New York, NY, USA
Dr A. Ruiz, Instituto Nacional de Diagnóstico e Investigación de la Enfermedad de Chagas "Dr Mario Fatala Chaben", Buenos Aires, Argentina

Dr M. Sadigurski, Instituto Gonçalo Moniz, Salvador, Bahia, Brazil
Dr E. Segura, Instituto Nacional de Diagnóstico e Investigación de la Enfermedad de Chagas "Dr Mario Fatala Chaben", Buenos Aires, Argentina
Scientific and Technical Advisory Committee, TDR: Members as of June 1987

Dr A. Texeira, University of Brasilia, Brasilia, Brazil
Dr G. Torrigiani, Director, Division of Communicable Diseases, WHO, Geneva, Switzerland
Dr P.I. Trigg, Research and Technical Intelligence, Malaria Action Programme, WHO, Geneva, Switzerland

Dr W.H. Wernsdorfer, Chief, Research and Technical Intelligence, Malaria Action Programme, and Secretary, Scientific Working Groups on the Immunology and on the Chemotherapy of Malaria, WHO, Geneva, Switzerland
Dr K.S. Warren, Rockefeller Foundation, New York, NY, USA
Dr C. Wisnivesky, Instituto Nacional de Diagnóstico e Investigación de la Enfermedad de Chagas "Dr Mario Fatala Chaben", Buenos Aires, Argentina

ANNEX III:

Text of the Committee's Solicitation of Comments on Issues of Key Concern

The following solicitation of comments was sent to:

Selected individuals knowledgeable of tropical diseases and TDR
Members of the Joint Coordinating Board, TDR
Members of the Scientific and Technical Advisory Committee, TDR.

"The second External Review Committee for the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases is now considering issues arising from its terms of reference and discussions at its first and second meetings. These include:

- What is the desirable scope of TDR activities, especially in relation to national control programmes: where should the boundary of primary responsibility for promoting action be drawn as a potential disease control "tool" progresses from laboratory concept through research, development and demonstration of probable utility in endemic areas (efficacy, safety, acceptability, practicability, operational research, cost effectiveness) to application?

- What methods could be used to achieve greater overall TDR Programme integration and Component interaction, particularly with regard to research capability strengthening activities and disease-specific Scientific Working Groups/Steering Committees?

- What methods or structures could be used for promoting the appropriate levels of integration of social and economic research into overall Programme activities?

- With whom should the Special Programme be "communicating"?

- What new methods might be used to ensure adequate and stable funding for TDR activities?

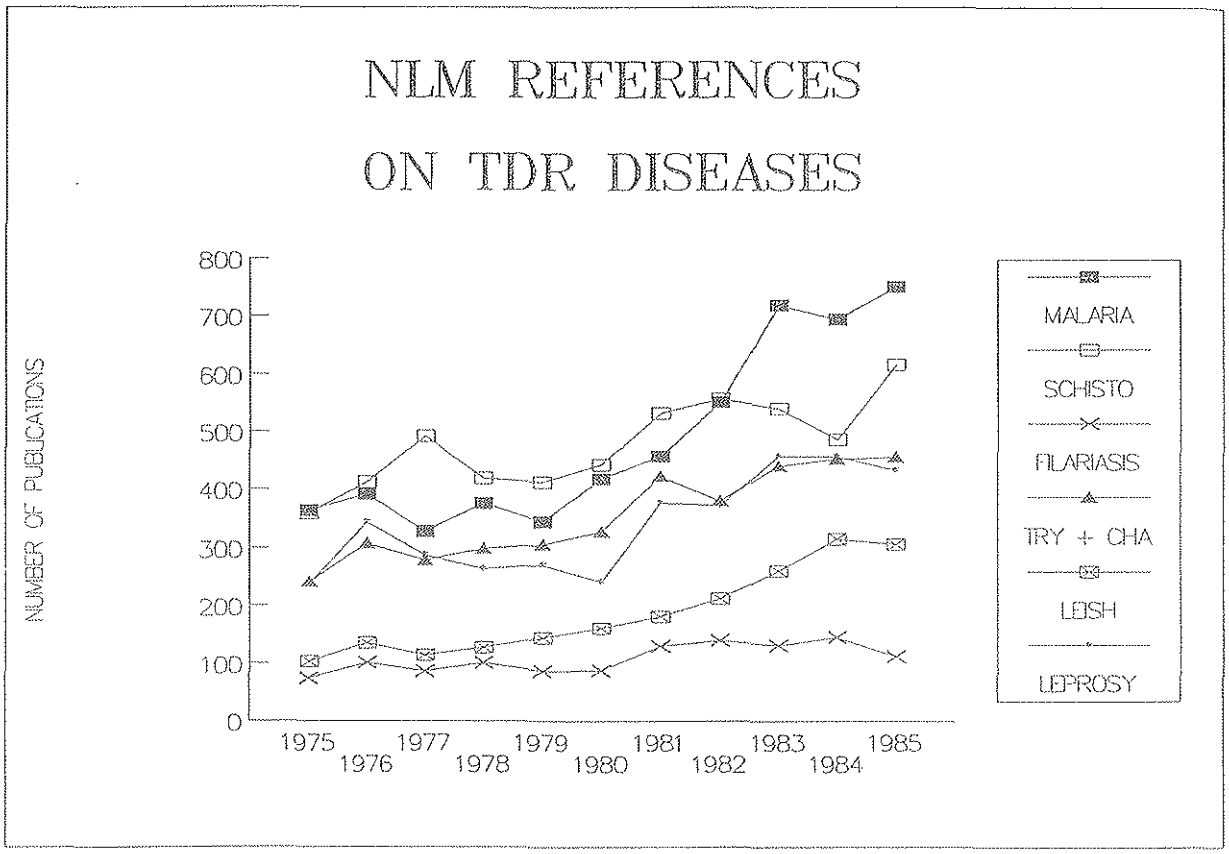
Your comments on any of these issues and those other topics which you consider the ERC should examine would be greatly appreciated.

The ERC's next meeting is 20-23 July 1987. Your comments would be most helpful if they arrived by 10 June 1987 so that they can be distributed prior to the meeting.

We look forward to receiving your views."

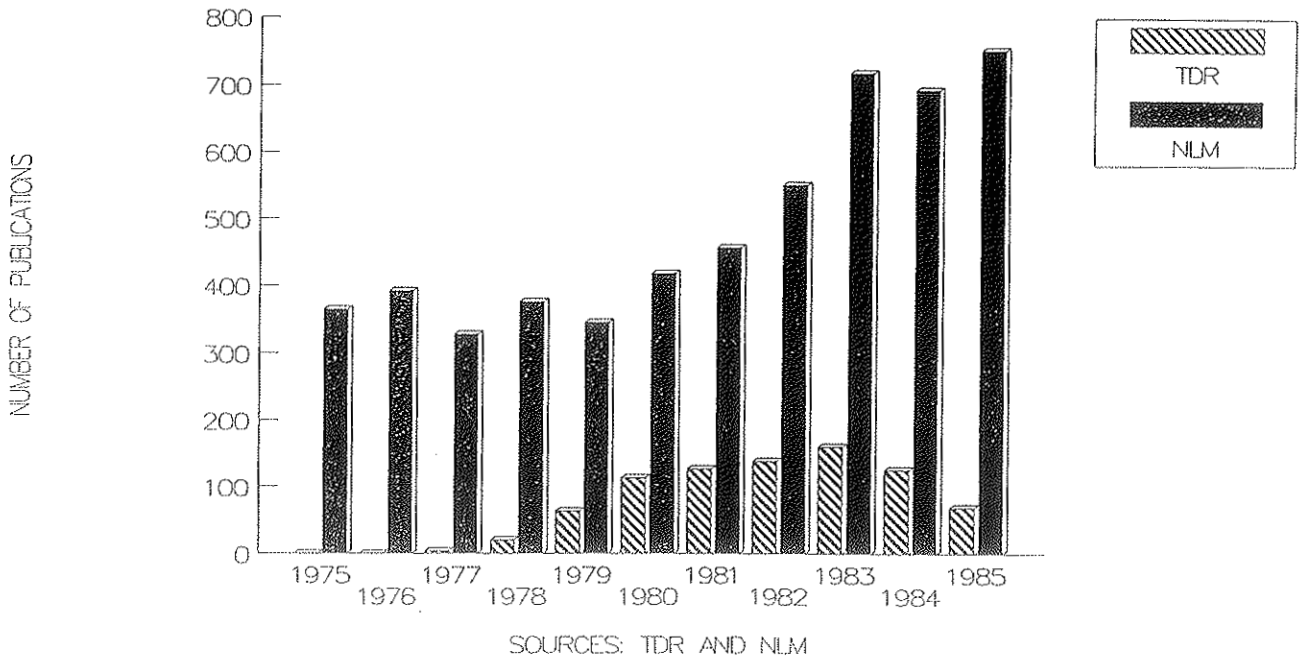
ANNEX IV:

Publications on TDR Target Diseases Identified by the US National Library of Medicine and Those Acknowledging TDR Support*

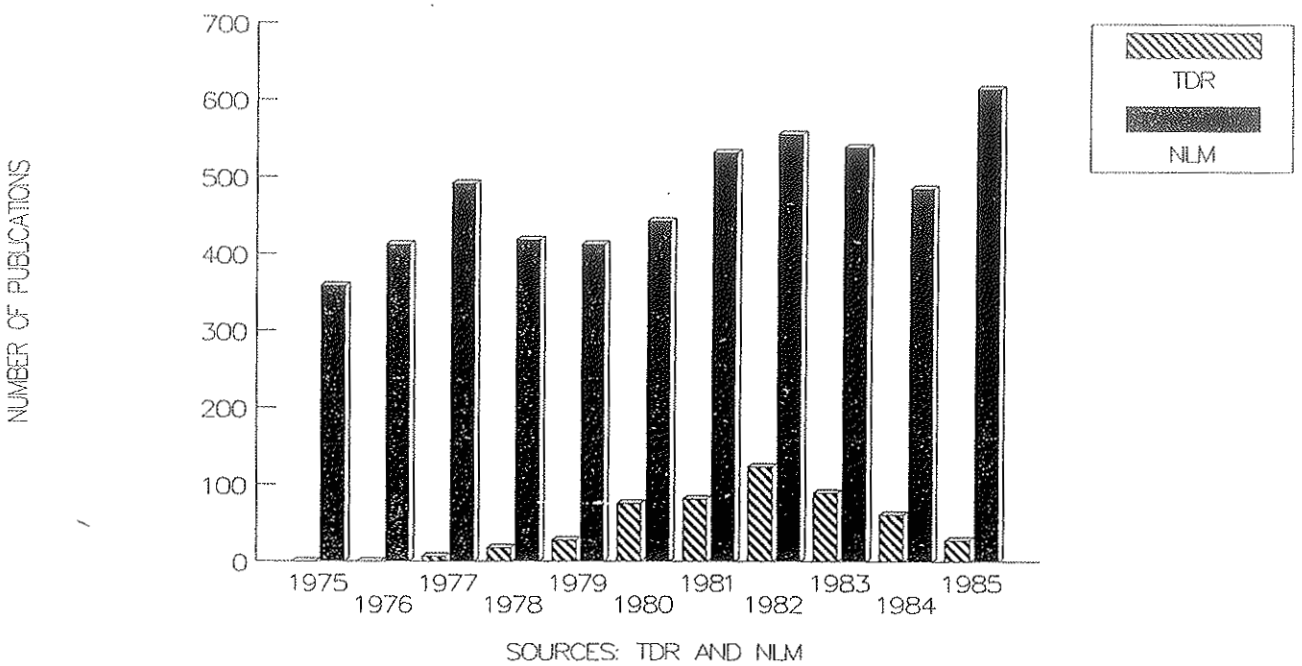


* The count of publications acknowledging TDR support is not complete for recent years owing to delay in verification; thus, the apparent decline is an artifact.

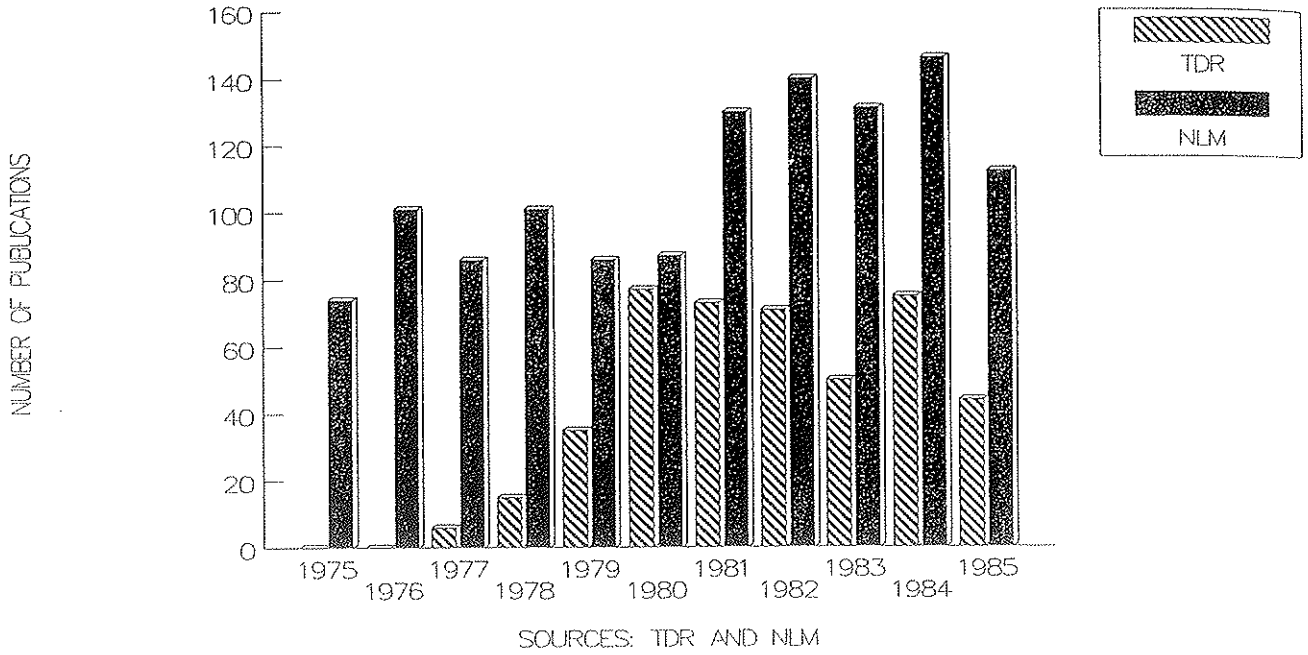
PUBLICATIONS ON MALARIA



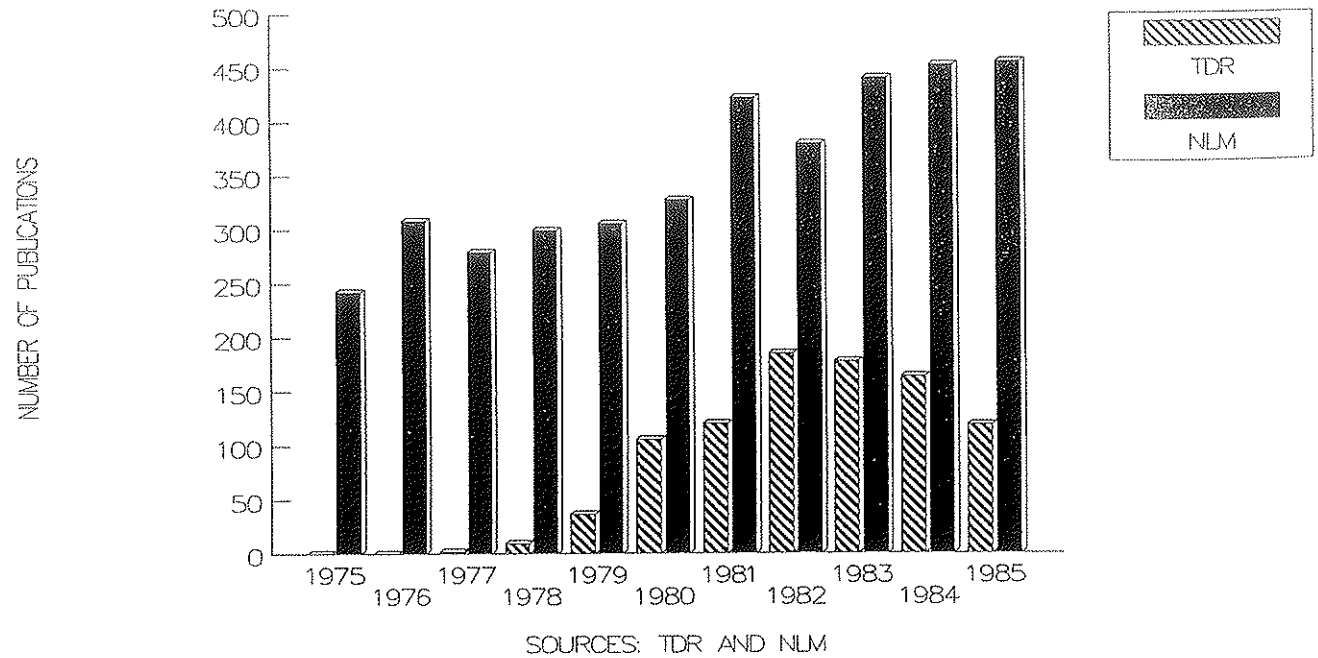
PUBLICATIONS ON SCHISTOSOMIASIS



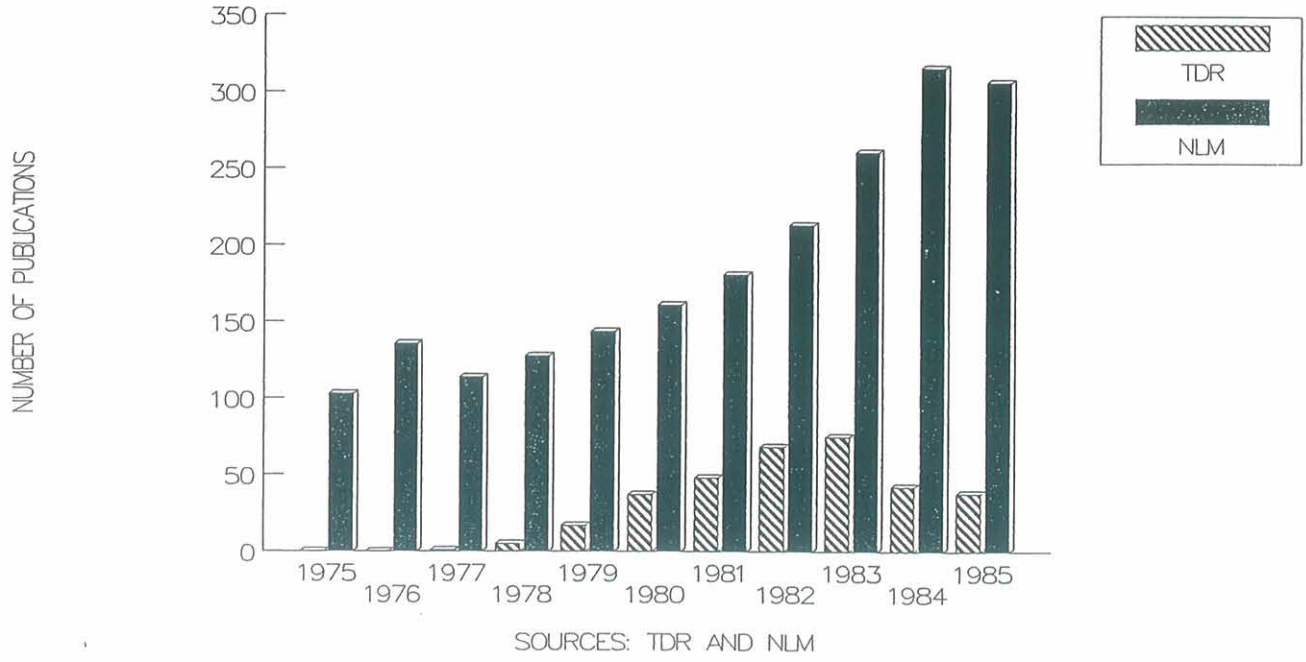
PUBLICATIONS ON FILARIASIS



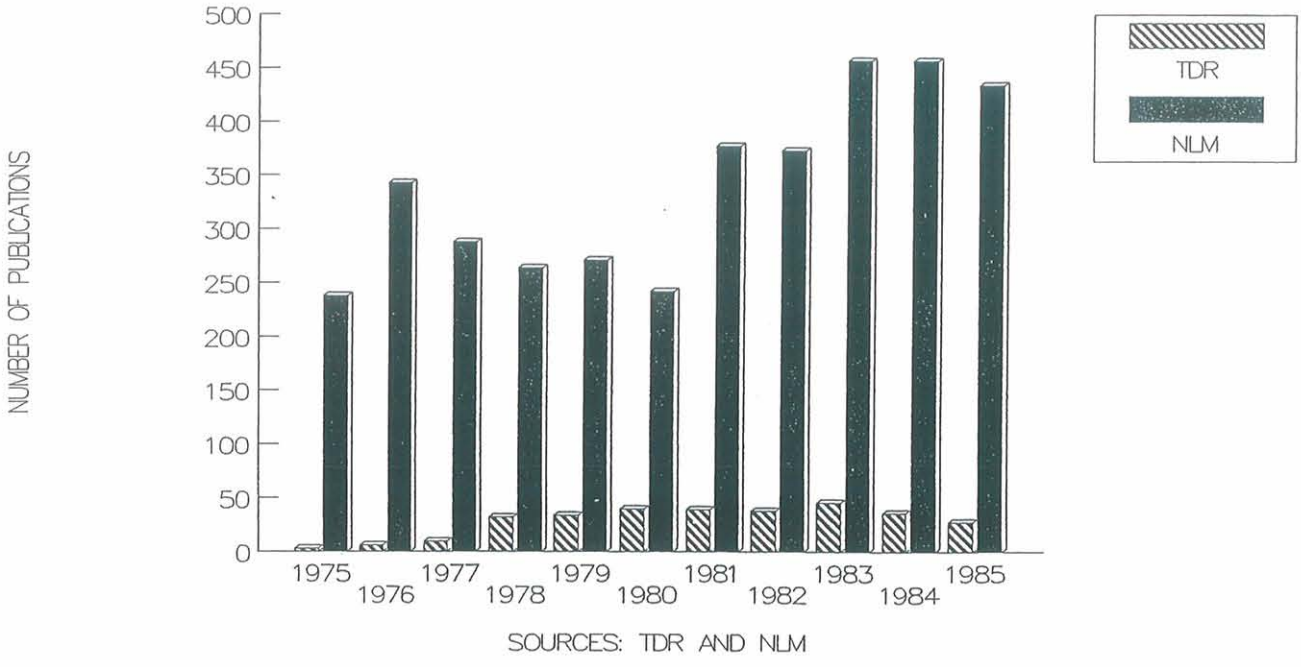
PUBLICATIONS ON TRYPANOSOMIASES



PUBLICATIONS ON LEISHMANIASES



PUBLICATIONS ON LEPROSY



ANNEX V:

Analysis of Publications Acknowledging TDR Support

18 NOV 1987 (REPORT P 04) — UNDP/WORLD BANK/WHO - SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES — PAGE 1

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
MOLECULAR AND BIOCHEMICAL PARASITOLOGY	212	44	42	24	33	46	13		25				3	11	16	257
TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE	210	62	31	32	17	14	41		7		4		1	30	19	258
AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE	130	45	18	22	4	23	13	2	2		3		3	11	17	163
PARASITOLOGY	109	23	37	23	13	2	18		6	7	1		1	4	4	139
MEMORIAS DO INSTITUTO OSWALDO CRUZ (RIO DE JANEIRO)	98	3		4		50	21		3				1	17	16	115
ANNALS OF TROPICAL MEDICINE AND PARASITOLOGY	92	34	6	44	7	9	21		1		4		4	7	5	142
SOUTHEAST ASIAN JOURNAL OF TROPICAL MEDICINE AND PUBLIC HEALTH	86	14	6	14							3	12		55	19	123
JOURNAL OF IMMUNOLOGY	82	19	33	7	2	7	9	9	6		1			2	9	104
JOURNAL OF PARASITOLOGY	82	30	17	18	2	15	4		4	1			2	6	9	108
INTERNATIONAL JOURNAL OF LEPROSY	78							95					2		1	98
JOURNAL OF PROTOZOOLOGY	78	25			10	17	14		7	2			1	5	6	87
INFECTION AND IMMUNITY	75	18	4	1	4	14	3	32	3		2				4	85
CLINICAL AND EXPERIMENTAL IMMUNOLOGY	72	13	8	10	2	4	6	30	5					12	12	102
TROPENMEDIZIN UND PARASITOLOGIE	65	3		42	24	1	3				2			8	3	86
BULLETIN OF THE WORLD HEALTH ORGANIZATION	61	48	2	9		3		2		2				2	6	74
EXPERIMENTAL PARASITOLOGY	61	12	22	12	1	6	9		3				1	2	9	77

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
ACTA TROPICA	60	3	7	18	12	13	4		3	2				8	5	75
NATURE	52	21	5	3	18	2		12	4				1		9	75
LEPROSY REVIEW	50						1	53			1		1	1	3	60
COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY	44	6	18		4	13	1							6	6	54
REVISTA CUBANA DE MEDICINA TROPICAL	43									5				32	8	45
PARASITE IMMUNOLOGY	42	8	17	16	1	1	5	2	3					4	4	61
ZEITSCHRIFT FUR PARASITENKUNDE	40	4	10	11	8	10	2							2	3	50
FEDERATION PROCEEDINGS	39	18	6		2	5	1		5				2		1	40
CAHIERS ORSTOM, SERIE ENTOMOLOGIE MEDICALE ET PARASITOLOGIE	37	1			28		2			1		4	5			41
ACTA PHARMACEUTICA SINICA	35	6												29		35
ANNALES DE PARASITOLOGIE HUMAINE ET COMPAREE	35	18	17				5									40
PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	35	22	1		7	1	3	4	1	2				1	1	43
JOURNAL OF INVERTEBRATE PATHOLOGY	34	1	3				1			36			1			42
ARQUIVOS DE BIOLOGIA E TECNOLOGIA	33		2			26	1		5							34
SCIENCE	32	23	1		2	3	3	2	1		1				4	40
BOLETIN CHILENO DE PARASITOLOGIA	31					31										31
LANCET	31	11	2	9		3	2	1					2	9	5	44

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
BIOCHEMICAL PHARMACOLOGY	29	8	4		7	7	6		1					3	1	37
JOURNAL OF HELMINTHOLOGY	29		8	20										6	1	35
INDIAN JOURNAL OF MEDICAL RESEARCH	26			6				1		2				19		28
MEDICINA (BUENOS AIRES)	26					25								8	1	34
JOURNAL OF EXPERIMENTAL MEDICINE	23	20		2			1	3	4					1	2	33
JOURNAL OF PARASITOLOGY AND PARASITIC DISEASES	23	1	1											22		24
BIOCHIMICA ET BIOPHYSICA ACTA	22	9	2			9		1					4	1	4	30
REVISTA DA SOCIEDADE BRASILEIRA DE MEDICINA TROPICAL	22					14						3		6	3	26
CIENCIA E CULTURA	21		3			9						2		7	3	24
FEBS LETTERS	21	2	3		3	9	2		3	2			1	4	2	31
ANNALES DE LA SOCIETE BELGE DE MEDECINE TROPICALE	20	8	3	1	4	1		1	1				2			21
EAST AFRICAN MEDICAL JOURNAL	20				5		8				1			13	5	32
INSECT SCIENCE AND ITS APPLICATION	20				8	3	14							8	1	34
BRITISH JOURNAL OF CLINICAL PHARMACOLOGY	19	6		3				2						8	4	23
COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES, SERIE D: SCIENCES NATURELLES (PARIS)	19	5	11			1	3			2				1		23
MOSQUITO NEWS	19	3		1						14			2	3	2	25
ACTUAL QUESTIONS OF MEDICAL PARASITOLOGY AND TROPICAL	18	17					1					15				33

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
SCANDINAVIAN JOURNAL OF IMMUNOLOGY	18		2			1		16							1	20
JAPANESE JOURNAL OF EXPERIMENTAL MEDICINE	17	2	4	12												18
ARCHIVOS DE BIOLOGIA Y MEDICINA EXPERIMENTALES	16					1								15	3	19
AUSTRALIAN JOURNAL OF EXPERIMENTAL BIOLOGY AND MEDICAL SCIENCE	16	11	3						5					3	1	23
JOURNAL OF IMMUNOLOGICAL METHODS	16	3	8	3		1	1	2					1	1	1	21
ACTA ACADEMIAE MEDICINAE SINICAE	15													15		15
ACTA PHARMACOLOGICA SINICA	15	4												11		15
BULLETIN DE LA SOCIETE DE PATHOLOGIE EXOTIQUE ET DE SES FILIALES	15		3	1	2		4			6	3			2		21
INTERNATIONAL JOURNAL FOR PARASITOLOGY	15		6	3	1	1	4		1	1				1	1	19
JOURNAL OF BIOLOGICAL CHEMISTRY	15	5			2	6	3							1		17
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY	14	4				5	5	2							1	17
CELLULAR IMMUNOLOGY	14		7				4	4								15
BULLETIN OF THE SOCIETY OF VECTOR ECOLOGISTS	13					7				6			1			14
NUCLEIC ACIDS RESEARCH	13				16		1								1	18
JAPANESE JOURNAL OF PARASITOLOGY	12		9	3												12

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
JOURNAL OF CHROMATOGRAPHY	12	8	5	1	1									1		16
JOURNAL OF INFECTIOUS DISEASES	12	2	3	1		2	2	2					1	2	2	17
JOURNAL OF MEDICAL ENTOMOLOGY	12	2		1		1	2			3				4	1	14
LEPROSY IN INDIA	12							12					1			13
CELL	11	4			16				1						1	22
JOURNAL OF CELL BIOLOGY	11	5			3				2				1			11
JOURNAL OF TROPICAL MEDICINE AND HYGIENE	11	3					3			1		1	1		3	12
REVISTA DO INSTITUTO DE MEDICINA TROPICAL	11					7	3							2	1	13
BIOCHEMISTRY INTERNATIONAL	10	2				9			2				1		1	15
ISRAEL JOURNAL OF MEDICAL SCIENCE	10	2					9	1								12
JOURNAL OF CELLULAR BIOCHEMISTRY	10	1	1				1		7							10
TROPICAL BIOMEDICINE	10	1		7										9	1	18
ANNALES D'IMMUNOLOGIE (INSTITUT PASTEUR)	9	3	3					2					1			9
APPLIED AND ENVIRONMENTAL MICROBIOLOGY	9	3							1	10					1	15
CHINESE MEDICAL JOURNAL	9						3			1				7	1	12
EUROPEAN JOURNAL OF BIOCHEMISTRY	9				5	4			2							11
IMMUNOLOGY	9	2	1	4	3	1									2	13
IRCS MEDICAL SCIENCE	9	1	1						3					3	4	12
KOREAN JOURNAL OF ENTOMOLOGY	9									11			2			13

ANALYSIS OF JOURNALS

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JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
MALACOLOGICAL REVIEW	9		4											5		9
MEDITSINSKAIA PARAZITOLOGIIA I PARAZITARNYE BOLEZNI (MOSKOVA)	9	2					6			2						10
SHANGHAI JOURNAL OF IMMUNOLOGY	9	2												8		10
BULLETIN OF ENTOMOLOGICAL RESEARCH	8	2			4		1								1	8
EUROPEAN JOURNAL OF IMMUNOLOGY	8		6	1			2						1			10
EXPERIENTIA	8	4				6								1	1	12
JOURNAL OF CLINICAL MICROBIOLOGY	8	1		2			2	1						3	1	10
PARASITOLOGIA	8	3											3	1	1	8
REPORT OF NATIONAL INSTITUTE OF HEALTH, KOREA	8									10						10
SUDAN MEDICAL JOURNAL	8			8												8
ACTA CIENTIFICA VENEZOLANO	7					6								1		7
AMERICAN JOURNAL OF VETERINARY RESEARCH	7	1		6				1								8
ANNALES DE MICROBIOLOGIE (INSTITUT PASTEUR)	7	1						4		5						10
BULLETIN OF THE PAN AMERICAN HEALTH ORGANIZATION	7					2								6		8
CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY	7	1	1	2		2		1								7
EMBO JOURNAL	7	3			5	1										9
IMMUNOLOGICAL REVIEWS	7	3	1	1				2	2						1	10
INTERNATIONAL ARCHIVES OF ALLERGY AND APPLIED IMMUNOLOGY	7	2	8													10

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT															PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
JOURNAL OF CLINICAL INVESTIGATION	7	5	1	1	1											8
JOURNAL OF THE AMERICAN MOSQUITO CONTROL ASSOCIATION	7									7						7
ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS	6	1				5								1	3	10
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS	6	1			1	1	2		1						1	7
BOLETIN DE LA DIRECCION DE MALARIOLOGIA Y SANEAMIENTO AMBIENTAL	6			2			4									6
BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH	6					6	1									7
BRITISH MEDICAL JOURNAL	6	3						1			2			3	1	10
ENTOMOPHAGA	6									5				1	1	7
HELVETICA CHIMICA ACTA	6	4	2													6
IMMUNOLOGY LETTERS	6		3			2							1	2	1	9
INTERNATIONAL JOURNAL OF BIOCHEMISTRY	6	2			1			1	2						1	7
JOURNAL OF HETEROCYCLIC CHEMISTRY	6			10					1							11
JOURNAL OF SUBMICROSCOPIC CYTOLOGY	6					5									2	7
PANS	6				6											6
ZOOLOGICAL RESEARCH	6									1				6		7
ACTA LEPROLOGICA	5			1			3	1						2	2	9
ACTA ZOOLOGICA SINICA	5													5		5

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
ANALYTICAL BIOCHEMISTRY	5	2	1		1		1									5
ANNALS OF TROPICAL MEDICINE AND HYGIENE	5	1		1	1	1	1							1		6
ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY	5	4	1	1									1	1		8
CELL BIOLOGY INTERNATIONAL REPORTS	5	4							1							5
CONTRIBUTIONS TO MICROBIOLOGY AND IMMUNOLOGY	5				4										2	6
CURRENT MICROBIOLOGY	5								2	4						6
FEMS MICROBIOLOGY LETTERS	5							1	2	2						5
INTERNATIONAL JOURNAL OF NUCLEAR MEDICINE AND BIOLOGY	5	5														5
JAPANESE JOURNAL OF SANITARY ZOOLOGY	5	5												3		8
JOURNAL OF MEDICINAL CHEMISTRY	5	1		5	1											7
JOURNAL OF MOLECULAR BIOLOGY	5				7											7
JOURNAL OF PHARMACEUTICAL SCIENCES	5	6			1											7
JOURNAL OF PHARMACY AND PHARMACOLOGY	5	3												2		5
MALACOLOGIA	5		7													7
MYCOPATHOLOGIA	5						1			4						5
NEW ENGLAND JOURNAL OF MEDICINE	5			3			1	1						1		6
PONTIFICIAE ACADEMIAE SCIENTIARUM SCRIPTA VARIA	5		3			1	1									5

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
REVISTA INSTITUTO MEDICA TROPICAL (SAO PAULO)	5					3	2							1	1	7
WALKERANA, TRANSACTIONS OF THE POETS SOCIETY	5													5	1	6
ZEITSCHRIFT FUR ANGEWANDTE ENTOMOLOGIE	5		1	2						2				1	1	7
BIOCHEMICAL JOURNAL	4			1		2								1	3	7
BOLETIN INFORMATIVO DEL CENETROP	4					1								3		4
BULLETIN OF THE HIGH INSTITUTE OF PUBLIC HEALTH (ALEXANDRIA)	4											4				4
CANADIAN JOURNAL OF MICROBIOLOGY	4									4						4
DRUG METABOLISM AND DISPOSITION	4	2						2								4
ENVIRONMENTAL ENTOMOLOGY	4									4						4
ETHIOPIAN MEDICAL JOURNAL	4							1						3		4
HEREDITAS	4		4													4
HETEROCYCLES	4			6												6
JOURNAL OF CELL SCIENCE	4	1			1	2										4
JOURNAL OF COMMUNICABLE DISEASES	4						1							3		4
JOURNAL OF ECONOMIC ENTOMOLOGY	4									3				1		4
JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS	4		7												1	8
JOURNAL OF SCIENCE SOCIETY OF THAILAND	4	2								2					1	5

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT														PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
LIFE SCIENCES	4	2	1				1									4
MOLECULAR AND CELLULAR BIOLOGY	4	1					1		2							4
PAPUA NEW GUINEA MEDICAL JOURNAL	4	4														4
PARASITOLOGY TODAY	4		1										1	2		4
PHARMACEUTICAL RESEARCH	4	3					1									4
PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY OF LONDON	4	2	2		1											5
REVIEWS OF INFECTIOUS DISEASES	4			1		3		1								5
REVISTA MEDICA DE MOCAMBIQUE	4													4		4
TROPICAL AND GEOGRAPHICAL MEDICINE	4	2	1								1				1	5
ACTA LEIDENSIA	3		2												1	3
ACTA MEDICA PHILIPPINA	3		2											1	1	4
ACTA PHARMACOLOGICA ET TOXICOLOGICA	3		2	1												3
AKTUALNII VOPROSI LEPROLOGII	3							3								3
AMERICAN JOURNAL OF PATHOLOGY	3			2									1			3
APPLIED MICROBIOLOGY AND BIOTECHNOLOGY	3									3			2			5
BIOCHEMICAL SOCIETY TRANSACTIONS	3		1	1	1											3
BOLETIN DE LA OFICINA SANITARIA PANAMERICANA	3						1							2		3
CANADIAN JOURNAL OF GENETICS AND CYTOLOGY	3	2								1						3

ANALYSIS OF JOURNALS

JOURNAL	PUBLI-CATION TOTAL	PROJECTS BY COMPONENT													PROJEC TOTAL
		MAL	SCH	FIL	TRY	CHA	LEI	LEP	BIO	VEC	EPD	SER	DIR	IST	TRN	
ZENTRALBLATT FUER MICROBIOLOGIE	3									3						3
ZENTRALBLATT FUR BAKTERIOLOGIE PARASITENKUNDE, INFEKTIONS-KRANKHEITEN UND HYGIENE	3			3												3