



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



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REPORT OF THE MEETING OF THE JOINT STEERING COMMITTEES
 OF THE SCIENTIFIC WORKING GROUP ON AFRICAN TRYPANOSOMIASIS

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Trypanosomiasis, Africa

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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 PNUQ/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.

1. INTRODUCTION

African trypanosomiasis shows a range of clinical manifestations in diverse ecological and epidemiological situations, requiring different approaches to control. Scientific progress during the past ten years, assisted by funding from the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR), has advanced our understanding of the disease and prompted the development of new tools for control.

The March 1988 meeting of the Joint Steering Committee reviewed past scientific achievements and suggested a strategy for future scientific work.

Speaking on behalf of Dr T. Godal, Director of TDR, and Dr H. Mahler, then* Director-General of the World Health Organization, Dr P. de Raadt, Chief of the Trypanosomiasis and Leishmaniasis Unit, WHO, emphasized the practical problems faced by health authorities in endemic countries in the face of frozen or shrinking health budgets. When establishing health care priorities under such conditions, trypanosomiasis has been treated as a priority only when it has reached epidemic levels, as currently in Zaire, Chad, and Uganda. Support to national health programmes from TDR/WHO has helped substantially to improve this situation. Dr A.R. Njogu, Director of the Kenya Trypanosomiasis Research Institute (KETRI), welcomed Working Group participants and thanked TDR/WHO for its support which has provided an important stimulus to KETRI development, and had spurred contributions from the Kenya government and other donor agencies.

Current activities and achievements of the research programmes supported by TDR as well as the problems of establishing effective field and research programmes were reviewed by Mr F.A.S. Kuzoe, Secretary of the Steering Committees on African Trypanosomiasis.

The Joint Steering Committees recommended that future strategy be based on a multidisciplinary approach with clearly defined priorities for each subprogramme and with particular emphasis on the development of new tools and their rapid evaluation and deployment. Such an approach will provide an effective link between the field and new developments in the laboratory towards the achievement of improved disease control.

2. EPIDEMIOLOGY AND VECTOR BIOLOGY AND CONTROL

2.1 Field Research

2.1.1 Protocols

There is an urgent need for standardized protocols for field epidemiological studies, prevalence studies (pilot reconnaissance studies) as well as for longitudinal prospective studies. Such standardized protocols should be developed by a multidisciplinary team, with field experience. Computerization would permit development of a software tool which would limit protocol development to actual data gathering and analysis, and also standardized and comparable data.

2.1.2 Epidemiological Analysis of Field Research

Limited progress has been made in epidemiological field research since the last SWG (1981), due to lack of standardized protocols, the high cost of prospective field studies and the lack of epidemiological knowledge and expertise in the endemic areas. Against this background it is appropriate to

* Note: Dr H. Mahler retired as Director-General, WHO, effective 20 July 1988.

emphasize recent developments in epidemiological methodology (design, sampling, data analysis) which remain to be applied in field epidemiological studies in sleeping sickness.

Epidemiological studies are the basis for approaching and analyzing biological phenomena, and provide insights into how and why disease occurs. Epidemiological studies on sleeping sickness have made major contributions in elucidating factors that determine host-fly relationships and the role of animal reservoirs in West and Central Africa.

It is also necessary to define the significance of asymptomatic carriers and their role in the maintenance of the disease, and to determine the role of human behaviour in the initiation and evolution of epidemics. To improve epidemiological research it will be necessary for the new technologies to be transferred to the field to improve the quality of data, to incorporate modelling as a part of our epidemiological investigations, and to ensure that integrated approach towards epidemiological research is adopted. This requires involvement of a variety of disciplines beginning with the planning phase of the research; such research is best undertaken by multidisciplinary teams linked to the health care system, working within well-defined geographic foci of the disease.

2.1.3 Socio-economic aspects

Few research projects have focused on the social and economic aspects of African trypanosomiasis. Available information suggests that knowledge of the disease in endemic areas remains poor, that there are negative attitudes towards hospitalization, and that population movement is a major constraint in the control of the disease. Attention must be given to the behavioural aspects of sleeping sickness epidemiology, in particular the coverage of vertical programmes, understanding of risk factors, strategies of integrated case detection (primary health care), follow-up of patients, surveillance of foci, and community participation in vector control activities. The behavioural information must be both qualitative and quantitative. Social scientists, preferably from the endemic areas, should be integrated into control teams.

More attention must also be given to the definition of the economic impact of sleeping sickness and its control at various levels -- foci, communities, families and individuals. In such studies the economic determinants cannot be expressed in monetary terms.

2.1.4 Multidisciplinary approach

To improve understanding of the epidemiology of sleeping sickness, a systematic approach must be adopted involving the integration of those scientific disciplines relevant to the different parameters and the definition of their interactions.

A multidisciplinary approach can only be introduced into field projects if it is based on management by objectives. This requires definition of problem(s) at all levels (from the individual to the government). This enables goals and objectives to be defined. The latter are quantifiable and time-limited and thus can be self-evaluated. Operational objectives, which are of short duration, can be defined, if required, to support the development objective.

Significant progress has been made in vector control methods in recent years with the development of traps and screens impregnated with insecticide; such methods can reduce riverine Glossina vector populations up to 99%, and maintain them at these low levels if such devices are regularly impregnated.

Community participation in vector control programmes is feasible and can be achieved through appropriate publicity campaigns. However, long-term motivation of communities remains a problem.

Vector control programmes are subject to certain constraints that must be overcome before satisfactory results can be achieved: knowledge of epidemiology, information on physical and human geography, entomological evaluations, etc. The programmes, which should last at least two years, must be planned in relation to available human resources and to the biology of Glossina.

A number of areas of research are pertinent to vector control programmes; these are

- trapping methods
- attractiveness and effectiveness of traps
- odour attractants
- management of various systems
- cost-effectiveness
- the presence of residual Glossina populations
- epidemiological significance of an animal reservoir
- studies on human behaviour
- the level of knowledge and awareness of the disease among local populations
- factors which may encourage or obstruct the participation of villagers in control programmes
- other possible control methods such as land-use management systems which either prevent the establishment of vector populations or reduce them to a minimum.

2.2 Laboratory Research

2.2.1 Vector and host-vector relationship

Laboratory colonies of Glossina have been used experimentally to study the olfactory responses of flies, using electroantennogram studies linked to gas liquid chromatography to measure the efficacy of candidate compounds as attractants. Laboratory analyses of fat and haematin to assess hunger state of flies, and analysis of the eye pigment, pteridine, as an indicator of fly age, will provide information relevant to trap development and population dynamics which will be essential components of any mathematical model.

Laboratory colonies of Glossina have been reared for Sterile Insect Technique (SIT) programmes; however, SIT is not an applicable technology in the control of human sleeping sickness. Simple devices, traps and targets with proven efficacy have been used with the objective of reducing or breaking disease transmission as rapidly as possible.

The finding that Glossina susceptibility to trypanosome infection is an inherited trait and that susceptibility is related to the presence of Rickettsia-like organisms (RLOs) mediated via lectin levels in the midgut, has provided an increased understanding of the underlying basis of fly infection rates and the mechanisms of parasite establishment in flies. These findings may have implications for the distribution of the disease and our understanding of infection rates in wild populations. Technique for DNA dot blots for parasite and RLO detection are now under development, and will provide tools to obtain more precise field data which can be applied to epidemiological models.

2.2.2 Parasite

Isoenzyme electrophoresis has been extensively used to characterize Trypanosoma brucei gambiense and T.b. rhodesiense from most endemic areas.

This has permitted the identification of human-infective trypanosomes in animal reservoir hosts and tsetse, and has provided information on the origin and spread of epidemics. Isoenzyme analysis has assisted in identifying the pig as a reservoir host of T.b. gambiense in West Africa, and highlighted the role domestic animals may play as reservoir hosts of T.b. rhodesiense in East Africa. It has also shown that sleeping sickness epidemics cannot generally be blamed on the introduction of new trypanosome stocks, and that trypanosomes circulating in any one outbreak are often heterogeneous. Isoenzyme electrophoresis will continue to generate valuable data on current and future outbreaks of trypanosomiasis provided adequate sampling is undertaken. Isoenzyme characterization also provided the first evidence that genetic exchange may occur among T. brucei in nature. The analysis of experimental crosses of trypanosomes in the laboratory will determine the mechanism of genetic exchange and demonstrate whether characters such as human infectivity and drug resistance are heritable.

Techniques of molecular biology have also been applied to characterization, and provide useful markers for T.b. gambiense. However, these methods require large numbers of trypanosomes and sophisticated analysis. Unfortunately, it is still not possible to distinguish T.b. gambiense by a simple dot blot test, as is possible with strains of T. congolense. It appears that the T. brucei group is fairly homogenous and the subspecies names are misleading. By all criteria so far used T.b. gambiense forms a much more cohesive group than T.b. rhodesiense, which is highly variable even in a focal epidemic.

However, in view of the recent discovery of genetic exchange in T. brucei and the possibility of marker reassortment, it would seem preferable to use the factor responsible for human-infectivity as a marker rather than some other character which may not be closely linked. The Blood Incubation Infectivity Test (BIIT) or the in vitro modification should be standardized, and efforts made to ascertain if a receptor for human-infectivity exists.

3. CHEMOTHERAPY AND DRUG DEVELOPMENT

3.1 Approaches in the search for new compounds

Because of the failure to discover new lead compounds by random synthesis and screening, researchers have concentrated on a more rational approach to drug development. This involves fundamental studies on the biochemistry and molecular biology of trypanosomes in a search for striking differences between host and parasite that could be exploited as targets for drug development. An increasingly sophisticated approach is being used involving gene sequencing, site-directed mutagenesis, mechanism-based enzymology, X-ray crystallography, and molecular modelling in an attempt to provide chemists with more precise information on likely structures for inhibitor design.

Several areas show potential for developing new compounds, improving existing drugs, or predicting combinations. These include:

- Inhibition of glycolysis (SHAM plus glycerol) or glycosomal assembly (suramin).
- Inhibition of polyamine metabolism (DFMO, pentamidine and triacetylbenzene trisguanylhydrazone), including biosynthesis of trypanothione.
- Interference with trypanosome functions (arsenicals, nitroheterocycles).
- Inhibition of protein synthesis using drugs coupled with anti-messengers to the spliced leader or mini-exon sequence of mRNA.

- Interference with antigenic variation by inhibiting activation or transfer of variant surface glycoprotein (VSG) genes.
- Interference with the anchoring of VSG in the plasma membrane by inhibition of the biosynthesis of glycosyl-phosphatidylinositol (GPI) or by activation of the VSG-releasing phosphokinase C.

Further support of research into the basic biochemistry and molecular biology of trypanosomes together with investigations into the mode of action of existing drugs will no doubt reveal other potential areas for drug development.

Screening of anti-cancer agents and natural products from plants and fermentation broths may also produce new leads for trypanocidal components.

3.2 Screening Activities

3.2.1 Animals models

3.2.1.1 Rodents

The mouse is the model of choice when testing drugs for immediate trypanocidal action: efficacy being assessed by survival. Minimal activity may be expressed as an increase in the prepatent period. The ability of drugs to cure chronic central nervous system infection is also best tested in the mouse. The mouse/T. brucei model also produces meningoencephalitis and is used as a model for preventing or alleviating encephalopathies. The vole, Microtus montanus, is used for T.b. gambiense infections which produce the same symptoms and encephalitis as the mouse model. The slow replication of some stabilates may be overcome by whole body irradiation of the mouse.

3.2.1.2 Ruminants

The sheep infected with T. brucei is also used as a model. The level of circulating parasites never reaches that of the mouse, but the disease progresses through early and late-stages where drug presentation and administration more closely parallels the treatment of human trypanosomiasis (except with orally administered drugs). Samples of cerebrospinal fluid (CSF) can be obtained relatively easily although there is a risk of blood contamination of the samples.

The goat model, with a cerebral catheter attached to the elliptical reservoir, is a similar model to the sheep, the advantage being that CSF samples can be repeatedly taken without trauma or contamination. This system is ideal for pharmacokinetic studies.

3.2.1.3 Dog model

The dog is an excellent model for the study of cardiac and optical pathology, as severe pancarditis develops similar to that described in man. The eye lesions are most marked in the dog and if untreated result in complete loss of vision.

3.2.1.4 Primate model

The primate is the only suitable intermediate model between the above-mentioned animals and man. An encephalitic late-stage disease is produced by non-curative Borenil chemotherapy and leads to a relapsing infection, with accompanying encephalitis. The model is expensive and a limited number of animals can be accommodated. Only compounds thoroughly investigated in other models should be extended to primates.

There is no substitute for in vivo experiments in the measurement of a drug's capability of crossing into the CNS because such studies allow the animal's normal immune responses to play their part in elimination of the trypanosomes. In in vivo experiments however, it is difficult to assess and overcome rapid inactivation by the animal; this problem might require continuous infusion of drug.

3.2.2 In vitro screening

The availability of culture systems to grow the mammalian stages of Trypanosoma brucei isolates has enabled the development of in vitro tests to determine the degree of sensitivity/resistance to trypanocidal drugs. Appropriate combinations of feeder layers and serum must be selected to assure good growth in control cultures. Trypanosome density can be determined either in a haemocytometer or with a Coulter Counter followed by inoculation into mice to assess viability. The development of a cell-free culture medium for the mammalian stages has enabled screening in the absence of feeder cells. Another method of drug evaluation is the incorporation of radiolabelled precursors such as labelled thymidine and leucine uptake in the presence of the drug. However, the incubation period is too short for some drugs to show cytotoxic action. A new test to measure the drug response of isolates is based on cell-free cultivation and involves in vitro assay of human isolates; H^3 -hypoxanthine is added after 24 h and inhibition curves established for different isolates and LC 50 determined (50% inhibition of incorporation compared with control cultures).

3.6. Drug Resistance

It is important to distinguish between drug resistance and refractoriness to drug treatment in the clinical testing. The former is the result of a genotypic or phenotypic change in the parasite whilst the latter involves factors such as the patient's tolerance to the drug, inadequate treatment, location of parasites in inaccessible sites or other pharmacokinetic considerations. Demonstration of drug resistance requires isolation of the parasite from the patient and the demonstration of a decreased sensitivity towards the drug in vitro or in vivo. This is usually not done, raising doubts as to the validity of some clinical reports of drug resistance. In order to produce a better understanding of the mechanisms of drug resistance it is necessary to know something about the mechanism of entry and mode of action of trypanocidal compounds. High levels of resistance observed in other micro-organisms frequently involves both. Surprisingly little is known about drug uptake and mode of action of trypanocidal agents. Elucidation of the mechanisms requires fundamental research which would be greatly aided by the availability of radio-labelled drugs.

4. IMMUNOLOGY AND PATHOLOGY

4.1 Immune Response

Antibodies produced in infections are specific to various antigens of the organisms -- predominantly the protective anti-VSG antibodies. Clonal exhaustion was previously considered to be an important component of the responses due to polyclonal activation by trypanosome antigen; however, it is now known that there is no clonal exhaustion and immunological recovery readily occurs after treatment. Responses previously thought to be non-specific on this basis have been shown to result from the presence of cross-reacting antigenic epitopes. Responses to some of the parasite antigens such as the cross-reacting determinants of the VSGs are depressed possibly due to intense antigenic competition. This is important when considering if there are other antigens that are accessible to immunological attack in the host. If they are

out-competed during infection, there will be no significant level of high avidity antibodies to exert their effect in the face of the highly immunodominant VSGs.

Such antigens include non-VSG moieties found on the trypanosome surface and parasite receptor molecules for essential host-derived nutrients, such as the transfer of high- and low-density lipoproteins. It is not known if these receptors are accessible to immunological attack or if they are sufficiently distinct immunologically from the host cell receptors for the same nutrients. It is important to address on a long-term basis if different animals and/or breeds recognize and respond better to these antigens, and if there is individual variation in response, mechanism of antigen presentation, relative immunogenicity of molecules if presented differently, and experimental suitability of antigen presenting systems. Serodeme-specific resistance is easily elicited in experimental conditions, particularly with chancre-inducing T. brucei and T. congolense stocks. Available evidence suggests the serodeme repertoire of T.b. gambiense to be more limited, but further studies on this topic are required. It is necessary to establish if the metacyclic VAT repertoire of T.b. gambiense is limited, and to determine the relative immunogenicity and stability of these antigens. Cultivation of defined metacyclic VATs of T.b. gambiense would be valuable for such studies.

4.2 Clinical signs

Studies conducted in recent years in clinical research programmes, especially at Daloa, in conjunction with the Faculties of Medicine at the Universities of Limoges and Abidjan, have accomplished the following:

- the identification of a large number of clinical signs of sleeping sickness;
- a more precise definition of the stage of CNS involvement; this was achieved by studying a number of clinical signs which, when present in a parasitologically-confirmed patient, enable a definition of the second phase of the disease;
- the compilation of clinical data for detailed study in collaborating centres; such clinical data should be made available in late 1988.

It is recommended that similar clinical data be compiled for T.b. rhodesiense trypanosomiasis and that a simplified version be produced to aid diagnosis where passive surveillance is undertaken in the field.

4.3 Experimental Pathology

Correlation between the signs of nervous system diseases and pathological alterations in the nervous system is still lacking. Recent studies on the localization of trypanosomes in the nervous system indicate that trypanosomes cause alterations in neurotransmitter receptor function in the brain.

Studies on T.b. brucei in rats, mice and deer-mice using immunohistochemical techniques (immunofluorescence and immunoperoxidase methods) revealed that the earliest invasion took place in those areas of the nervous system that lack a 'tight' blood-brain barrier: the choroid plexus, spinal root ganglia and cranial nerve, and the circumventricular organs. The involvement of this latter area may be related to the pathogenesis of the disease as severe disturbance in urinary melatonin secretion is associated with certain types of depression and disturbances in the sleep pattern. The median eminence is involved in secretion of a releasing factor for pituitary gland hormones, and parasites invade this area. The secretion from the median eminence is modulated by a strong dopaminergic innervation in this area. Immunohistochemical techniques enable the neurotransmitters and neuropeptides in these

regions as well as certain of their receptors to be investigated in association with trypanosome infection. Monoclonal antibodies against subsets of lymphocytes and major histocompatibility complex antigens also provide methods for studying immune reactions in the brain. Brisk induction of class I MHC is observed in experimental trypanosomiasis in the median eminence and in two distinct hypothalamic nuclei -- the median supraoptic and median paraventricularus. This indicates that these hypothalamic neurons are signalled through retrograde axonal external transport of factors from the infected areas either derived from the trypanosomes or from monocytes or lymphocytes. These results provide an interesting area for future research on trypanosomiasis, providing a better understanding of the link between signal molecules and their receptors in the immune and nervous systems as well as linking pathogenesis to clinical disease.

4.4 Models for Clinical and Pathological Evaluation of Treatment

Vervet monkeys (Cercopithecus aethiops) provide a good model of the human disease because two phases of CNS infection can be observed in T. rhodesiense infection in vervets; first, where the parasite is established in CSF but not in brain parenchyma and second, where the parasite is in the brain and encephalitis results. Both phases can be used in trials of established drugs or of new compounds and regimens. Ten drugs have so far been tested in the vervet monkey and promising results have been found with reduced dosages of melarsoprol, MelCy, and the nitroimidazoles, MK 436 and Ro 15 2016.

The dog is another model used in studies in comparative medicine. Pancarditis is a prominent feature of trypanosome infection in both monkey and dog and is being studied in detail in dogs. The dog could also be used as a model of trypanosome-induced encephalitis.

Future requirements include more standardized screening through the various models. The suggested lineage might be mouse acute, mouse chronic, goat, sheep, dog, monkey.

There is an urgent need for a T.b. gambiense model, possibly in C. mitis (Sykes monkeys) as reactive encephalopathy following therapy is poorly understood.

The vervet model requires improvements to overcome the need to "induce" encephalitis with a drug and to improve diagnosis during the post-treatment follow-up period in order to identify potential relapse cases.

Criteria for treatment on the basis of different CNS stages need revision and might be developed through the vervet model. A drug is needed which will ideally treat both late-stage phases. Manipulation of the blood-brain barrier with drugs might be investigated in these models.

5. PROSPECT FOR THE APPLICATION OF NEW TOOLS IN DISEASE CONTROL

A number of effective tools have been developed for improved diagnosis of trypanosomiasis, as alternative drugs in cases refractory to melarsoprol, and for effective vector control. When these tools have been assessed and tested in the field, large-scale evaluations have then been conducted to confirm the laboratory results. Evaluation of the CATT was conducted in six African countries using a standard protocol which confirmed the high sensitivity and specificity of the test. Clinical trials with DFMO are being conducted in several centres with highly satisfactory results. Large-scale evaluation of vector control tools have been made in several countries with and without community participation.

Nevertheless, in a few countries results from subsequent use have been at variance with earlier assessments. Such occurrences may be due to either poor implementation resulting from inadequate training, defective equipment, inadequate material produced by doubtful methods, or misinterpretation of results due to incorrect definition of terms.

It is recommended, therefore, that all new tools be subject to appropriate evaluation at every level, and protocols be developed which will give reliable and comparable results irrespective of where or by whom they are used.

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ANNEX

REPORT ON THE WORKSHOP ON MODELLING SLEEPING
SICKNESS EPIDEMIOLOGY AND CONTROL

This workshop took place at the Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium from 25-29 January 1988 and was organized by Dr A. de Muynck on behalf of TDR. The aim of the workshop was to bring laboratory scientists, modellers and field scientists together to discuss the logical structure of causal and analytical models for sleeping sickness, the use of the models, the choice of parameter values, the benefits of the models in epidemiological studies of sleeping sickness and its control and the place of modelling in the planning of control activities.

The workshop was organized as a plenary session, combined with expert meetings, where specialists presented and discussed their position papers and examined the current situation in their groups. The Workshop recommended:

1. The use of models in the planning, monitoring and evaluation of control programmes.
2. The hypothesis generating function of models in different disciplines.
3. The need to gather past data sets and publications.
4. The need for multidisciplinary studies in particular geographical areas.
5. That due attention should be given to the human behavioural aspects.
6. That there is need to integrate a transmission model into an expert systems framework that also incorporates separate models for human behaviour, economics, chemotherapy and vector populations and their control, together with data sets, both published and unpublished, that would be most relevant to informed decision-making.
7. That field workers be educated in the use of models. This requires packaging of models for PC use, coupled with appropriate teaching in the understanding and use of models as components of decision support systems.

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