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

Geneva, 29 February to 3 March 1988

REPORT OF THE TENTH MEETING OF THE
 SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-10)

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This report contains the collective views of an International group of experts convened by the UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR). It does not necessarily reflect the views of TDR/WHO. In the interests of rapid communication it has been submitted to only minimal editorial revision. Moreover, any geographical designations used in the report do not imply the expression of any opinion whatsoever on the part of TDR or WHO concerning the legal status of any country, territory, city or area or of its authorities concerning the delimitation of its frontiers or boundaries.

Ce rapport exprime les vues collectives d'un groupe international d'experts réuni par le PROGRAMME SPECIAL PNUD/BANQUE MONDIALE/OMS DE RECHERCHE ET DE FORMATION CONCERNANT LES MALADIES TROPICALES (TDR). Il ne représente pas nécessairement les vues du TDR/OMS et, en vue d'une diffusion accélérée, il n'a pas été l'objet d'une mise en forme particulièrement soignée. En outre, les noms géographiques utilisés dans le présent rapport n'impliquent, de la part du TDR ou de l'OMS, aucune prise de position quant au statut juridique de tel ou tel pays, territoire, ville ou zone, ou de ses autorités, ni quant au tracé de ses frontières.

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1. SUMMARY AND MAJOR CONCLUSIONS

The tenth meeting of the Scientific and Technical Advisory Committee (STAC-10) of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) took place in Geneva, Switzerland, from 29 February to 3 March 1988. STAC reviewed the draft report on the transfer to national health services of technology developed with TDR support, commented on the Programme Director's report on TDR activities during the past year and carried out in-depth reviews of the activities of the Scientific Working Groups (SWGs) on Leprosy, Malaria, and Social and Economic Research. STAC held discussions with the Chairman and Vice-Chairman of the second External Review Committee (ERC) and reviewed their report.

STAC commended the continuing scientific progress of the Programme, the newly established programme-based grants, the newly created joint TDR-Rockefeller Foundation grants and the new initiatives for field research.

STAC decided that it would continue its biennial review of all Programme activities but would use a more efficient procedure. Five-yearly in-depth reviews would be continued in 1988 in modified form. STAC introduced a new type of Programme analysis, "Prospective Thematic Reviews", to identify new directions for research common to several disease-specific Components.

2. RECOMMENDATIONS

2.1 Programme Development Fund

As requested by JCB(10), STAC discussed the use of the US \$1 million which had been suggested for the Programme Development Fund in the proposed Programme budget for the 1988-89 biennium. STAC endorsed the proposal of Director, TDR, that the amount available in the budget for the 1988-89 biennium be used to finance the urgently needed strengthening of field research activities and the initiation of the new approaches in field research.

2.2 Leprosy

- a) The TDR Leprosy Component should draw up a long-term global agenda of research needs and publicize it widely, and should encourage other bodies, such as governments and nongovernmental organizations, to contribute to this agenda.
- b) Collaboration between the Components on the Immunology (IMMLEP) and the Chemotherapy (THELEP) of Leprosy should be strengthened. This process has already been started by the creation of a joint committee on molecular biology and should be extended to include all field projects.
- c) IMMLEP and THELEP must prepare themselves for the possible implications of success in the vaccine trials now under way. Contingency plans for different outcomes must be made in relation to the availability of vaccines, target group identification and second-generation vaccines.
- d) Molecular biology should be given priority, in particular the development of sensitive methods of identifying viable Mycobacterium leprae in patients.
- e) Priority areas within IMMLEP should be (a) methods for the detection of infection and (b) the development of second-generation vaccines.
- f) Within THELEP, therapeutic trials of the fluoroquinolones should be given priority, and THELEP should renew its efforts to involve the pharmaceutical industry in the development of antileprosy drugs.
- g) In commending the restructuring of TDR's Research and Development and Research Capability Strengthening Programme Areas, STAC noted that field trials in leprosy constituted unique opportunities for training. More local scientists should be encouraged to move to the field in order to optimize the potential for operational research.

2.3 Malaria

- a) The clinical trial centres in Bangkok, Thailand, Ndola, Zambia, and Medellin, Colombia, must be maintained. In the event of any one centre having to close down, an alternative site in the same continent must be found without delay.
- b) An effort should be made to bring at least two of the most promising artemisinin derivatives to Phase II clinical trials.
- c) If preliminary studies do not reveal any intrinsic toxicological or other side-effects associated with the trioxane moiety, a major effort should be started on the development of this class of compounds.

- d) The Components on the Immunology of Malaria (IMMAL) and Applied Field Research in Malaria (FIELDMAL) must work together on the epidemiological assessment of humoral (serological) and cell-mediated (T-cell) immune responses. IMMAL should provide clear directives about the information required for the selection of vaccine candidates among the newly characterized merozoite molecules.
- e) IMMAL should commit itself as soon as possible to a clearly defined plan for blood-stage vaccine development, including a time-frame and criteria for antigen selection.
- f) IMMAL should work with FIELDMAL on the design of studies on the variability of candidate vaccine molecules.
- g) In entering into commercial arrangements on TDR-supported products, WHO should ensure for developing countries public sector rights on subsequent modifications introduced by industry.
- h) The Component on the Chemotherapy of Malaria (CHEMAL) and IMMAL should alert STAC well in advance to planned clinical trials of new drugs and vaccines to allow time for the necessary appropriation of funds.
- i) Knowledge of vector population genetics and ecology has reached a point where scientifically based intervention can be contemplated. A special effort is required to study ways in which the substantial body of knowledge which has been acquired in these fields can be applied to vector control.
- j) FIELDMAL should, in coordination with the WHO Malaria Action Programme, focus on operational research relevant to national malaria control programmes, so as to become a resource to control programmes.

2.4 Social and Economic Research

- a) A major future contribution of the Component on Social and Economic Research (SER) to the goals of TDR will be its involvement with other Scientific Working Groups (SWGs) in disease control projects, as is now the case for the Epidemiology SWG. It is essential that the relevant social and economic questions be posed at the earliest appropriate stage of research and development. This may best be done by a member of the SER Steering Committee being involved with each of the disease-oriented Steering Committees.
- b) To ensure the availability of scientists, special attention must be paid to expanding training in the related scientific disciplines, ranging from short courses to formal programmes for higher degrees. Attention should be given to training across disciplines, such as economics for epidemiologists and vice versa. Special attention should be given to the utilization of ongoing field research projects for training purposes and support should be given to graduate students to conduct research within this framework.
- c) Efforts should be intensified to attract scientists experienced in social and economic and other related disciplines into TDR's field of activities. Communication between researchers should be facilitated by meetings, cooperative research projects and early dissemination of research findings.

- d) The extension of SER responsibilities will require strengthening of the Secretariat in addition to a substantial budget increase.

2.5 Second External Review and Evaluation of TDR

- a) As recommended by the ERC, the diseases falling within TDR's mandate should continue to be only the six target diseases.
- b) Continued efforts should be made to link research and development activities with social and economic research and with research capability strengthening. Such links are now the key to the success of the Programme and will provide the basis for long-term tropical disease control.
- c) TDR staffing requirements would need to be considered within the context of the global and goal-oriented nature of the Programme's activities, with attention being given to demands on the number and expertise of the staff.
- d) With regard to the expansion of SER activities, a scientist with expertise in health economics should be appointed.
- e) With regard to the roles of SWGs in coordinating activities within a disease-specific Component and with WHO disease control activities, there should be only one SWG for each disease-specific Component.
- f) With regard to the ERC's detailed suggestions on Steering Committee review procedures for incoming proposals, existing procedures had evolved under the close scrutiny of STAC and continued to meet requirements effectively. Some flexibility was needed, however, in special situations and was indeed essential in dealing with proposals submitted by scientists inexperienced in the preparation of formal research proposals.
- g) STAC supported the ERC's proposal to expand the Director's Initiative Fund from US \$262 000 to US \$1 million per year and agreed that limits not be set for the amounts which could be granted from this fund for start-up activities or increases of a Component's budget.

2.6 Mode of Operation of STAC

- a) In order to increase the effectiveness of STAC's biennial review of all Components, in 1988 each STAC member will attend the meetings of one of the Steering Committees or of the Research Strengthening Group (RSG) and will prepare a report for STAC-11 on the activities of the assigned Committee or Group.
- b) The Filariasis and Schistosomiasis Components will submit their five-yearly reports on their activities to STAC-11. After reviewing these reports, STAC will decide whether an in-depth review by a Scientific and Technical Review Committee (STRC) is necessary in each case and, more generally, whether to continue this modified five-yearly review process.
- c) In order to enhance the scientific direction given by STAC to the Programme, STAC introduced "Prospective Thematic Reviews" (PTRs). Their

purpose would be to examine problems and new scientific advances relevant to a number of Programme Components. Ad hoc committees to conduct these reviews will be chaired by members of STAC and include international experts.

3. OPENING OF THE MEETING

The tenth meeting of the Scientific and Technical Advisory Committee (STAC-10) UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was held at WHO headquarters in Geneva, Switzerland, from 29 February to 3 March 1988. The meeting was opened by Dr H. Mahler, Director-General of WHO, who in his remarks briefly traced the history of TDR. The Programme had always kept its main objectives -- the development of new tools and the strengthening of research capability in tropical countries to improve the control of tropical diseases -- clearly in focus. Equally it had responded to changing circumstances, such as the spread of parasite resistance to drugs and vector resistance to insecticides, and population movements, which exposed people to new disease risks. As TDR matured, so increasing emphasis was given to the field-testing of new products, to community involvement in field projects and to stronger ties with national disease control programmes. This was part of the drive towards the transfer of technology, and it was appropriate that this was also the topic of the STAC symposium.

3.1 Transfer to National Health Services of Technology Developed with TDR Support

3.1.1 Symposium

Professor D. von Wettstein, Chairman of STAC, conducted the proceedings of the symposium. In his introductory remarks Dr T. Godal, Director, TDR, noted that the evolution of TDR fell broadly into five-year cycles. From 1977 to 1982 the foundations were laid by establishing the basic structure of the Programme, by defining what had to be done and by getting projects under way. Over the next five years TDR established itself as a promoter of high-quality research. Now, in the third five-year cycle, the focus is on the production of disease control tools. This symposium set the scene for the 1990s, when the usefulness and use of the tools will be the focus. The document "Transfer to National Health Services of Technology Developed with TDR Support" had been prepared by the Secretariat as a basis for discussion.

The following talks were presented:

- Multidrug therapy in leprosy - Dr M. Christian, Schieffelin Leprosy Research and Training Centre, Karigiri, North Arcot District, India
- The operational introduction of mefloquine, a new antimalarial drug, by the Antimalarial Programme in Thailand - Dr S. Finichpongse, Ministry of Public Health, Bangkok, Thailand
- Ivermectin in onchocerciasis - Dr K.R. Brown, Merck Sharp and Dohme Research Laboratories, West Point, PA, USA
- The use of Bacillus thuringiensis in the Onchocerciasis Control Programme (OCP) in West Africa - Dr D. Kurtak, Onchocerciasis Control Programme in West Africa, Bouaké, Côte d'Ivoire

Summaries of the papers are included in Annex II. In the discussion it was stressed that the success of these four products was in a large measure due

to the commitment of national governments and/or their agencies in the deployment of the tools. It was emphasized that these products should now be evaluated and promoted through regular government health services.

3.1.2 Discussion of the Director's Report on the Transfer to National Health Services of Technology Developed with TDR Support

This report covered the basic policy issues of the role of TDR in the development of tools and transfer of technology for their production and/or use, training activities, dissemination of scientific and technical information and twelve examples of the transfer of technology developed with TDR support.

STAC was appreciative of the steps that TDR had taken to make available the benefits of the new tools and methods to target populations in developing endemic countries. In general, TDR should be responsible for research and development of new tools up to and including the stage of field-testing in the intended setting of use, after which national governments should take over. This recommendation is similar to that of the ERC. It was suggested that suitable links be established with appropriate national agencies on a case-to-case basis so that technology could be transferred smoothly.

In view of the growing importance of biotechnology, it was suggested that developing endemic countries be encouraged to establish Master's-level courses in this area.

4. CHAIRMAN'S REPORT

The Chairman of STAC reported on the Tenth Session of the Joint Coordinating Board [JCB(10)] held in Geneva on 24-25 June 1987. The Board had expressed its pleasure with TDR's achievements during its first decade of operations. These had been excellently presented in the Eighth Programme Report. JCB(10) had noted that the situation with regard to tropical diseases was as serious as it had been ten years ago and that the role of TDR remained as urgent and crucial as before. The JCB had decided to take a more active role in raising funds and had appointed an ad hoc committee to recommend to JCB(11) strategies towards this end. The target was to increase funds by at least 25% to allow for increases in social and economic research and field research. It was gratifying to note that the funds anticipated for the current biennium had increased by US \$7 million or 13.4% of the total budget.

JCB(10) had accepted the Report of the Ninth Meeting of STAC and approved its recommendations. In its discussion of the budget for the 1988-89 biennium, JCB(10) had decided not to establish a Programme Development Fund during this period. JCB(11) would reconsider the matter in 1988 in the light of recommendations of STAC(10) and the ERC.

5. DIRECTOR'S REPORT

5.1 Overview of Scientific Progress 1987-88

In his overview of progress of the Programme in the past year, Director, TDR, began by describing recent developments in basic biology germane to the understanding of parasite-host relationships and parasite differentiation. It had been found that the maturation of trypanosomes in the Glossina midgut was dependent on species-specific lectins that could be blocked by glucosamine.

An epidermal growth factor (EGF) receptor on the surface of Trypanosoma brucei was recognized by antiserum to the human EGF receptor. Stress ("heat-shock") proteins had been shown to be major antigens in parasites and mycobacteria, and appeared to be highly conserved in evolution; one of these, an antigen with a relative molecular weight of 65 000 (65 K), had been shown to be related to a human mitochondrial protein. Repeated DNA sequences, already well known in plasmodia, had been found in T. cruzi and Leishmania, and might be an attribute related to the ability of the parasite to survive in both host and vector.

A potentially important advance related to malaria vaccine development had been the observation by M.E. Patarroyo et al. from Colombia that a hybrid vaccine constructed with synthetic peptides from blood-stage parasites and the repeat peptide from the circumsporozoite protein provided protection against malaria infection in Aotus monkeys and in humans; an IMMAL collaborative study with Patarroyo for validation in Aotus monkeys was under way. Further insight into mechanisms of immune protection against sporozoite-induced infection was provided by the observation that protection following injection of x-rayed sporozoites was dependent on γ -interferon and cytotoxic T cells, probably active against the liver stage of infection. A major step towards making BCG a vector for mycobacterial vaccine constructs was made by B. Bloom et al. in New York, USA, who had achieved lysogeny in M. smegmatis.

Amongst major developments in drug development had been the demonstration of impressive in vivo antimalarial activity by trioxane compounds (which incorporate a peroxide group) by C.W. Jefford et al. in Geneva and the completion of clinical trials with pefloxacin (a fluoroquinolone) in 20 lepromatous patients, with 99.9% killing of M. leprae at eight weeks without any side-effects. A new formulation of 2-nitroimidazole, RO 15-0216, from F. Hoffmann-La Roche and Co., Switzerland, had exhibited antitrypanosomal activity in experimental infections.

A major advance in diagnostics had been the use by C.M. Morel et al. in Rio de Janeiro of DNA polymerase chain reactions (PCR) to improve the sensitivity of the detection of kinetoplast DNA. With this amplification a DNA probe was able to detect less than one parasite. The method could be adapted for preparation of probes in large quantities and offered great possibilities for epidemiological studies on infections, such as Chagas' disease, malaria and sleeping sickness, in which highly sensitive tests might be required. Rapid progress continued to be made in DNA probe methodology for characterization of malaria, filarial and Leishmania infections; DNA probes had been used successfully to differentiate between forest and savanna onchocerciasis. A very simple direct agglutination test had been developed for visceral leishmaniasis. A new specific serological test for schistosomiasis developed by E. Beck et al. in Heidelberg was based on a cloned 31/32 K antigen and had shown promising results.

Progress in vector control included large-scale field trials of formulations of B. sphaericus in Côte d'Ivoire, India, Thailand and the United Republic of Tanzania against Culex mosquitos: 100% mortality and a residual effect of five to eight weeks had been observed. Insecticide-impregnated mosquito nets had been used to reduce mosquito bites in Burkina Faso, as had impregnated house curtains in mining communities in Brazil.

STAC Comments

STAC commended Director, TDR, on progress achieved during the last year and noted with satisfaction the research and development results of the

Programme.

Concern was expressed over the increasing obstacles to experimentation with animals. STAC affirmed the continuing need for animal experimentation for the development of vaccines, drugs and other purposes in health research, and requested Director, TDR, to take up this matter with the appropriate WHO bodies.

5.2 New Approaches to Research Capability Strengthening (RCS)

Director, TDR, described at length the guiding principles and strategy for research capability strengthening under the Special Programme and the steps that had been taken to implement recommendations made last year. The various approaches and schemes are described in the booklet "Tropical Disease Research, A Global Partnership at Work. New Approaches to Research Capability Strengthening". The guiding principles are to develop self-reliance for indigenous problem solving and to provide training at the cutting edge of science to take advantage of the latest developments in science and technology. The formation of linkages is encouraged between institutions and scientists of developing countries with those of developed countries in order to generate and maintain momentum in research.

From a first phase of institution strengthening, the Programme is now entering a second phase of programme-based grants, in which support is oriented towards research objectives. The management of science and the development of human resources through job and career opportunities in developing countries are critical. Various supporting measures introduced by TDR, such as research fellowships and career development grants, were described by Director, TDR.

STAC Comments

Following discussion of the Director's report, of the report of the twelfth meeting of the Research Strengthening Group (RSG) and of the booklet on new approaches to research capability strengthening, STAC considered that a successful start had been made in integrating TDR's research capability strengthening and research and development activities.

The booklet presents the mechanisms by which the RSG will operate to strengthen research institutions and develop human resources. The RSG has supported almost 100 institutions and close to 600 scientists over the last decade. International partnerships and interdependence of research groups are the key directions of the future.

STAC considers that the various types of grants now available are capable of providing the flexibility needed to meet the varied needs of different institutions in different circumstances.

5.2.1 Institution Strengthening Grants

Capital grants are awarded on a once-only basis to augment current research capabilities or ongoing postgraduate and postdoctoral research.

Long-term support grants are given for periods of up to five years to enable an institution to obtain most of what it needs to participate in TDR's research and research training network.

Programme-based grants, a novel type of grant, are awarded for a period

of up to five years to help institutions with adequate material resources carry out high-quality research focused on clearly defined objectives. They are also intended to give groups of investigators working in different institutions and scientific disciplines a better chance of making significant contributions to a scientific problem related to one or more of the TDR target diseases. They can cover salaries, equipment, supplies, field research, data handling, collaborative arrangements and central facilities for services such as monoclonal antibody production or social and economic research activities.

Joint TDR-Rockefeller Foundation grants are awarded to quality institutions willing to work as partners in applying the latest advances in biomedical sciences, epidemiology and social sciences to the development, testing and application of new ways of preventing, treating and controlling the TDR target diseases. The partnerships should be so formed as to offer the best chances of an effective exchange of expertise and resources with a view to increasing clinical and epidemiological understanding of tropical diseases and to facilitating the transfer of advanced biomedical research capabilities to laboratories in tropical countries.

Over 200 applications for this type of grant have been reviewed by a joint TDR-Rockefeller Foundation committee and 30 have been selected to submit detailed applications.

5.2.2 Human Resource Development

Research training grants are awarded for periods ranging from three weeks to three years to enable trainees to acquire skills in research on one or more of the TDR target diseases.

Visiting scientist grants enable senior scientists to upgrade their knowledge outside their own countries for periods ranging from one to 11 months.

Postgraduate fellowships for advanced epidemiological field research training are awarded for two- to three-year periods. These novel fellowships are intended to enable health and health-related professionals to acquire experience in field research by joining large ongoing field projects or disease control programmes in endemic countries. Community-based trials of new disease control tools developed with TDR support and long-term epidemiological field studies sponsored by TDR and other international organizations offer excellent opportunities for the kind of research training covered by these fellowships.

Re-entry grants are given on a once-only basis to support scientists from developing countries returning home after a period of training.

Career development grants -- a novel type of research support for up to five years -- is awarded to outstanding investigators who, despite strong determination and motivation and excellent qualifications, might be prevented from continuing their work by the harsh conditions prevailing in many developing countries or by their appointment to senior governmental administrative posts.

Short-term group training grants are given to institutions for one- to three-week training courses.

Long-term group training grants are given to institutions for four years

to implement postgraduate Master's degree courses in disciplines such as entomology, epidemiology and the social sciences.

5.3 TDR Project Funding in Developing Endemic Countries

STAC-9 had noted that the percentage of Programme funding to tropical disease-endemic countries had declined in 1986 and 1987 and had requested a report on the situation to STAC-10. This report (Annex IV) was presented by Director, TDR. The decline had occurred primarily in the Research and Development Programme Area, and appeared to be due to lack of promotion and a consequent reduction in grant applications. In recent months, the number of applications from developing countries had increased. Steps taken to correct the imbalance included an increase in TDR's scientific activities in developing countries -- Steering Committee meetings, the introduction of project development grants (designed to assist scientists from developing countries in formulating technically sound research proposals) and increased research capability strengthening activities.

STAC comments

STAC endorsed these initiatives, which they considered adequate at the present time to promote resource allocation to developing endemic countries. STAC will continue to keep this aspect of the Programme under close review.

5.4 New Approaches to Field Research

The achievements of the field research component of TDR programme and further plans to strengthen it were described. It was emphasized that on-the-spot development of study designs and protocols in field projects was an important part of training and an invaluable way of building research capability in field research. The RSC intends to promote local field research resource centres in developing countries, which would play a major role in local networking and in the training of scientists in field research. Steering Committees would have the responsibility of outlining research protocols and designing trials of new tools developed with TDR support (see Annex III).

Field research would be given top priority, as this was the most important step in carrying the benefits of research and development to target populations. It was proposed that the budgeted Programme Development Fund of US \$1 million be used by Steering Committees to fund new field research projects. It was also suggested that an additional US \$0.5 to 1 million be made available during the biennium for research capability strengthening activities in support of field research.

5.5 Initiative for the Implementation of Biotechnology

As part of a new initiative for the promotion of biotechnology, collaboration is being considered with a limited number of laboratories in Africa, Asia and Latin America to enable them to collaborate with scientists who have developed DNA probes, monoclonal antibodies, etc., and become producers of such tools for the Programme.

STAC Comments

STAC was impressed by the initiatives that had been taken by Director, TDR. It endorsed the direction this planning was taking and stressed the importance of training field research scientists within developing endemic

countries.

5.6 Programme Development Fund

In its report, STAC-9 had welcomed the establishment of a Programme Development Fund of US \$1 000 000 for the 1988-89 biennium in order to provide sufficient flexibility for the initiation of new lines of research and development after approval of the Programme budget by the JCB. In the course of the biennium, Director, TDR, would recommend to STAC the allocation of amounts from the Programme Development Fund to specific Components. JCB(10) did not support the establishment of a Programme Development Fund, but accepted the proposal by Director, TDR, that STAC-10 would discuss the use of the resources budgeted for this fund in the 1988-89 biennium.

STAC-10 endorsed the proposal of Director, TDR, that the amount available in the budget for the 1988-89 biennium be used to finance the urgently needed strengthening of field research activities and the initiation of the new approaches in field research.

Future provisions for budget flexibility were then discussed. STAC supported the ERC's proposal to expand the Director's Initiative Fund from US \$262 000 to US \$1 million per year and agreed that limits not be set for the amounts which could be granted from this fund for start-up activities or increases of a Component's budget.

6. REVIEWS OF SCIENTIFIC AND TECHNICAL REVIEW COMMITTEES

During the previous year, Scientific and Technical Review Committees (STRCs) had examined in detail the work of the SWGs on the Immunology (IMMLEP) and the Chemotherapy (THELEP) of Leprosy over the period 1983 to 1987; the Chemotherapy (CHEMAL) and the Immunology (IMMAL) of Malaria and Applied Field Research in Malaria (FIELDMAL) over the period 1983 to 1987; and on Social and Economic Research (SER) over the period 1982 to 1987.

STAC was joined by Steering Committee Chairmen for a discussion of the STRC reports: for IMMLEP, Professor J. Grosset; for CHEMAL, Dr C.J. Canfield; for IMMAL, Major General P.K. Russell; for FIELDMAL, Dr R.L. Kaiser; for SER, Dr R.K. Davidson and Professor B. Singer, the incoming Chairman.

STAC accepted the reports of its STRCs and made the following comments and recommendations:

6.1 Leprosy

STAC was most impressed by the leadership shown by the two Steering Committees, IMMLEP and THELEP, and for the great progress achieved with few resources over the years.

STAC noted that there were still some 10-12 million cases of leprosy in the world. Less than 50% of these were identified, and at least one third progressed to an advanced, disabling state of disease. STAC highlighted the following contributions of TDR-supported projects and indicated some remaining high-priority problems.

6.1.1 Immunology of Leprosy (IMMLEP)

The provision of M. leprae was a vital ingredient in the TDR programme. The continuous supply of armadillo-derived M. leprae and purified reagents still remained a most valuable resource. IMMLEP had added a highly impressive number of reliable agents, such as: monoclonal antibodies to defined M. leprae antigens; recombinant DNA clones and sequences; T-lymphocyte clones with defined specificity; synthetic peptides, as well as complex polysaccharides and glycolipids of diagnostic relevance. The sharing of these reagents and the ability to move simultaneously in a coordinated fashion in the field and in the laboratory were pivotal in speeding up global research.

Development of immunoassays based on defined T-cell stimulatory epitopes from M. leprae antigens had progressed satisfactorily. Skin tests were still in need of improvement, however.

Humoral immunodiagnostic tests were being developed against a large variety of antigens. The development of a simple, reliable test for early infection remained a high priority.

Vaccine trials in Malawi and Venezuela were well on the way and STAC considered the protocols for these to be excellent. It remained a major concern to maintain adequate record-keeping for the necessary period, which might extend for a decade or more.

Success in the ongoing vaccine trials would put WHO under great strain to produce large amounts of M. leprae antigens cheaply. Production was likely to require recombinant DNA technology, already successfully applied to research on M. leprae. STAC considered that genetic manipulation of BCG strains to enable them to produce leprosy-derived antigens was a research line of great promise.

6.1.2 Chemotherapy of Leprosy (THELEP)

Multidrug therapy (MDT), designed to reduce the development of drug resistance, is now firmly established in the control of leprosy. No drug-resistant strains had arisen after correctly administered MDT. It remained urgent, however, to monitor closely the possible onset of resistant strains.

STAC considered the new fluoroquinolones a most promising group of substances, whose place in leprosy therapy should now be determined.

STAC identified the lack of suitable in vitro methods to cultivate M. leprae as a major factor in slowing chemotherapeutic research and the understanding of resistance. Molecular biology now offered alternative approaches.

6.1.3 Research strengthening and training

STAC noted that the restructuring of the TDR Programme would allow Steering Committees and SWGs to add more input into research strengthening and training. STAC was impressed with the role the SWGs have already played in bringing younger workers with advanced technical skills from outside tropical disease research into the field of leprosy. So far, this has happened chiefly in the developed countries. STAC believed a similar effort was required in the developing countries, where there was an urgent need to recruit and train leprosy experts, particularly for field trials and other operational research.

6.1.4 Budget

STAC noted the limited resources currently available for new research initiatives. For 1988, IMMLEP had only US \$300 000 and THELEP US \$150 000 not already committed to ongoing programmes.

6.1.5 Recommendations

- a) The TDR Leprosy Component should draw up a long-term global agenda of research needs and publicize it widely, and should encourage other bodies, such as governments and nongovernmental organizations, to contribute to this agenda.
- b) Collaboration between IMMLEP and THELEP should be strengthened. This process has already been started by the creation of a joint committee on molecular biology and should be extended to include all field projects.
- c) IMMLEP and THELEP must prepare themselves for the possible implications of success in the vaccine trials now under way. Contingency plans for different outcomes must be made in relation to the availability of vaccines, target group identification and second-generation vaccines.
- d) Molecular biology should be given priority, in particular the development of sensitive methods of identifying viable M. leprae in patients.
- e) Priority areas within IMMLEP should be (a) methods for the detection of infection and (b) the development of second-generation vaccines.
- f) Within THELEP, therapeutic trials of the fluoroquinolones should be given priority, and THELEP should renew its efforts to involve the pharmaceutical industry in the development of antileprosy drugs.
- g) In commending the restructuring of TDR's Research and Development and Research Capability Strengthening Programme Areas, STAC noted that field trials in leprosy constituted unique opportunities for training. More local scientists should be encouraged to move to the field in order to optimize the potential for operational research.

6.2 Malaria

STAC noted that the global malaria situation remained highly unsatisfactory, with many millions of persons at risk of infection. Population movements, deforestation and occupational exposure had increased the incidence of the disease in some regions, such as the Amazon basin. In some large cities of tropical Africa the situation had deteriorated due to uncontrolled urbanization, with destitute populations living in shanty towns. About 50% of anopheline vector species had developed resistance to DDT. The most worrying problem, however, was chloroquine- and multidrug-resistant Plasmodium falciparum malaria.

Against this bleak background, STAC considered the positive results achieved by the SWGs and highlighted the following contributions of TDR-supported projects in malaria research:

- the results of the clinical trials of mefloquine in Thailand, including trials involving children and pregnant women;

- the advances in fundamental research on purine metabolism achieved by local Thai investigators in cooperation with the Walter Reed Army Institute of Research (WRAIR), USA;
- the north-south linkages in immunoepidemiology, specifically the cooperative studies done by the Lamco Hospital (Liberia) with the Karolinska Institute (Sweden) and by the National University of Colombia with the University of Stockholm; jointly these studies have demonstrated that human T cells respond to the Pf 155 (RESA) parasite molecule and have clarified the value that this antigen may have for a future merozoite vaccine;
- the speed with which basic knowledge obtained from molecular cloning of parasites can be carried into field work; the standardization of parasitic diagnosis using DNA probes had enormous potential for epidemiological studies;
- the demonstration, in a field study involving 3500 people in Sri Lanka, that transmission-blocking antibodies are regularly detectable in P. vivax-infected individuals;
- the impact of recombinant DNA technology on malaria research: impressive progress has been made in the molecular characterization of the malaria genomes and the major parasite antigens.

6.2.1 Chemotherapy of Malaria (CHEMAL)

The clinical facilities established in Bangkok, Thailand, Belém, Brazil, and Ndola, Zambia, played a major role in the clinical evaluation of mefloquine and the mefloquine/sulfadoxine/pyrimethamine combination. The Belém centre had ceased functioning and a new centre was created in Medellín, Colombia. STAC considered that it was essential to maintain one centre in each of these regions.

STAC expressed disappointment over the long delay in establishing clinical trials of artemisinin and its derivatives.

STAC considered that the most promising group of new drugs, the trioxanes, should be the object of toxicological studies and eventually of clinical trials.

Floxacrine derivatives required further evaluation of possible toxicity in animals. Pyronaridine required further evaluation of efficacy and toxicity. Studies should also be continued on hydroxynaphthoquinones and on halofantrine.

The STAC suggested a series of guidelines to prevent problems related to the development of new drugs within TDR, with respect to contracts with non-industrial investigators (e.g., universities).

6.2.2 Immunology of Malaria (IMMAL)

Major efforts have been made towards the development of malaria vaccines. Despite the disappointing results of the first trials, STAC considered the findings an important step forward.

Sporozoite vaccines were being developed largely outside the ambit of TDR. Nevertheless, the Programme exerted a useful and much appreciated

coordinating function and provided qualified manpower.

A major step forward in the development of blood-stage vaccines had been the identification and characterization of 28 parasite antigens. STAC suggested criteria for selecting candidate vaccine antigens.

TDR is the major agency active in the development of transmission-blocking vaccines. There has been notable progress in this direction.

The discovery of an antigen expressed on the surface of infected liver cells has opened up the possible development of a liver-stage vaccine.

There is now sufficient information on antigenic variability to sound a cautionary note in vaccine development.

6.2.3 Applied Field Research in Malaria (FIELDMAL)

Despite the constraints identified by the previous in-depth review in 1983, steady and, in some instances striking, progress had been made in various aspects of FIELDMAL activities.

Chemotherapeutic trials were carried out (in collaboration with CHEMAL) in Africa and in China and Thailand.

Immunoepidemiological studies were carried out in Thailand to build a database to assess the value of serological testing as an early warning of malaria outbreaks.

In Liberia, the age-specific prevalence of antibodies to a 155 K *P. falciparum* antigen was determined.

Electrophoretic genetic analyses and chromosomal examinations were successfully incorporated into TDR-supported field investigations on *Anopheles* sibling species in Benin, Burkina Faso, Mali, Sudan and the United Republic of Tanzania, in Africa, and in India and Thailand, in South-East Asia.

Large-scale trials of pyrethroid-impregnated bednets had shown considerable promise for malaria control.

The range of topics supported by FIELDMAL had been very wide and the time had now come for a more selective approach in certain areas:

- a) the rational use of antimalarial drugs within the primary health care context;
- b) the role of vaccines in malaria control;
- c) field-testing of DNA probes;
- d) vector biology and control.

6.2.4 Composition of Steering Committees and outside interactions

While the participation in Steering Committees of scientists from tropical disease-endemic countries had increased in the last few years, there was still room for improvement, particularly in the balance of the IMMAL Steering Committee. There was, however, a deplorable lack of women scientists in the three Steering Committees and appropriate action should be taken to correct this unjustified gender imbalance.

There had been efforts to increase the interaction between the Malaria Component and the RSG. It was felt that similar efforts must be made to increase cooperation with the SER Component, particularly regarding studies on the socioeconomic determinants of malaria.

Interaction with the pharmaceutical industry had been required for the commercial development, manufacture, regulatory approval and widespread distribution of new drugs. Some aspects of new antimalarial drug and vaccine development would present potential problems that merited the prompt attention of TDR. Such was the case with chemical modifications introduced by industry on TDR supported and patented structures which might result in new or better products not covered by the original patent.

6.2.5 Budget

All the SWGs considered the present level of funding satisfactory, although they made it clear that TDR goals would be achieved more rapidly if funds could be expanded. The demand for additional funds might rise sharply when TDR started to take a vaccine through safety testing and clinical trials.

6.2.6 Recommendations

STAC approved the workplans of the three Malaria Steering Committees and made the following recommendations:

- a) The clinical trial centres in Bangkok, Thailand, Ndola, Zambia, and Medellin, Colombia, must be maintained. In the event of any one centre having to close down, an alternative site in the same continent must be found without delay.
- b) An effort should be made to bring at least two of the most promising artemisinin derivatives to Phase II clinical trials.
- c) If preliminary studies do not reveal any intrinsic toxicological or other side-effects associated with the trioxane moiety, a major effort should be started on the development of this class of compounds.
- d) IMMAL and FIELDMAL must work together on the epidemiological assessment of humoral (serological) and cell-mediated (T-cell) immune responses. IMMAL should provide clear directives about the information required for the selection of vaccine candidates among the newly characterized merozoite molecules.
- e) IMMAL should commit itself as soon as possible to a clearly defined plan for blood-stage vaccine development, including a time-frame and criteria for antigen selection.
- f) IMMAL should work with FIELDMAL on the design of studies on the variability of candidate vaccine molecules.
- g) In entering into commercial arrangements on TDR-supported products, WHO should ensure for developing countries public sector rights on subsequent modifications introduced by industry.
- h) CHEMAL and IMMAL should alert STAC well in advance to planned clinical trials of new drugs and vaccines to allow time for the necessary appropriation of funds.

- i) Knowledge of vector population genetics and ecology has reached a point where scientifically based intervention can be contemplated. A special effort is required to study ways in which the substantial body of knowledge which has been acquired in these fields can be applied to vector control.
- j) FIELDMAL should, in coordination with the WHO Malaria Action Programme (MAP), focus on operational research relevant to various national malaria control programmes so as to become a resource to control programmes.

6.3 Social and Economic Research

STAC drew special attention to the following points:

- The social and economic research disciplines relevant to TDR covered a very wide field that included sociology, anthropology, geography, economics, psychology and political science. These were essential disciplines for an understanding of the spread of the six diseases and for the development of methods for their control, including the acceptance and use of the products of TDR research and development.
- Many past disease control projects had failed because those who sought to introduce a new vaccine, drug or other control measure did not take into account the knowledge, attitudes and beliefs of the target populations, nor local constraints to change.
- Remarkable progress had been made by SER over the past nine years despite the paucity of resources both in WHO and in the scientific community and in the face of the need to involve the interest of experienced research workers in research of this type. As a result, starting almost from scratch, 67 research projects had been mounted in 25 countries. The possibilities for applying social and economic research to the improvement of disease control were many and involved; STAC noted that an extensive list of recommendations had been made in the STRC report. Nonetheless, it was difficult to see how all these could be accomplished, given the limited resources of TDR. STAC therefore made the following recommendations for research priorities:

Recommendations

- a) A major future contribution of SER to the goals of TDR will be its involvement with other SWGs in disease control projects, as is now the case for the Epidemiology SWG. It is essential that the relevant social and economic questions be posed at the earliest appropriate stage of research and development. This may best be done by a member of the SER Steering Committee being involved with each of the disease-oriented Steering Committees.
- b) To ensure the availability of scientists, special attention must be paid to expanding training in the related scientific disciplines, ranging from short courses to formal programmes for higher degrees. Attention should be given to training across disciplines, such as economics for epidemiologists and vice versa. Special attention should be given to the utilization of ongoing field research projects for training purposes and support should be given to graduate students to conduct research within this framework.

- c) Efforts should be intensified to attract scientists experienced in social and economic and other related disciplines into TDR's field of activities. Communication between researchers should be facilitated by meetings, cooperative research projects and early dissemination of research findings.
- d) The extension of SER responsibilities will require strengthening of the Secretariat in addition to a substantial budget increase.

7. SECOND EXTERNAL REVIEW AND EVALUATION OF TDR

7.1 The seven-member External Review Committee (ERC) had prepared a report (document TDR/JCB(11)/88.6) on the accomplishments of the first decade of TDR activities with recommendations for future directions. STAC discussed this report in detail with Dr E. Otero, Chairman of the ERC, Professor H. Danielsson, Vice-Chairman, and Dr R. Widdus, Executive Secretary.

According to the report, TDR "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 the global efforts in research and development for tropical disease control tools".

The ERC concluded that the continuing enormous health and economic burden of tropical diseases, especially of the TDR target diseases, compellingly justified the continued existence of the Programme for at least another ten years. The report endorsed the basic strategies of TDR, with special mention of TDR's catalytic and facilitating roles, the management by outside scientists and the strengthening of existing national institutions in the developing countries. The many successful contributions of the Programme to the control of the target diseases, to product development and to progress in the "trans-disease" areas were detailed. In addition, the following general achievements were highlighted:

- increased awareness of the significance of tropical diseases as major public health problems;
- recruitment to tropical disease research of experienced scientists and young investigators from the forefront of other rapidly advancing disciplines;
- provision of a model for the management of targeted research;
- stimulation of the involvement of pharmaceutical companies;
- funding of investigators from developing countries in social and economic research.

The report stated that the SER Component had demonstrated the institutional, economic and behavioural interdependence of the spread and the control of tropical diseases in endemic countries, at the level of individuals, households, communities or larger groupings within societies. Within the world's social science research community, the Programme's SER Component is the largest (and for several developing countries, the only) source of support and stimulation for social science research in the field of tropical diseases. Such a pre-eminent position of intellectual leadership and primary funding is

unlikely to change in the years immediately ahead. The SER Component has trained the first sizeable cadre of social scientists and funded the first projects in social and economic research in tropical diseases conducted in endemic countries by local scientists.

After reviewing in detail the results of research on the individual diseases, STAC noted the ERC's conclusion that TDR has an impressive record of accomplishments in promoting and speeding the development of products for disease control.

STAC noted that many ERC recommendations regarding field studies, social and economic research, research capability strengthening and linkages of other research and development efforts with these activities were already being implemented (as described in the Director's report).

7.2 Recommendations

- a) As recommended by the ERC, the diseases falling within TDR's mandate should continue to be only the six target diseases.
- b) Continued efforts should be made to link research and development activities with social and economic research and with research capability strengthening. Such links are now the key to the success of the Programme and will provide the basis for long-term tropical disease control.
- c) TDR staffing requirements would need to be considered within the context of the global and goal-oriented nature of the Programme's activities, with attention being given to demands on the number and expertise of the staff.

STAC noted that Director, TDR, had already streamlined the management and reorganized the staff to adapt to the new situation.

- d) With regard to the expansion of SER activities, a scientist with expertise in health economics should be appointed.
- e) With regard to the role of SWGs in coordinating activities within a disease-specific Component and with WHO disease control activities, there should be only one SWG for each disease-specific Component, i.e., one SWG might relate to several Steering Committees.
- f) With regard to the ERC's detailed suggestions on Steering Committee review procedures for incoming proposals, existing procedures had evolved under the close scrutiny of STAC and continued to meet requirements effectively. Some flexibility was needed, however, in special situations and was indeed essential in dealing with proposals submitted by scientists inexperienced in the preparation of formal research proposals.
- g) STAC supported the ERC's proposal to expand the Director's Initiative Fund from US \$262 000 to US \$1 million per year and agreed that limits not be set for the amounts which could be granted from this fund for start-up activities or increases of a Component's budget.

8. ONCHOCERCIASIS CHEMOTHERAPY PROJECT

STAC took note of the Onchocerciasis Chemotherapy Project (OCT) Progress Report for 1987 [document JPC8.8(A)] and the Review of the Independent Group [document JPC8.8(B)], and endorsed the following major recommendations of the review:

- a) The OCT must place its major emphasis on the development of a macrofilaricide. Basic research and exploration for new candidate drugs must be phased out by 1991, with subsequent focus on advanced development and clinical evaluation of candidate drugs.
- b) The drug development effort must be sharply focused and rigorously managed to assure the accomplishment of objectives within the limited constraints of time and funding.

STAC was informed that OCT funding would be integrated with the operation of the Onchocerciasis Control Programme in West Africa (OCP). The scientific management of the OCT was under review, and STAC-11 will consider information on the outcome of this review in 1989.

9. MODE OF OPERATION OF STAC

9.1 STAC examined in detail its procedures for review of Programme Components. These comprised:

- a biennial review of all Programme activities, preparatory to the preparation of the Programme's budget for the next biennium;
- an in-depth evaluation of the activities of individual Components by the examination of Steering Committee reports and by site visits by specially convened STRCs, usually once every five years.

There was concern that the conduct of the five-yearly reviews was unduly disruptive of the work of the Secretariat. Moreover, a heavy load was placed on STRC members at no inconsiderable cost to the Programme. Often the STRC reviews highlighted the quality of work of Steering Committees, attributable to the commitment and labour of their members. In these circumstances, further examination by an STRC of the Steering Committee's report often added little of substance.

9.2 Recommendations

The following recommendations reflect the concern of STAC for greater efficiency in close surveillance of Programme Components and the importance of close integration of the Programme as a whole.

- a) In order to increase the effectiveness of STAC's biennial review of all Components, in 1988 each STAC member will attend the meetings of one of the Steering Committees or of the Research Strengthening Group and will prepare a report for STAC-11 on the activities of the assigned Committee or Group.

- b) The Filariasis and Schistosomiasis Components will submit their five-yearly reports on their activities to STAC-11. After reviewing these reports, STAC will decide whether an in-depth review by a Scientific and Technical Review Committee (STRC) is necessary in each case and, more generally, whether to continue this modified five-yearly review process.
- c) In order to enhance the scientific direction given by STAC to the Programme, STAC introduced "Prospective Thematic Reviews" (PTRs). Their purpose would be to examine problems and new scientific advances relevant to a number of Programme Components. Ad hoc committees to conduct these reviews will be chaired by members of STAC and include international experts.

In 1989, a PTR on "New Directions in Research on Methods for the Control of Vectors", chaired by Professor J. Duarte de Araujo, and another on "New Directions in Drug Development", chaired by Professor A. Cerami, will take place. Specific terms of reference for each of these PTRs will be prepared by the Chairperson for discussion by STAC-11.

10. PROGRAMME BUDGET

Dr P. Ladouceur, Responsible Officer, Programme Management, TDR, informed STAC that the Joint Coordinating Board (JCB) had approved a Programme budget of US \$59 349 000 for the 1988-89 biennium, as recommended by STAC and the Standing Committee. As previously discussed by STAC, the Board did not, however, approve the proposed Programme Development Fund, but requested that STAC make a recommendation concerning the allocation of the US \$1 million which had been suggested for this fund in the proposed Programme budget for the 1988-89 biennium.

In previous biennia it had been necessary to make substantial reductions in the budget approved by the JCB, since TDR's income was insufficient to finance the full amount approved. With the improvement of TDR's finances in 1986 and 1987, it would be possible to proceed on the basis of the budget as approved by the JCB. This assumed that there would not be a significant appreciation of the US dollar in relation to other major currencies and that contributions to TDR would continue to increase.

STAC welcomed the improvement in TDR's finances and noted that this would permit the implementation of the scientific and technical programme as recommended by STAC-9 to the JCB in 1987. STAC also commended the Programme Secretariat for the clear and informative presentation of TDR's financial situation and requirements in the "Programme Budget for the 1988-89 Biennium and Estimates for 1990-91".

ANNEX I

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- OTERO, Dr E., Asociación Médica de los Andes, Bogota, Colombia (CHAIRMAN)
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ANNEX II

SYMPOSIUM SUMMARIES:

TRANSFER TO NATIONAL HEALTH SERVICES
OF TECHNOLOGY DEVELOPED WITH TDR SUPPORT

Multidrug Therapy in Leprosy

Dr M. Christian, Schieffelin Leprosy Research and Training Centre, Karigiri, North Arcot District, India

The introduction of dapsone to the chemotherapy of leprosy in the early 1950s was a major advance in the control of leprosy. For the first time it became possible to control leprosy through domiciliary treatment of patients. However, dependence on the single drug, dapsone, inevitably led to the emergence of drug resistance and, in the 1970s, the problem of dapsone resistance steadily intensified.

Established by TDR in 1976, the Scientific Working Group (SWG) on the Chemotherapy of Leprosy (THELEP) took major initiatives to systematically map primary and secondary dapsone resistance and seek better ways of using available drugs in the treatment of leprosy. Through such initiatives it became possible for a WHO Study Group on the Chemotherapy of Leprosy for Control Programmes, meeting in 1981, to recommend standard multidrug regimens aimed at preventing and managing dapsone resistance and at reducing the duration of treatment. Multibacillary patients required a combination of three drugs -- rifampicin, clofazimine and dapsone -- for a minimum of two years, paucibacillary patients a combination of two drugs -- rifampicin and dapsone -- for six months.

Field trials of multidrug therapy among multibacillary patients at two Indian centres, Karigiri and Polambakkam, have shown the treatment to be effective and associated with minimal side-effects, to be highly acceptable to the patients, to increase compliance with treatment and to reduce the frequency of ENL reactions. In over 5000 patient-years of follow-up not a single case of relapse has been observed. Field trials in paucibacillary patients in Indonesia and Malawi have shown that side-effects are minimal and acceptability is high. However, reversal reactions appear to occur more frequently among paucibacillary patients.

Following the recommendations of the Study Group, WHO, nongovernmental organizations and others have actively promoted multidrug therapy in national leprosy control programmes. The results are gratifying. Several countries have increased their commitment for leprosy and resources for leprosy control from donor agencies are on the increase. Introduction of multidrug therapy has generated increased enthusiasm among both patients and health workers. In several situations the prevalence of leprosy has shown a dramatic decline. According to data available from the Leprosy Unit of WHO, by January 1988 more than 2.1 million patients in about 88 leprosy-endemic countries were under multidrug therapy or had already completed multidrug therapy. This figure is likely to increase further in the next years, leading to a major decline of leprosy in several countries.

The Operational Introduction of Mefloquine, a New Antimalarial Drug, by the Antimalaria Programme in Thailand

Dr S. Pinichpongse, Chief Medical Officer, Department of Communicable Disease Control, Ministry of Public Health, Bangkok, Thailand

Mefloquine is an antimalarial drug of the quinoline methanol class, first developed by the Walter Reed Army Institute of Research (WRAIR), USA. Initial testing of this drug against chloroquine-resistant falciparum malaria in Thailand began in 1974. Following the first studies, further research conducted in Bangkok by the Faculty of Tropical Medicine of Mahidol University provided information on pharmacokinetics and optimal dosage regimens. The use of mefloquine in children and in pregnant women was also studied at the Faculty.

As the problem of drug resistance in Thailand worsened and extended to the sulfadoxine/pyrimethamine combination, a seven-day course of quinine had to be used, and even this regimen was associated with progressively decreasing cure rates. The side-effects of quinine administration also caused poor patient compliance and often resulted in under-dosing, followed by recrudescence and, potentially, selection for drug-resistant parasites. There was therefore an urgent need to use mefloquine operationally. The Malaria Division of the Ministry of Public Health, in collaboration with the TDR Components on the Chemotherapy of Malaria (CHEMAL) and Applied Field Research in Malaria (FIELD-MAL), carried out a number of field studies on the efficacy, tolerance and acceptability of mefloquine, both as a single drug and in combination with sulfadoxine/pyrimethamine and with primaquine (as a gametocytocide). Mefloquine appeared to be an ideal drug for field use: it was highly effective, well tolerated and acceptable to patients.

Because of general concern that widespread use of mefloquine would quickly result in selection of resistant parasites, and following experimental evidence from a mouse malaria model suggesting that a mefloquine/sulfadoxine/pyrimethamine combination (MSP) would delay the appearance of resistance, WHO recommended that mefloquine be deployed only as such a combination.

Since mid-1985, MSP has been the standard treatment for all slide-positive cases of *P. falciparum* malaria in Thailand. To date over 300 000 patients have been treated with the combination.

In early 1985, there were several reports of severe and even fatal cutaneous side-effects related to sulfadoxine used for malaria prophylaxis. The Thai Malaria Division initiated a prospective monitoring system designed to detect such toxicity resulting from treatment with MSP. Several cases were discovered, none of which were fatal. WHO convened a meeting in 1986 to reconsider the recommendation that mefloquine should only be used in MSP combination, and further research was recommended. The Malaria Division of Thailand has undertaken a double-blind comparative trial of the monodrug mefloquine vs. MSP and to date, in over 370 patients, both regimens were equally effective in producing cure and similar in the incidence of mild side-effects.

The Malaria Division, with WHO assistance, is planning a large-scale double-blind comparison of mefloquine vs. MSP in 3000 additional patients to confirm the findings of the study already under way, and then to monitor closely treatment with mefloquine in 100 000 patients over the next year.

Ivermectin in Onchocerciasis

Dr K.R. Brown, Merck Sharp and Dohme Research Laboratories, West Point, PA, USA

After extensive safety testing and use in animals for a variety of applications, ivermectin was first given to patients with onchocerciasis in 1981. With safety the first consideration, dosing was started at 5 µg/kg on a single-dose basis. Ultimately, extensive studies were done with 50, 100, 150, or 200 µg/kg on a single-dose basis in patients with light to heavy Onchocerca volvulus infections. Both open and double-blind studies were performed; by the time of product licensure in France in October 1987, 1163 patients had received ivermectin, 50 diethylcarbamazine (DEC) and 385 placebo in the various trials conducted by the different groups, the principal of which were Merck Sharp and Dohme Research Laboratories (MSDRL) and WHO, including both TDR and the OCP.

Studies were done initially in lightly infected patients. As trials continued, it was possible to show that ivermectin was equally effective in heavily infected persons. The initial trials were done to demonstrate the utility of ivermectin given once every six months; later trials documented the possibility of extending the dose interval to 12 months but not significantly beyond that. Furthermore, a study which was allowed to include children from five years of age demonstrated that the safety, efficacy and tolerability in 103 children in that age-group were generally comparable to those previously documented in adults.

The Mazzotti reaction was not completely absent in persons treated with ivermectin, but its frequency and severity were often dramatically and significantly less than in the DEC-treated patients (both historically and concomitantly in comparative trials). The qualitative nature of the reactions was similar and it was not unusual to see some patients with itching, fever, headache and adenopathy with or without tenderness. A major advantage of ivermectin treatment was the absence of significant eye reactions or aggravation of existing eye disease, both of which may occur in DEC-treated patients.

The approved physician's circular for Mectizan (ivermectin, MSD), which was approved by the French regulatory agency, states that Mectizan is indicated for the treatment of onchocerciasis, whether diagnosed or suspected, at a dose of 1-2 tablets (150 µg/kg) on a single-dose basis every six months. The drug was not approved for use in pregnancy, and nursing mothers were requested to wait three months before using the drug; initially children under 12 years of age were excluded. MSDRL has submitted to the regulatory agency additional data supporting a dose interval of 12 months and inclusion of pediatric patients from five years of age.

Evidence suggests that in single doses ivermectin has no deleterious effect on the adult worms per se; however, changes to the microfilariae in utero can be seen when adult worms are examined one, two and three months after treatment; up to 85% of the forms are found in a degenerated state. Future studies will address the issue of possible macrofilaricidal activity after repeated doses of ivermectin. Data in hand suggest the possibility of decreasing transmission of the microfilariae by reducing counts to below five microfilariae/mg of tissue.

The drug has been approved for use in onchocerciasis by the French regulatory agency. Merck and WHO (the OCP and TDR) continue, however, to enter patients in a variety of trials in endemic areas in order to broaden the base of experience, so that by the time the drug is released for more general use in endemic areas between 80 000-140 000 patients will have been treated. To date

over 40 000 persons have been treated and, in the community-based trials, only 37 serious adverse clinical effects have been reported.

Merck has established a Mectizan Expert Committee (C-MEC) to review applications from countries with endemic onchocerciasis to receive the drug as a donation. C-MEC is chaired by Dr W. Foege of the Carter Presidential Center, USA, and its members include Dr A.O. Lucas, formerly of TDR and now with the Carnegie Foundation, USA; Dr G. Zea-Flores of the Servicio Nacional de Erradicación de la Malaria y Programas Adscritos (SNEM), Guatemala; Dr M. Larivière of the University of Paris, France; Dr B. Greene of Case Western Reserve University, USA; and Dr E.A. Ottesen of the National Institutes of Health, USA. Non-voting members include WHO, represented by Dr A. Davis; the Centers for Disease Control (CDC) in the USA, represented by Dr R. Kaiser; and MSDRL, represented by Dr K.R. Brown.

C-MEC has had its first meeting and anticipates having guidelines for use by WHO Member States as well as applications for receipt of Mectizan after its April 1988 meeting. The expected route of approval and distribution is as follows: Member State submits application directly to the C-MEC Secretariat for duplication and distribution to WHO, Merck and C-MEC members. WHO advises Member State on technical aspects of application, offering, where appropriate, suggestions for improvement. C-MEC exercises final approval authority. Following approval of application, C-MEC requests Merck to ship the drug to the Member State.

The Use of *Bacillus thuringiensis* in the Onchocerciasis Control Programme in West Africa (OCP)

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Formulations of *Bacillus thuringiensis* H-14 (B.t. H-14) have been an essential part of the inventory of insecticides used by the Onchocerciasis Control Programme in West Africa (OCP) since 1980. This product offers unique advantages for OCP use in terms of combating resistance and low mammalian toxicity. However, the relatively large quantity needed and the low order of activity make it prohibitively expensive for use at high river discharges. It is likely that improved formulations will be available in the near future to overcome some of these problems. For OCP use, where a product with a high and uniform active ingredient content is needed, as well as high-performance formulations, it is doubtful that local production would be cost-effective, and the OCP will continue to purchase the product from the major manufacturers and benefit from their expertise in improving it and in keeping the price low. B.t. H-14 will thus have played an important role in the successful fight against a major parasitic disease.

ANNEX III

PLANNING MEETING ON THE DEVELOPMENT OF FIELD
RESEARCH NETWORKS AND CENTRES

Geneva, 15-16 February 1988

SUMMARY

The purpose of this small working group meeting was to develop a five-year plan for the establishment of field research networks and centres in each WHO Region. These networks would: facilitate communication among field researchers in order to strengthen their capacity for multidisciplinary field studies; facilitate continuing training and consultation through regular workshops and short training courses; serve as a focus for collaborative research and provide a mechanism to develop protocols for high-priority field studies; foster links between field researchers and national disease control programmes; disseminate information on new advances in field research methods and tools; provide a focus for the strengthening of regional resource centres that would furnish continuing multidisciplinary expertise for neighbouring field research projects; promote further field research by expanding the network to involve additional researchers and institutions; and link those in endemic areas with their colleagues in technically advanced countries and so contribute to the transfer of skills to endemic areas.

Several issues received emphasis:

1. Field studies generally require expertise from many disciplines; networks with regular workshops provide an effective means of integrating social scientists, economists, entomologists, parasitologists, clinicians and epidemiologists during the planning and analysis of field research.
2. Those responsible for national disease control programmes should be included in the networks and, where possible, be directly involved in the field research itself, especially that concerned with the introduction of new intervention methods.
3. The networks could have an informal structure, with emphasis on dissemination of skills and knowledge to the field research areas. Selected institutions within the network, however, may need strengthening in order to serve as multidisciplinary resource centres for field research projects.

Criteria were developed for including groups in a network and for an institution to qualify as a regional field research resource centre. Three groups of participants set out specific plans for networking, respectively, in Africa, Asia and Latin America. Timetables for network activities for the next two years were established for each of the three Regions. Although the basic functions and structural characteristics outlined above are common to all three plans, the detailed arrangements vary in relation to the great differences in disease patterns, the underlying factors that contribute to them and the resources available in each Region to combat them.

1. BACKGROUND

There is a paucity of well-conducted field research in the tropical disease-endemic areas. Few good proposals have been submitted to TDR Steering Committees, and other groups supporting research on tropical diseases (e.g., the WHO Diarrhoeal Diseases Control Programme) have faced similar problems. Although such studies are vital for the assessment of new tools and interventions against tropical diseases, this has been one of the weakest areas of TDR activities. Several initiatives have been made in the past to try to remedy this situation, including institution strengthening with emphasis on postgraduate courses in epidemiology in endemic countries; sponsorship of individuals for postgraduate training at master's and doctoral levels; workshops involving training in preparing research protocols; and commented reviews by Steering Committee members and others of epidemiology protocols submitted to TDR, sometimes with site visits by Secretariat members or consultants.

These strategies have met with only limited success and additional ways of improving the quality and quantity of field research in the endemic areas are needed. With this end in view several new initiatives have been proposed.

First, support has been provided for fellowships for training in advanced epidemiological field research. Many of the skills needed for successful field research are not taught on epidemiology courses. In developed countries, epidemiological skills are usually learned by junior researchers working under the supervision of experienced workers, as is also the case with the laboratory sciences. Opportunities are limited for such apprenticeship training in developing countries, where there are often no established traditions of field research and where there are few experienced field epidemiologists. It is proposed, therefore, to make use of ongoing, well-conducted, epidemiological studies in the endemic areas as training opportunities for young epidemiologists. Fellowships have been advertised for advanced "on-site" training in field epidemiological research. Fellows will be attached for a period of two or three years to successful ongoing field projects, often in countries other than their own, to develop their epidemiological skills in the design, conduct and analysis of intervention trials and other epidemiological field research. The fellowships are intended for those who have a basic grounding in epidemiology but who lack supervised field experience.

Second, it is proposed that TDR Steering Committees develop outline protocols for field research. The traditional passive method of allocating funds for research, in which Steering Committees review submitted proposals according to scientific merit and relevance to Programme priorities, does not work well for epidemiological field research. Not only is the quality of submitted proposals generally poor but the objectives of the research proposed are often not those of the highest priority. It is proposed that TDR Steering Committees play a more active role in defining field research priorities, not only by listing the important research issues but also by developing outline protocols for studies on these issues. Each Steering Committee will have an associated "field studies subcommittee", consisting of several Steering Committee members and additional ad hoc members, as necessary. Each subcommittee will, in close liaison with the parent Steering Committee, list priorities and outline protocols for field research. Where possible, scientists from endemic areas in a position to conduct research of the kind likely to be proposed will be included in the subcommittees and take an active part in the drafting process.

Third, it is proposed to launch a major new initiative aimed at strengthening the capacity for field research in the endemic areas through the creation and promotion of networks of field researchers and centres. In outline, links will be built up between field researchers in endemic areas through local (regional or subregional) networks. To this end, regular regional workshops will bring together investigators conducting TDR-related field studies so that they can exchange ideas and information on methods developed in their own field studies, design protocols for new studies, be briefed by "experts" on new developments (e.g., on priority research issues, new field tools, etc.), and present for critical review preliminary results from field studies. Short instructional courses on the use of particular techniques might be run in conjunction with these workshops. Workers in developed countries might participate in the networks in order to promote the transfer of skills in field research methods and organization.

A small meeting of scientists with considerable field experience was convened in Geneva to review and further develop an outline plan for the development of field research networks. The list of participants is given in section 7, below.

2. OBJECTIVES

The main objective of the meeting was to develop a five-year plan for the development of field research networks and centres. Specific objectives were:

- 2.1 to review critically and revise a draft document distributed in advance of the meeting;
- 2.2 to formulate a detailed plan of activities for the next two years for the development of field research networks and centres;
- 2.3 to plan workshops to be held in East Africa, West Africa, Asia and Latin America in the next 12 to 18 months;
- 2.4 to develop a budget and plan funding mechanisms for the proposed activities;
- 2.5 to make a preliminary list of potential network participants, regional centres and linkages with developed country individuals/institutions.

Objectives 1, 2, 3 and 5 were addressed in some detail. Uncertainties about how the networks would develop and lack of time at the meeting did not permit a detailed costing to be made, though several funding mechanisms were discussed. There was general agreement that the kinds of research networks considered were likely to need long-term support, possibly for a decade or more, but at this stage it would be difficult to develop a detailed long-term plan, as the networks would have to "evolve" and their evolution would probably vary in different regions.

3. BASIC STRATEGY

Following a review of previous TDR efforts to strengthen field research capacity, detailed consideration was given to the proposal for the development of field research networks. There was strong support for the proposal and the general approach outlined. A lack of field studies in tropical disease-endemic

areas was recognized as a problem for many groups besides TDR, especially national disease control programmes, but initially the initiative should focus on the TDR diseases. Other groups and diseases might be incorporated at a later stage.

The networks would function at different levels, but should bring together those working on similar problems within countries. Links should be formed between those doing or planning field research on the TDR target diseases and this would normally also involve the fostering of links between their home institutions. By including disease control programmes in the linking process, new interventions could be put to use at a national level and evaluated through field studies. One means of ensuring good links with control programmes would be either to include them directly in the networks or at least ensure that other institutions chosen for the networks have close links with control programmes.

Networks of field researchers in different countries would probably best be organized on a regional or subregional basis, but in some circumstances wider links might be envisaged, possibly with respect to field research specific to a disease or topic (e.g., between groups conducting large-scale vaccine trials). An informal structure would be most appropriate, with emphasis on decentralization of skills to the field research areas. "Resource centres" may, however, be needed in endemic areas to develop special skills in individuals who would be available on a consultant basis within a network. In the early stages, some regional networks may need to form links with centres in developed countries.

The networks should be used to develop multidisciplinary studies and thereby facilitate the integration of socioeconomic and entomological components into field research projects, especially those involving control programmes in which such components are usually of special relevance.

The exact role developed country institutions would play in the networks would probably vary considerably between regions. Some regions would be able to operate autonomous networks from an early stage, whereas others may need to import skills initially (e.g., for help in designing studies and developing protocols). Developed country institutions should be chosen for their regional linkages and commitment to the transfer of skills to network participants. It was unlikely that any one institution would have individuals with sufficient skills in all required areas and such individuals would have to be co-opted as required.

Following the plenary discussions of the general form the networks should take, participants separated into three groups to discuss plans for networks in, respectively, Africa, Asia and Latin America. Some common themes emerged from these group discussions but it was apparent that networks were likely to take different regional forms.

4. FUNCTIONS OF FIELD RESEARCH NETWORKS

The functions of field research networks were summarized as follows:

- 4.1 to facilitate communication between field researchers in the endemic areas in order to strengthen their capacity to conduct multidisciplinary field studies;
- 4.2 to facilitate continuing training in field research through regular workshops and short training courses organized at regional centres;

- 4.3 to serve as a focus for collaborative research and to provide a mechanism for developing protocols for high-priority field studies;
 - 4.4 to foster links between field researchers and national disease control programmes;
 - 4.5 to disseminate information through the network on new advances in field research methods and tools;
 - 4.6 to provide a focus for the strengthening of regional resource centres to enable them to provide assistance or advice to individual researchers on special aspects of field studies;
 - 4.7 to promote further field research studies by appropriate expansion of the network to include additional researchers and institutions;
 - 4.8 to link field researchers in the endemic areas with those in developed countries, with the objective of transferring skills to the former.
5. CRITERIA FOR INCLUSION IN A NETWORK AND FOR THE SELECTION OF FIELD RESEARCH RESOURCE CENTRES
- 5.1 The institute/project should have on its staff at least one trained or experienced epidemiologist or public health specialist with epidemiological interests.
 - 5.2 There should be ongoing or planned field research activities on a TDR disease.
 - 5.3 Where possible, there should be a link with a disease control programme, preferably not only at a national but also at a district level.
 - 5.4 There should be a potential for developing local data processing and analysis capabilities that allow rapid evaluation and feedback.
 - 5.5 There should be facilities and manpower structures that allow large-scale processing of laboratory tests and ensure overall logistic support and management backing.

In general, network participants should be scientists involved directly with the conduct of field research and also trainees associated with field projects. One or more regional field research resource centres would be associated with each network. The requirements for such a centre should include:

- a "critical mass" of well-trained epidemiologists, themselves involved in field research projects;
- adequate data processing facilities and statistical support;
- well-managed, adequate laboratory facilities;
- high-level managerial competence;
- logistic support for vehicles, equipment maintenance and communications;
- established linkages with disease control programmes.

Well-trained staff in the social sciences and entomology would also be desirable.

It was recommended that a comprehensive list be drawn up of ongoing field projects involving the TDR diseases in each region. The list should include both institutions and projects involved in applied field research focusing on local (district) health problems and priorities. The meeting drew up regional lists based on participants' personal knowledge, to be subsequently augmented with information from the TDR data bank and other sources.

6. REGIONAL NETWORKS

6.1 Africa

To initiate networks in Africa it was proposed that two workshops be held in late 1988, one for East Africa, the other for West and Central Africa, to bring together scientists undertaking field research in different endemic settings. Workshop participants should present their ongoing studies and plans for future studies and identify their needs for epidemiological backing and training for the projects presented. The workshops should not be limited to one disease. Using outlines for priority field studies provided by TDR Steering Committees, the workshops could develop protocols to be submitted for funding in early 1989.

The demand for further training among participants should be assessed from the results of the first workshops. Short courses might then be developed to meet the express needs of the participants with the involvement of developed country epidemiologists as necessary. Courses might be based on a one- or two-week module, organized in conjunction with future workshops. Issues that might be addressed through such modules include:

- choice of research priorities;
- choice and planning of intervention studies;
- questionnaires and cultural context;
- data handling and the use of microcomputers;
- clinical epidemiology;
- entomological techniques;
- immunodiagnostic tools;
- report writing;
- use and place of anthropological studies.

Modules should be selected by workshop participants and be directly relevant to the strengthening of field research activities. They would build on an assumed basic epidemiological training rather than instruct participants in elementary epidemiological methods, knowledge of which would be a requirement for participation. Module development might be coordinated by TDR but other institutions should be encouraged to develop modules.

Subsequent workshops would probably be necessary on an annual basis. As the number of participants would increase over time, the first workshops should probably be kept quite small. A regular sequence of workshops, with associated training modules, should strengthen informal links between researchers and various field projects. Workshops could be combined with national or regional research meetings.

A tentative timetable for the development of network activities is outlined as below.

| Time | Activity | Organised by |
|--------------|--|---------------------------------------|
| 03.88 -09.88 | Selection of participants for initial workshops and preparation of workshops | TDR |
| 12.88 | Initial workshops | TDR, consultants and regional centres |
| Spring 89 | Protocols developed at workshops to be submitted to Steering Committees | |
| Later in 89 | Workshops and associated training modules | Regional centres and consultants |

6.2 Asia

To identify institutions that might serve as regional resource centres for field research, the group reviewed the activities of the various institutions that had been strengthened by TDR in Asia, as well as other large projects which had been funded by TDR Steering Committees. These centres would be expected to provide technical support to field researchers in the design, execution and analysis of field studies.

TDR should strengthen one or more of the following centres: in India, the ICMR Tuberculosis Research Centre, Madras; in the Philippines, the College of Public Health, Manila; in Thailand, the Faculty of Tropical Medicine, Mahidol University; and in Malaysia, the Institute of Medical Research, Kuala Lumpur. These institutions should also be involved in planning the development of a field research network and should aim to hold a meeting later in 1988 to draw up a detailed plan of action and a budget for the development of a network. (Efforts are under way to strengthen the Institute of Parasitic Diseases in Shanghai, which might serve as a resource centre for field research activities in China.)

Concurrently with these activities, an effort should be made, in collaboration with TDR Steering Committees, to identify and bring together potential researchers on filariasis and malaria, at least six on each topic, for a workshop in August or October 1988. At this workshop, TDR priorities for field research on these two diseases would be reviewed in the light of regional priorities and protocols for field research studies developed either at this workshop or at a subsequent workshop). The first workshop participants would also be expected to elaborate activities for the development of a network of researchers/institutions in field research areas of common interest. It may be necessary for the first workshop to involve the directors of the relevant institutes in order to decide priorities.

Early in 1989 a workshop on field research methods would be conducted for field researchers participating in the research projects that were drawn up at the earlier workshop on detailed site-specific protocols.

A draft timetable for regional activities was drawn up:

| Time | Activity |
|-----------|--|
| Immediate | Elicit interest in different centres in strengthening their capacity for field research to enable them to become resource centres. |
| 06-12.88 | Develop a proposal for RSG support of resource centres. Compile a list of potential malaria and filariasis field researchers, in collaboration with Steering Committees. |
| 08-09.88 | Convene a meeting of researchers and representatives of resource centres. Formulate protocols for submission to the Steering Committees on Applied Field Research in Malaria (FIELDMAL) and Filariasis (FIL). Identify needs for local strengthening in field research capacities. |
| Spring 89 | Submission of proposals to Steering Committees. |
| Early 89 | Workshop in research methodology for field workers. |
| 01-03.89 | Development of field research project on schistosomiasis in the Philippines (after the Scientific Working Group on Schistosomiasis has defined field research priorities in September 1988). |

6.3 Latin America

The group reviewed ongoing field activities on TDR diseases in Latin America. A number of research networks are functioning or planned in Latin America, although few include field studies as a major component. The most notable of these is the network for research on Chagas' disease, which had been formed with TDR support and involved 11 centres, but few epidemiologists.

Several diseases should be incorporated in the proposed field research networks, which should be geographically focused. Two were suggested initially, one centred on Cali, Colombia, the other on Rio de Janeiro, Brazil (at the FIOCRUZ School of Public Health).

The Cali-based network might consist initially of researchers and institutions in Colombia, Venezuela, Mexico and Central America. It was suggested that the first meeting of this network might be held in October 1988. FIELDMAL would be asked to provide outline research protocols for priority field studies for consideration at this meeting, at which Steering Committee representatives might participate. Protocols suitable for submission for funding to FIELDMAL might be developed at the workshop. Researchers working on other TDR diseases would also be invited to the workshop. While Mexico might participate initially in this network, a separate Mexican network might be formed at a later date.

The Rio-based network might initially include researchers from Argentina, Brazil, Paraguay and Peru. The first meeting of this network might take place shortly after the Cali workshop, in late 1988 or early 1989, in order that Dr A. Alzate, who would coordinate the Cali workshop, might also attend the Rio meeting. The development of the Rio-based network would be discussed further by Dr Alzate at the FIELDMAL meeting in Brasilia, Brazil, in April 1988 and

by Dr R.H. Morrow and Dr P. Smith during their visit to Rio in May. It was envisaged that epidemiologists involved in the Chagas' disease network would participate in the Rio-based network.

7. PARTICIPANTS

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ANNEX IV

FUNDING OF RESEARCH AND DEVELOPMENT
IN TROPICAL DISEASE-ENDEMIC COUNTRIES

1. Introduction

The Special Programme for Research and Training in Tropical Diseases (TDR) has two interdependent objectives:

- 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.

By its nature, TDR is a development assistance programme that funds activities of benefit to developing countries, whether they are conducted in developing or in developed countries. However, in order to ensure their maximum development impact, TDR encourages activities that are conducted in the developing countries themselves. In general, activities directed specifically towards TDR's second objective are carried out either in countries where tropical diseases are endemic (e.g., institution strengthening activities), or involve training in developed countries of nationals of the endemic countries. Research and development activities, on the other hand, may be conducted anywhere in the world, since TDR seeks to enlist the best scientists and institutions in the search for new disease control tools. Exceptionally, in the case of social and economic research, TDR funds only projects whose principal investigators are developing country researchers based in institutions in tropical disease-endemic countries.

TDR has always closely monitored the geographic distribution of funded activities. After a number of years of stability, the proportion of funding in tropical disease-endemic countries (developing endemic countries or DEC) appeared to decline in 1986 and 1987. The purpose of this document is to examine this decline and describe measures being taken or proposed to increase funding in DEC.

The information in section 2 is based on data from TDR's Management Information System (MISTR), which uses a number of definitions and conventions, notably:

- DEC ("Developing Endemic Countries"): developing countries endemic for one or more TDR target diseases; "non-DECs" refers to developed countries.
- Country "attribution": projects are attributed to a country on the basis of the country of the institution with which TDR concludes a research agreement, regardless of whether the project is carried out partly or even largely in another country;
- Programme Areas: in line with the basic structure of the TDR budget, Programme Area II includes research and development

activities conducted by disease and trans-disease Components and Programme Area III refers to research capability strengthening activities.

MISTR data are organized in such a way that a project is assigned to a particular country, but they may not permit ready identification of projects in which developed country scientists or institutions act as principal investigators or collaborating institutions (frequently for administrative reasons) but in which activities are carried out entirely or primarily in DECs. Thus, trends in the data are more important than absolute figures.

2. Review of Statistical Data

From the inception of TDR until the end of 1987, 54.7% of TDR project funding went to DECs (Table 1 and Figure 1). Between 1978 and 1985, the proportion ranged from 61.1% (1981) to 53.4% (1978), with an average of 57.1%. However, in 1986 and 1987, the proportion decreased to 49.4% and 45.4%, respectively.

Nearly all projects funded under Programme Area III (Research Capability Strengthening) are considered DEC projects (Table 2). Some are recorded under developed countries because group training activities occasionally occur in a developed country collaborating institution. (Individual training grants, on the other hand, are always recorded against the country of origin of the

TABLE 1 PROJECT FUNDING IN DEVELOPING ENDEMIC COUNTRIES (DECs) AND DEVELOPED COUNTRIES: TOTAL PROGRAMME (PROGRAMME AREAS II AND III)

| Year | Developing Endemic Countries | | Developed Countries | | All Countries |
|--------------|------------------------------|--------------|---------------------|--------------|--------------------|
| | Amount (US\$) | Per Cent | Amount (US\$) | Per Cent | Amount (US\$) |
| 1975 | 53 928 | 34.5% | 102 300 | 65.5% | 156 228 |
| 1976 | 8 500 | 3.3% | 252 850 | 96.7% | 261 350 |
| 1977 | 1 002 381 | 28.0% | 2 574 653 | 72.0% | 3 577 034 |
| 1978 | 6 724 337 | 53.4% | 5 870 129 | 46.6% | 12 594 466 |
| 1979 | 9 949 287 | 56.4% | 7 704 469 | 43.6% | 17 653 756 |
| 1980 | 10 487 204 | 56.5% | 8 060 713 | 43.5% | 18 547 917 |
| 1981 | 11 615 533 | 61.1% | 7 403 524 | 38.9% | 19 019 057 |
| 1982 | 9 399 905 | 54.9% | 7 728 351 | 45.1% | 17 128 256 |
| 1983 | 11 633 752 | 60.4% | 7 625 771 | 39.6% | 19 259 523 |
| 1984 | 9 075 424 | 59.3% | 6 223 073 | 40.7% | 15 298 497 |
| 1985 | 10 346 274 | 55.4% | 8 341 119 | 44.6% | 18 687 393 |
| 1986 | 7 250 231 | 49.4% | 7 440 592 | 50.6% | 14 690 823 |
| 1987 | 8 373 148 | 45.4% | 10 077 635 | 54.6% | 18 450 783 |
| TOTAL | 95 919 904 | 54.7% | 79 405 179 | 45.3% | 175 325 083 |

Fig. 1 Project Funding in DECs

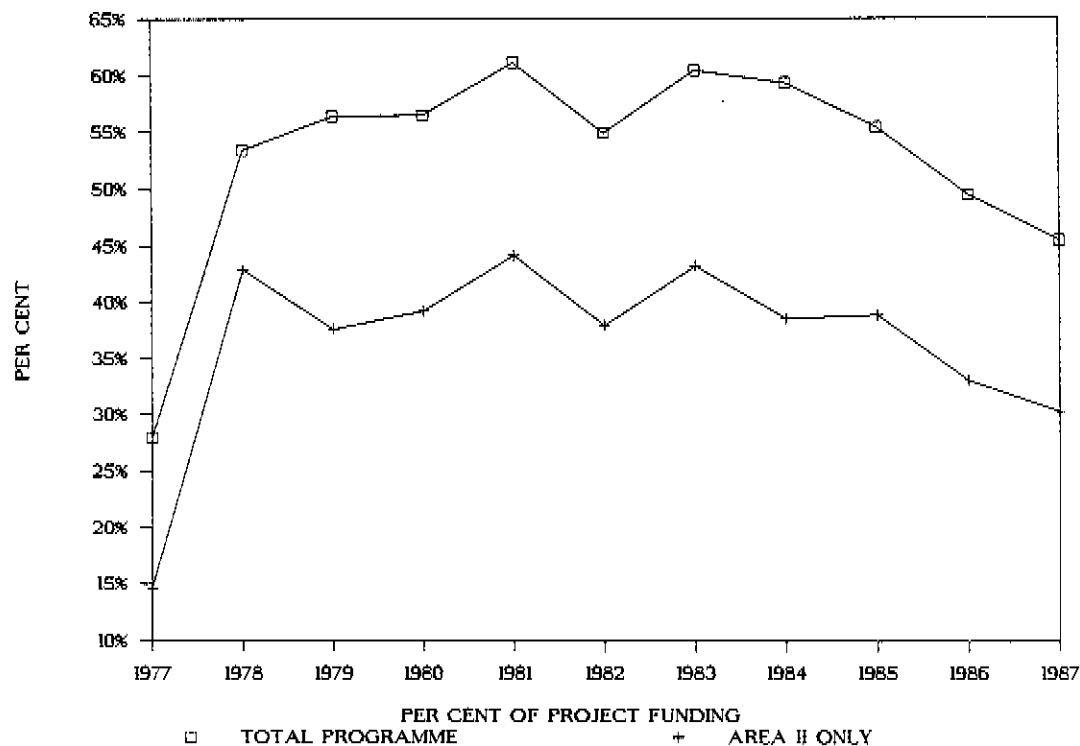


TABLE 2 PROJECT FUNDING IN DEVELOPING ENDEMIC COUNTRIES (DECs) AND DEVELOPED COUNTRIES: RESEARCH CAPABILITY STRENGTHENING (PROGRAMME AREA III)

| Year | Developing Endemic Countries | | Developed Countries | | All Countries Amount (US\$) |
|--------------|------------------------------|--------------|---------------------|-------------|--------------------------------|
| | Amount (US\$) | Per Cent | Amount (US\$) | Per Cent | |
| 1975 | 28 928 | 100.0% | 0 | 0.0% | 28 928 |
| 1976 | 0 | 0.0% | 0 | 0.0% | 0 |
| 1977 | 560 651 | 100.0% | 0 | 0.0% | 560 651 |
| 1978 | 2 314 237 | 99.6% | 9 000 | 0.4% | 2 323 237 |
| 1979 | 5 310 819 | 100.0% | 0 | 0.0% | 5 310 819 |
| 1980 | 5 365 084 | 98.0% | 111 011 | 2.0% | 5 476 095 |
| 1981 | 5 868 723 | 98.2% | 110 250 | 1.8% | 5 978 973 |
| 1982 | 4 793 490 | 96.6% | 167 770 | 3.4% | 4 961 260 |
| 1983 | 5 895 817 | 98.8% | 73 607 | 1.2% | 5 969 424 |
| 1984 | 5 194 601 | 99.8% | 12 850 | 0.2% | 5 207 451 |
| 1985 | 5 051 980 | 100.0% | 0 | 0.0% | 5 051 980 |
| 1986 | 3 593 531 | 99.7% | 10 000 | 0.3% | 3 603 531 |
| 1987 | 4 082 363 | 96.7% | 141 200 | 3.3% | 4 223 563 |
| TOTAL | 48 060 224 | 98.7% | 635 688 | 1.3% | 48 695 912 |

trainee and not the country of training.) Although almost all expenditures for research capability strengthening are shown as DEC expenditures, they influence the overall DEC/developed country ratio (Table 1), since the proportion of total project funding accounted for by research capability strengthening varies from year to year and has in fact decreased slightly in recent years: the overall average was 27.8% from 1975 to 1987, 24.5% in 1986 and 22.9% in 1987. This magnifies the overall decrease in project funding in DECs for 1986 and 1987, as shown in Table 1.

Most of the variation in project funding in DECs is the result of changes in funding in the Research and Development Components in Programme Area II (Table 3 and Figure 1). The average of research and development funding in DECs since the inception of TDR has been 37.8%, ranging from 44.1% in 1981 to 37.9% in 1982, with an average of 40.2% between 1978 and 1985. In 1986, the figure dropped to 33.0% and in 1987, to 30.2%.

Three factors have been used to analyse the decrease in DEC project funding in 1986 and 1987:

- (1) the number of project proposals received from DECs in comparison with that received from developed countries;
- (2) the relative "approval rate" between projects originating in DECs and those in developed countries, i.e., the number of projects approved or funded as a proportion of all projects on which funding decisions have been made;
- (3) the relative size or average dollar value of projects funded in DECs in comparison with that in developed countries.

TABLE 3 PROJECT FUNDING IN DEVELOPING ENDEMIC COUNTRIES (DECs) AND DEVELOPED COUNTRIES: RESEARCH AND DEVELOPMENT (PROGRAMME AREA II)

| Year | Developing Endemic Countries | | Developed Countries | | All Countries |
|--------------|------------------------------|--------------|---------------------|--------------|--------------------|
| | Amount (US\$) | Percent | Amount (US\$) | Percent | Amount (US\$) |
| 1975 | 25 000 | 19.6% | 102 300 | 80.4% | 127 300 |
| 1976 | 8 500 | 3.3% | 252 850 | 96.7% | 261 350 |
| 1977 | 441 730 | 14.6% | 2 574 653 | 85.4% | 3 016 383 |
| 1978 | 4 410 100 | 42.9% | 5 861 129 | 57.1% | 10 271 229 |
| 1979 | 4 638 468 | 37.6% | 7 704 469 | 62.4% | 12 342 937 |
| 1980 | 5 122 120 | 39.2% | 7 949 702 | 60.8% | 13 071 822 |
| 1981 | 5 746 810 | 44.1% | 7 293 274 | 55.9% | 13 040 084 |
| 1982 | 4 606 415 | 37.9% | 7 560 581 | 62.1% | 12 166 996 |
| 1983 | 5 737 935 | 43.2% | 7 552 164 | 56.8% | 13 290 099 |
| 1984 | 3 880 823 | 38.5% | 6 210 223 | 61.5% | 10 091 046 |
| 1985 | 5 294 294 | 38.8% | 8 341 119 | 61.2% | 13 635 413 |
| 1986 | 3 656 700 | 33.0% | 7 430 592 | 67.0% | 11 087 292 |
| 1987 | 4 290 785 | 30.2% | 9 936 435 | 69.8% | 14 227 220 |
| TOTAL | 47 859 680 | 37.8% | 78 769 491 | 62.2% | 126 629 171 |

Table 4 shows the number and proportion of new research and development project proposals received from the inception of TDR until the end of 1987 (see also Figures 2 and 3). The proportion of proposals from DECs increased in the early years of TDR, from 35.6% in the 1975-77 period, to a high of 48.6% in 1981, remaining fairly constant between 44.0% and 46.6% up to 1985. In 1986, the proportion decreased to 41.3% and dropped to 40.5% in 1987. These are significant decreases, especially when combined with the drop in the actual number of proposals received from DECs in 1986 (from an average of 175 a year in the preceding four years to 136 in 1986). Although the actual number of proposals received in 1987 increased to 159, this did not prevent a further slight decrease in the ratio, since the number of proposals received from developed countries also increased significantly in 1987. The larger number of proposals from DECs in 1987 is nonetheless a positive development, which should influence funding ratios for DECs in future years.

As a general conclusion, there was a significant decrease in the number and proportion of project proposals received from DECs in 1986 and 1987 in comparison with earlier years.

Although there are variations from year to year in the "approval rate" or funding ratio for projects from DECs and developed countries (Figure 4), on the whole, the proportions of projects funded or approved from both DECs and developed countries in relation to all projects either funded or rejected (adjudicated) during the year have remained relatively constant, averaging 60.9% and 61.9%, respectively.

In 1986 the funding ratio for developed country projects exceeded that for DECs, but the reverse was true in 1987. This suggests that the funding ratio is not a significant factor in accounting for the overall changes in the geographic distribution of project funding.

TABLE 4 RESEARCH AND DEVELOPMENT PROJECT PROPOSALS RECEIVED: PROGRAMME AREA II

| Year | From DECs | From Developed Countries | From All Countries | Per Cent DECs | Per Cent Developed Countries |
|-------|-----------|--------------------------|--------------------|---------------|------------------------------|
| 1975 | 3 | 10 | 13 | 23.1% | 76.9% |
| 1976 | 2 | 10 | 12 | 16.7% | 83.3% |
| 1977 | 107 | 183 | 290 | 36.9% | 63.1% |
| 1978 | 178 | 263 | 441 | 40.4% | 59.6% |
| 1979 | 178 | 249 | 427 | 41.7% | 58.3% |
| 1980 | 157 | 203 | 360 | 43.6% | 56.4% |
| 1981 | 158 | 167 | 325 | 48.6% | 51.4% |
| 1982 | 179 | 228 | 407 | 44.0% | 56.0% |
| 1983 | 171 | 196 | 367 | 46.6% | 53.4% |
| 1984 | 177 | 205 | 382 | 46.3% | 53.7% |
| 1985 | 171 | 204 | 375 | 45.6% | 54.4% |
| 1986 | 136 | 193 | 329 | 41.3% | 58.7% |
| 1987 | 159 | 234 | 393 | 40.5% | 59.5% |
| TOTAL | 1 776 | 2 345 | 4 121 | 43.1% | 56.9% |

Fig. 2 Research and Development Proposals from DEC's

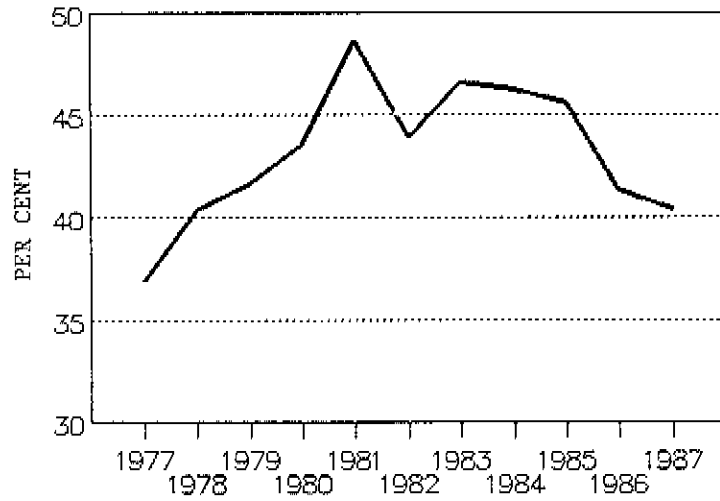


Fig. 3 New Research and Development Proposals Received

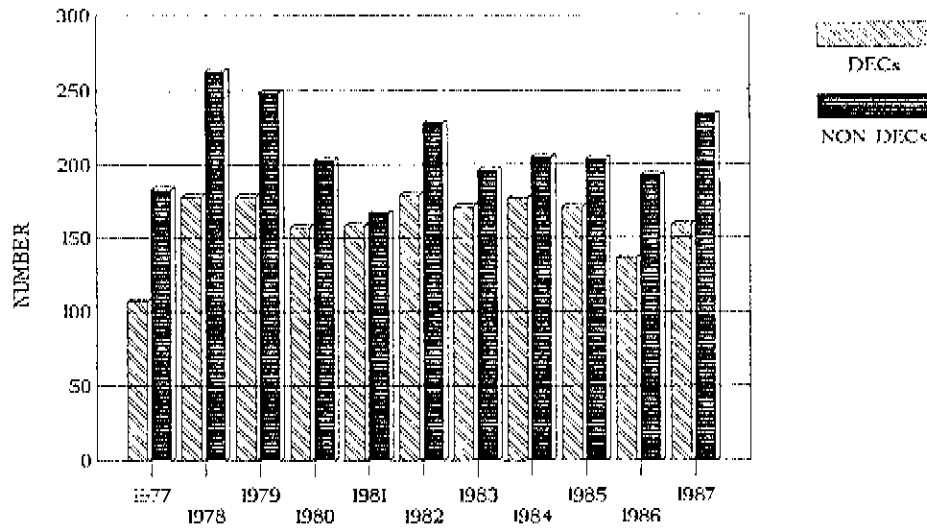
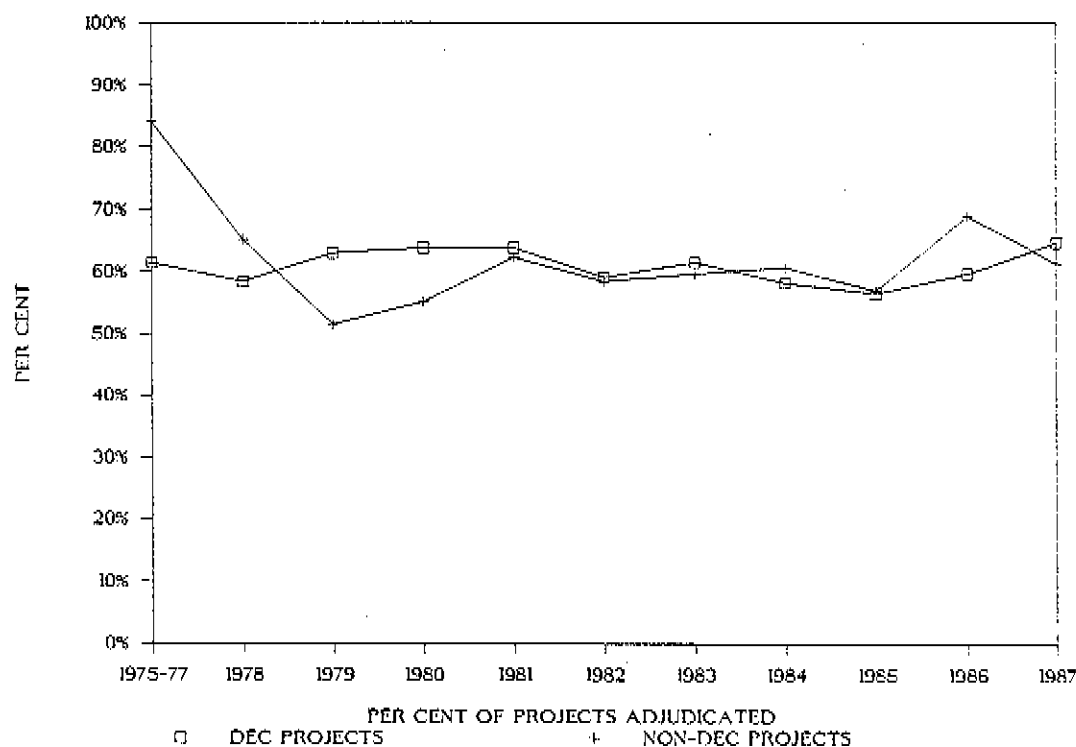


Fig. 4 Projects Funded: Programme Area II

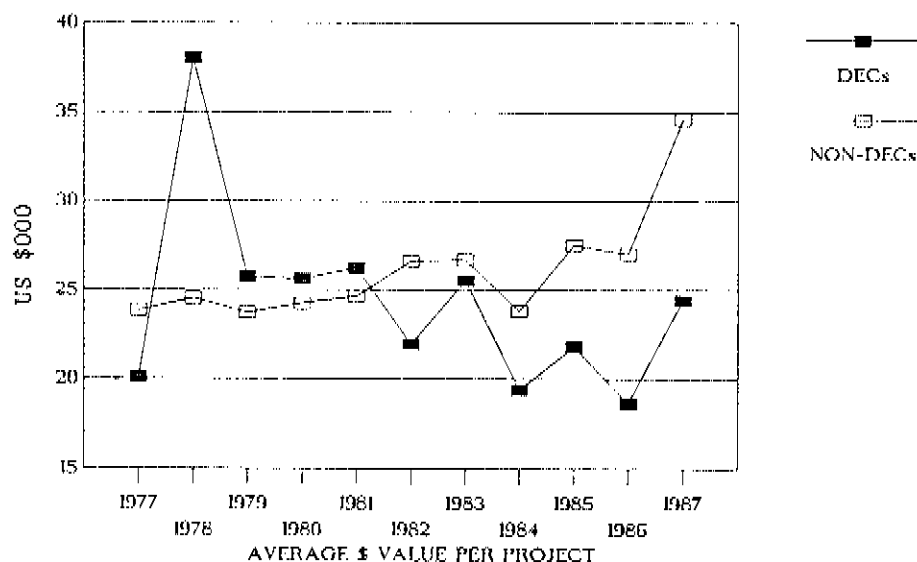


From 1978 to 1981 the average annual funding or approved dollar value of DEC projects (Table 5 and Figure 5) actually exceeded that for projects in developing countries, but the opposite has been true since 1982 and the "gap" increased significantly in 1986 and 1987, when the ratio of funding for DEC projects to that for developed country projects fell to about 0.7:1.0. This is also, therefore, an important factor in the geographic distribution of project funding, since developed country projects are now significantly "larger" (in dollar terms) than DEC projects.

TABLE 5. AVERAGE ANNUAL PROJECT FUNDING IN US\$: PROGRAMME AREA II

| Year | Developing Endemic Countries | Developed Countries | Difference in US\$ | Funding Ratio DECs:NonDECs |
|-------|------------------------------------|------------------------|-----------------------|-------------------------------|
| 1975 | 8 333 | 9 300 | (967) | 0.896 |
| 1976 | 2 833 | 12 040 | (9 207) | 0.235 |
| 1977 | 20 079 | 23 839 | (3 761) | 0.842 |
| 1978 | 38 018 | 24 524 | 13 495 | 1.550 |
| 1979 | 25 769 | 23 706 | 2 063 | 1.087 |
| 1980 | 25 611 | 24 237 | 1 374 | 1.057 |
| 1981 | 26 241 | 24 639 | 1 602 | 1.065 |
| 1982 | 21 935 | 26 622 | (4 686) | 0.824 |
| 1983 | 25 502 | 26 686 | (1 184) | 0.956 |
| 1984 | 19 404 | 23 794 | (4 390) | 0.816 |
| 1985 | 21 787 | 27 528 | (5 741) | 0.791 |
| 1986 | 18 657 | 27 020 | (8 364) | 0.690 |
| 1987 | 24 379 | 34 622 | (10 242) | 0.704 |
| TOTAL | 24 014 | 26 074 | (2 060) | 0.921 |

Fig. 5 Average Annual Project Funding: Programme Area II



3. Basic Factors

Analysis of the data points to the existence of more basic factors underlying the significant changes in the pattern of project funding in 1986 and 1987. Most of these factors are difficult to quantify.

In 1986 and to a less extent in 1987 TDR continued to suffer the effects of severe budgetary constraints, which dominated the period from 1982 to 1985. It was only towards the end of 1986, when contributions to TDR increased, that budgetary pressure began to ease. For the previous four years or so, TDR had reduced its project promotion activities, and many potential researchers undoubtedly turned to other funding sources and even to other fields of research. In 1987, TDR began to encourage more project proposals: 393 proposals were received during that year, the highest number since 1982.

As noted above, a high proportion of the 1987 proposals were from developed country scientists, who responded more quickly to the improvement in TDR's finances than scientists in developing endemic countries. Indeed, there has been a notable increase in tropical disease research in developed countries in recent years, in part because of TDR and in part because of more sources of funds for tropical disease research. In developing endemic countries, there has been an increase in the number of tropical disease researchers and improvements in the scope and quality of research activities as a result of TDR training and institution strengthening activities. However, for several reasons this is not yet reflected in an increased number of project proposals reaching TDR. In many DEC's, there is a continuing lack of good researchers with a long-term commitment to tropical disease research and in some DEC's,

national restrictions on external funding of research hinder TDR involvement with local scientists and institutions. At the same time, TDR is no longer the sole external source of funding for tropical disease research in developing countries and significant national funding is available in some countries.

Another major factor influencing the geographic distribution of research funding in recent years is the increase in the number and value of molecular biology and basic drug development projects funded by TDR. These projects tend to be concentrated more in developed countries than in DEC countries and also to be costly. This undoubtedly contributes to the rapid growth in the average size of projects funded in developed countries in the last two years and thus also to the growing project funding gap between developed countries and DEC countries. Some Components, such as those on the Immunology of Malaria and the Immunology of Leprosy, are by their nature largely focused on molecular biology and genetic engineering, and a high proportion of the research supported under them has necessarily been conducted in developed countries. In recent years, modern approaches to biology have increased in other Components, such as those on Schistosomiasis (particularly the immunology of schistosomiasis), African Trypanosomiasis (the molecular biology of trypanosomes) and Epidemiology (the development of immunodiagnosics). The Chemotherapy of Malaria and African Trypanosomiasis are also increasingly involved in more basic approaches to drug development, again involving primarily sophisticated laboratories in developed countries.

In the case of the Chemotherapy of Malaria Component, there has also been a shift in activities affecting the geographic distribution of project funding. In the early 1980s, the Chemotherapy of Malaria Component was deeply involved in clinical trials of mefloquine in many DEC countries, whereas in recent years the focus has been on more basic research and the development of new antimalarial drugs, such as those derived from Qinghaosu.

4. Possible Solutions

The TDR Secretariat has considered a number of measures to improve the distribution of project funding in favour of developing endemic countries. Some are long-term in nature, while others are intended to have more immediate effects.

The most important long-term activities are of course those directed towards improving the research capabilities of the developing endemic countries by increasing the numbers of institutions and researchers involved in tropical disease research and by improving the scientific quality of the institutions. Recent initiatives in the Research Capability Strengthening Programme Area, which include a broadening of the scope of available Programme mechanisms to support institution strengthening and training, should have a growing effect in the next few years. They should also result in increased expenditures in Programme Area III, which will improve the funding ratio for DEC countries for the Programme as a whole. Included in these initiatives is increased emphasis on the transfer of the new biotechnologies to developing endemic countries.

It is anticipated that there will be a substantial increase in field research in the next few years, especially in field trials of new disease control products emerging from the various disease-oriented Components, as well as in epidemiology and social and economic research. Such field research takes place in DEC countries, and it will be important to ensure that the lead role in projects involving field trials is assumed by developing country researchers and institutions. This will require careful preparation of field trials, including early identification of potential sites, investigators and institutions and, if necessary, the timely strengthening of institutions to enable them to conduct field research.

In addition, certain recurring TDR activities carried out in developed countries will be reviewed in terms of both technical feasibility and financial implications to determine if some could be carried out equally well in developing endemic countries. These activities include the production and distribution of reagents (e.g., DNA probes and monoclonal antibodies), the analysis of samples, the conduct of early phases of clinical trials, the maintenance of reference centres and laboratories, and the organizing of training workshops.

Finally, as a measure with considerable potential for immediate impact, it is proposed to establish project development grants (see section 4.1, below) to assist DEC researchers in designing research projects and in preparing funding proposals for consideration by TDR Steering Committees. Funding would be available for DEC researchers to seek advice and assistance from recognized experts in the subject of the proposed research, to gather preliminary data and even to initiate preparatory research. Project development grants would provide up to US \$10 000 and would not be renewable. It is suggested that an initial amount of US \$150 000 be set aside from the Director's Initiative Fund, with possible further funding from Component operations budgets if required.

4.1 TDR Project Development Grants

Purpose: To assist developing country researchers to prepare and to present sound research proposals for consideration by TDR Steering Committees.

Eligibility: Developing country scientists and researchers who wish to present a project proposal for TDR funding may apply.

Funding: Up to US \$10 000 (non-renewable).

Use of funds: To seek advice from recognized experts concerning the development of research proposals of interest to TDR, to gather baseline or other preparatory data and to initiate preliminary research.

Application procedure: Applications must originate from developing country researchers and be endorsed by their institutions. Pending the development of special forms, the existing application form for the Director's Initiative Fund will be used.

Review procedure: Applications will be reviewed by the Chairman, the Secretary and one other member of the relevant Steering Committee, who will provide their assessments and recommendations to Director, TDR, for his consideration.

Source of funds: Initially, an amount of US \$150 000 will be set aside from the Director's Initiative Fund for this purpose. Should additional funds be required in the 1988-89 biennium, an amount of up to one per cent (1%) of the operations budget of each Component will be reserved for this activity.

Administrative procedures: The standard Technical Services Agreement and normal project and financial reporting procedures will apply. Funds may be administered by WHO/TDR for the provision of external visiting experts if required.