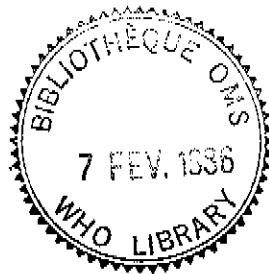


special programme for research and training in tropical diseases

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LEISHMANIASIS COMPONENT REVIEW FILE - 1986

This file has been assembled to assist STAC-8 in their review of the leishmaniasis component.

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LEISHMANIASSES WORKPLAN 1986 - 1989

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

TABLE I: LEISHMANIASIS WORKPLAN 1986 - 1989 (contd.)

OBJECTIVES	PLANS	ACTIVITIES
CHEMICAL	Optimize treatment with existing drugs and develop new non-toxic drugs	Investigation of fundamental biochemistry and physiology of <i>Leishmania</i> and their interactions with host cells with attention to possibilities for drug action, diagnosis of disease, and tests for cure.
	Conduct clinical trials	Clinical trials of new and existing drugs. This includes standardizing antimony preparations, experimental agents which may be developed, and topical therapy.
	Search for new drugs	Data analysis of compounds already screened by outside agencies; continued screening of compounds in tissue culture; tests of promising agents to be done later in appropriate animal models
	New delivery systems	Formulation to improve the biological activity of compounds to permit more efficient anti-parasite activity and/or increased bio-availability in the human host
	Identification and characterization of parasites	Support of reference centres

2. TECHNICAL REVIEW GROUP I - SEPTEMBER 1976

4. The Selected Diseases

4.9 Leishmaniasis (TDR/WP/76.14 and 76.15)

a) As noted above, the TRG recommended that leishmaniasis be retained among the six diseases, with emphasis on those aspects of the disease in which research showed potential at relatively low cost, and which were also relevant to research in other diseases among the six.

b) Leishmaniasis had considerable research potential for the investigation of immunological aspects of the host response - the different persistent chronic forms being likely to depend on defects of response which were open to investigation.

c) The current chemotherapy of leishmaniasis is most unsatisfactory. Because of the general similarity to trypanosomiasis, drugs shown to be effective against this (and other parasites) should be tested against leishmania, and vice versa.

d) In view of these considerations, some reallocation within the present budget was desirable, but no increase in the overall budget was necessary. Limited funds should be available for chemotherapeutic trials. Clinical pathology (budget item 3.3) should be advanced to priority A. Work on clinical pathology and the experimental studies indicated under budget item 2, should be coordinated, and directed in an attack on the persistent forms of the disease.

5. The Balance of Priorities Between the Six Diseases

Leishmaniasis did not have the same status as the preceding infections as a problem of public health importance, although it was a major concern especially in parts South America. There were very promising research leads, especially in certain aspects of the host/parasite relationship. The diseases caused by infection with leishmania were similar in a number of respects to others of the six diseases, and the inclusion of leishmaniasis promoted the coherence of the Special Programme. There was a great need for improved chemotherapy.

3. TECHNICAL REVIEW GROUP II - SEPTEMBER 1977

3. Progress Made in 1977

3.3 Research and Development

The SWGs on filariasis, schistosomiasis, epidemiology and biological control of vectors held their first meetings and defined their objectives and plans of action. Research projects of these SWGs have been funded or approved for funding and, in filariasis, joint projects on drug development are being negotiated with the pharmaceutical industry. The SWGs on African trypanosomiasis, Chagas' disease, leishmaniasis and trans-disease biomedical research will be convened within the next few months. A group to consider operational research on malaria, and Research Capability Strengthening Working Group will also be convened shortly.

4. Recommendations

4.3 Operational Recommendations

4.3.6 Leishmaniasis

This disease is now resurgent in a number of areas and current drugs are not sufficiently effective. High priority should therefore be given to the search for new therapeutic agents along with greater emphasis on epidemiological and control studies. Further metabolic studies of the parasite are desirable to define points of attack which could be used as a basis for drug development. There is a need for better serodiagnostic tests to detect infection at an early stage. Clinical manifestations observed in leishmaniasis should be correlated with immunological status and with increasingly precise parasitological definition of species and strain. The possibility of developing improved vaccines should be explored. Studies of the ecology of the vectors and the implications for control are also required.

Planning is sufficiently advanced to permit major funding of research during the last half of 1978. The proposed budget should reflect this and expenditures may need to be re-examined in 1979 to ensure their adequacy.

4. TECHNICAL REVIEW GROUP III - AUGUST-SEPTEMBER 1978

3. Progress in 1977-78

3.2 Research and Development

The SWG on Leishmaniasis initiated research on vaccines and new drugs. Resurgence of the disease in a number of countries underscored the need to study its epidemiology and thus establish its significance as a public health problem.

A start was made in collaboration with the pharmaceutical industry and academic institutions in the development and testing of drugs for the control of malaria, schistosomiasis, filariasis, African trypanosomiasis, leishmaniasis and leprosy. Such collaboration is essential for the success of this aspect of the Programme, in view of the unique capabilities of industry in drug synthesis and the capacity of the Special Programme to carry out both biological and clinical evaluations. In circumstances where industry is active in drug development, as in schistosomiasis, the objectives of the Programme may be met best by collaboration in the later stages of development, especially in clinical trials in endemic areas. If there is only limited industrial interest, as in drugs for filariasis, the Programme may initiate and support all stages of drug development, seeking to involve industry at any stage where it is appropriate.

4. Recommendations

4.4 Operational Recommendations

4.4.6 Leishmaniasis

The Group noted various reports of a sharp increase in the incidence of leishmaniasis following the interruption of antimalarial spraying programmes or the opening of newly developed areas. Increasing concern about

leishmaniasis as a public health problem in South America, Asia and Africa underscored the need to obtain as rapidly as possible, accurate and timely information on the prevalence, distribution and importance of leishmanial infections.

The Group considered the greatest immediate need was for more information on the epidemiology of leishmaniasis, to include a better understanding of host-parasite relationships and pathology and the ecology of animal reservoirs and vectors. The need to develop and use common approaches in conducting epidemiological studies was emphasized.

Programmes on the immunology, immunopathology, biochemistry and chemotherapy of leishmaniasis should focus on activities likely to be fruitful in the short run or which elucidate pertinent aspects of other diseases included in the Special Programme.

The operational budget for 1979 should reflect the above priorities; approximately 50% of the operating funds should be spent in the area of epidemiology, and the total budget should be increased to US\$653,000.

5. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-1)
AUGUST-SEPTEMBER 1979

3. Progress in 1978-79

3.2 Research and Development

Epidemiological studies on leishmaniasis were initiated in several countries and preliminary groundwork was laid for improved serodiagnostic tests. A small drug development programme was started.

4. Recommendations

4.2 Research Recommendations for 1980

4.2.6 Leishmaniasis

The Committee reaffirmed the recommendation of TRG III, that main efforts should be focused on epidemiology, since the evaluation of new control procedures will depend upon achievements in this area. Drug screening operations should be continued. Despite their long-term importance, in view of the financial constraints on the Programme, immunological investigations should be decreased for 1980.

To permit the SWG to carry out an effective programme of research, it was recommended the budget for 1980 should be increased by approximately 20%.

6. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-2) - SEPTEMBER 1980

2. Recommendations

2.1 Research and Development

Leishmaniasis

The main emphasis should be on efforts to gain better information on the epidemiology of the different forms of disease. A workshop should be held on the chemotherapy of visceral leishmaniasis including clinical trials of allopurinol. Priority should be given to collaborative international trials on allopurinol. Necessary professional secretariat services should be provided to serve the Steering Committee of the SWG on Leishmaniasis.

4. Progress in 1979-80

4.2 Research and Development

Concern has been expressed repeatedly on the seriousness of the leishmaniasis as a public health problem. The main effort of the small research activity within the Special Programme has been to define the incidence and prevalence of the different forms of disease in several parts of the world. A protocol has been prepared for assessment of drugs for the treatment of mucocutaneous leishmaniasis, work is in progress to improve diagnostic methods, and suggestive evidence has been obtained that immunization against non-healing forms of disease can be achieved.

5. STAC Review and Conclusions

5.2 Review of SWG Activities

5.2.4 Leishmaniasis

STAC recommended that:

a) The main emphasis should be on efforts to gain better information on the epidemiology of the different forms of the disease.

b) A workshop be held on chemotherapy of visceral leishmaniasis, including clinical trials of allopurinol. Priority should be given to collaborative international drug trials on allopurinol.

c) Necessary professional Secretariat services should be provided to serve the Leishmaniasis Steering Committee.

9. Programme Activities Over the Next Five-Year Period, 1981-85

9.1 Priorities

Having in mind Research and Development advances achieved to date, and the promise for the future, the Committee reached the following conclusions regarding research priorities:

1. Over the next five years developments in chemotherapy will provide new tools for treatment of the six diseases in the Special Programme. Long acting formulations of currently available antimalarials and new antimalarials now under development should reach the stage of clinical testing by the end of the quinquennium. Expanded clinical trials of drug combinations for the treatment of malaria and leprosy can be expected by 1984-85, and a promising lead in the chemotherapy of leishmaniasis may reach a stage of development requiring clinical trials by about the same time.

2. The contribution of advances in immunology to the diagnosis and treatment of the six diseases is potentially enormous, but new immunological tools for treatment and prevention cannot be expected to reach the stage of application within the next quinquennium. It now seems likely, however, that a leprosy vaccine will be field tested in the next five years, probably in 1984-85, and this development should be given high priority. Recent advances indicate that production of an effective malaria vaccine is feasible; the potential benefits from such a vaccine are so large that development of it must be given high priority. Work on the development of vaccines for the other diseases (filariasis, African and American trypanosomiasis, schistosomiasis and leishmaniasis) is much less advanced, but application of the techniques of modern biology has already begun to have a significant impact. For the next five years, development of vaccines for these other diseases should be maintained at approximately the present levels, expressed in 1980 US dollars, and must be highly focused on the most relevant lines of research leading to the probable development of vaccines.

7. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-3) - SEPTEMBER 1981

1. Summary and Major Conclusions

The Committee:

- concluded that leishmaniasis is a public health problem in many parts of the world of much greater magnitude than previously considered; noted that the Special Programme plays an important role in conducting and stimulating research and training in this field; recommended enhanced support for this component.

2. Recommendations

2.1 Research and Development (Programme Area II)

Leishmaniasis:

a) To strengthen the immunology subcomponent, a new SWG on immunology should meet to redefine goals and the means of achieving them; in view of the possibility of developing effective and reliable vaccines, additional funds should be allocated to the immunology subcomponent.

b) Funding of the chemotherapy subcomponent should be maintained at the present level.

c) Major emphasis should continue on epidemiology; such research should focus on in-depth studies in selected geographic areas representative of the major foci of the disease and of specific ecological situations.

d) Emphasis should be placed on standardization of research methodology and protocol development.

e) Close contact should be developed with national research agencies and control programmes.

f) Research on social and economic factors should be stressed; close contacts with the Social and Economic Research (SER) component are essential.

g) Training should be emphasized through close relationships between the SWG and the RSG.

4. Progress in 1980-81 and Recommendations for the 1982-83 Biennium

4.2 Research and Development

4.2.7 Leishmaniasis

This component was examined by an STRC.

STAC noted that leishmaniasis is spreading in several areas of the world. The Special Programme plays an important role in research on its control by stimulating and coordinating research and training. The contribution of the Special Programme thus is in reality much greater than the financial input might indicate. STAC was of the firm view that leishmaniasis is an important component of the Special Programme, and merits additional support.

Recommendations

STAC concurred with the conclusions of the STRC report and on this basis recommended:

a) To strengthen the immunology subcomponent, a new SWG on immunology should meet to redefine goals and the means of achieving them. In view of the possibility of developing effective and reliable vaccines, additional funds should be allocated to the immunology subcomponent;

b) Funding of the chemotherapy subcomponent should be maintained at its present level;

c) Major emphasis should continue to be placed on the epidemiology subcomponent; such research should focus on in-depth studies in selected geographic areas representative of the major foci of the disease and of specific ecological situations;

d) Emphasis should be placed on standardization of research methodology and protocol development;

e) Close contact should be developed with national agencies and control programmes;

f) Research on social and economic factors should be stressed; close contact with the SER component is essential;

g) Training should be emphasized through a close relationship between the SWG and the RSG; and

h) A permanent Secretary for the SWG Steering Committee (SC) on Leishmaniasis should be appointed.

7. Programme Activities Over the Next Four-Year Period, 1982-85

Priorities:

STAC noted with concern the evidence that leishmaniasis is a much more serious public health problem in many parts of the world than had previously been recognized. Increased priority must be placed on leishmaniasis research over the next four years. Major emphasis should be given to epidemiological

aspects of the disease complex, but additional resources should also be provided for immunology investigations, in the hope of developing an effective vaccine.

8. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-5) - MARCH 1983

2. Recommendations

2.1 Research and Development (Programme Area II)

(f) Leishmaniases

- In accordance with plans of the SWG, increasing emphasis should be given to developing preventive vaccines and better treatment;

- studies on vector biology should be carried out, with special reference to experimental transmission studies, parasite characterization and field research in a few selected locations for each of the major disease groups; and

- funding for the 1984-85 biennium should be maintained at current levels.

8. Reports of Progress Made by SWGs

8.6 Leishmaniases

8.6.1 A valuable global review has been completed of all forms of leishmaniases including information on aetiologic agents, forms of disease in man and known or suspected reservoir hosts and vectors. STAC commended an anticipated shift in emphasis within the Programme subcomponents, with increasing focus on developing preventive vaccines and better treatment. There is still a need for studies on vector biology, with special reference to experimental transmission studies, parasite characterization and field research in a few selected locations for each of the major disease groups.

8.6.2 The goals and priorities of the immunology subcomponent have been re-examined by the SWG, and strategies for vaccine development, diagnostic tests and basic immunology have been outlined. Vaccine development is now considered a realistic goal in the light of recent developments in immunology.

8.6.3 Guidelines for preparing protocols for clinical trials on chemotherapy of visceral leishmaniasis were developed. They should prove helpful in testing the therapeutic efficacy of newly-developed antileishmanial compounds. Through pharmacokinetic studies carried out outside the Programme at the Walter Reed Army Institute of Research, and at the Programme-supported Clinical Research Centre in Nairobi, existing treatment schedules using pentavalent antimonials have been improved. Two new candidate drugs are now available for human trials - a pentavalent antimonial liposomal preparation, and allopurinol riboside. The Programme has been invited to assist in further development of a third product for treatment of Old World cutaneous leishmaniasis which is based on a synergistic effect of two drugs.

8.6.4 STAC recommended that the SWG continue its present research programme.

10.1.13 Subject always to the appearance of new and promising research opportunities and leads, and changing disease patterns, STAC recommended that research on schistosomiasis, African trypanosomiases, Chagas' disease, filariasis and leishmaniases should be maintained at approximately the same resource levels as during the 1982-83 biennium.

9. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-7)
MARCH 1985

1. Summary and Major Conclusions

1.7 Leishmaniasis

STAC approved the current workplan. Coded isolates of parasites should be distributed by the recently established International Reference Strain Laboratories.

- In-depth studies of selected foci should receive particular attention, with the objective of developing simple control measures, and research on social and economic aspects should continue.

- Research with the ultimate aim of developing effective vaccines should be promoted, under conditions laid down by the Steering Committee.

6. Reports of Progress made by other Scientific Working Groups and the Research Strengthening Group

6.5 Leishmaniases

STAC approved the current workplan. It commended the establishment of International Reference Strain Laboratories (IRSL), and the exchange of standard strains of parasites which has taken place. STAC recommended that coded isolates be distributed by the IRSLs in order to implement the process of international identification.

Particular attention should be paid to in-depth studies of selected disease foci for elucidation of transmission cycles involving man, with the objective of developing simple control measures. The importance, as laid down in the 1981 STRC report, of continuing research on social and economic factors that play a part in the epidemiology of leishmaniases was re-emphasized. High-risk areas are particularly important for study.

A new chemotherapeutic agent, allopurinol riboside, is currently undergoing trial as an ointment for topical treatment. Both developments arose out of research conducted by the Programme. STAC noted that serious attempts now are underway to develop research on the immunology of leishmaniases, with the ultimate aim of developing effective vaccines. It supported this initiative, under conditions laid down by the Steering Committee.

10. STRC REPORT ON LEISHMANIASIS, MARCH 1981

1. Recommendations

The STRC deliberations resulted in a number of significant recommendations for the Leishmaniasis Programme which are incorporated at the end of the various sections of the report. However, there were several of the recommendations which the Committee felt were especially important - these are listed below:

1.1 The STRC is concerned about the suggestions that the TDR programme on Leishmaniasis might be discontinued. On the contrary, the STRC strongly recommends the continuation of the programme. Leishmaniasis is a world wide problem which is increasing in several areas. Recent advances in pharmacology, immunology and molecular biology have considerably improved the chances of success in conquering this serious group of diseases compared to the prospects a few years ago. Far from stopping this venture, it should be continued with enthusiasm and even expanded.

1.2 Throughout the meeting the STRC came up against constraints in the Leishmaniasis Programme that could be directly attributed to lack of a Permanent Secretary. It is, therefore, quite clear to the STRC that this is the main deficiency in the Programme and should be rectified as soon as possible. The STRC feels that the presence of a permanent Secretary should not be linked to budget considerations - the Programme cannot continue to function effectively without this element in its organization.

1.3 The STRC endorsed the relative proportions of the operating budget previously allocated to the 3 components of the Programme (EPILEISH, IMMLEISH, and CHEMLEISH). Except for minor readjustment, the STRC was in accord with the new budget figures proposed by the Joint Steering Committee. Although this would boost the budget so slightly over one million dollars, it is felt that such an increase is justified.

1.4 The STRC recommends that up to date existing data on geographical distribution, prevalence and incidence of the leishmaniasis be compiled. For areas where adequate information is not available, investigation should be promoted to properly identify the parasites, reservoirs and vectors. Studies on the interactions of these epidemiological elements are needed for the development of rational control programmes.

1.5 Traditional control measures which have proven effective in the past in certain areas should be implemented more thoroughly. In areas in which such measures do not appear feasible (Neotropical forests) new approaches should be investigated. These would include development of vaccines or prophylactic drugs and outdoor insecticide spraying procedures.

1.6 To strengthen the IMMLEISH Programme, the STRC recommends that a meeting of a new SWG on Immunology be convened to redefine the goals of IMMLEISH and determine how these goals can best be achieved. The SWG would include persons familiar with the newly developed technologies including the production of monoclonal antibodies, isolation of antigens, and genetic engineering; these methods are needed to obtain pure antigens to be used for producing vaccines, and developing specific reagents useful both for diagnosis and elucidation of basic immunologic mechanisms in pathogenesis of the disease.

1.7 The STRC recommends that, in addition to developing animal models to test antigens as potential vaccines and to understand the basic immunoprotective mechanisms, it is important to carry out further studies, using recently developed technology, on the immune response, (and lack of

response) to Leishmania in human subjects with leishmaniasis. Such investigations must of course comply with WHO ethical standards.

1.8 CHEMLEISH - The STRC wants to stress the importance of improvement in the use of known compounds, as well as the necessity for development of novel drugs for the treatment of Leishmaniasis. Therefore, studies on the metabolism of the parasite, establishing well standardized in vitro and in vivo models for drug action and the attraction of highly qualified scientists to work on Leishmaniasis, should be considered.

1.9 Training activities already initiated by the TDR which include set courses of varying duration, training grants for scientists in developing countries, medium term facilitation of able scientific workers and teachers, seminars, workshops and the exchange of study visits of scientists in institutions of the endemic countries, need to be strengthened with closer interaction between the SWG and the RSG and the application of ample resources as the Programme can make available. The endemic countries themselves need to make every effort to identify and facilitate junior scientists to be absorbed in research institutions collaborating with TDR, so as to provide a permanent base for the strengthening of their own institutions and the continuation of the research and training programmes.

1.10 Research on social and economic factors that play a part in the epidemiology of the Leishmaniasis should be emphasized. A better understanding of these factors could provide useful new tools to enhance the effectiveness of medical, biological and ecological measures of control.

11. FIFTH ANNUAL REPORT - JULY 1980 - JUNE 1981

4.1 Strategic Plan

The priorities developed by the SWG in 1977 included a range of objectives covering improvement in the use of existing compounds, discovery of novel antileishmanial compounds and investigation of the biochemistry of the parasite.

There is potential for improvement in the use of existing compounds, especially the antimonials. More pharmacokinetic and metabolic data are required to permit the assessment of the relative efficacies of the two antimony compounds - sodium stibogluconate and meglumine antimoniate. The priorities for clinical investigation, were (1) to find out if parasitological relapse after treatment was due to the development of acquired drug resistance, and (2) to pursue more effective targetting of known drugs.

Development of new anti-leishmanial compounds involved the establishment of in vivo and in vitro models and methods. Compounds for examination would be derived from compounds already in use for treatment of other diseases, from existing novel compound banks and from inhibitors of specific parasite enzyme pathways. Increased potency may be revealed by a study of potentiation between known chemotherapeutic agents and investigation of the mode of action of anti-leishmanial compounds.

Biochemistry of the amastigote and amastigote/macrophage complex was also given high priority, with the aim of developing new anti-leishmanial compounds non-toxic to the patient. The studies of the biochemistry of the parasite were to include both development of techniques for obtaining parasite material and the characterization of specific amastigote metabolic pathways.

When a second SWC meeting was convened (May 1979) to narrow the priorities, all long-term fundamental biochemical studies were deferred and priorities were restricted to detailed development of known antileishmanial compounds, in particular the development of protocols for clinical trials and experimental studies on drugs in clinical use for other diseases.
