



REPORT OF THE EIGHTH MEETING OF THE  
 SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-8)

Contents

|   | <u>Page</u> |
|---|-------------|
| 1. SUMMARY AND MAJOR CONCLUSIONS . . . . .  | 2           |
| 2. RECOMMENDATIONS . . . . .  | 2           |
| 2.1 African Trypanosomiases . . . . .   | 2           |
| 2.2 Chagas' Disease . . . . .   | 3           |
| 2.3 The Leishmaniases . . . . .   | 3           |
| 3. OPENING OF THE MEETING . . . . .   | 4           |
| 4. DIRECTOR'S REPORT . . . . .  | 5           |
| 4.1 Introduction . . . . .  | 5           |
| 4.2 Scientific Progress, 1984-85 . . . . .  | 5           |
| 4.3 STAC Comments . . . . .   | 7           |
| 5. CHAIRMAN'S REPORT . . . . .  | 7           |
| 6. SCIENTIFIC AND TECHNICAL REVIEW COMMITTEE (STRC) REVIEWS . . . . .   | 8           |
| 6.1 African Trypanosomiases . . . . .   | 8           |
| 6.2 Chagas' Disease . . . . .   | 10          |
| 6.3 The Leishmaniases . . . . .   | 12          |
| 7. ONCHOCERCIASIS CHEMOTHERAPY PROJECT . . . . .  | 14          |
| 8. DESIGNATED FUNDS . . . . .   | 15          |
| 9. PROGRAMME BUDGET . . . . .   | 15          |
| 10. STRC PROCEDURES . . . . .   | 15          |
| 11. COMMITTEE ASSIGNMENTS FOR STAC MEMBERS . . . . .  | 16          |
| ANNEX 1: SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE MEMBERS . . . . .  | 17          |
| ANNEX 2: SCIENTIFIC WORKING GROUP REPRESENTATIVES (FOR<br>SCIENTIFIC AND TECHNICAL REVIEW COMMITTEE DISCUSSIONS)<br>FOR AFRICAN TRYPANOSOMIASES, CHAGAS' DISEASE AND<br>THE LEISHMANIASES . . . . . | 19          |
| ANNEX 3: COMPONENT WORKPLANS . . . . .  | 20          |
| ANNEX 4: REVIEWERS OF ACTIVITIES OF SCIENTIFIC WORKING GROUPS<br>DURING THE COURSE OF THE MEETING OF STAC-9 (1987) . . . . .  | 25          |

This report contains the collective views of an international group of experts convened to advise on the UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES.

Ce rapport exprime les vues collectives d'un groupe international d'experts réuni pour donner des avis au sujet du Programme SPECIAL PNUD/BANQUE MONDIALE/OMS DE RECHERCHE ET DE FORMATION CONCERNANT LES MALADIES TROPICALES.

## 1. SUMMARY AND MAJOR CONCLUSIONS

The eighth meeting of the Scientific and Technical Advisory Committee (STAC-8) of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) took place in Geneva from 18-20 March 1986. STAC received and commented on the Director's report of activities during the past year and carried out in-depth reviews of the activities of the Scientific Working Groups (SWGs) on African Trypanosomiasis, Chagas' Disease and the Leishmaniases. STAC reviewed the role of designated funds in expediting progress and considered the impact of anticipated budgetary constraints on future Programme activities. STAC also made recommendations to improve the effectiveness of its in-depth review processes and to reduce their cost.

STAC commended the progress achieved during the past year; the Committee especially noted the central position now occupied by TDR in coordinating research on malaria vaccine development, the success of the drug ivermectin in the treatment of onchocerciasis, and the pioneering role of TDR in the application of the new tools of molecular biology. A striking recent example has been the cloning and expression of the entire genome of Mycobacterium leprae.

## 2. RECOMMENDATIONS

STAC made the following recommendations:

### 2.1 African Trypanosomiasis

In view of current financial constraints, STAC recommended that a limited number of first-level priorities should be selected by the Steering Committees for the Programme to concentrate on, while at the same time supporting other priorities at reduced levels.

Basic research to identify new diagnostic methods for sleeping sickness, techniques for trypanosome identification, new drug targets and new therapeutic lead compounds should continue.

Concerned by a decrease of one-third in expendable funds between the 1980-81 and the current biennia, STAC noted that further development of promising leads in chemotherapy will require additional funds.

Continued high priority should be given to the support of the Daloa Centre for pre-clinical and clinical trials on existing and newly discovered compounds. A second clinical centre in East Africa is urgently required.

The development and application of improved simple diagnostic tests, including tests for antigen detection, should be continued with emphasis on Trypanosoma brucei rhodesiense.

Research on pathogenesis should focus on the immunopathology of human sleeping sickness to improve management of patients with CNS involvement and monitoring of chemotherapy. Studies should be conducted on natural and acquired resistance in human trypanosomiasis.

Integrated epidemiological studies should be continued for T.b. gambiense and expanded for T.b. rhodesiense as funds are available. They should include clarification of both the taxonomic status of the T. brucei species and the role of reservoirs.

Large-scale evaluation of trapping to control tsetse flies should be continued.

## 2.2 Chagas' Disease

Insecticidal paints and the fumigant cartridge, the new tools of vector control, should be evaluated in two or three other areas on a large scale. At the same time negotiations with potential manufacturers should be started.

The development of a trypanocidal compound to replace crystal violet for disinfecting blood intended for transfusion in endemic areas should be pursued.

Of prime importance are analytical epidemiological studies to disclose factors responsible for geographical variations of Chagas' disease.

The following studies should be continued with maximal effort:

- basic biochemistry of the parasite in order to seek targets for chemotherapeutic attack;
- molecular biology of the parasite to identify mechanisms for antigen expression;
- identification of protective antigens;
- use of DNA probes and monoclonal antibodies for direct detection of circulating parasites;
- studies of immune mechanisms of chronic lesions;
- the detection of antigens in urine for diagnostic purposes.

Immunopathology remains a difficult area, in which a scientific strategy has not yet been established. The proposal of the SWG Steering Committee (SC) to hold a meeting discussing all aspects of the chronic development of the disease and appropriate experimental approaches to study cellular immunity was therefore warmly welcomed.

## 2.3 The Leishmaniases

### 2.3.1 Epidemiology

In anticipation of future vaccination studies, baseline epidemiological studies should be developed in candidate trial areas as soon as possible.

Contact should be maintained and scientific exchange encouraged with the SWG on the Biological Control of Vectors (BCV), particularly in connection with new findings in vector biology.

Projects oriented towards control (of reservoirs and vectors) should be encouraged in areas where the epidemiology is sufficiently well known.

The number of human behavioural (social and economic) studies should be increased in relation to the cause and impact of disease in different communities, in collaboration with the SWG on Social and Economic Research (SER).

### 2.3.2 Immunology and biochemistry

A vaccine trial against Old World cutaneous leishmaniasis should be initiated as rapidly as possible along the lines indicated in a recent SWG report. STAC considered that safety criteria could be adequately met, that the potential benefits were great and that the risks were slight.

In this connection, STAC welcomed the scrutiny that any vaccine plan will necessarily receive from the WHO in-house Secretariat Committee on Research Involving Human Subjects (SCRIHS), and recommended that the Scientific Advisory Group of Experts (SAGE) also be consulted. In addition, the close exchange of information should be maintained with other vaccine trials under way in TDR, notably in leprosy, and elsewhere in WHO.

In this connection also, STAC recommended information be exchanged and collaboration fostered with industry and/or other bodies with experience in vaccine development.

The application to man of the understanding of basic immunology acquired in animal studies has long been an aim of the Programme. STAC endorsed this aim and recommended that in the future greater emphasis be placed on elucidation of human immunological responses to the leishmaniases, particularly in relation to leishmanization.

Efforts to treat cutaneous lesions by means of local immunotherapy, such as those already under way outside TDR with interferon-containing ointment, should be kept under review. Future vaccine trials, as mentioned above, would provide an opportunity for exploring local treatment by means of immunotherapeutic or chemotherapeutic agents.

### 2.3.3 Chemotherapy

Major efforts should be made in the following areas:

- an evaluation of the use of purine analogues with or without the addition of transport-blocking compounds as new chemotherapeutic agents against the leishmaniases;
- the possibility of developing other (oral) compounds with selective antileishmanial activity.

Efforts to elucidate the biochemistry and physiology of Leishmania, both intracellular and extracellular, should be continued.

Consideration should be given to developing new facilities and new screening methods, including tissue culture, for identifying potential antileishmanial compounds.

Efforts should be made to identify the structures of those drugs which on animal screening were found to have antileishmanial activity equal to or greater than the reference compound (glucantime) and to further develop them.

### 2.3.4 General

STAC noted the important diagnostic potential of tests on urine, and recommended that their development be pursued, as appropriate, for all six groups of diseases.

## 3. OPENING OF THE MEETING

The eighth meeting of the Scientific and Technical Advisory Committee of the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was convened at WHO Headquarters in Geneva from 18-20 March 1986. In opening the meeting, Mr W.W. Furth, Assistant Director-General of WHO, pointed out that this is a time of change for TDR, with the imminent departure of the current Director and the appointment of his successor. He paid special tribute to Dr A.O. Lucas, the distinguished current Director, who

more than anyone has been responsible for building up TDR to its position as a Programme of high reputation internationally. The incoming Director, Dr Tore Godal, has been associated with TDR from its inception, and has been untiring in support for it.

Mr Furth noted that the environment of change in TDR applies also to its accomplishments. Many important new products for disease control -- vaccines, drugs and diagnostic tests -- are now becoming available for assessment and use in the field. TDR's role in coordination of research activities is becoming increasingly important.

In some areas, such as the development of leprosy vaccines or research on the chemotherapy of African trypanosomiasis, TDR-supported research dominates the world picture. In others, such as the development of malaria vaccines, TDR is a partner, relatively small in terms of financial input, within an extensive research programme which is heavily funded by several other agencies. TDR's collaborative relationships with industry have contributed in very significant ways to the development of new drugs, vaccines, diagnostic tests and vector control agents.

#### 4. DIRECTOR'S REPORT

##### 4.1 Introduction

As in previous years the Director of TDR pointed out substantial progress in the development of drugs, vaccines and diagnostic methods concerning all target diseases of the Special Programme: malaria, schistosomiasis, filariasis, African and American trypanosomiasis, the leishmaniases and leprosy. Exciting advances also are being made in the control of vectors involved in the transmission of malaria, onchocerciasis, African trypanosomiasis and Chagas' disease. TDR's catalytic and coordinating role in the development of malaria vaccines based on the application of recombinant DNA technology and synthetic peptides was outlined. The success of TDR's efforts is closely linked to constructive cooperation with the pharmaceutical industry, and the Director reported on the establishment of several new joint ventures. TDR's scientific results and goal-oriented projects have generated new opportunities for the control of all of the diseases included within its scope.

TDR has continued to strengthen research capability in developing countries in the tropics through training and direct institutional support. Scientists from these countries continue to play a major role in the activities of the Special Programme.

##### 4.2 Scientific Progress, 1984-85

Development of malaria vaccines based on antigens from sporozoites, asexual blood stages and sexual stages is progressing. Phase I clinical trials of two anti-Plasmodium falciparum sporozoite vaccines based on the repetitive sequence of the major surface protein of this species will commence in the United States this year. One vaccine is based on a synthetic peptide, the other includes the same peptide produced from the cloned gene in Escherichia coli. Guidelines for field trials are being worked out by staff of TDR and the Malaria Action Programme of WHO, and will be published.

There are reasonable grounds for hope that the sporozoite vaccine against P. falciparum will be usable worldwide, since evaluation of the gene structure and primary structure of the peptide on which the vaccine is based reveals high conservation in 18 different falciparum strains.

The gene encoding the immunodominant epitope of the circumsporozoite protein of P. vivax has been cloned and the amino acid sequence of the

repetitive unit determined. This provides the basis for the anti-P. vivax vaccine which is now being developed.

Sporozoite vaccines are primarily intended to block access of sporozoites to the liver. However, recent evidence indicates that anti-sporozoite antibodies can also impede parasite development within liver cells.

Alternative candidates for inclusion in vaccines are antigens found in the asexual blood stages and the sexual stages of the parasites. Molecular analysis of a wide array of antigens of the asexual blood stages is under way. It has been shown that antibodies to the sexual stages, when ingested by a mosquito in a blood meal, can prevent further development of the parasite in the vector. A target antigen has been identified for P. falciparum and gene cloning studies are in progress.

Chemotherapy of malaria remains precarious because of the further spread of chloroquine-resistance by P. falciparum. During the year, confirmed cases of drug-resistant malaria were encountered in Cameroon, indicating that the problem of drug resistance continues to intensify in Africa. It is therefore gratifying that mefloquine has been registered for use alone and in combinations. However, occasional severe adverse reactions have been attributed to the sulfadoxine component of antimalarial drug combinations. These findings further accentuate the need for new, safe and effective drugs. In the light of these findings, recommendations for malaria chemotherapy and chemoprophylaxis are currently under review. Formulations for halofantrine, artemisinin derivatives and a naphthoquinone compound are being developed in collaboration with the Walter Reed Army Institute of Research and with industry. Intensification of the search for new antimalarials has now led to the identification of several major new families of promising compounds.

The development of DNA probes for the highly sensitive and specific diagnosis of malaria is in an advanced stage. The Zavala test, a sensitive, specific test using a monoclonal antibody for detecting sporozoites in mosquitos, is being evaluated in the field. Early results are encouraging, and, if successful, this test will provide a new tool for the identification of mosquito vector species.

TDR collaborates closely with the Onchocerciasis Chemotherapy Project (OCT) of the Onchocerciasis Control Programme in West Africa (OCP). Ivermectin is being developed in collaboration with a major pharmaceutical company as a safe, long-acting microfilaricide for the treatment of onchocerciasis. Its registration for human use is expected in about a year. Two other compounds (CGP 6140 and 20376), which kill adult worms in experimental models, are being evaluated in man. Promising additional compounds from two multidisciplinary industrial groups associated with academia and funded by the OCT are to be screened in cattle.

Important contributions to the control of Chagas' disease include the completion of epidemiological studies which form the basis for control programmes in several endemic areas and the successful development of two vector control devices for use in houses: fumigant cartridges and paints which slowly release insecticide over a period of two years. Field testing of both these technologies is in progress. Immunodiagnosis of T. cruzi infections has been improved by standardization of tests and the establishment of a continental network of test centres. Promising new serological tests are being evaluated.

There is increasing evidence that the different forms of leishmanial infections constitute a major public health hazard. A wide variety of Leishmania species are responsible, and isoenzyme techniques, DNA probes and monoclonal antibodies are now being used to identify them. Highly susceptible

animals can be protected by vaccination with non-living, irradiated or avirulent parasites, suggesting that it may be possible to produce an effective vaccine. The immunological processes involving protection or exacerbation of disease are being investigated. Formulations and therapeutic schedules of antimony drugs are being improved and new drugs are under investigation.

In African trypanosomiases, a major new advance has been the successful treatment of patients unresponsive to conventional therapy with DL- $\alpha$ -difluoromethylornithine (DFMO). Low-cost tsetse control by trapping is being evaluated at the village level.

With respect to leprosy, field trials of killed, armadillo-derived M. leprae vaccine are continuing in Malawi and Venezuela. A similar trial is planned in India. A striking advance has been the cloning and expression of the entire genome of M. leprae. This opens the way for the development of second generation vaccines based on well-defined antigens produced by recombinant DNA technology. A simple diagnostic test based on a specific phenolic glycolipid of M. leprae has been developed and is now being evaluated. It could be particularly useful in monitoring the progress of patients with the lepromatous form of the disease.

Several strains of Bacillus sphaericus have been identified as potentially important biological larvicides, highly effective against culicine mosquitos. The strain 2362, identified through TDR support, shows special promise. In a trial in the United Republic of Tanzania, one application of B. sphaericus 2362 controlled the breeding of culicine larvae in pit latrines for six to ten weeks, much longer than with conventional larvicides.

#### 4.3 STAC Comments

STAC commended the Director on progress achieved during the last year and congratulated him on his conspicuous successes in obtaining the cooperation of increasing numbers of industrial companies with the Programme.

STAC noted with satisfaction that the catalytic role of TDR in research on malaria vaccines has now evolved into a central position in coordinating the various efforts towards identifying candidate vaccine antigens. TDR plays an important role in providing guidelines for vaccine evaluation, including field trials.

The successful treatment of onchocerciasis patients with ivermectin is to be regarded as a major achievement.

STAC commented on the pioneering role which TDR plays in the use of recombinant DNA technology and other tools of molecular biology. A striking example is the cloning and expression of the genome of M. leprae.

Other Components, not specifically mentioned in this brief summary, are similarly making progress.

#### 5. CHAIRMAN'S REPORT

5.1 The Chairman of STAC reported on the Eighth Session of the Joint Coordinating Board [JCB(8)] held in Geneva on 26-27 June 1985. The Board had accepted the report of STAC-7, approved its recommendations and commended STAC for the quality of its report. JCB noted that the impact of TDR is being increasingly recognized, as is its importance for the social and economic development of tropical endemic countries.

The Chairman reported that JCB(8) had discussed in some detail the use of designated funds in expediting the work of the Programme. This matter was taken up again by STAC-8, whose views on this issue are presented in section 8 of this report.

5.2 The tasks of STAC-8 included the following:

- receive and evaluate a report on progress made and problems encountered during the year;
- consider in-depth reviews of the Programme's Components on African trypanosomiases, Chagas' disease and the leishmaniases;
- consider and make recommendations regarding designated funding of activities;
- consider the impact of the approved 1986-87 budget on the activities of TDR.

## 6. SCIENTIFIC AND TECHNICAL REVIEW COMMITTEE (STRC) REVIEWS

### 6.1 African Trypanosomiases

The STRC examined in detail the work of the African Trypanosomiases Scientific Working Group for the period 1981 to 1985 and made a number of visits to project sites. It noted with satisfaction that, as far as possible, all recommendations of the previous Review Committee (1981) had been implemented. The Committee was highly impressed by the results achieved and their relevance to the needs of the endemic countries.

The Committee noted that the human trypanosomiases constitute a serious and growing threat to the health of some 50 million people. Experience has shown that where medical surveillance is inadequate or lacking serious epidemics can occur which are difficult to control. The number of reported cases has, indeed, doubled in the past few years. There is considerable research being conducted on the trypanosomiases of African livestock, but the human disease has specific problems in epidemiology, vector control, diagnosis and therapy. The Special Programme has been unique in stimulating and supporting research and collaboration in this field. The STRC noted with much concern that TDR funds available for research on African trypanosomiases had decreased by 40% since 1981.

In the field of immunology and pathology, the Card Agglutination Test for Trypanosomiasis (CATT) for the serological diagnosis of T.b. gambiense infection is now commercially available and is being introduced for general use by 10 countries.

Autopsy material obtained at the clinical centre at Daloa in the Côte d'Ivoire is being used to evaluate the causes of encephalitis in patients treated with melarsoprol. Reference banks for serum and CSF of infected patients and for trypanosome stocks have been set up.

Remarkable results have been achieved in chemotherapy and drug development. The search for new drugs has led to the identification of several lead compounds. The most significant finding has been the activity of DFMO in advanced human sleeping sickness. The drug is being developed in collaboration with a pharmaceutical company and has been successfully used in 100 patients with T.b. gambiense infection, including some with melarsoprol-resistant infection. Other new compounds active in animal models are triacetylbenzene tris(guanylhydrazone) (TBG), a nitroimidazole derivative (MK 436) and a new

arsenical. Some of these compounds showed synergism when used in combination with suramin in animal models. Additional funding will be required for further development of these lead compounds.

Doses of melarsoprol, considerably lower than those used conventionally in man were effective in curing encephalitis in vervet monkeys. This observation is being followed up in human patients in the Côte d'Ivoire, in combination with appropriate pharmacokinetic studies. The STRC emphasized the significance of the work of the clinical centre in Daloa and stressed the need for a centre in East Africa for studies on T.b. rhodesiense infection.

Longitudinal studies on the epidemiology of infection in man were carried out in the Côte d'Ivoire and Zambia. Major gaps remain in knowledge concerning the ecology of the vector, the nature and extent of animal reservoirs, and the identification of trypanosomes which are pathogens to humans. Progress was achieved on trypanosome characterization using isoenzyme electrophoresis, immunological techniques and DNA hybridization. It is hoped that a "dot test" for the characterization of parasite strains can be developed. Traps for use at the village level are being evaluated in several locations.

#### 6.1.1 STAC comments

STAC noted with concern the reports of recent major outbreaks of sleeping sickness in several countries. This situation demands increased research efforts to develop further the leads found by the SWG, to enable control programmes to operate on a more secure basis. STAC noted the progress made in introducing newly developed methods of diagnosis and control in health services, including the publication by WHO of a manual on trypanosomiasis control for health workers.

STAC noted with some concern that relatively few applications for research project funding came from research workers in the endemic countries.

STAC congratulated the SWG on progress made, approved the workplans, (Annex 3) accepted the STRC report and made the following recommendations.

#### 6.1.2 Recommendations

In view of current financial constraints, STAC recommended that a limited number of first-level priorities should be selected by the Steering Committees for the Programme to concentrate on, while at the same time supporting the other priorities at reduced levels.

Basic research to identify new diagnostic methods for sleeping sickness, techniques for trypanosome identification, new drug targets and new therapeutic lead compounds should continue.

Concerned by a decrease of one-third in expendable funds between the 1980-81 and the current biennia, STAC noted that further development of promising leads in chemotherapy will require additional funds.

Continued high priority should be given to the support of the Daloa Centre for pre-clinical and clinical trials on existing and newly discovered compounds. A second clinical centre is urgently required in East Africa for the study of T.b. rhodesiense.

The development and application of improved simple diagnostic tests, including tests for antigen detection, should be continued with emphasis on T.b. rhodesiense.

Research on pathogenesis should focus on the immunopathology of human sleeping sickness to improve the management of patients with CNS involvement

and monitoring of chemotherapy. Studies should be conducted on natural and acquired resistance in human trypanosomiases.

Integrated epidemiological studies should be continued for T.b. gambiense and expanded for T.b. rhodesiense as funds are available. They should include clarification of both the taxonomic status of the T. brucei species and the role of reservoirs.

Large-scale evaluation of trapping to control tsetse flies should be continued.

## 6.2 Chagas' Disease

The STRC examined in detail the work of the SWG on Chagas' Disease over the period 1982-85 and visited a number of project sites. The STRC noted with satisfaction that 73% of the research budget was expended in the endemic countries themselves. The projects are being pursued with competence and skill by enthusiastic senior and junior investigators together with their students. TDR has played a catalytic role in establishing excellent collaboration among laboratories, clinics and government control programmes in South and Central America. The high scientific standard of the training, research and clinical investigations is attested by two important publications: A Laboratory Manual on Genes and Antigens of Parasites, (C.M. Morel, ed.), Fundação Oswaldo Cruz, Rio de Janeiro, 1984, and the report of the Meeting on Standardization of Methods for Trypanosoma cruzi Classification, published in the Revista da Sociedade Brasileira de Medicina Tropical, 18, Supplement, 1985. In addition, the publication of a Bibliography listing 2457 publications on Chagas' disease over the period 1968-84 has been jointly supported with the Pan American Health Organization and the US National Institutes of Health. Close collaboration in all the work of the SWG is maintained with the Pan American Health Organization.

### 6.2.1 Vector control

At present, the only practical measures of controlling the disease are those aimed at interrupting the domestic and peridomestic vector-host cycles by attacking triatomine bugs with insecticides. Two new approaches which should confer greater efficacy on previously known and potentially new insecticides have been assessed in the Programme: (i) a fumigant cartridge (production cost of US \$1) is being field tested; (ii) slow-release of malathion over a period of two years is achieved by its incorporation into polyvinyl acetate, which can be painted as transparent films on walls and roofs. This procedure is being tested on 5000 houses. Comparative large-scale studies in additional areas are required and negotiations with potential manufacturers are to be initiated.

### 6.2.2 Chemotherapy

Chemotherapy of Chagas' disease relies at present on nifurtimox (a nitro-furan derivative) and benzidazole (nitroimidazole) in addition to crystal violet, the latter being used as a trypanocidal compound for disinfection of blood intended for transfusion. From 700 drugs already accepted for human use, several compounds with trypanocidal activity in vitro have been identified. Some of these are neuroleptics, and minor modification of chemical structures appears to eliminate their neuroleptic effect, while retaining antitrypanocidal activity. A short list of these has been prepared, and these drugs are being further evaluated to determine whether they meet the necessarily stringent requirements for addition to blood for transfusion. Screening for new compounds with curative potential is being carried out in a collaborative effort between a pharmaceutical company, the Walter Reed Army Institute of Research and the University of Georgia.

### 6.2.3 Diagnosis

The development of a continental network comprising 14 laboratories in 11 countries for the standardization and improvement of the quality of Chagas' disease serodiagnosis is proceeding. The network represents a major training effort and has made an invaluable contribution in epidemiological surveys. It has been discovered that enzyme-mediated immunoassays can be carried out on inexpensive polyester-coated textile discs. Prepared discs can be stored dry at room temperature for 18 months.

Two antigens have been studied for their suitability in standard immuno-enzymatic reference tests. The 25 000 MW glycoprotein fragment originating from a 60 000 MW T. cruzi surface protein shows excellent specificity but in some cases sensitivity is low. Monoclonal antibodies against T. cruzi antigens have been successfully used to identify parasite antigens in the urine of Chagasic patients after concentration of the urine on nitrocellulose beads. Three synthetic DNA probes are being tested for detection of trypanosome DNA in the blood of Chagasic patients. These probes are expected to provide a highly sensitive parasite detection device.

### 6.2.4 Epidemiology

Country-wide surveys of the prevalence of the disease and of vectors have been made in Ecuador, Honduras, Paraguay and Uruguay, while longitudinal studies have been initiated in Bolivia, Chile, Colombia and Panama. The findings are being used for the design and improvement of control programmes. The stage is now set for analytical in-depth studies of areas which differ in prevalence, morbidity and ecological patterns. Attention is being given to the need for better standards for objective interpretation of electrocardiograms.

### 6.2.5 Biochemistry and molecular and cell biology

The changes occurring in the protein composition of the parasite surface coat during the conversion of trypomastigotes to epimastigotes in the insect and during differentiation of the epimastigote into the metacyclic trypomastigote -- the infectious form for the vertebrate host -- have been worked out. cDNA sequencing for deduction of the primary structure of the major protein species involved in these parasite coat changes is in progress. The parasite coat changes which occur in the triatomine bugs can be duplicated in cultures of epimastigotes, and conversion to metacyclic trypomastigotes has been achieved on a culture medium fortified with proline. Immune modulators with which the parasite evades the human humoral immunological system as well as the human defence systems for intracellularly located parasites have been identified.

Biochemical characterization of strain specificity is being utilized to determine if T. cruzi strains isolated from Chagasic patients with differing syndromes of disease are lines with different genotypes and if multiplication of several genotypes in the same insect affects the composition of the parasite population. More basic knowledge is required of T. cruzi genetics and chromosome sequence transpositions.

Upon infection of a human subject, the trypomastigotes invade cells, including macrophages and muscle cells, by endocytosis. It has been found that removal of certain proteins, inhibition of their glycolysation or application of rabbit polyclonal as well as monoclonal antibodies can inhibit cellular invasion. To what extent antigenic components identified in these studies can be used as vaccine components and whether a vaccine would be relevant to the control of Chagas' disease are being carefully scrutinized.

#### 6.2.6 Immunology and immunopathology

It is of great importance to determine the extent to which humoral and cellular immune responses participate in the protective and pathological phenomena observed in the chronic phase of the disease. The STRC and the SWG are in agreement that current projects do not form a cohesive integrated plan.

In the acute phase of the disease, protective and nonprotective antibodies are produced. The former mediate activation of the alternate complement pathway leading to lysis of trypomastigotes and enhanced cytotoxicity or phagocytosis. They remain in the human body during the chronic stage of the disease. The first encouraging results on immunoprotection with fractions of T. cruzi epimastigotes have been reported in mice. In this animal, heart lesions can be produced by injection of antigenic fractions of the parasite.

#### 6.2.7 STAC comments

STAC commended the SWG for its excellent progress, approved the workplans (Annex 3) and accepted the STRC report.

#### 6.2.8 Recommendations

Insecticidal paints and the fumigant cartridge, the new tools of vector control, should be evaluated in two or three other areas on a large scale. At the same time negotiations with potential manufacturers should be started.

The development of a trypanocidal compound to replace crystal violet for disinfecting blood intended for transfusion in endemic areas should be pursued.

Of prime importance are analytical epidemiological studies to disclose factors responsible for geographical variations of Chagas' disease.

The following studies should be continued with maximal effort:

- basic biochemistry of the parasite in the search for targets for chemotherapeutic attack;
- molecular biology of the parasite to identify mechanisms for antigen expression;
- identification of protective antigens;
- use of DNA probes and monoclonal antibodies for direct detection of circulating parasites;
- studies of immune mechanisms of chronic lesions;
- the detection of antigens in urine for diagnostic purposes.

Immunopathology remains a difficult area, in which a scientific strategy has not yet been established. The SC proposal to hold a meeting discussing all aspects of the chronic development of the disease and appropriate experimental approaches to study cellular immunity was therefore warmly welcomed.

#### 6.3 The Leishmaniases

The STRC reviewed the scientific progress of the SWG on the Leishmaniases over the period 1981-85. It noted with satisfaction that good progress had been made in the three subcomponents of epidemiology, immunology

and biochemistry, and chemotherapy, and in particular that new procedures and products have been developed to the point where they are now ready to enter field trials. It drew attention to the following points.

Field studies carried out by the Programme have played a major part in identifying disease vectors and reservoirs in Bolivia, China, Greece, Israel and Peru, and sandfly breeding sites in Sardinia.

New methods of parasite species and strain identification based on monoclonal antibodies and DNA probes are beginning to have a significant impact on field studies.

Sufficient progress has been made in studies of human resistance to the diseases, and of immunization in man and animals, to justify small-scale vaccine trials.

While the immunological mechanisms responsible for host resistance remain incompletely understood, good progress has been made in sorting out the antigens and lymphocyte subsets involved.

Regimens of pentavalent antimonial treatment have been improved, and the newer purine analogues, in particular allopurinol riboside, have so far fared well in in vitro tests, animal tests and small-scale trials in man.

Topical treatment, either with immune modulators ( $\gamma$ -interferon) or drugs, now looks promising.

#### 6.3.1 STAC comments

STAC expressed concern that reported outbreaks of visceral leishmaniasis have increased in number throughout the New and Old World, and that the epidemic in parts of South-East Asia, possibly associated with reduction in malaria control, continues and is spreading.

STAC commended the progress made by the SWG, approved the workplans (Annex 3), accepted the STRC report and made the following recommendations.

#### 6.3.2 Recommendations

##### 6.3.2.1 Epidemiology

In anticipation of future vaccination studies, baseline epidemiological studies should be developed in candidate trial areas as soon as possible.

Contact should be maintained and scientific exchange encouraged with the SWG on the Biological Control of Vectors (BCV), particularly in connection with new findings in vector biology.

Projects oriented towards control (of reservoirs and vectors) should be encouraged in areas where the epidemiology is sufficiently well known.

The number of human behavioural (social and economic) studies should be increased in relation to the cause and impact of disease in different communities, in collaboration with the SWG on Social and Economic Research (SER).

##### 6.3.2.2 Immunology and biochemistry

A vaccine trial against Old World cutaneous leishmaniasis should be initiated as rapidly as possible along the lines indicated in a recent SWG report. STAC considered that safety criteria could be adequately met, that the potential benefits were great and that the risks were slight.

In this connection, STAC welcomed the scrutiny that any vaccine plan will necessarily receive from the WHO in-house Secretariat Committee on Research Involving Human Subjects (SCRIHS), and recommended that the Scientific Advisory Group of Experts (SAGE) also be consulted. In addition, the close exchange of information should be maintained with other vaccine trials under way in TDR, notably in leprosy, and elsewhere in WHO.

In this connection also, STAC recommended that information be exchanged and collaboration fostered with industry and/or other bodies with experience in vaccine development.

The application to man of the understanding of basic immunology acquired in animal studies has long been an aim of the Programme. STAC endorsed this aim and recommended that in the future greater emphasis be placed on elucidation of human immunological responses to the leishmaniasis, particularly in relation to leishmanization.

Efforts to treat cutaneous lesions by means of local immunotherapy, such as those already under way outside TDR with interferon-containing ointment, should be kept under review. Future vaccine trials, as mentioned above, would provide an opportunity for exploring local treatment by means of immunotherapeutic or chemotherapeutic agents.

#### 6.3.2.3 Chemotherapy

Major efforts should be made in the following areas:

- an evaluation of the use of purine analogues with or without the addition of transport-blocking compounds as new chemotherapeutic agents against the leishmaniasis;
- the possibility of developing other (oral) compounds with selective antileishmanial activity.

Efforts to elucidate the biochemistry and physiology of Leishmania, both intracellular and extracellular should be continued.

Consideration should be given to developing new facilities and new screening methods, including tissue culture, for identifying potential antileishmanial compounds.

Efforts should be made to identify the structures of those drugs which on animal screening were found to have antileishmanial activity equal to or greater than the reference compound (glucantime) and to further develop them.

#### 6.3.2.4 General

STAC noted the important diagnostic potential of tests on urine, and recommended that their development be pursued, as appropriate, for all six groups of diseases.

### 7. ONCHOCERCIASIS CHEMOTHERAPY PROJECT

STAC welcomed progress in the development of new compounds for the chemotherapy of onchocerciasis, as indicated in the Director's Report. STAC authorized its Chairman to review the forthcoming scientific report of the OCT to the Expert Advisory Committee of the Onchocerciasis Control Programme. A formal review of OCT will be undertaken in 1987.

## 8. DESIGNATED FUNDS

8.1 STAC noted that on two previous occasions it had commented on the place of designated funds in expediting progress in high priority areas. It reiterated the view presented by STAC-7, that designated funds should be accepted, subject to the following conditions:

- the scientific balance of the Programme must not be disturbed;
- the role of STAC in providing independent, objective advice to the JCB must not be compromised;
- designated funds should be devoted to areas identified by STAC as ready for effective expansion.

8.2 Previous STAC meetings had designated four areas as candidates for the receipt of designated funds, viz: immunology of malaria, leprosy vaccines, field trials of biological control agents and training. STAC confirmed that these remain high priority for this purpose and added clinical trials on new drugs for the treatment and control of African trypanosomiasis to the list.

## 9. PROGRAMME BUDGET

9.1 STAC noted that JCB(8) had approved a budget for 1986-87 of US \$55 745 000 for the Special Programme. Of this amount, US \$36 398 000 and US \$13 271 000 had been allocated for Research and Development and Research Capability Strengthening respectively.

It appeared that contributions received during the biennium probably would be somewhat less than the total budget levels approved. Prudent expenditure of funds was therefore of particular importance. STAC commended the Director for his careful monitoring and control of the financial situation. It noted that the three Research and Development Components examined in detail (African trypanosomiasis, Chagas' disease and the leishmaniasis) are all at bare minimum levels of financial support. Further reductions in funding provided for their support below levels approved by JCB could reduce the research programmes to below critical mass levels and seriously jeopardize the continued viability of the research efforts. This is perhaps particularly so for the leishmaniasis, but in the field of human African trypanosomiasis also, where TDR is far and away the major funding source for research on a world-wide basis, further reductions in funding would prevent the Programme from taking advantage of promising new leads for disease control. In the light of these concerns, STAC asked the Director to ease the financial constraints on these three Components so far as he is able to do so within the framework of the approved budget and established research priorities.

9.2 In an era of financial constraint, wise advice from STAC to JCB on scientific and technical priorities for TDR is of particular importance. To assist it in carrying out this responsibility, STAC asked the Director, in consultation with his successor, to consider those areas of Research and Development and Research Capability Strengthening where TDR makes, or could make, a unique contribution. This information should be presented in the form of a paper to STAC-9.

## 10. STRC PROCEDURES

STAC reviewed current procedures and recommended the following modifications to reduce costs and increase effectiveness:

- Appoint STRC Chairmen two years in advance of the STAC in-depth review meeting. During the following six months the Chairman, in collaboration with the secretariat, establishes a plan for all STRC activities including site visits. This plan and its budget are then approved by Chairman, STAC.
- Establish a budget ceiling of US \$30 000 (1986) for the operation of any one STRC, other than malaria (US \$35 000). Exceptional increments over these figures would require approval of Chairman, STAC.

#### 11. COMMITTEE ASSIGNMENTS FOR STAC MEMBERS

In preparation for STAC-9, to be held in 1987, STAC designated members to review the activities and progress made by SWGs other than those subject to in-depth review at that time. These include Malaria, Schistosomiasis, Filariasis and OCT, African Trypanosomiasis, Chagas' Disease, Leishmaniasis, the Immunology and Chemotherapy of Leprosy, Biological Control of Vectors, Epidemiology and Social and Economic Research. The list of STAC members assigned to the various review groups is appended as Annex 4.

ANNEX 1

SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE MEMBERS

- BRUCE-TAGOE, Professor Alexander A., Prince Salman Bin Abdulaziz Hospital,  
Riyad, Saudi Arabia
- BUTNER, Professor D.W., Scientific Director, Department of Helminthology,  
Bernhard-Nocht-Institute for Maritime and Tropical Medicine, Hamburg,  
Federal Republic of Germany
- D'ALESSANDRO, Professor A., Professor, Department of Tropical Medicine, Tulane  
Medical Center, New Orleans, Louisiana, USA
- \* DAVIES, Professor A. Michael, Director, School of Public Health and Community  
Medicine, Faculty of Medicine of Hebrew University and Hadassah,  
Jerusalem, Israel
- DIGGELMANN, Dr Heidi, Head of Department of Molecular Biology, Swiss Institute  
for Experimental Cancer Research, Epalinges, Switzerland
- DJERASSI, Professor C., Professor of Chemistry, Stanford University, Stanford,  
CA, USA
- DUARTE DE ARAUJO, Professor José, Ministério da Ciência e Tecnologia (MCT),  
Brasilia, Brazil
- EL HASSAN, Professor A.M., Department of Medicine, Colleges of Medicine and  
Medical Sciences, King Faisal University, Dammam, Saudi Arabia
- \*\* MASON, Dr James O., Assistant Surgeon General, Director, Centers for Disease  
Control, Department of Health and Human Services, Atlanta, GA, USA
- MITCHISON, Professor N.A., Head, Department of Zoology, University College  
London, London, UK
- MORRISON, Professor A.B., Chairman, Department of Food Science, University  
of Guelph, Guelph, Ontario, Canada (CHAIRMAN)
- MOUCHET, Dr J., Inspecteur général honoraire, Office de la Recherche  
Scientifique et Technique d'Outre-Mer (ORSTOM), Paris, France
- NAKANE, Professor Chie, Professor of Social Anthropology, The Institute of  
Oriental Culture, University of Tokyo, Tokyo, Japan
- NOSSAL, Professor Sir Gustav J.V., Director, The Walter and Eliza Hall  
Institute of Medical Research, Royal Melbourne Hospital, Melbourne,  
Victoria, Australia
- RAMALINGASWAMI, Professor V., Director-General, Indian Council of Medical  
Research, New Delhi, India

---

\* Unable to attend

\*\* Attended only for 20 March

\* SUKADJI, Professor Ranuwihardjo, Director-General of Higher Education,  
Ministry of Education and Culture, Jakarta, Indonesia (co-opted)

\* SUPRONOV, Professor F.F., Director, Martsinovsky Institute of Medical  
Parasitology and Tropical Medicine, Moscow, USSR

VARNAL, Professor F., Head, Chair of Tropical Medicine, Post-Graduate Medical  
School, and Director-General, Laszlo Hospital for Infectious and  
Tropical Diseases, Budapest, Hungary (co-opted)

VON WETTSTEIN, Professor D.H., Professor of Physiology and Head, Department of  
Physiology, Carlsberg Laboratory, Copenhagen, Denmark (RAPPORTEUR)

---

\* Unable to attend

ANNEX 2

SCIENTIFIC WORKING GROUP REPRESENTATIVES  
(FOR SCIENTIFIC AND TECHNICAL REVIEW COMMITTEE DISCUSSIONS)  
FOR AFRICAN TRYPANOSOMIASSES, CHAGAS' DISEASE AND THE LEISHMANIASSES

African Trypanosomiasis

- FREZIL, Dr J.-L., Mission de l'Office de la Recherche Scientifique et  
Technique d'Outre-Mer (ORSTOM), Brazzaville, Congo [Epidemiology of  
African Trypanosomiasis (EPIAF)]
- MURRAY, Dr M., Glasgow University Veterinary School, Glasgow, UK [(Immunology  
and Pathology of African Trypanosomiasis (IMMAF))]
- NJOGU, Dr A.R., Kenya Trypanosomiasis Research Institute, Kikuyu, Kenya  
[Chemotherapy of African Trypanosomiasis (CHEMAF)]

Chagas' Disease

- MOREL, Dr C.M., Director, Instituto Oswaldo Cruz, Rio de Janeiro, Brazil  
[Chemotherapy and Parasitology and Immunology and Immunopathology of  
Chagas' Disease (CHEMCHA/IMMCHA)]
- SOUSA, Dr O.E., Gorgas Memorial Laboratory, Panama, Panama [Epidemiology and  
Vector Biology and Control of Chagas' Disease (EPICHA)]

The Leishmaniasis

- ASHFORD, Dr R.W., Department of Parasitology, Liverpool School of Tropical  
Medicine, Liverpool, UK [Epidemiology, Parasitology and Vector Biology  
and Control of the Leishmaniasis (EPILISH)]
- MARR, Professor J. Joseph, Director, Division of Infectious Diseases,  
Department of Medicine, University of Colorado Health Sciences Center,  
Denver, CO, USA [Chemotherapy of the Leishmaniasis (CHEMLEISH)]
- MAUEL, Dr J., WHO Immunology Research and Training Centre, Institute of  
Biochemistry, University of Lausanne, Epalinges, Switzerland [Immunology  
and Biochemistry of the Leishmaniasis (IMMLEISH)]

ANNEX 3  
COMPONENT WORKPLANS

January 1986

Workplan for African Trypanosomiasis

TDR

OBJECTIVES

To gain a better understanding of epidemiology as a basis for improved disease control

PLANS

To conduct long-term multidisciplinary studies

To improve diagnostic tests

To improve methods for parasite identification

To assess significance of animal reservoirs and asymptomatic infection in man

To assess vector/parasite relationships

To assess aspects of vector biology and control

To evaluate role of community participation in disease control

To study basic biology of parasites and host/parasite differences

To identify potential new leads and compounds

To assess pharmacokinetics and pharmacodynamics of drugs now in use

To assess effectiveness of drug combinations and methods of combating drug resistance

To improve dosage and regimens of drugs now in use

To assess pathogenesis of disease in man

To assess effects of other concomitant infections on pathogenesis

To establish a network of clinical centres in Africa

To improve clinical management

To establish facilities for clinical research in endemic areas

ACTIVITIES

Studies of *T. gambiense* infection in Central Africa and *T. rhodesiense* in Ethiopia and Zambia

Development of improved parasitological and serological tests for blood and CSF for epidemiological and clinical use; development of serological tests for *Rhodesiense* infection; establishment of serum banks

Exploitation of the blood incubation infectivity test (BLIT) and isoenzyme markers; development of DNA probes

Surveys in Burkina Faso, the Congo, the Ivory Coast and Zambia

Studies of factors related to vector susceptibility to infection and behavioural changes, and methods for detecting infection in vectors

Identification of vectors based on new taxonomic tools, and of vector attractants; studies of vectorial capacity and of vector control methods, including impregnated screens and traps

Studies in Central and West Africa

Biochemical, genetic and cultivation studies, including studies of antigenic variation, and differentiation and growth regulation in trypanosomes

Screening of compounds for activity, assessment of toxicity and effectiveness

Studies on *in vitro* uptake and *in vivo* distribution of trypanocides, using conventional methods, and development of simple methods for estimating drug concentration

Studies on animal models, trials in man

Studies on effectiveness of reduced doses of melarsoprol, and improved solvents for arsenicals

Studies on immunological, pathophysiological and biochemical features of infection in man

Studies in man

Centres established in the Ivory Coast, Mozambique, Uganda, Zaïre and Zambia

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

OBJECTIVES

To develop better methods for the design and evaluation of control programmes

To develop better vector control strategies (agents, formulations and methods)

To improve understanding of the course of infection and disease

To develop better drugs to prevent and treat disease

To develop substances to kill parasites in transfusion blood

PLANS

To conduct distribution and prevalence studies

To identify ways to improve control using community participation

To identify methods to prevent or eliminate house infestation

To study mechanisms for vector resistance to insecticides

To identify, describe and quantify clinical and geographical varieties of disease

To relate clinical and geographical varieties of disease to parasite population

To screen available compounds to carry out basic metabolic studies to identify targets for drug action

To screen available compounds

To test selected compounds in endemic areas

ACTIVITIES

Country-wide surveys on prevalence of human infection and house infestation by vectors (currently under way in Ecuador, Honduras, Paraguay and Uruguay)

Behavioural and community participation studies (being carried out in Brazil under the Scientific Working Group on Social and Economic Research)

Laboratory and field trials in endemic areas of Brazil of conventional and new formulations of insecticides (paite) (underway in collaboration with the Brazilian Control Programme (SUCAM))  
Field trial in endemic areas of Argentina of a new method of insecticide application -- the fumigant canister (underway in collaboration with Argentina's Chagas' Disease Control Programme)  
Studies on mode of action of insecticides to improve selectivity and efficacy

Studies on development of mechanisms of vector resistance to insecticides  
Determination of baseline data for detecting vector resistance to ICH

Descriptive and analytical epidemiological studies (under way in selected areas of Bolivia, Chile, Colombia and Panama)

Multicentre, analytical epidemiological studies to identify risk factors leading to manifest disease and to assess the importance of morbidity and mortality and their public health importance

One screening system in operation  
Projects on modes of action of current drugs; protein glycosylation, purine metabolism, control of cell division

One screening system in operation  
Two trypanocidal compounds identified for further evaluation in comparison with gentian violet

Appropriate trials

OBJECTIVES

To obtain better tests for diagnosis, monitoring of therapy and evaluation of control activities

To obtain better cultivation and harvesting techniques

To obtain better methods for species and strain characterization

To achieve a better understanding of the host/parasite relationship at the cellular level

To improve understanding of the immunopathogenesis of chronic lesions

To develop vaccines against disease

PLANS

To standardize current methods of serodiagnosis

To develop kDNA probes and monoclonal antibodies, and identify appropriate antigens

To obtain parasites in quantities sufficient for biochemical analysis and antigen preparation

To standardize *T. cruzi* characterization techniques

To conduct studies of structural and functional factors involved in the host/parasite interaction

To clarify the role of autoimmune mechanisms

To identify protective antigens and those related to immunopathology

ACTIVITIES

A new test using specific monoclonal antibody being field tested  
A new ELISA test using a stage-specific antigen being assessed  
Network of Collaborating Laboratories in operation in 11 countries  
Reference Centre in Sao Paulo evaluates network performance  
Distribution of standard serum samples under way

Research projects in progress

Mechanism of multiplication of strains and clones in parasite vectors being studied  
Study of factors involved in metacyclogenesis, including specific requirements for cultivation media

Ongoing projects to establish morphological, functional, isozymic, immunological and kDNA restriction characteristics of *T. cruzi* subpopulations

Ongoing projects on biochemical analysis of parasite surface proteins and their role in penetration of host cells and parasite infectivity

Identification of antigens common to parasites and host nervous tissue  
Study of cell-mediated immunity  
Study of cytotoxicity of lymphocytes from Chagas' patients in animal models

Antigen analysis including studies of flagellar antigens (under way)  
Antigen production using molecular biological techniques (under way)

| <u>OBJECTIVES</u>  | <u>PLANS</u>  | <u>PRIORITY</u>   | <u>ACTIVITIES</u>  |
|--|---|---|--|
| <p><b>EPITHELIUM</b></p> <p>To develop and improve methods for disease control through epidemiologically based studies</p>   | <p>To conduct in-depth field research</p>   | A   | <p>Studies of selected foci to elucidate transmission cycles with the objectives of developing simple control measures and identifying sites for carrying out trials of vaccines, new drugs or new diagnostic tests as they are developed</p>  |
|  |   | B   | <p>Initiation of field studies designed to answer selected specific questions (reservoirs, vectors, etc.)</p>  |
|  |   | B   | <p>Epidemiological studies in selected potentially high-risk areas</p>   |
|  |   | A   | <p>Isolation, characterization and cryopreservation of parasites with detailed documentation and coordinated exchange of information between laboratories; maintenance of present centres and encouragement of the development of regional and/or national reference strain laboratories and cryobanks</p> |
|  |   | A   | <p>Field trials of new diagnostic tests, drugs and vaccines</p>  |
|  | <p>To apply new control tools</p> <p>To investigate vector/parasite relationships</p> | B   | <p>Study of vector/parasite relationships relevant to the development of simple control measures</p>   |
|  |   | B   | <p>Basic sandfly biology and taxonomy</p>  |
|  |   | A   | <p>Purification and standardization of immunogens protective in animal models and <u>in vitro</u> assessment of human immune responses to them</p>   |
|  |   | A   | <p>Vaccine trials with standardized materials against cutaneous leishmaniasis</p>  |
|  |   | A   | <p>Development of primate models</p>   |
| <p><b>INTELLECTUAL</b></p> <p>To develop vaccines</p> <p>To improve diagnosis</p> <p>To understand host-parasite relationships with the aim of developing new control tools/approaches</p> | B   | <p>Mechanism of protective immunity in humans</p>   |  |
|  | B   | <p>Standardization of leishmanization</p>   |  |
|  | A   | <p>Development of simple tests for case detection and parasite identification</p>                                       |  |
|  | B   | <p>Standardization of serological tests</p>   |  |
|  | B   | <p>Standardized leishmanin</p>  |  |
|  | A   | <p>Continued studies of host-parasite relationships with emphasis on protective mechanisms and pathogenic responses</p> |  |
|  | B   | <p>Genetic analysis in humans and mice</p>  |  |
|  | B   | <p>Support of reference centres</p>   |  |



OBJECTIVES

CHENLEISH

To develop new non-toxic drugs and optimize treatment with existing drugs

PLANS

To design drugs

To conduct clinical trials

To search for new drugs

To develop new delivery systems

To continue studies on parasite identification and characterization

PRIORITY ACTIVITIES

A Investigation of fundamental biochemistry and physiology of Leishmania and their interactions with host cells with regard to drug action, diagnosis and tests for cure

A Clinical trials of new and existing drugs, including standardization of antimony preparations and further development of combined drug therapy and topical treatment

A Data analysis of compounds already screened by outside agencies; continued screening of compounds in tissue culture; subsequent tests of promising agents in appropriate animal models

B Development of new formulations to improve the biological activity of compounds and to permit more efficient anti-parasite activity and/or bio-availability in the human host

B Support of reference centres

ANNEX 4

REVIEWERS OF ACTIVITIES OF SCIENTIFIC WORKING GROUPS  
DURING THE COURSE OF THE MEETING OF STAC-9 (1987)

|   |   |
|---|---|
| Malaria (MAL)   | Professor J. Duarte de Araujo<br>Dr J.O. Mason<br>Professor Sir Gustav J.V. Nossal<br>Professor F.F. Supronov |
| Schistosomiasis (SCH)   | Professor A.A. Bruce-Tagoe<br>Professor N.A. Mitchison  |
| Filariasis (FIL) and Oncho-<br>cerciasis Chemotherapy Project | Dr Heidi Diggelmann<br>Professor Chie Nakane<br>Professor D. Von Wettstein                                    |
| African Trypanosomiasis (TRY)                                 | Professor A.A. Bruce-Tagoe<br>Dr Heidi Diggelmann   |
| Chagas' Disease (CHA)   | Dr Heidi Diggelmann<br>Professor N.A. Mitchison   |
| The Leishmaniases (LEISH)                                     | Professor A.A. Bruce-Tagoe<br>Professor N.A. Mitchison<br>Professor F.F. Supronov                             |
| Leprosy (IMMLEP and THELEP)                                   | Professor A.A. Bruce-Tagoe<br>Professor Chie Nakane<br>Professor Sir Gustav J.V. Nossal                       |
| Biological Control of<br>Vectors (BCV)                        | Dr Heidi Diggelmann<br>Professor Chie Nakane<br>Professor Sir Gustav J.V. Nossal                              |
| Epidemiology (EPD)  | Professor J. Duarte de Araujo<br>Dr J.O. Mason<br>Professor D. Von Wettstein                                  |
| Social and Economic<br>Research (SER)                         | Professor N.A. Mitchison<br>Professor Chie Nakane<br>Professor D. Von Wettstein                               |

\* \* \* \* \*





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

INTRODUCTION TO THE REPORT OF THE EIGHTH MEETING  
OF THE SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-8)

A. B. Morrison  
University of Guelph  
Guelph, Ontario, Canada  
(STAC Chairman)

Once again it is a great pleasure for me to introduce the report of the Scientific and Technical Advisory Committee, which met in Geneva in mid-March of this year. STAC's major task this year related to a consideration of in-depth reviews of the activities of the Scientific Working Groups on the African trypanosomiases, Chagas' disease and the leishmaniases. The Committee also commented once more on the impact of budgetary constraints on the ability of the Special Programme to meet its objectives.

TDR continues to be an extremely successful programme. In some areas, such as the development of leprosy vaccines or new chemotherapy for African trypanosomiasis, TDR-supported research dominates the world picture. In others, such as the development of malaria vaccines, the Programme is not by any means the major financial donor. Nevertheless, it continues to play a crucially important coordinating role in these areas - a role which is aided by constructive and mutually respectful relationships with the pharmaceutical industry. The outstanding success of the drug ivermectin in the treatment of onchocerciasis in West Africa is a vivid example of how rapidly major advances can be made through active collaboration between WHO and a major pharmaceutical company. Exciting advances also are occurring in research leading to improved control of the insect vectors responsible for malaria, onchocerciasis, Chagas' disease and the African trypanosomiases. Substantial progress continues to be made in the development of drugs, vaccines and diagnostic methods concerning all six target diseases of the Special Programme.

TDR continues to have a heavy investment in the application to the six target diseases of the new tools of molecular biology. Striking examples of its success in this area include the cloning and expression of the entire genome of *M. leprae*, and TDR's catalytic and coordinating role in the development of malaria vaccines based on the application of recombinant DNA technology and synthetic peptides. TDR has also enjoyed unusual success in more applied fields, including the use of insecticidal paints to control the triatomine vectors of Chagas' disease and simple traps for tsetse flies.

STAC noted with deep concern the continued intensification of disease control problems in endemic countries. Chemotherapy of malaria remains in a precarious situation because of the further spread of chloroquine resistance in *Plasmodium falciparum*. Confirmed cases of drug-resistant malaria have now been encountered in Cameroon. Drug resistance is thus becoming more deeply entrenched across Africa. Thankfully, mefloquine is now registered for use, alone and in combinations, but disturbing reports have been received of severe

The issue of this document does not constitute formal publication. It should not be reviewed, abstracted or quoted without the agreement of the World Health Organization. Authors alone are responsible for views expressed in signed articles.

Ce document ne constitue pas une publication. Il ne doit faire l'objet d'aucun compte rendu ou résumé ni d'aucune citation sans l'autorisation de l'Organisation mondiale de la Santé. Les opinions exprimées dans les articles signés n'engagent que leurs auteurs.

adverse reactions to the sulfadoxine component of certain antimalarial drug combinations. The need for new safe and effective antimalarial drugs remains high. Several major new families of promising compounds have been identified and formulations of halofantrine, artemisinin derivatives and a naphthoquinone compound are being tested. In the absence of their availability for use in the field, however, we remain in a very precarious position vis-à-vis the effective chemotherapy of malaria.

Recent major outbreaks of African sleeping sickness in several countries are of major concern, particularly in light of the severe limitations of current chemotherapeutic agents from the point of view of both safety and effectiveness. A significant new lead has appeared from TDR-sponsored research. The drug difluoromethylornithine (DFMO) has been successfully used in 100 patients with advanced disease caused by T.b. gambiense, including some with melarsoprol-resistant infection. Several other new compounds active in animal tests have also been identified. Additional funding will be required for further development of these lead compounds. Furthermore, there is an urgent requirement for a clinical centre in East Africa where much needed work on T.b. rhodesiense infection can be carried out.

This was not a budget year, but STAC nonetheless felt it necessary to comment on certain of the financial aspects of the Programme. All three of the R & D Components examined in detail (African trypanosomiasis, Chagas' disease and leishmaniasis) are at bare minimum levels needed for viability. Many exciting and important leads cannot now be followed up. Further reductions in funds would seriously jeopardize the future of the research efforts of these fields. STAC commended the Director for his wise and prudent control of the financial situation and asked that, insofar as possible within budget and priority frameworks, he should ease the financial constraints on these three Components.

STAC reiterated its views, expressed previously, concerning designated funds. These should be accepted only if they do not disturb the scientific balance of the Programme, nor compromise the independent role of STAC in providing objective advice to JCB. Furthermore, they should be devoted to areas identified by STAC as ready for effective expansion. To the list of those areas previously designated as acceptable candidates - viz. immunology of malaria, leprosy vaccines, field trials of biological control agents and training, STAC added a new item - clinical trials on new drugs for the treatment and control of African trypanosomiasis.

This is my last report as Chairman of STAC. It has been a great privilege over the years for me to represent so many distinguished colleagues from all over the world. They have made my task easy. I must also pay tribute to the distinguished retiring Director of the Programme. Dr Adetokunbo Lucas has more than anyone else been responsible for the success of TDR. The international scientific community owes him a great debt for his skill, knowledge and wisdom, coupled with untiring effort.

Finally, I wish to extend best wishes to Dr Tore Godal, the incoming Director, who is no stranger to TDR and brings his own excellent reputation in leprosy research and long-term interest in tropical diseases to his new responsibilities.

= = =