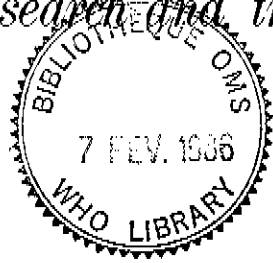


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FILARIASIS COMPONENT REVIEW FILE - 1986

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

Table of Contents of Excerpts

	<u>Page</u>
1. 1.1 Revised Workplan.....	1-3
1. 1.2 List of Priorities.....	4-5
2. TECHNICAL REVIEW GROUP I - SEPTEMBER 1976.....	6
4. The Selected Diseases.....	6
4.6 Filariasis.....	6
5. The Balance of Priorities Between the Six Diseases.....	6
3. TECHNICAL REVIEW GROUP II - SEPTEMBER 1977.....	6
3. Progress Made in 1977.....	6
3.3 Research and Development.....	6
4. Recommendations.....	7
4.3 Operational Recommendations by Disease and Trans-Disease Components.....	7
4.3.3 Filariasis.....	7
4. TECHNICAL REVIEW GROUP III - AUGUST-SEPTEMBER 1978.....	7
3. Progress in 1977-78.....	7
3.2 Research and Development.....	7
4. Recommendations.....	7
4.4 Operational Recommendations by Disease and Trans-Disease Components.....	7
4.4.3 Filariasis.....	7
4.6 Programme Review and Evaluation.....	8
4.6.2 Large projects.....	8

...ii

5.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-1) AUGUST-SEPTEMBER 1979.....	8
	3. Progress in 1978-79.....	8
	3.2 Research and Development.....	8
	4. Recommendations.....	8
4.2	Research Recommendations by Disease and Trans-Disease Components for 1980.....	8
	4.2.3 Filariasis.....	8
6.	REPORT OF THE SCIENTIFIC WORKING GROUP ON FILARIASIS, 1975-80...	9
	7. Projections for the Future.....	9
	7.1 Chemotherapy.....	9
	7.2 Immunological Work.....	10
	8. Plan of Action and Budget Projections.....	10
	8.1 Plan of Action.....	10
7.	REPORT OF THE STRC ON FILARIASIS, 1980.....	11
	10. Recommendations.....	11
	10.2 Chemotherapy.....	11
	10.3 Immunology.....	12
	10.4 Field and Laboratory Research on Epidemiology and Vectors..	12
8.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-2) SEPTEMBER 1980.....	12
	2. Recommendations.....	12
	2.1 Research and Development.....	12
	4. Progress in 1979-80.....	12
	4.2 Research and Development.....	12
	4.3 Research Capability Strengthening.....	13
	5. STAC Review and Conclusions.....	13
	5.1 Scientific and Technical Review Committee (STRC) Reports...	13
	5.1.3 Filariasis SWG.....	13
	9. Programme Activities Over the Next Five-Year Period, 1981-85.....	13
	9.1 Priorities.....	13
9.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-3) SEPTEMBER 1981.....	14
	2. Recommendations.....	14
	2.1 Research and Development.....	14
	4. Progress in 1980-81 and Recommendations for the 1982-83 Biennium.....	14
	4.2 Research and Development.....	14
	4.2.3 Filariasis.....	14
	7. Programme Activities Over the Next Four-Year Period, 1982-85.....	15
	7.1 Priorities.....	15

10.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-4) MARCH-APRIL 1982.....	15
	4. Progress in 1981-82.....	15
	4.2 Director's Report.....	15
11.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-5) MARCH 1983.....	15
	2. Recommendations.....	15
	2.1 Research and Development.....	15
	4. Progress in 1982-83.....	16
	4.2 Director's Report.....	16
	8. Reports of Progress made by Scientific Working Groups.....	16
	8.3 Filariasis.....	16
	10. Programme Activities Over the Next Four Year-Period, 1984-87.....	17
12.	FIFTH ANNUAL REPORT: 1 JULY 1980 - 30 JUNE 1981.....	17
	3. Research and Development (Excerpt from Summary Overview).	17
	3.4 Filariasis.....	17
	1. Objectives (Excerpt from Chapter 4: Filariasis).....	18
	2. Strategic Plan (Excerpt from Chapter 4: Filariasis).....	18
13.	SIXTH PROGRAMME REPORT: 1 JULY 1981 - 30 JUNE 1982.....	19
	3. The Six Diseases (Excerpts from Overview).....	19
	3.3 Filariasis.....	19
14.	REPORT OF THE SCIENTIFIC WORKING GROUP ON FILARIASIS, 1980-83.	20
	3. Projected Activities.....	20
	3.1 Chemotherapy.....	20
	3.2 Immunology.....	21
	3.3 Field Research.....	21
15.	REPORT OF THE STRC ON FILARIASIS, 1984.....	21
	Overview.....	21
	Major Recommendations.....	22
16.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-6) MARCH 1984.....	24
	1. Summary and Major Recommendations.....	24
	1.2 Filariasis.....	24
	5. Scientific and Technical Review Committee (STRC) Reviews.	25
	5.2 Filariasis.....	25
	5.3 Onchocerciasis Chemotherapy Project (OCT).....	25
	Table 1 - Activities with Filaricidal Compounds Which Found Place Between 1980 and Fall 1983: Type of Activity (Stage of Development).....	27
	Table 2 - Flow Chart for Therapeutic Trials in Filariasis.....	28

17.	SEVENTH PROGRAMME REPORT 1 January 1983 - 31 December 1984.....	
	1. Overview.....	29
	1.2 Filariasis.....	29
18.	SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-7).....	
	6.2 Filariasis.....	30



Workplan for Filariasis

1 January 1986

- 1 -

OBJECTIVES

Chemotherapy*

To develop new filaricides (L/O**) especially macrofilaricides (O)

PLANS

To carry out lead-directed chemical synthesis (L/O)

To conduct studies on filarial biochemistry and metabolism (L/O)

To screen candidate compounds (L/O)

ACTIVITIES

Support for and coordination of ongoing research on chemical synthesis (L/O)

Support for research groups and individual researchers studying synthesis, biochemistry and screening (O), under the Onchocerciasis Chemotherapy Project (OCT)

Support for and improvement of primary and secondary screens and improvement of B. malayi leaf-monkey screen (L)

Development of W. bancrofti leaf-monkey screen (L)

Maintenance and improvement of Onchocerca cattle screen (O), under the OCT

Maintenance of nodule supply (O), under the OCT

Improvement of in vitro culture and development of small-animal Onchocerca screen (O), under the OCT

Studies on mutagenicity, absorption, distribution, metabolism and excretion of CCP 20376 (in progress or planned) (L)

Phase I/IIA trials of CCP 20376 under consideration (L)

Phase II trials of ivermectin under consideration (L)

Phase I/IIA trials of CCP 6140 under way (O), under the OCT

Phase II/III trials of ivermectin under way (O), under the OCT

Clinical trials of benzimidazoles (flubendazole) envisaged (O), under the OCT

To conduct studies on pharmacokinetics, toxicology, etc.

To conduct clinical trials of drugs

* Some activities are carried out in collaboration with the Onchocerciasis Chemotherapy Project (OCT) (as noted above in the "Activities" column). For further information on TOR and OCT activities, please write to the Office of the Director of the Special Programme.

** L = Lymphatic filariasis; O = Onchocerciasis

Workplan for Filariasis (cont.)

1 January 1986

<u>OBJECTIVES</u>	<u>PLANS</u>	<u>ACTIVITIES</u>
<p>To improve the use of currently available drugs (L/O*)</p> <p><u>Immunology and Pathology</u></p> <p>To improve immunodiagnostic techniques, especially by the detection of parasite antigens in body fluids, in relation to active infection (L), prepatent infection (L/O), occult filarial syndromes (L) and monitoring of responses to chemotherapy (L/O)</p>	<p>To conduct field trials (L/O)</p> <p>To assess primary health care approach to chemotherapeutic control of lymphatic filariasis (L)</p> <p>To assess the effect of widely-spaced low-dose regimens in controlling disease and in reducing transmission</p> <p>To develop more specific and more sensitive tests, with emphasis on antigen detection and the use of monoclonal antibodies (L/O)</p>	<p>Field trials of ivermectin envisaged (O)</p> <p>Assessment of cost-effectiveness of new DEC regimens for early treatment of acute lesions to prevent development of chronic disease (L)</p> <p>Assessment of widely-spaced low-dose DEC regimens (L)</p> <p>Study of the effect of low-dose sunitin regimens on anterior and posterior segments of the eye in ocular onchocerciasis (O)</p> <p>Studies under way on: selection and testing of the most suitable techniques for detection of antigens and antibodies for differentiation between active and past infection and of different disease spectra (L/O); development of nonisotopic assays for field use (L/O); diagnosis of negatives in lymphatic infection (L); assessment of conversion in children exposed to onchocerciasis (O); definition of conditions under which antigen and antigen/antibody complexes occur in blood and examination of conditions under which antigen becomes detectable (L/O)</p> <p>Comparison and exchange of monoclonal antibodies for use in diagnostic tests and study of characterized patients, with longitudinal follow-up (under way) (L/O)</p> <p>Immunological monitoring during drug trials (under way) (L/O)</p>
<p>To determine the mechanisms of both natural and treatment-induced immunopathology and to identify predictive factors for individuals at risk of developing disease (L/O)</p>	<p>To study the pathology of pulmonary lesions (L)</p> <p>To study ocular pathology (O)</p> <p>To conduct research on the Mazzotti reaction (O)</p>	<p>Required activities to be defined (L)</p> <p>Studies in progress (O)</p> <p>Studies in progress (O)</p>
<p>To study the mechanisms of both natural and treatment-induced immunopathology and to identify predictive factors for individuals at risk of developing disease (L/O)</p>	<p>To conduct research on obstructive lesions of the lymphatic system (L)</p>	<p>Required activities will be identified at the meeting of the Scientific Working Group on Filariasis to be held in November 1985</p>

* L = Lymphatic filariasis; O = Onchocerciasis

Workplan for Filariasis (cont.)

1 January 1986

OBJECTIVES	PLANS	ACTIVITIES
<p>To develop better animal models (L/O)*</p> <p>To assess the possibility of protection by vaccination (L/O)</p>	<p>To develop the models mentioned above under "Chemotherapy" activities (L/O)</p> <p>To establish reliable criteria for measuring protective immune responses in animals and man (L/O)</p> <p>To identify antigens modifying host responses to filariae (L/O)</p>	<p>Development of leaf-mosquito (L) and snail-animal (L/O) models</p> <p>Required activities to be defined (L/O)</p> <p>Required activities to be defined (L/O)</p>
<p><u>Field Research</u></p>	<p>To identify risk factors for microfilaraemia (L) and disease (L/O)</p> <p>To evaluate methods used for assessing control programmes (L/O)</p> <p>To assess (i) risk factors for blindness (O); (ii) annual transmission potential and annual biting rates associated with "tolerable levels of transmission" in different epidemiological settings (O/L)</p> <p>To conduct appropriate longitudinal studies (L/O)</p>	<p>Required activities to be defined (L)</p> <p>Required activities still to be identified (L/O)</p> <p>Studies of risk factors for blindness planned (O)</p> <p>Studies in progress (L)</p>
<p>To determine the predictive value of immunological tests with respect to the development of disease and to the clinical and parasitological responses to therapy (L/O)</p>	<p>To detect and differentiate infective larvae in vectors (L/O)</p>	<p>Research under way using DNA probes to distinguish human from animal parasite species, especially <i>B. malayi</i> (L) and <i>O. volvulus</i> (O), and between forest and savanna forms of <i>O. volvulus</i> (O)</p>
<p>To improve methods of controlling vectors (L/O)</p>	<p>To explore the effectiveness of localized vector-control measures (L/O)</p> <p>To develop methods of trapping vectors for control purposes (L/O)</p>	<p>Studies done or under way (L/O)</p> <p>Required activities still to be identified (L/O)</p>

* L = Lymphatic filariasis; O = Onchocerciasis

CURRENT RESEARCH PRIORITIES OF THE SCIENTIFIC WORKING GROUP ON FILARIASIS
 [Including associated activities of the Onchocerciasis Chemotherapy Project (OCP)]
 (this table amplifies priority activities listed in the current workplan)

1 January 1986

AREA OF RESEARCH	LYMPHATIC FILARIASIS	ONCHOCERCIASIS
<p>CHEMOTHERAPY (Laboratory/hospital/field studies)</p>	<p>Search for and development of new macrofilaricides:</p> <ul style="list-style-type: none"> - Lead-directed chemical synthesis - Filarial biochemistry and metabolism - Screening 	<p>BOX: ASSOCIATED ACTIVITIES OF THE OCT</p> <ul style="list-style-type: none"> - Maintain support of Wellcome and Upjohn research groups and ancillary investigators (synthesis, biochemistry, screening) - Maintain and improve Onchocerca cattle screen - Maintain module supply - Improve in vitro culture and develop small-animal Onchocerca screen
<p>Search for and development of new macrofilaricides:</p>	<ul style="list-style-type: none"> - Maintain and coordinate chemical synthesis - Improve primary and secondary screens - Maintain and improve <u>B. malayi</u> leaf-monkey screen - Develop <u>M. bancrofti</u> leaf-monkey screen 	<ul style="list-style-type: none"> - CCP 6180 (Phase I/IIA) - Ivermectin (Phase III) - Benzimidazoles (Flubendazole) - New schedules of DEC or suramin - Other new drugs as available - Prepare for field trials of ivermectin
<p>- Pharmacokinetics, toxicology, etc.</p>	<ul style="list-style-type: none"> - CCP 20376 (mutagenicity, ADME studies) 	<ul style="list-style-type: none"> - Study effects of low-dose suramin regimens on anterior and posterior segments of the eye in ocular onchocerciasis
<p>- Clinical trials</p>	<ul style="list-style-type: none"> - New schedules of DEC - CCP 20376 (Phase I/IIA) - Ivermectin (Phase II) - Other new drugs as available 	<ul style="list-style-type: none"> - Study effects of low-dose suramin regimens on anterior and posterior segments of the eye in ocular onchocerciasis
<p>Field drug trials</p>	<ul style="list-style-type: none"> - Primary health care approach to chemotherapy control of lymphatic filariasis: trials of new DEC regimens on cost-effective basis: (i) early treatment of acute lesions to prevent development of chronic disease (ii) widely spaced, low-dose regimens to control disease and reduce transmission 	<ul style="list-style-type: none"> - Study effects of low-dose suramin regimens on anterior and posterior segments of the eye in ocular onchocerciasis

2. TECHNICAL REVIEW GROUP I - SEPTEMBER 1976

4. The Selected Diseases

4.6 Filariasis

a) The TRG considered that the proposed filariasis research programme comprised a series of well-balanced practical proposals, covering all important aspects. The proposals are based in the main on specific costed projects to be carried out with existing personnel and laboratories, and would provide additional support to a number of ongoing projects as well as initiating several new lines.

b) The TRG considered that the proposal for priority A was correct with regard to chemotherapeutic research, but that priority A should also be accorded to research on animal models and on in vitro culture as essential supplements and precursors to the chemotherapeutic programme. Additional support should be given towards establishing centres in endemic areas for clinical trials of filaricides.

c) The TRG considered that the overall budget for filariasis was unduly low. Since almost all the funds requested were allocated to specific projects, additional funds should be established to cover other projects which would almost certainly require support in the near future and which would be established on the basis of a Scientific Working Group report.

d) The TRG recognized that the research programme of the Onchocerciasis Control Programme (OCP) was pursuing some of the same goals as the filariasis component of the Special Programme. They recommended that the existing close planning liaison between the two programmes should continue, and that, in general, whenever a division of effort was necessary, the Special Programme accept responsibility for the more basic aspects of the research and the OCP for the more applied aspects. Details of OCP research should regularly be available to the filariasis Scientific Working Group and to the Special Programme's Scientific and Technical Advisory Committee.

5. The Balance of Priorities Between the Six Diseases

Combining the specific disease review with the above considerations, the TRG considered that the budget for filariasis was too low and that for schistosomiasis too high. They should be made more nearly comparable and the Scientific Working Groups on these subjects should develop detailed proposals with this in mind.

2. 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.

4. Recommendations

4.3 Operational Recommendations by Disease and Trans-Disease Components

4.3.3 Filariasis

The Group approved the SWG's plans for research and development.

Coordination between the onchocerciasis (OCP) and the filariasis programmes should be maintained and strengthened. Full use should be made of several OCP-supported centres in West Africa in carrying out field trials on antifilarial drugs. It is recommended that funds allocated to the filariasis programme for 1978 should be approximately 50% greater than those expended and obligated in 1977.

3. TECHNICAL REVIEW GROUP III - AUGUST-SEPTEMBER 1978

3. Progress in 1977-78

3.2 Research and Development

Research on the chemotherapy of onchocerciasis, including basic screening of new chemotherapeutic agents, was stressed. An international network of biological screening procedures was set up to test filaricidal compounds. Relationships between the Special Programme and the Onchocerciasis Control Programme (OCP) were close, and availability of the OCP Clinical Research Centre in Tamale, Ghana, should be of considerable value in expediting the clinical evaluation of new antionchocercal drugs.

A start was made in collaboration with the pharmaceutical industry and academic institutions in the development and testing of drugs for the control of filariasis. 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 by Disease and Trans-Disease Components

4.4.3 Filariasis

Research on the chemotherapy of onchocerciasis should remain the number one priority in the filariasis component. In the immunology subcomponent, development of vaccines, serodiagnostic tests and research on exoantigens should be pursued actively. Emphasis should be placed on development of appropriate animal models, epidemiology and vector control. Applied or field

research should have priority over basic research studies.

The Group noted that almost all research grants funded to date have gone to investigators from developed countries. The Group recommended that the SWG intensify its efforts to identify institutions and scientists involved in filariasis research in affected countries. It pointed to the Workshop Meeting on Methods to be Used in Chemotherapeutic Trials against Onchocerciasis as a useful way to involve and identify such investigators. The balance within the filariasis component, with greatest emphasis on chemotherapy, should be maintained as proposed. Funds provided in 1979 should be increased by approximately 20%, to US\$1 890 000.

As previously noted, the Special Programme has now developed close links with the Onchocerciasis Control Programme (OCP). Additional activity by the Special Programme in the development of chemotherapeutic agents for onchocerciasis would require additional funds. The Group recommended that such funds, if needed, should be sought outside the established funding mechanism of the Special Programme.

4.6 Programme Review and Evaluation

4.6.2 Large projects

The Group noted that the following five large field research projects and their associated budgets were transferred from other WHO programmes to the Special Programme on 1 January 1978.

(The filariasis project was)

	<u>1978 Budget - US\$</u>
- Epidemiology and control of filariasis in relation to urbanization (Tanzania).....	148 000

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

3. Progress in 1978-79

3.2 Research and Development

In the search for new filaricidal drugs, over 1 000 compounds have been screened at primary level, and a promising secondary Onchocerca screen in cattle was developed. Clinical research was conducted to improve the treatment of ocular onchocerciasis, including reduction of adverse side effects of currently available drugs, assessment of new drugs and improved methods of drug administration. The development of in vitro and in vivo culture systems as a source of parasitic antigens received attention.

4. Recommendations

4.2 Research Recommendations by Disease and Trans-Disease Components for 1980

4.2.3 Filariasis

Chemotherapy was considered of the highest priority, and the proportion

of total funds allocated to it should be increased by approximately one-third in 1980. Major emphasis should be placed on screening of new drugs, and the cattle model for onchocerciasis should be further developed and exploited.

The Committee noted that a close relationship with the Onchocerciasis Control Programme resulted in the Tamale Chemotherapeutic Centre (Ghana) being handed over to the Special Programme for clinical trials against onchocerciasis. This should strongly reinforce other trials in progress in Nigeria, Sudan, Togo and Upper Volta.

Investigations should be continued on administration schedules for large-scale treatment of lymphatic filariasis and onchocerciasis, and on methods to prevent or control adverse reactions to treatment.

In the early phase of the filariasis programme, immunological research received a high priority; but, after two years of activity, the Committee considered it advisable to concentrate research activities on those areas where there is the greatest opportunity for progress: the mechanisms and control of tissue damage caused by filariae, and the development of serodiagnostic tests. Vaccine studies should take a lower profile. In consequence, funds recommended for allocation to the immunology/pathology section of the programme should be reduced somewhat.

The recommended budget for work on epidemiology, field research and vectors during 1980 should be reduced to approximately one-half of that for 1979, pending the development of additional high quality research proposals.

It was recommended that the total budget for filariasis in 1980 should remain at the 1979 level.

6. REPORT OF THE SCIENTIFIC WORKING GROUP ON FILARIASIS, 1975-1980

7. Projections for the Future

7.1 Chemotherapy

The search for a non-toxic macrofilaricide effective against O. volvulus will continue to be given top priority as it is the general view of the Steering Committee that perhaps the most pressing need in this disease is for a safe drug which will kill or permanently sterilize the adult worms, without at the same time rapidly destroying the microfilariae, with resultant tissue damage from allergic responses.

The programmes on the chemotherapy of onchocerciasis will also need support from the pathological and immunological side of the programme in order to study the pathogenesis of the lesions caused by death of microfilariae, especially during treatment of the disease, as well as the development of means to control the inflammatory reactions encountered.

For the lymphatic filariases, on the other hand, the better use of DEC for large-scale treatment, and even for chemoprophylaxis, can be of value for

control. A better, and a slower-acting, microfilaricide is needed.

Although at the outset of the programme the main emphasis was placed on onchocerciasis, the Committee has recently been planning to increase its research effort on the lymphatic forms of filariasis. The identification of several chemotherapeutic centres in the South-East Asian and Western Pacific Regions has already been made, following three important Regional meetings on sub-periodic Bancroftian filariasis (WPRO, Western Samoa), on Brugian filariasis (WPRO/SEARO, Kuala Lumpur), and Bancroftian filariasis (SEARO/WPRO, New Delhi), and visits by the SWG Secretary to countries in these Regions. As a result a number of new research proposals have been submitted on these lines, and more are in the pipeline, from institutions in India, Indonesia, Thailand and Malaysia. These will include work on (a) various low-dosage treatment schedules of DEC, (b) DEC-medicated salt studies, (c) chemoprophylactic studies with DEC, and (d) the acceptability and efficacy of mass versus selective sampling and chemotherapy in DEC campaigns.

7.2 Immunological Work

With regard to immunological work, as well as the "inflammatory" studies mentioned above, the Committee feels that antigen development should go on, particularly with the aim of obtaining potent and specific antigens for serodiagnostic tests.

However, the development of a vaccine for man is felt to be a long-odds and expensive shot which will have to await further work on the isolation and characterization of stage-specific antigens, together with evidence that these can excite a protective immunity, which will probably need to be both humoral and cellular. In this connexion, while the prime target would be the infective larvae, consideration should also be given to the apparent role of microfilariae in inducing stage-specific immunity. Although for human use a killed vaccine would seem to be a sine qua non, progress towards a live irradiated Onchocerca vaccine in cattle has been so satisfactory that the Committee feels that this study on the feasibility of a filarial vaccine should be followed to its conclusion.

8. Plan of Action and Budget Projections

8.1 Plan of Action

Chemotherapy

Support for existing screening centres will have to continue with greater emphasis on leads identified so far, e.g. benzimidazoles, avermectins, etc. New leads will be followed by appropriate synthetic chemistry which may have to be stepped up and combined with toxicity studies leading to clinical trials. The results of screening and successes with compounds will necessarily have to be translated to clinical trials in onchocerciasis and the lymphatic filariases.

In lymphatic filariasis, low-dosage trials of intermittent DEC treatment, the effects of DEC treatment on immune responses, the testing of DEC as a chemotherapeutic (causal and clinical), and comparison of the efficacy and acceptability of DEC in mass and selective surveys and treatments are likely to prove invaluable in the better use of DEC.

An increased number of such projects, some of which are already coming in as proposals from India, Malaysia and Indonesia, are expected in the next triennium and will need increased funding.

Immunology

Basic studies will have to be stepped up on exoantigens and surface antigens, which show promise for serodiagnosis and vaccine development, and the greater involvement of hybridoma techniques is expected. The results of vaccination studies now going on with onchocerciasis in cattle will need field trials in developing countries where these infections are common. All these studies will justify the suggested increase in the budget.

Field Research

Increased participation of workers in endemic areas is expected in the next triennium, especially after the three Regional and Bi-Regional Working Group meetings (see 4.4). Thus, a proportionately greater increase of funding of field projects on lymphatic filariasis and onchocerciasis is envisaged to provide information on the epidemiology and vectors of both these infections.

7. REPORT OF THE STRC ON FILARIASIS, 1980

10. Recommendations

10.2 Chemotherapy

10.2.1 The pharmaceutical industry be encouraged to select, develop and perfect promising candidate compounds with backing from the SWG and, in this connection, should accelerate the development of new benzimidazole and amoscanate derivatives for systemic use in filariasis;

10.2.2 The possibility of developing a trans-disease clinical trials centre in Tamale, Ghana, with links with the Liverpool School of Tropical Medicine and the University of Liverpool, be looked at by both the RSG and SWGs, and the OCP be approached at an appropriate time regarding assistance for the proposed trans-disease centre;

10.2.3 The possibility of a trials centre such as the Tamale Centre be considered for lymphatic filariasis in Malaysia, Indonesia or India;

10.2.4 The mode of action of drugs and drug combinations be further studied using better prepared in vitro culture systems;

10.2.5 Top priority be given to developing a compound that will kill or, for a prolonged period of time, sterilize adult Onchocerca volvulus;

10.2.6 Action be taken urgently to determine whether activity found in the majority of experimental screens correlates with that in man;

10.2.7 New knowledge on the prevention of the Mazzotti reaction be confirmed and made known to physicians in endemic areas;

10.3 Immunology

10.3.1 The first priority should be to develop highly sensitive serodiagnostic methods for field use;

10.3.2 Studies on immune complexes be encouraged;

10.3.3 The nature of antigens in immune reactions involved in immunopathological processes in lymphatic filariasis be explored;

10.3.4 Transplantation of adult Onchocerca from animal sources or even from man to laboratory animals be encouraged;

10.3.5 O. dewittei of the pig in Malaysia be investigated further with a view to establishing a laboratory model;

10.3.6 Particular emphasis be laid on assays to detect circulating antigens, with the possibility of detecting antigens in urine;

10.3.7 Studies continue on protective immunization using rodent and other laboratory models, and also on natural models such as bovine Onchocerca;

10.4 Field and Laboratory Research on Epidemiology and Vectors

10.4.1 With the development of more effective drugs and new serodiagnostic tests, detailed information on vector ecology and disease epidemiology is necessary and should be encouraged;

10.4.2 Action be taken urgently to augment the present research on the taxonomy of filariasis vectors, both descriptive and for provision of techniques for field identification.

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

2. Recommendations

2.1 Research and Development

Filariasis

The filariasis SWC has shown good progress and should continue along current lines.

4. Progress in 1979-80

4.2 Research and Development

In filariasis the major emphasis has continued to be on the development of new drugs, and improved methods for the use of existing ones. Over 1 500

compounds have now passed through primary and secondary screens. Encouraging results in chemotherapy have been obtained at Tamale, Ghana.

4.3 Research Capability Strengthening

A computerized listing has been obtained, based on traditional medicine, of over 500 plant products used for treatment of filariasis. This list is available to scientists who operate biological screens for filarial infection, and selected products will be examined.

5. STAC Review and Conclusions

5.1 Scientific and Technical Review Committee (STRC) Reports

5.1.3 Filariasis SWG - The STRC supported the general objectives of the SWG. Good results have been achieved in the treatment trials which were undertaken to establish correlations between animal screening results and effects of the drugs involved in human subjects. An important advance has been the establishment of appropriate screening centres and development of an animal model for onchocerciasis. Although field research has been less successful, there has been excellent cooperation with the pharmaceutical industry. The research is well planned and executed. Consideration should be given to establishing a trans-disease clinical trial centre at Tamale, Ghana. Taxonomic studies on filarial vectors need to be emphasized as part of the epidemiologic aspects of the programme.

STAC concluded that the filariasis programme has shown good progress and should continue along current lines.

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.

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.

3. The need for improved procedures for the diagnosis of all six diseases will remain high during the next five years. Those presently available often lack specificity and precision, are costly, and not readily applicable to field conditions in affected countries.

4. The need to improve the epidemiologic data base for all six diseases will continue to be high. Such information is essential to assess the effects of new control modalities on the incidence, severity and prevalence of the six diseases.

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

2. Recommendations

2.1 Research and Development

Filariasis

a) Financial support should continue at the present level.

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

4.2 Research and Development

4.2.3 Filariasis

In a study at the Tamale Centre in Ghana, it was found that mebendazole was effective in temporarily sterilizing adult onchocercal worms and that mebendazole with levamisole reduced microfilarial density by 88% with no inflammatory reactions. Approximately 3 000 compounds were screened for filaricidal activity; four compounds having activity as microfilaricides and one with macrofilaricidal activity were identified. Significant progress was made in elucidating the pharmacodynamics of diethylcarbamazine (DEC) in man and a chemoprophylactic action of DEC against filarial infection was observed in leaf monkeys. In the field of immunology, emphasis was placed on studies of secreted and surface filarial antigens and the detection of circulating antigens in the host. As recommended by STAC-2, more attention was paid to lymphatic filariasis. (Note by the Secretariat: THIS RECOMMENDATION WAS MADE BY THE STRC, NOT BY STAC)

Recommendations

To maintain the current steady progress towards the achievement of Programme objectives, STAC recommended that financial support should be continued at the present level. If a breakthrough is obtained in the filaricidal screening programme, additional resources may be required on a high priority basis.

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

7.1 Priorities

Subject always to changes in the threat posed by the disease and by the appearance of promising research leads, research on schistosomiasis, filariasis, African trypanosomiasis and Chagas' disease should be maintained at approximately the same resource levels as at present, expressed in 1981 US dollars.

10. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-4) - MARCH-APRIL 1982

4. Progress in 1981-82

4.2 Director's Report

During the last five years, progress in filariasis research has increased to the extent that there is now a valid animal (cattle) test for screening of onchocercal drugs; there are several new promising leads and some ten pharmaceutical companies are now collaborating with the Programme in this area.

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

2. Recommendations

2.1 Research and Development

c) Filariasis

- Investigations on the in vitro cultivation of B. pahangi and B. malayi should be developed further;

- research on the chemotherapy of filariasis should be strengthened to include more work on the development of drugs against lymphatic filariasis, as well as against onchocerciasis;

- close collaboration must be maintained with the newly established onchocerciasis chemotherapy project of the Onchocerciasis Control Programme, and every effort made to maximize use of common programmes of synthesis and screening;

- in this connexion the Chairman of STAC should review on behalf of STAC plans produced during 1983 by the Steering Committee on the Chemotherapy of Onchocerciasis, and the forthcoming STRC in-depth examination of filariasis should include consideration of this activity in its review; and

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

4. Progress in 1982-83

4.2 Director's Report

4.2.3 A major success of the Programme has been the coordination of the activities of scientists in a number of ways:

b) by establishing and supporting networks for screening drugs, e.g. antimalarials, filaricides;

d) by establishing of reference banks of biological agents including monoclonal antibodies;

4.2.5 Advances arising from Programme activities include the following:

f) stimulation of the pharmaceutical industry to collaborate in the evaluation of potential drugs to control diseases such as onchocerciasis.

4.2.7 Among other activities reported were the development of improved diagnostic tests for all diseases in the Special Programme, and the first successful in vitro culturing of Brugia malayi and B. pahangi larvae to the young adult stage.

8. Reports of Progress made by Scientific Working Groups

8.3 Filariasis

8.3.1 Filariasis will be the subject of an STRC review in 1983-84.

8.3.2 The major achievements of the Special Programme to date have been the establishment and support of a screening network for filaricidal drugs and the stimulation of a significant industrial interest in the search for new drugs. Progress in screening was reviewed during the year and several drugs with some potential, especially for onchocerciasis were identified. The screen was improved by the introduction of an in vitro test with Brugia pahangi and the establishment of a third stage screen for B. malayi in Presbytis monkeys in Malaysia.

8.3.3 STAC noted the establishment of an onchocerciasis chemotherapy project within the Onchocerciasis Control Programme to accelerate the development of safe and effective macrofilaricidal drugs. STAC has been requested to participate in the technical review of this project. The SC of the project will meet for the first time in late April 1983. STAC authorized the Chairman to review on their behalf plans produced by the SC during the coming year. The forthcoming STRC in-depth review of filariasis should include consideration of this activity in its review.

8.3.4 In research on immunology of onchocerciasis, important advances have been made especially in relation to monoclonal antibodies, surface antigens and new serological tests. The successful in vitro cultivation of B. malayi and B. pahangi larvae to early adult worms is a considerable stimulus

for studies on lymphatic filariasis. STAC recommended such investigation be developed further.

10. Programme Activities Over the Next Four-Year Period, 1984-87

10.1.9 The research programme on filariasis must be strengthened to include more work on the development of new chemotherapeutic agents against lymphatic filariasis, as well as against onchocerciasis. Close collaboration with the newly established onchocerciasis chemotherapy project of OCP must be maintained, and every effort made to maximize use of common programmes of chemical synthesis and screening facilities.

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 trypanosomiasis, Chagas' disease, filariasis and leishmaniasis should be maintained at approximately the same resource levels as during the 1982-83 biennium.

12. FIFTH ANNUAL REPORT: 1 JULY 1980 - 30 JUNE 1981

3. Research and Development (Excerpt from Summary Overview)

3.4 Filariasis

The Filariasis SWG continues to give priority to the problem of onchocerciasis and is also expanding its work on lymphatic filariasis. With regard to chemotherapy and drug development, the Group aims to improve the use of existing filaricides and to find new ones; it seeks also to find means of reducing the inflammatory reactions that occur in the human host in response to the presence and death of filarial worms. Immunological research is aimed at identifying filarial antigens to be used in serodiagnostic tests, and perhaps for the development of vaccines. The Group is also supporting work on the natural history, epidemiology and vectors of filarial infections with a view to improving methods for controlling their transmission.

During the reporting period, over 3 000 compounds have been tested in various screens. An SWG meeting held during the year provided a useful forum for the scientists involved in screening to exchange information. Compounds which show activity in the primary screens are subjected to further evaluation and the promising ones are put through the cattle screen of infection with Onchocerca gibsoni and O. gutturosa. So far three compounds have shown high macrofilaricidal activity in this screen. Flubendazole suppressed embryogenesis in the cattle screen, more markedly in O. gibsoni than in O. gutturosa, and was found to be more effective when given by injection than by the oral route. New chemical compounds, synthesized around existing leads, are being screened for antifilarial activity.

Microfilarial density was markedly reduced (88% reduction) in patients treated with mebendazole in combination with levamisole. Mebendazole alone or in combination with levamisole has a chemosterilant effect as shown by nodules which were examined after treatment. Studies using radiolabelled

diethylcarbamazine have provided new information about the handling of this drug in the human body. The rate of excretion of the drug is apparently influenced by the pH of urine. Most of the drug is excreted as unchanged drug but 8% is excreted in the urine as DEC-N-oxide. Work has continued on the identification and characterization of antigens for serodiagnosis. Some models have been designed to study the pathogenesis of ocular lesions in onchocerciasis. Some progress has been made with regard to the vectors of both lymphatic filariasis and onchocerciasis, and some epidemiological studies have been funded. An onchocerciasis mathematical model, which gives predictive simulations of control strategies, has been developed.

Chapter 4: Filariasis

1. Objectives

The objectives of the Filariasis SWG remain the same, namely:

- To improve the use of existing filaricides and to find new ones. Here the main needs are:

a) to determine the safest and most practical schedules for the immediate treatment of patients with ocular onchocerciasis who are at high risk of blindness;

b) to find and develop new macrofilaricidal compounds, the most pressing need being for a safe drug which will kill or permanently sterilize the adult worms of *Onchocerca volvulus*, but which does not at the same time cause tissue damage as a result of allergic responses to the rapid destruction of microfilariae; and

c) to determine the most practical dosage schedules for large scale treatment to control the lymphatic filariases.

- To find means of reducing the inflammatory reactions that occur in the human host in response to the presence and death of filarial worms, particularly tissue-dwelling microfilariae; and to identify filarial antigens of sufficient potency and specificity to be used in serodiagnostic tests, and perhaps for the development of preventive vaccines.

- To gain knowledge of the natural history, epidemiology and vectors of filarial infections in man with a view to improving methods for controlling their transmission. Since these problems vary from country to country and region to region, they are more susceptible to a local rather than a global approach. On the other hand, a global overview may be necessary in order to assess priorities when funds are limited.

2. Strategic Plan

The strategic plan remains the same; it has two main lines of activity: the treatment of filariasis, and the prevention of filarial diseases.

13. SIXTH PROGRAMME REPORT: 1 JULY 1981 - 30 JUNE 1982

3. The Six Diseases

3.3 Filariasis

In drug development, further clinical trials with flubendazole and mebendazole, including mebendazole citrate, have confirmed their embryostatic activity in onchocerciasis and lymphatic filariasis and suggested a possible macrofilaricidal effect on the lymphatic parasites. Dosage schedules for the better use of DEC-C and suramin in onchocerciasis and of DEC-C in lymphatic infections have been developed. The prophylactic effect of DEC-C in lymphatic infections has been confirmed in the monkey-B.malayi model and is being tested in humans.

Several new compounds have been synthesized on a lead-directed basis. Some benzimidazole derivatives and some coded compounds provided by Ciba-Geigy appear promising. Three or four of the latter will undergo toxicological and other tests.

More than 50 compounds have shown some activity in the various screens, and 13 of these have been selected for further testing and titration at secondary and tertiary levels.

Ivermectin, which was identified earlier in primary and secondary screens as a microfilaricide and prophylactic, has now been confirmed as a prophylactic in the cattle-Onchocerca screen. It has also been tested (outside the Programme) against O.volvulus in man and found to cause prolonged reduction of microfilariae.

Research and development of new compounds for the therapy of onchocerciasis is conducted in close coordination with the Onchocerciasis Control Programme in the Volta River Basin Area.

In research on immunology and immunopathology, excretory-secretory (ES) and surface antigens are being assessed for use in immunodiagnosis. Monoclonal antibodies have been produced and tests for detection of antibodies and circulating antigens are being developed.

Associations between clinical status and a) levels of T lymphocytes and b) cellular reactions in lymphatic infections have been demonstrated, and a higher percentage of suppressor T lymphocytes has been shown in microfilaraemics than in amicrofilaraemics.

A successful in vitro culture technique for B. malayi and B.pahangi from infective larvae to the young adult stage has paved the way for progress in chemotherapeutic and immunological studies of all filarial parasites.

Research in the field has provided information on population and transmission dynamics of the vectors of onchocerciasis in Congo and Sudan and of the Mansonia vectors of lymphatic infections in Thailand, Indonesia and Malaysia.

14. REPORT OF THE SCIENTIFIC WORKING GROUP ON FILARIASIS, 1980-1983

3. Projected Activities

Projected activities were summarized in the original workplan (pages 3-4).

3.1 Chemotherapy

The search for a non-toxic macrofilaricide for O. volvulus still remains the top priority of the SWG and therefore existing screening activity must continue with greater emphasis on leads identified so far from screening, synthesis and metabolic studies.

At present the benzimidazoles have shown promise in all screens as embryostatic agents and those already available for human use, such as mebendazole and flubendazole, need further follow up with a view to increasing bioavailability, reducing the duration of treatment and, for flubendazole, developing a less painful and more acceptable injectable formulation for use in both onchocerciasis and lymphatic filariasis. Synthesis around the benzimidazole ring as well as replacement of the benzimidazole nucleus with other heterocyclic systems will continue in the hope that more promising compounds will emerge.

The Ciba-Geigy coded compounds that have already been identified and gone through the cattle screen, as well as the promising melanylthioarsenites need more careful investigation with regard to their effects on the parasites and their toxicity. If any of these coded compounds are cleared for human use, Phase I and II trials in man will take place, especially at the OCRC, Tamale, once suitable protocols have been agreed on.

A more pragmatic approach to the biochemical studies and the studies on folate and related metabolism including the enzyme inhibitor studies on suramin and its analogues will be necessary by further identification of possible lead compounds. Further studies on avermectins (Ivermectin) are indicated in view of microfilaricidal effects reported recently in man and chemoprophylactic activity in animal screens.

In all the above activities, it is clear that the Onchocerciasis Chemotherapy Project will play an important role in accelerating development of a macrofilaricide or embryostatic agent.

Some of the above compounds must also go through the tertiary screen for lymphatic infections (Presbytis/B. malayi) before being considered for human trials. In this connection more clinical trial centres for onchocerciasis drug trials will be sought, and one or more such centres for lymphatic infections will need to be identified.

Studies on improving the use of known drugs like suramin for onchocerciasis and DEC-C for lymphatic filariasis will continue. Low dosage administration for the former compound and low dosage schedules, slow release and prophylactic studies for the latter will continue to be funded in the short term until more suitable compounds become available in the longer term.

3.2 Immunology

The progress already made in the identification, characterization and testing of ES and surface antigens must continue until suitable antigens are identified which could not only diagnose "resident" or active infection, but which could distinguish between various categories of the clinical spectrum of disease and even predict disease and clinical courses of infection.

Also foreseen in the next biennium are the development of monoclonal antibodies and DNA hybridization techniques with some sophisticated immunochemical methods for obtaining material for immunodiagnostic tests and improving them and for tests for circulating antigens both in serum and urine. Such tests will eventually have to be modified suitably for application in the field, which is the ultimate aim. A "monoclonal antibody bank" may need to be considered in addition to the "serum bank".

Studies to understand more fully the Mazzotti reaction and the ocular pathology of onchocerciasis will be followed by those for the prevention of adverse effects. Similar investigations in lymphatic infections are needed to overcome the effects of DEC-C which at present is the most satisfactory drug available.

Animal models for O. volvulus and W. bancrofti are still necessary for both chemotherapeutic and immunological purposes and these and some basic studies towards vaccine development will continue but with lower priority.

3.3 Field research

The Steering Committee will encourage field research by eliciting more proposals, by identifying investigators in developing countries and by assisting them in the development of protocols for longitudinal field research studies and case-control studies to assess risk factors for infection and disease. With this in mind workshop meetings, such as the one planned for Madras and for Bamako in 1984, will be held during the next four years.

It will be necessary to identify infective larvae in vectors and to distinguish between larvae of animal and human origin in order to estimate transmission potentials not only in the OCP and other onchocerciasis areas, but also in areas of lymphatic filariasis, especially where Mansonia and other vectors share parasites of human and animal origin. Accordingly DNA probe studies and immunological test systems will need to be encouraged.

15. REPORT OF THE STRC ON FILARIASIS, 1984

Overview

Since the last STRC report in March 1980, significant advances have occurred in the field of filariasis research. Thanks to the sustained efforts of the directorate of the Special Programme, the Secretariat staff and the Steering Committee of the Scientific Working Group (SWG) on filariasis,

several pharmaceutical companies (Ciba-Geigy Ltd, Janssen Pharmaceutica, Merck Sharpe & Dohme, Upjohn Ltd, Wellcome Foundation, etc.) have become interested and now participate actively in the search for new antifilarial drugs. University research institutions and other non-academic bodies have also become involved in this field.

The recent creation of the Onchocerciasis Chemotherapy Project (OCT) by the Onchocerciasis Control Programme (OCP), has brought substantial financial resources to the drug programme and there are now several promising new drugs under study. These have reached the stage of requiring extensive trials on humans, and even more substantial funds will be required in order to hasten the time when such agents could become available as a major tool for control of these diseases. In this regard, the Committee proposes that the STAC consider the possibility of appointing a monitor on a consultant basis, who would co-ordinate and supervise the clinical trials. This would ensure that potentially useful agents are tested with the best possible quality control under a variety of circumstances.

The immunology of filariasis has continued to receive close attention in first-rate immunology laboratories. The search for a simple, effective and cheap sero-diagnostic test continues, and the workshop to be organized in Lille in November 1983 may clarify the present state of the art on this subject. Studies to understand and eventually control the immune reactions that complicate treatment have also been pursued with vigor, but no final solution to this problem appears to have emerged. The development of an effective vaccine against filariasis must await a better understanding of filarial antigens as well as a means to identify and quantitate host-protective immune responses against each stage of filarial parasite infection.

Field research, by comparison to the period up to 1980, has increased significantly. Lymphatic filariasis research, as was recommended, is now receiving more attention, as a result of the increasing use of the SWG of the existing research infra-structure that is available in some of the South-east Asian countries where lymphatic filariasis is endemic. In spite of this relative improvement, there is still a need to increase and to strengthen field research in endemic areas. The Committee is aware of the problems that are peculiar to field research and appreciates efforts that have been made to solve them. Nevertheless, the Committee believes that research objectives in this field need to be better defined, and the RSG support for training in epidemiology and other field research should be considered in concert with the needs in filarial diseases endemic areas.

Major recommendations

In the light of the progress achieved in 1980-83, and the current state of development of research in chemotherapy, immunology and in the field, the following recommendations are made.

- Reaffirming the recommendation of STRC (1980), it is imperative that a clinical trial centre should be established for lymphatic filariasis, preferable in an Asian country where the disease is a serious problem.

- New clinical trial centres for onchocerciasis with good ophthalmological facilities should be established outside the OCP area by

OCT. In order to avoid overwhelming the centres in endemic areas, Phase I trials should be carried out in other facilities, in or close to the target areas, which have clinical pharmacology capabilities.

- Based on the positive experience of the SWG-MALARIA, STRC recommends that a clinical research monitor should be appointed, on a consulting basis, to co-ordinate the current and planned chemotherapy trials for filariasis.

- Linkages should be pursued actively between indigenous and foreign high-technology immunology laboratories and field-level clinical and parasitological staff, especially for longitudinal studies.

- Emphasis should be placed on upgrading the quality of clinical and parasitological information on human patient status and temporal changes so that better correlations can be made with the increasingly sophisticated range of immunological assays which are being applied. The opportunity to undertake such work in parallel with chemotherapy trials should not be overlooked.

- The SWG Filariasis should be encouraged to elaborate a comprehensive field research programme including investigations on such topics as human behavioural factors and health care structures, in concert with other TDR research strategies.

- The SWG Filariasis should maintain closer links with other existing TDR structures, such as TDR/SER/SWG, TDR/EPD/SWG, and RSG, and should seek their active support, in particular for the identification and funding of appropriate field researchers or teams in endemic areas.

- The evaluation of research proposal for support by the FIL/SWG through independent external reviewers must be encouraged whenever possible. Project critiques should have an objective basis and be articulated clearly to ensure that investigators can receive and understand the foundations on which decisions have been made concerning funding or recommended structural changes. This obligation requires a more extended time commitment on the part of the FIL/SC and budgetary adjustments must be made in anticipation of this change.

- The STRC recommends that the FIL/SC in close cooperation with RSG, the Programme for the Prevention of Blindness and possibly OCT and OCP, should identify an existing ophthalmology department of a university or research institution in a country, where onchocerciasis is endemic, which can be strengthened sufficiently to undertake research on ocular onchocerciasis.

- The Steering Committee should be requested to prepare an up to date strategic plan for research on filariasis and establish priorities in accordance with instructions contained in the hand book. STRC recommends systematic reference to and review of this plan in its operational and evaluation processes.

- The STRC recommends that the activities of the SWG on filariasis should continue at least on the level of 1982/83 during the next two biennial periods until 1987 with appropriate budgetary adjustments for inflation. Provisions have to be made for a considerable increase, of probably more than 20% in real terms, for the second biennial 1986/1987 for toxicology studies

and clinical trials for the drugs being investigated at present, if the results justify further development.

- The STRC recommends pursuit of outside funds for the further development of promising drugs, if the necessary funds cannot be provided by TDR. For drugs for onchocerciasis, OCP should be approached. In case other funds are not available from other sources, at least the most promising drug for filariasis should be developed as quickly as possible, even if activities in immunology or field research have to be reduced.

Table 1 - Activities with Filaricidal Compounds Which Found Place Between 1980 and Fall 1983: Type of Activity (Stage of Development), and Table 2 - Flow Chart for Therapeutic Trials in Filariasis are annexed to this document.

16. SCIENTIFIC AND TECHNICAL ADVISORY COMMITTEE (STAC-6) March 1984

1. Summary and Major Conclusions

1.2 Filariasis

- a) It is imperative that a clinical trial centre be established for lymphatic filariasis, preferably in an Asian country where the disease is a serious problem.
- b) New clinical trial centres for onchocerciasis with good ophthalmological facilities should be established outside the Onchocerciasis Control Programme (OCP) area. In order to avoid overloading trial centres in endemic areas, Phase I trials should be carried out at centres other than these.
- c) A clinical monitor should be appointed, on a continuing basis, to coordinate the current and planned chemotherapy trials for filariasis.
- d) An existing ophthalmology department of a university or research institution should be identified in a country where onchocerciasis is endemic. The centre selected should be strengthened to undertake research on ocular onchocerciasis.
- e) Long-term collaborative relationships between basic immunologists and molecular biologists, on the one hand, and clinicians and parasitologists working in the field, on the other should be strengthened further, recognizing that all concerned have unique scientific contributions to make.
- f) Emphasis should be placed on upgrading the quality of clinical and parasitological information on human patients so that better correlations can be made with sensitive and specific immunological assays. The opportunity to undertake such work in parallel with chemotherapy trials should not be overlooked.
- g) The SWG on Filariasis, in collaboration with the SWG on Epidemiology, should be encouraged to develop a field research programme which includes investigations on human behavioural factors, health care structures and integration of multiple approaches to vector control.

The Committee endorsed the research activities of the Onchocerciasis

Chemotherapy Project (OCT). A more detailed examination of these activities will be carried out by a subcommittee of STAC in October 1984.

5. Scientific and Technical Review Committee (STRC) Reviews

5.2 Filariasis

The STRC examined work done in the Programme during the period from January 1980 to June 1983.

Primary, secondary and tertiary SWG-funded drug screens have been established and nearly 7500 compounds have been processed. Appropriate relationships were developed between producers of compounds in industry and academia and screening laboratories. A number of promising compounds have been identified for further toxicological assessment. Ivermectin, a drug marketed for veterinary use, is being tested clinically in collaboration with the manufacturer, Merck, Sharpe and Dohme. It had previously shown promise in drug screens sponsored by the Special Programme. If present small-scale clinical testing of ivermectin shows favourable results, substantial funds will be required for large-scale field tests.

Longitudinal studies were started on the chemoprophylactic effects of diethylcarbamazine on filarial infections.

Technical advances have been made in areas such as the collection and cryopreservation of viable parasite material, the laboratory generation of infective Onchocerca larvae, the in vitro cultivation of filariae, especially Brugia, and the use of surrogate vectors for Onchocerca.

In the area of immunology, projects have focused on the following:

- a) immunological reactions which are responsible for pathological changes during the natural course of infection or as a result of treatment;
- b) detection, identification and isolation of antigens for the production of specific antibody reagents for use in immunodiagnostic assays; and
- c) host protective immune responses to various developmental stages of filarial parasites.

Considerable progress has been made at the Onchocerciasis Chemotherapy Centre in Tamale, Ghana, on the quantitation of clinical reactions to microfilaricides, permitting comparison of different drugs and evaluation of drugs suitable to block adverse reactions.

Substantial progress has been achieved with reference to Simulium taxonomy and bionomics.

STAC accepted the STRC report and, based on its review of the report, made the above recommendations (1.2 page 23).

5.3 Onchocerciasis Chemotherapy Project (OCT)

The Onchocerciasis Chemotherapy Project (OCT) was established by decision of the Joint Programme Committee of the Onchocerciasis Control Programme (OCP) in the Volta River Basin area at its meeting in December 1982. The decision

followed the recommendations in the report of the Onchocerciasis Chemotherapy Working Group. An OCT Steering Committee was set up early in 1983, and a suitable candidate for the post of Secretary has been identified. A plan of action identifying areas of priority and budget proposals for 1984 have been prepared along with projections to 1987.

Three groups of drugs, which emerged from the research of the SWG on Filariasis, are presently being studied in clinical trials. Phase II trials of ivermectin, a possibly long-acting microfilaricide, are under way (see section 5.2 above).

A small Phase II trial on flubendazole in Mexico gave promising therapeutic results, but produced severe local reactions at the injection site. The manufacturer, Janssen Pharmaceutica, is attempting to prepare a more acceptable preparation.

Among a new group of macrofilaricidal compounds produced by Ciba-Geigy, two have been selected for Phase I clinical trials.

The research activities of the OCT were endorsed by STAC. A more detailed examination of the OCT will be carried out by a subcommittee of STAC in October 1984, and the results will be reported to the Joint Programme Committee of the OCP in December 1984. The members of this subcommittee are Drs A.B. Morrison (Chairman), D. Büttner, C. Djerassi and J. Mouchet.

TABLE 1: ACTIVITIES WITH FILARICIDAL COMPOUNDS WHICH FOUND PLACE BETWEEN 1980 AND FALL 1983
TYPE OF ACTIVITY (STAGE OF DEVELOPMENT)

Compound	Indication o = oncho- cerciasis ly = lymphatic filariasis	Experimental trials	Human pharma- cology pharma- cology pharma- cokinetics	Dose-finding trials	Phase III/IV comparative trials + field trials
Suramin	o		pharmacokinetics planned		
DEC-C	o ly		pharmacokinetics + DEC N-oxide	eye damage	field studies, prophylactic use planned
Metrifonate	o		stop: Mazzotti reaction.		
M-citrate (better bioavailability)					
Mebendazole		teratogen in animals	poor bioavailability		
Levamisole + M combinations	o ly			stop	
oral Fibendazole	o	planned toxicology	poor biovai- ability	stop: poor local tolerance	
i.m.	o	with new galenical formulation			
Ivermectin	o ly		planned	in progress	planned trials in other indications including loiasis planned
Amoscanate	o	stop: liver toxicology poor bioavailability			
Ciba-Geigy 6140	o ly		phase I planned	phase II foreseen	
		further test- ing required			
Ciba-Geigy 20376	ly		phase I planned	phase II foreseen	
Ciba-Geigy 24914			stop: toxicity		
Ro 05-9963	o			stop: results not yet assessed	
Furaprimidone	ly	(data not yet assessable)			

TABLE 2: FLOW CHART FOR THERAPEUTIC TRIALS IN FILARIASIS

Drugs resp. compounds	Indication o = oncho- cerciasis ly = lymphatic filariasis	Trials completed				Trials planned			
		1980	1981	1982	1983	1984	1985	1986	1987
Suramin	o	optimal dosage / mode of action / pharmacokinetics							
DEC-C	o ly	phase IV trials phase IV fields trials: control and prophylaxis				standard for comparative trials			
Metrifonate Amodiaquine Furazolidone Nitrofurantoin	o	phase IV adverse effect screening, inactive							
Mebendazole (* Levamisole)	o ly	phase 0 / I and II							
Flubendazole	o					new i.m. formulation			
Ivermectin	o ly					phase I, II, III and field trials			
Amoscanate	o	phase 0 / I							
Ciba-Geigy 6140	o	Toxicology				phase I / II			
Ciba-Geigy 20376	ly	Toxicology				phase I / II			
Ciba-Geigy 24914		Toxicology							
Ro 05-9963	o	phase II							
Furaprimidone	ly					?			

17. SEVENTH PROGRAMME REPORT 1 JANUARY 1983 - 31 DECEMBER 1984

1. Overview

1.2 Filariasis

In collaboration with the Onchocerciasis Chemotherapy Project, TDR has accorded highest priority to the development of new drugs, especially for the treatment of onchocerciasis. Currently available drugs are of limited efficacy: they have unpleasant side-effects and unless used under the careful supervision of an ophthalmologist, may cause permanent eye damage. In collaboration with industry, major advances have been made in the search for safe and effective drugs.

The most promising compound is ivermectin, a drug originally developed by industry for veterinary purposes and now undergoing clinical trials for the treatment of human onchocerciasis. WHO is collaborating with the manufacturer in the evaluation of this compound. Early results are encouraging: a single dose has an apparently strong microfilaricidal effect, and the limited evidence so far available suggests that ivermectin is better tolerated than existing drugs. If preliminary safety and efficacy findings are confirmed, ivermectin would represent a major advance in the treatment of river blindness.

Other anti-onchocerciasis drugs are in the pipeline. One which would kill or permanently sterilize the adult onchocercal worm is still needed. In a study carried out in Mexico (in an institution receiving a TDR long-term support grant), parenteral flubendazole produced a marked, sustained fall in microfilarial counts in onchocerciasis patients, but the injection was painful. The drug is currently being reformulated before being further evaluated in man.

Two experimental compounds, CGP 6140 and CGP 20376, have been found to kill filarial worms in animal experiments. They are now ready to be submitted to Phase I clinical trials: CGP 6140 will first be tested against onchocerciasis and CGP 20376, against lymphatic filariasis.

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

6.2 Filariasis

The Filariasis SWG was reviewed in depth by STAC in 1984. Most of the recommendations have been acted upon, and STAC endorsed the current workplan. Highest priority is being given to improved chemotherapy. A clinical trial centre for lymphatic filariasis has been established at the Tuberculosis Research Centre in Madras, India, and two more centres in endemic areas are planned. A clinical monitor for the coordination of chemotherapy trials has been appointed on a part-time basis.

Clinical trials for the chemotherapy of onchocerciasis have commenced outside the Onchocerciasis Control Programme (OCP) area, but a site for the development of a new clinical trial centre with ophthalmological facilities has not yet been identified.

In collaboration with OCP, a meeting was held in November 1984 in Bamako, Mali, to review the relationship between Onchocerca and Simulium, focusing on links between laboratory and field research. Because uncontrolled forest areas lie next to controlled savanna areas, highest priority was given to the development of methods to distinguish between forest and savanna forms of O.volvulus in man and the Simulium vector. The use of isoenzyme analysis, DNA probes and monoclonal antibody techniques on all stages of the parasite were planned.

Establishment of a serum bank in Basel, Switzerland, will accelerate research on the development of immunodiagnostic tests. Studies have commenced on serum samples from patients participating in drug trials.

A workshop on epidemiological research in lymphatic filariasis was held early in 1984 in Varanasi, India. Protocols for case control studies of risk factors were developed. An international training programme on molecular approaches to research on filariasis and biological control of insect vectors was held in October 1984 in Madurai, India, under the auspices of the BIOS SWG.
