CHEMOTHERAPY
(FOR ONCHO)

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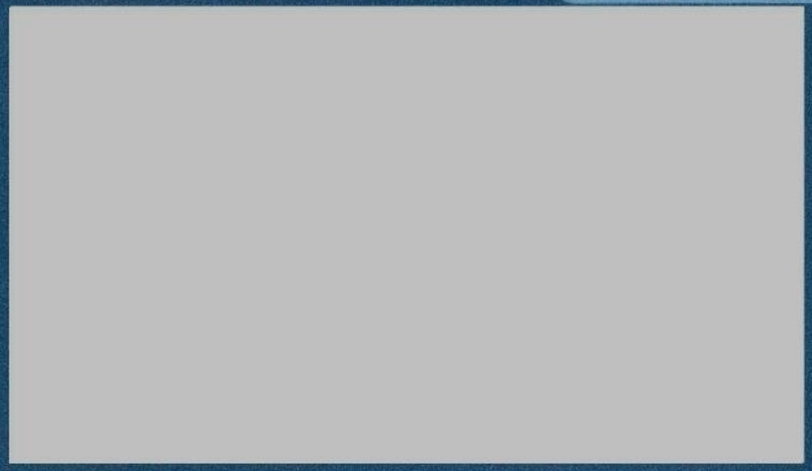

August 1987

REVIEW OF THE ONCHOCERCIASIS CHEMOTHERAPY PROJECT

1. In order to determine the future course that the Onchocerciasis Chemotherapy Project (OCT) should follow after its present funding support comes to an end in 1988, a review has been undertaken by an independent Group established for this purpose.

A. MEMBERSHIP OF THE INDEPENDENT REVIEW GROUP

2. The membership of the Independent Review Group was as follows:

Colonel D. Davidson, Jr. (Chairman)
Walter Reed Army Institute of Research
Washington, D.C., USA

Dr A.B. Morrison
University of Guelph
Guelph, Ontario, Canada

Dr Edward F. Rogers
Middletown, New Jersey, USA
(recently retired from Merck, Sharp & Dohme, USA)

Professor Asbjorn M. Tonjum
University Eye Department
Rikshospitalet, Oslo, Norway

Dr D.H.G. Wegner
Neuried, Federal Republic of Germany
(recently retired from Bayer, Federal Republic of Germany)

B. TERMS OF REFERENCE OF THE INDEPENDENT REVIEW GROUP

3. The Group was given the following terms of reference:

(1) Evaluate the progress and accomplishments of OCT to date and determine how effective OCT has been in following its mandate of developing a macrofilaricide.

(2) Assess whether progress on any compound has reached a level to indicate that an effective drug may be forthcoming in time to be of use to OCP.

(3) In view of ivermectin becoming available in 1987, consider whether a macrofilaricide is

(a) still top priority for OCP for devolution/maintenance;
(b) a useful back-up to ivermectin;
or (c) not necessary.

(4) If OCT is to continue after 1988, indicate the probability of discovering a new drug and the time frame as well as for the research emphasis necessary to ensure most efficient use of funds.

(5) In light of financial constraints facing OCP and other priorities for OCP expenditures, identify the level of financial support and expenditure priorities necessary for OCT to continue on an appropriate pathway following 3 and 4 above until the end of the third financial phase in the first instance.

(6) Determine how OCT will continue in relation to the Special Programme for Research and Training in Tropical Diseases (TDR)'s activities.

(7) Review possibility of alternative funding sources outside OCP.

(8) Submit a report of its recommendations to WHO by end-May 1987 for consideration by EAC.8 and CSA before forwarding, with comments as appropriate, to JPC.8.

C. REPORT OF THE INDEPENDENT REVIEW GROUP

4. Introduction

4.1 The Group established to carry out a review of OCT met in Geneva, Switzerland from 23-26 March, and in London from 1-3 May 1987. Members of the Group also met with participants in the Upjohn - Michigan State University consortium at Kalamazoo, Michigan, USA and with their counterparts in the Wellcome Foundation, Beckenham, Kent, UK in order to assess the contributions of the industrial groups involved in the OCT project. While in Geneva the Group met with the Steering Committee of OCT and received extensive recommendations from it regarding OCT's future. Detailed discussions also were held with staff members of the Onchocerciasis Control Programme (OCP) and with the Director of TDR.

4.2 The Group had before it the guidelines established for OCT by the Onchocerciasis Chemotherapy Project Working Group (OCP/82.4/Rev.2). The objective of OCT is to develop an effective, low-cost and safe drug for treatment of onchocerciasis which would permanently sterilize or kill adult female Onchocerca volvulus, without at the same time causing severe allergic reactions in recipients from microfilaricidal action. Considerable progress has been made in the development of onchocerciasis chemotherapy since OCT was initiated. The Group concluded, however, that available evidence indicates that the objective of OCT still has not been met.

5. Progress and accomplishments of OCT to date

5.1 Overview

5.1.1 OCT is organized and is functioning as recommended by the Onchocerciasis Chemotherapy Project Working Group (OCP/82.4/Rev.2) in 1982. The OCT multidisciplinary steering committee has been composed of experts in relevant disciplines, including parasitology, biochemistry, medicinal chemistry, pharmacology, pharmacokinetics, toxicology, ophthalmology and clinical pharmacology. Although it had been anticipated that OCT would emphasize development of a macrofilaricide, the discovery of ivermectin as a long-acting microfilaricide has, most appropriately, diverted a substantial portion of OCT resources to its development with a corresponding reduction in resources available for development of macrofilaricides.

5.1.2 OCT has recruited participation by chemical and pharmaceutical companies in drug development. Companies have been encouraged to provide chemical samples for testing in model test systems established and supported under OCT and TDR-funded contracts. Candidate compounds also have been solicited from academia, from national and international institutions such as Walter Reed Army Institute of Research and International Organization for Chemical Development, and by funding of research contracts to synthesize compounds based upon biochemical rationale or lead-directed synthesis. OCT should be encouraged to continue to obtain candidate drugs by these mechanisms.

5.1.3 OCT has established and funded multidisciplinary groups in the pharmaceutical industry to pursue macrofilaricidal drug development projects. Two such groups have been established, one at the Wellcome Foundation, UK, and one at the Upjohn Company, USA. Selection of these groups was based upon their historical strengths in parasite chemotherapy, availability of a critical mass of multidisciplinary expertise and other resources, strength of the proposed development strategy and cost. Progress of these industrial efforts is described below.

5.1.4 Progress has been made in the development and utilization of improved animal models for testing potential drugs. Methods for <u>in vitro</u> cultivation of <u>Onchocerca volvulus</u>, including relatively long-term preservation and transport is a major accomplishment of OCT.

5.1.5 Fundamental research supported by OCT to elucidate the biochemistry, molecular biology and other functional characteristics of onchocerca and closely related species of filaria has increased knowledge of biochemical targets which might be exploited chemotherapeutically. Continued support of fundamental research is needed to provide knowledge to guide drug discovery and drug design. Since OCP will "go out of business" by 1997, and in light of the time needed to evaluate drugs in man prior to their release for general use, work on the basic aspects of drug development should be completed by the end of the third Financial Phase of OCP (1991). This would permit OCT to concentrate thereafter on the further development of candidate drugs at the clinical level.

5.1.6 The Group recognized that OCT had proved to be an excellent mechanism for promoting drug development in collaboration with the pharmaceutical industry. A substantial scientific and financial investment would have been made in this activity by 1991 and it was important that the momentum gained by then was not lost. Therefore, the Group recommended that by 1991 alternative means be identified within TDR, with the necessary financial support, to ensure thereafter the continuation of this effort related to the long-term development of drugs against filarial diseases.

6. Progress by industrial collaborators

6.1 Ciba-Geigy, Switzerland

6.1.1 The most advanced of the candidate macrofilaricidal drugs under development has arisen through a collaborative agreement with Ciba-Geigy established by OCT in 1982. The leading candidate in the Ciba-Geigy series is CGP 6140, a compound which was known to have activity against filaria, schistosomes and hookworms. Phase I and Phase IIA clinical evaluations of CGP 6140 have been conducted with OCT support at the Onchocerciasis Chemotherapy Research Centre (OCRC) in Tamale, Ghana, and at the Medical School in Bamako, Mali. No severe side effects were encountered with single or multiple oral dosage regimens to a total dose of 1600 mg. and marked suppression of microfilariae was observed. Effects of CGP 6140 on adult worms currently are being evaluated.

6.1.2 Additional Phase II clinical trials are required with CGP 6140 before its potential value as a macrofilaricide in man can be assessed. High-dose animal subchronic toxicology studies suggest the need for careful monitoring of the safety of this compound in human subjects.

6.2 The Wellcome Foundation, UK

6.2.1 A research group at Wellcome has been funded by OCT since 1982. Early work of this multidisciplinary group identified biochemical targets for drug development. A series of antimycin analogues shows promising macrofilaricidal activity in laboratory studies, although no choice of a clinical candidate can yet be made.

6.2.2 The other Wellcome series under active investigation, the phenylamidines, was derived from a systematic programme of lead-directed synthesis based upon prior knowledge of the action of levamisole on filariae. The lead compound in this series has been selected for the final definitive efficacy evaluation in the cattle onchocerca model. Further support of work on this novel and potentially important series of macrofilaricidal compounds is clearly warranted.

6.2.3 The Group was particularly impressed with the progress of the Wellcome project, with the strength of the biochemical expertise and chemical synthesis effort, and with the cohesiveness of this group. It has been creative and has overcome major obstacles and technical setbacks. Of particular merit is the ability of this group to develop and utilize animal filarial models and in vitro assays which are tailored to the needs of their specialized synthetic effort. Continued support of this productive and well-directed group is encouraged.

6.3 The Upjohn Company, USA

6.3.1 The Upjohn project was established as a multi-institutional consortium in 1985. At the outset the Company identified 45 classes or sub-classes of "active" compounds from their prior programme for evaluation in filarial models. Access to filarial testing models was provided and the series of compounds "of interest" has subsequently declined to 14, and ultimately to 4 or 5. While there appears to be macrofilaricidal activity in at least some of these surviving classes, none of these compounds is considered to be sufficiently effective to warrant optimism. Feedback of screening data has been slow, and reliability of data has been poor at times. This has impaired the strategy of lead-directed synthesis which depends upon responsive feedback of quantitative biological information of good reliability. Upjohn has recently recommended an adjustment of its strategy to place greater reliance on biochemical rationale.

6.3.2 A noteworthy accomplishment of the Upjohn group is the application of a "micromotility meter" as a drug assay system for filarial worms, including onchocerca. The Upjohn group also, in its emphasis on development of in vitro techniques for drug assessment, established field methods which were applied in Sudan, Sierra Leone, Ecuador and Guatemala to measure drug effects against Onchocerca volvulus adult worms freshly isolated from nodules.

6.3.3 It is the opinion of the Group that the Upjohn "consortium" of geographically separated collaborating institutions has not proved to be effective. While constraints of technology are a major factor limiting accomplishment, difficulties in managing this multi-institutional effort are also apparent. This effort should either be extensively restructured or abandoned. Strengths in in vitro model technology are worthy of preservation, and a more highly focussed synthesis-based drug development effort of limited scale is supportable.

7. Clinical Research Centre

7.1 In 1983 OCT assumed responsibility for financial support and technical direction of the OCRC in Tamale, Ghana. As noted previously, work on CGP 6140, the Ciba-Geigy candidate macrofilaricide, has been carried out at this Centre. In addition, Phase II and Phase III clinical trials of ivermectin have been successfully completed at the OCRC. Continuing vector control activities of OCP have made the Tamale site increasingly less useful for the evaluation of macrofilaricides.

7.2 The Group noted with pleasure that the Ghanaian Ministry of Health has agreed to finance the construction of a new OCRC facility at Hohoe in the Volta region of Ghana. Construction is well advanced, including senior staff and nurses' quarters, laboratories, and renovation of a clinical ward. Completion is expected by the summer of 1987. Hohoe is expected to be a suitable location which has good access to patients, and which should be suitable for studies of candidate macrofilaricides.

7.3 In addition to the permanent OCRC in Ghana, an additional Centre in Bamako, Mali (Professor P. Ranque) was used during the development of ivermectin, and more recently for clinical studies of CGP 6140.

7.4 The Group noted that the currently supported clinical research centres may not be sufficient to support future trials of candidate macrofilaricides now beginning to emerge. OCT continues to search for additional centres which have the existing, or potential, resources of expertise, physical facilities, and accessibility to subjects in byperendemic areas. Effective vector control in much of the savanna region precludes siting centres in these areas. It seems most likely that physical facilities and/or staffing of centres in hyperendemic areas will have to be augmented to render them suitable for clinical trials.

8. Mobile clinical team

8.1 The OCT Steering Committee in 1984 funded a consortium of workers from the Johns Hopkins University and the University Hospitals of Cleveland (USA) to operate an ophthalmological and clinical group, with appropriate statistical and logistical back-up, as a "mobile team" which could operate in any area where conditions made it possible to undertake chemotherapeutic studies. The group has been effective in supporting the rapid development of ivermectin, usually being the first to publish results.

8.2 However, the group has so far worked only in Liberia, and the original "mobile" concept thus has not been fulfilled. Additionally, the costs of a base outside the endemic area and in the USA are relatively expensive.

8.3 The Group recognizes the contributions and accomplishments of the mobile team during a time when alternative resources to support clinical trials in the endemic area were extremely limited. Although centres in the region are still limited, some improvement is noted. In accordance with the stated objective of OCP to turn responsibility for control over to the regional governments in 1997, it is imperative that efforts be made to develop centres and strengthen clinical research capacity in Africa. The "mobile team" concept does not further the achievement of that objective, and it should no longer be funded.

9. The role of ivermectin in onchocerciasis control

9.1 Ivermectin, an antibiotic derivative developed by Merck, Sharp & Dohme, USA, for the veterinary market as a wide-spectrum anthelminthic against gastrointestinal nematodes and as an ectoparasiticidal drug, has been demonstrated to have potent and long-lasting microfilaricidal activity against Onchocerca volvulus.

9.2 In tests in more than 2 000 adult onchocerciasis patients, ivermectin administered orally in a single 6-12 mg dose (150-200 µg/kg), reduced skin microfilarial counts to a very low level. There is reason to hope that this dosage, repeated at twelve month intervals, will reduce disease transmission, although the minimum skin microfilarial count required to arrest transmission is not known. Although ivermectin was well tolerated in clinical trials to date, more work is needed to assess its safety. Although there is no evident reason for concern, broader, controlled clinical studies are needed to assess its safety for children, pregnant women, for individuals with intercurrent diseases or poor nutritional status, and those taking other medications.

9.3 There is no clinical evidence to date that ivermectin kills adult worms, nor is it known to permanently sterilize adult female worms. Thus, ivermectin is palliative, and annual administration to infected, and potentially infected individuals, would be required in transmission areas. In areas in which vector density is high, it will very likely be necessary to maintain ivermectin coverage of a very high percentage of the resident population to minimize transmission. It is hoped that the development of blindness associated with onchocerciasis will be substantially retarded by long-term administration of ivermectin. This important potential benefit has been demonstrated in short-term clinical trials, but confirmation over longer periods of several years is required. Since adult female worms are known to survive for twelve years on average, long-term ivermectin treatment will be required to minimize eye damage in infected individuals, unless a macrofilaricidal drug is also used to terminate the infection.

9.4 The long-term suppression of microfilarial counts by ivermectin results from a reversible action on the adult female worm, which is rendered incapable of releasing microfilariae for a prolonged period. Further studies of the long-term administration of ivermectin, including the effects of repeated dosage, are required.

9.5 Community trials of ivermectin are planned by OCP in seven locations within the Programme area beginning in 1987 and 1988. These locations represent a spectrum of transmission situations from areas of no vector control to areas in which vector control is, or has been, effective. Some of these trials may be initiated prior to licensing in France, and will thus represent an extension of Phase III trials. Informed consent, the appropriate level of monitoring, and preparation of regulatory documents are essential. Because of the large size of the population (40 000 to 50 000) involved, compared to only 2 000 patients studied to date, close surveillance of both acute and subacute side-effects must be provided to obtain the safety data needed to support future large-scale use. Strategies to deliver the drug to the target population and to avoid overdosing must be developed.

9.6 The Group concluded that ivermectin shows considerable promise to be an important component of onchocerciasis control. Systematic assessment of the optimal strategy of utilization and a full understanding of the limitations of its utility, must be obtained as quickly as possible.

10. The need for additional drugs in the future

10.1 Macrofilaricides versus microfilaricides

10.1.1 Despite the fortuitous development of ivermectin as a microfilaricidal drug, the Group was of the firm view that there still remains a need for an effective, safe, low-cost macrofilaricide. Because ivermectin has not been shown to be macrofilaricidal, it will require repeated annual administration. The logistical organization and strategy to accomplish such an ambitious long-term programme have not been developed, although proposed community-based trials, if adequately designed and monitored, will provide information to permit definition of the problem. If a macrofilaricide were available to treat infected individuals as they were identified, the cost of maintaining health teams and providing treatment would be reduced substantially.

11. The OCT Steering Committee

11.1 OCT is in transition. As drug products such as ivermectin reach the clinical level of development, links between OCT and OCP will need to be strengthened. Furthermore, OCT must be managed in ways which maximize the likelihood of developing a useful drug, within the time-frame and financial realities involved. This requires that the Steering Committee focus very tightly on the attainment of the objectives of OCT. The Steering Committee must have a high degree of mission-orientation and be composed of individuals with experience in, and strong orientation towards, drug development, including regulatory aspects thereof. At the same time, the Steering Committee must possess necessary expertise in relevant basic and clinical medical sciences. In light of these factors, the Group was of the view that the OCT Steering Committee should include experts in clinical aspects of drug development, preferably with individuals having relevant industrial and regulatory experience. One or more scientists from the endemic area should be included on the Committee. Of perhaps greatest importance, the Steering Committee should be continuously oriented towards the timely achievement of its objective. It must be adamant in recommending funding only for projects which meet its objectives, and must reject proposals, regardless of their general scientific merit, which will not assist materially in moving the work along towards timely achievement of the goal.

12. Relationships between OCT, OCP and TDR

12.1 The Group reiterated the original recommendation that management of OCT must be such that decisions can be taken rapidly, with adequate controls to ensure that funds are expended effectively and efficiently.

12.2 The Group noted that at present OCT is financed by OCP, but acts on the scientific and technical guidance of the Director of TDR. Membership of the Steering Committee overlaps with that of the Steering Committee on Filariasis in order to ensure coordinated action. The Secretary of the OCT Steering Committee is an OCP staff member.

12.3 Although the present management structure of OCT has permitted significant progress to be made, the Group considered it appropriate to re-examine relationships between OCT, OCP and TDR. Now is an opportune time to do so, given the current status of OCP. In essence, OCT sits somewhere in between OCP and TDR, receiving funding from one and technical guidance from the other.

12.4 Furthermore, technical advances in the OCT project increasingly must be considered in the more general framework of OCP. Thus, the role of chemotherapy vis-à-vis vector control in eliminating the threat to public health of onchocerciasis in the OCP area must be considered. Ways to integrate the two operationally in order to provide the most efficient and effective control of the disease, must also be developed. The Group thus considered it essential that OCT be more closely related functionally to OCP. This could best be done by transferring full programme responsibility for OCT to OCP, to go with the already existing financial responsibility which OCP bears for the project. If this were done it would seem advisable to establish a Drug Development and Clinical Evaluation Unit in OCP, with responsibility for drug development, testing and application. Continued close collaboration with TDR would be essential to avoid duplication and ensure the most efficient and effective utilization of expertise and resources.

13. Financial aspects

13.1 Projected annual funding requirements to assure optimal function of the OCT project from 1989 onwards are estimated as follows:

	US $ (000)
- Support of two interdisciplinary groups	1 200
- Basic biochemistry and model development	250
- Chemical synthesis and screening	750
- Pre-clinical toxicology	400
- Phase I and Phase II clinical studies	750
- Secretariat, administration, travel and meetings	250
Total	US $ 3 600

This optimal funding would thus be US $3 600 000 per annum for the 1989-1991 period, or a total for the remainder of the third Financial Phase of US $10 800 000. Many of the Programme costs can be uniformly budgeted on an annual cycle. The funding must be flexible to permit the project management to take full advantage of opportunities to advance specific candidates on a timely basis.

D. RECOMMENDATIONS

(1) Continue funding of the OCT project to the end of the third Financial Phase of the OCP programme (1991).

(2) Transfer full responsibility for the OCT project to OCP, as a Drug Development and Clinical Evaluation Unit within OCP.

(3) Establish a Steering Committee to provide guidance to this unit on drug development and application. The composition of the Steering Committee should include members with expertise in industrial drug development, clinical investigation, field trials, epidemiology and regulatory affairs.

(4) Maintain effective channels of technical communication and co-operation between OCT, TDR and WHO disease control programmes to avoid duplication of effort and to achieve maximum efficiency and effectiveness in use of available resources.

(5) OCT must place its major emphasis on development of a macrofilaricide. Basic research and exploration for new candidate drugs must be phased out by 1991, with subsequent focus on advanced development and clinical evaluation of candidate drugs.

(6) By 1991 alternative means should be identified within TDR, with the necessary financial support, to ensure the continuation thereafter of the basic research effort related to the long-term development of drugs against filarial diseases.

(7) The drug development effort must be sharply focussed and rigorously managed to assure timely accomplishment of objectives within limited constraints of time and funding.

(8) Cooperation and collaboration with the pharmaceutical industry must be maintained.

(9) Terminate support of the Upjohn consortium. Consider continued support of individual projects within the consortium on their own merits. Encourage Upjohn and other pharmaceutical companies to submit focussed project proposals.

(10) Continue efforts to develop improved screening methods to increase the capability to reliably identify candidate drugs for trial in man.

(11) Expand the output of existing animal test systems to keep pace with project objectives.

(12) Expand clinical testing capacities in Africa.

(13) Pending implementation of recommendation number 2, encourage OCP to rapidly complete the clinical assessment of ivermectin to determine its safety and value for use in onchocerciasis control.

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K. REVIEW OF ONCHOCERCIASIS CHEMOTHERAPY PROJECT

The Project Manager, in introducing the subject, highlighted points of particular importance from Document OCP/EAC 11.3 "Report of the Onchocerciasis Chemotherapy Project, with a plan for the continuation of research on a macrofilaricide during the period 1992-1997". EAC commended the Project Manager on the report and its presentation.

At present, only two compounds are under consideration for clinical use as macrofilaricides, and both have potential problems of toxicity such that they might not meet all requirements of efficacy, safety and applicability.

Clinical trials with the first compound, CGP 140, remain in the hands of Ciba Geigy, and full results from a multiple dose treatment are expected by August 1990. Previous OCT trials using a slightly different regimen, encountered unacceptable toxicity, and the drug cannot be recommended for further studies by OCT/OCP until its safety has been clearly demonstrated.

The second compound, CGI 18041, is macrofilaricidal in Ciba Geigy animal studies, and has an acceptable safety pharmacology profile. The company has agreed to procede with preclinical development, and first clincial studies in volunteers are envisaged for July 1991 with patient studies following if Phase I studies are satisfactory.

Other active compounds from various sources are at an early stage of preclinical investigation. Meanwhile, studies on ivermectin, given in combination with another drug - initially albendazoe - are being undertaken at the Onchocerciasis Clinical Research Centre in Hohoe.

The approach followed by OCT in response to CSA recommendations in 1988, has not resulted in the identification of additional macrofilaricides, and the provision of test compounds by the pharmaceutical industry has been poor. In view of the longer term approach recommended by JPC.10, OCT proposes to solicit a limited amount of target-oriented research to facilitate its approaches to industry.

Following the successful operation of the joint Preclinical Drug Development Team (PDDT), OCP and TDR propose to amalgamate their programmes of macrofilaricide development, as recommended by EAC at its last meeting.

The Directors of OCP and TDR tabled a joint proposal outlining the administration of the combined programme, which should greatly enhance efficiency.

EAC commended the proposal of Director OCP and TDR, and recommended that OCP procede with the arrangement. The Project Manager was asked to provide EAC, at its next meeting, with a detailed budget separating the contributions of OCP from those of TDR.

The EAC also agreed, after lengthy discussion, that a limited amount of targeted research was essential within OCT to facilitate the necessary approaches to industry.

EAC reconfirmed its view that the development of a macrofilaricide was essential if the mandate of OCP was to be fulfilled, and expressed its determination to do all it could towards its development.

EAC deferred the question of budget allocation to OCT until the overall plans and budget of OCP for Phase IV were discussed.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

THE MACROFIL CHEMOTHERAPY PROJECT. 1996-99

BACKGROUND

The Independent Commission, reporting in 1981 on the long term prospects for the Onchocerciasis Central Programme in West Africa (OCP) recommended that the Onchocerciasis Chemotherapy Project (OCT) be set up to develop a safe and effective macrofilaricidal drug, which would both help OCP to bring its programme to an end within the allocated 20 year time period, and to maintain disease control thereafter. OCT began operations in 1982, and pursued a multidisciplinary drug discovery and development programme, initially with the collaboration of two multinational pharmaceutical companies (Wellcome and Upjohn). In these early years of OCT, Merck and Co initiated human clinical trials of ivermectin (Mectizan^{R}) as a microfilaricidal drug for onchocerciasis, and in collaboration with OCT, successfully registered Mectizan as a treatment for onchocerciasis in 1987. With a very safe drug available for control of morbidity, mainly in preventing blindness and skin changes, the OCT again turned its full resources towards development of a macrofilaricide to kill the long-lived adult Onchocerca worms (mean lifespan of a female worm is 10-12 years).

The OCT has always been based in Geneva, and has operated in the same way as Steering Committees of the Special Programme for Research and Training in Tropical Diseases (TDR), and scientific work has been under the day-to-day control of Director, TDR, although funding for the project came from the OCP budget. OCT always collaborated closely with the Filariasis Steering Committee of TDR, which also had a drug development component for both onchocerciasis and lymphatic filariasis, and it was suggested that all work on drug development for onchocerciasis should be carried out within one programme. Thus in 1991, OCT became the Macrofil Chemotherapy Project (MACROFIL) and the drug development projects of TDR-FIL were transferred to the new project.

The Fourth Financial Phase of OCP (1992 - 1997) comes to an end in 1997, and a Mid-Term Prospective Evaluation was carried out by the Expert Advisory Committee (EAC) of OCP in June 1994. Macrofil, as a component of OCP, was included in this review, and when the review was discussed by the Joint Programme Committee (JPC) of OCP later in the year, "the Chairman of EAC stressed that a field-applicable macrofilaricide was unlikely to materialize before the end of OCP operations in time to reduce the duration of vector control and that his Committee had therefore recommended the cessation of OCP funding of Macrofil by the end of 1997. Several delegations emphasized in this connection the importance of continuing the search for a field-applicable macrofilaricide beyond 1997."

JPC was informed that "Director, TDR, intended to support continued search for a macrofilaricide to control onchocerciasis and lymphatic filariasis. Proposals would be made in that respect to the TDR Governing Body within a 1996-1999 four-year plan."

Such a 4-year plan was produced by the Macrofil secretariat, and the document was considered during 1995 by both the Scientific and Technical Advisory Committee (STAC) and the Joint Coordinating Board (JCB) of TDR.

"STAC considered that an effective and affordable macrofilaricidal drug would be of potentially great importance in maintaining control in the OCP area after vector control efforts are discontinued and in the expanded African Programme for Onchocerciasis Control in which ivermectin will be employed with minimal vector control. STAC also considered that the availability of a macrofilaricide, in addition to ivermectin, can be expected to be a vital tool in future efforts to reduce morbidity in lymphatic filariasis." "STAC recommends the continued development of a candidate macrofilaricide by TDR after OCP funding is withdrawn. TDR will have to identify sources of new funds to support this activity." JCB endorsed this recommendation in 1995.

At an ad hoc meeting of TDR on "Prospects for eradication of some of the TDR target diseases" (September, 1995), it was suggested that onchocerciasis could be eliminated as a public health problem by the use of ivermectin, and lymphatic filariasis by the use of combinations of diethylcarbamazine, ivermectin and albendazole; in both cases complemented by local vector control, "but not without an investment of new funds for a finite period of time". For a further discussion of this topic, see Appendix I.

CURRENT OBJECTIVES AND WORKPLAN OF MACROFIL

The objectives of the Programme are to discover adulticidal (macrofilaricidal) drugs for onchocerciasis and lymphatic filariasis with the following profile:

- Effective (>70% Kill);
- Safe (for community use with limited medical supervision);
- Acceptable dosing regimen (oral dosing over no more than 3 days, or single intramuscular injection);
- Long shelf life (>2 years at ambient temperatures).

The value to the patient of such drugs would be:

- Permanent removal of the source of pathology (Microfilariae in onchocerciasis; adult worms in lymphatic filariasis);
- Removal of need to take ivermectin continuously.

The value to the community is:

- Control or elimination of transmission; sustaining and consolidating OCP's achievements to date in onchocerciasis control;
- Elimination of needs for, and costs of, continuous ivermectin treatment;
- Reduction in the likelihood of acquired resistance to ivermectin;
- An alternative to larviciding, which is no longer an affordable option;

- Providing a fully effective adulticidal drug to replace diethylcarbamazine in lymphatic filariasis.

Two complementary strategies are being followed to discover new lead molecules:

- Characterization and validation of potential drug targets in filariae, leading to both rational, computer-aided design, and identification of novel ligands by interaction with parasite enzymes/receptors;

- In vivo assays (against B. pahangi and A. viteae in the gerbil) of novel molecules obtained from as wide a range of novel compounds as possible. Two compound screening centres are currently supported for these activities.

Once active molecules are identified, chemical synthesis may be supported when analogues are not available, to optimize promising leads.

Details of how the Macrofil Project is carrying out work to achieve these objectives can be found in the current Macrofil Workplan (July, 1995).

During the period 1995-1997, MACROFIL will primarily pursue the objectives outlined by EAC of OCP, namely to bring to field use, as quickly as possible, the two drugs with identified macrofilaricidal activity, amocarzine and UMF 078, and to study the possibility of resistance to ivermectin in onchocerciasis and how it could be detected at an early stage.

AMOCARZINE - CLINICAL DEVELOPMENT

Ciba Geigy have now terminated all work on amocarzine (CGP 6140), and by formal legal agreement have transferred all documentation relating to the drug, and all available supplies of bulk drug and tabletted material to WHO. All future development of amocarzine will therefore need to be carried out by the Macrofil Project.

Ciba-generated preclinical data indicated that amocarzine could be given safely to patients at a level of 10mg/kg/day. Pregnant females should not be treated. However, existing clinical data from over 2000 patients with amocarzine in Africa and Latin America, showed that above a total dose of 20 mg/kg, reversible central nervous system effects became limiting, and the optimal dose schedule, developed in Ecuador, was 3mg/kg p.p., b.i.d., for 3 days, i.e. a total dose of 18mg/kg. Protocols for future clinical trials in onchocerciasis and lymphatic filariasis using this dose regimen, have been developed at Macrofil sponsored meetings.

The Onchocerciasis Chemotherapy Research Centre in Hohoe, Ghana has almost completed enrollment in a Phase II study in onchocerciasis patients to examine the safety and efficacy of the optimum dosing schedule on a "forest" strain of O. volvulus. In order to separate the adverse effects of the Mazzotti reaction from any intrinsic toxicity of amocarzine, a subgroup of patients has been pretreated with the standard dose of ivermectin (150 μg/kg) one week prior to dosing with amocarzine, to remove macrofilariae.

If reasonable efficacy (70% kill of adult worms) is shown in the trial, (which will be reviewed at the February, 1996, meeting of MACROFIL), then further development will proceed by way of a pivotal, possibly multicentre, Phase III trial during 1996-97. Key issues with amocarzine relate to its efficacy against African strains of onchocerciasis, and its narrow therapeutic index. If all items of safety and efficacy are resolved in the multicentre clinical trials then a registration dossier will be prepared during 1997-98, for submission, and hopefully approval during 1998.

For lymphatic filariasis, where optimal dosing schedules are unknown, a Phase I safety, tolerance and pharmacokinetic study is being carried out in India, prior to Phase II studies against Brugian and Bancroftian filariasis in the same country. The Phase I study will begin soon, and a report could be available early in 1996. Phase II studies in infected patients would begin in early 1996 (dependant upon Indian government approval). Multi-centre trials would then take place during 1997 and the first half of 1998. If good clinical results are available by the end of 1998, preparation of the registration dossier could begin, and a submission made during 1999. Thus the earliest approval of amocarzine use for lymphatic filariasis would be the end of 1999.

UMF 078 - PRECLINICAL DEVELOPMENT

UMF 078, which came from a TDR-Supported programme of research, is a derivative of flubendazole which in animals, unlike the parent compound, is significantly bio-available via the oral route, and is not an irritant when given by the parenteral route. Recent assays have shown that, unlike most benzimidazole carbamates, it is not mutagenic in the Ames test. Work during 1996 will concentrate on preclinical toxicological studies such as the acute toxicity in rats to augment that already obtained from mice, and the muscle irritancy study to allow a final decision to be made on preferred routes of administration. Efficacy and dosing regimens of UMF 078 were worked out in the Brugia/dog model, and thus during 1995, the efficiency against Onchocerca ochengi is being studied in the cattle model.

If all studies have a successful outcome, chronic toxicity studies in rat and dog will be initiated in 1996, and plans made for a Phase I study in man. The earliest date for clinical trials would be late 1996, continuing into 1997. Phase II studies in infected patients (onchocerciasis and lymphatic filariasis) could then take place in 1997 and Phase III in 1998. Analysis of clinical data and assembly of a registration dossier would then take place in 1998 and 1999, giving 2000 as the earliest possible time for approval.

THE POSSIBILITY OF IVERMECTIN RESISTANCE IN ONCHOCERCIASIS

As ivermectin is the only drug currently used for control of onchocerciasis, appearance of resistance would be a major problem both for OCP, and the recently created African Programme for Onchocerciasis Control, which is based on the widespread use of ivermectin.

Ivermectin resistance has already occurred in several gastrointestinal parasitic nematodes in the veterinary field, where ivermectin has been in widespread use since 1981, and in insects. Macrofil was therefore asked by EAC of OCP, to study the mechanism by which nematodes became resistant to ivermectin, and if possible to develop

a diagnostic method by which resistance genes could be identified in Onchocerca before resistance had become a problem in the field.

Initial work has utilized resistant mutants of the free-living nematode Caenorhabditis elegans, and the animal parasite of sheep Haemonchus contortus. Several resistance genes have now been cloned and sequenced from these parasites, and the mechanisms of mutation studied. Genetic studies are now being extended to other parasitic nematodes and to O. volvulus itself. Additionally, support has been given to the Rotterdam group who have developed the robust and predictive model of onchocerciasis in man - ONCHOSIM. Computer simulations over a 50 year time span have been developed to model the spread of dominant or recessive resistance genes through the worm population under various programmes of ivermectin distribution. A MACROFIL-sponsored meeting on ivermectin resistance took place in 1995, to determine the most productive way to continue these investigations, and the recommendations which emerged were brought into action at the September, 1995 meeting of the Macrofil Steering Committee.

DRUG DISCOVERY

MACROFIL, as part of the TDR Product Development Unit, collaborates with the two major chemotherapy programmes (CHEMAL and I-CHEM) via the in-house CHEMCORE group. The same strategy is followed; i.e. potentially lethal molecular targets are identified in parasites, and then the genes for these are cloned and expressed, with the objective of generating a robotic screening assay capable of high-throughput screening of molecules to be done in collaboration with pharmaceutical companies.

Additionally, compounds obtained from pharmaceutical companies and elsewhere are tested in the various in vivo models available to Macrofil:

Primary testing against	B. pahangi and A. viteae in gerbils,
Secondary testing against	B. pahangi in dogs, and
	O. ochengi in cattle.
In vitro testing against	O. volvulus adult worms.

Successful compounds from such assays go on to preclinical development involving scale-up chemistry, assay development, metabolism, toxicology, pharmacokinetics, formulation, etc., as appropriate, in laboratories identified able to carry out such work to international recognized GLP standards. Four such lead compounds have been identified, and are under development.

FINANCIAL SUPPORT FOR MACROFIL 1996-99

Prior to 1991, OCT/MACROFIL was fully funded by OCP, and funds were earmarked for the full cost of the project i.e. salaries of personnel, cost of meetings, duty travel etc were all to be paid from the funds allocated, in addition to the operational costs of the research and development of macrofilaricidal drugs. In 1986, just prior to registration of ivermectin for onchocerciasis, OCT costs peaked to just over US$ 3 million. In the late 1980's with structural changes taking place within the project annual costs fell to about US$ 1.5 million. In the 1990's JPC requested an acceleration

the Fourth financial phase of OCP budgets were planned to peak in 1993-4 and to fall steadily thereafter to the termination of OCT/OCP in 1997.

Since 1991, TDR has contributed to the operations budget at a level of approximately US$ 400,000 per annum. STAC-17 has recommended that this be increased to US$500,000 per annum for the biennium 1996-97. Thus (see Table 1 - MACROFIL PROJECT - FUNDING 1995-99) the total budget of MACROFIL for 1995 is just below US$ 3 million, but will fall to about US$ 2.3 million by 1997. If TDR wishes to continue to operate the Macrofil Chemotherapy Project beyond 1997 at even that minimal level, it will need to meet the total annual costs of $2.2-2.3 million. This allows for approximately $0.5 million per annum for administrative costs, and gives an operational budget of $1.7-1.8 million broken down as indicated in the budget table. Note that TDR funding for MACROFIL during the 1996-97 biennium is set at US$500,000 per annum. To date, TDR has not needed to supply funds for clinical trials of new drugs in lymphatic filariasis, but this year amocarzine will enter into such clinical trials in India and specific funds need to be earmarked for this purpose in the next biennium.

Thus it can be seen that the Macrofil Chemotherapy Project has a balanced programme of work with identified clinical and preclinical candidates, which will carry it to 1999 and beyond. It is therefore hoped that as recommended by participating and donor countries at JPC-15 and JCB-18, TDR can continue to support a programme of macrofilaricide development, for both onchocerciasis and lymphatic filariasis, within its overall chemotherapy programme.

Table 1.

PRODUCT RESEARCH AND DEVELOPMENT MACROFIL PROJECT - FUNDING 1995-99
ANNUAL BUDGET IN US$

OPERATIONS

	1995 OCP	1995 TDR	1996 OCP	1996 TDR	1997 OCP	1997 TDR	1998 TDR	1999 TDR
Clinical	603 500	-	654 925	75 000	485 671	50 000	1 000 000	1 000 000
Preclinical	700 000	18 000	800 000	50 000	550 000	100 000	200 000	300 000
Screening	300 000	150 000	150 000	200 000	100 000	200 000	300 000	300 000
Target Identification IVM resistance	300 000	210 000	100 000	175 000	75 000	150 000	200 000	200 000
Sub-totals	1 903 500	378 000	1 704 925	500 000	1 210 671	500 000	-	-
Total Operations	2 281 500		2 204 925		1,710,671		1 700 000	1 800 000

ADMINISTRATION

Personnel	271 500	-	285 075	-	299 329	-	270 000	280 000
Meetings/Duty Travel etc.	335 000	-	305 000	-	275 000	-	230 000	220 000
Total Administration	606 500	-	590 075	-	574 329	-	500 000	500 000
Total Costs Macrofil	2 888 000		2 795 000		2 285 000		2 200 000	2 300 000

At a recent (September 1995) "Ad hoc meeting on prospects for eradication of some of the TDR target diseases. Modelling the tools and time frame required.", Professor Habbema (Rotterdam) summarized results of computer simulations which examined the "macrofilaricidal" properties of ivermectin, and also of a theoretical macrofilaricide (parameters used were based on data from Suramin and amocarzine).

Originally, when ivermectin was considered to have only microfilaricidal activity, ONCHOSIM modelling predicted that even after 25 years of annual treatment recrudescence would still occur if drug treatment was then stopped (Habbema JDF et al. Parasitology Today 8 99, 1992). Then, when data from a detailed study of 5 years of annual ivermectin treatment in Asubende Ghana, were modelled, it was shown that during a period of about 10 months following each drug treatment, the rate of microfilarial production increased, but at one year post treatment, this rate was still about 35% less than that prior to the last treatment. The most acceptable hypothesis was that all adult females had suffered an irreversible loss in fecundity due to ivermectin treatment. (Plaisier, A.P. et al. Journal of Infectious Diseases 172, 204, 1995).

Taking this finding into account, with relatively low community microfilarial loads (20mf/snip) and 65% coverage of the population, modelling predicted that after 15 years of annual treatment with ivermectin, the risk of recrudescence would be slightly less than 1%. If biannual treatments were to be given, the risk of recrudescence, after even 10 years, was negligible. If the community microfilarial loads were higher (60mf/snip), then the risk of recrudescence is high even after 20 years of annual ivermectin treatments.

Professor Habbema also presented previously unpublished simulations comparing biannual ivermectin treatments with a hypothetical macrofilaricide at high community microfilarial levels (70mf/snip). These simulations (see Fig. 1) indicate that if drug coverage is maintained at the levels possible with ivermectin, i.e., 65%, even a relatively ineffective macrofilaricidal drug (60% or 75% adulticidal activity) would reduce the risk of recrudescence to less than 1% within a 5 to 10-year period, while ivermectin would require 10 - 20 years of treatment. Fig. 2 demonstrates that a macrofilaricide with 75% efficacy could control the parasite population in five years if given twice a year.

One important factor which could greatly influence the success of drug treatment when coverage is incomplete is systematic non-compliance of certain persons requiring treatment, rather than assuming random non-compliance, and the former situation is shown in Fig. 3. Five years of treatment with a macrofilaricide showing unacceptable adverse effects could then result in treatment failure due to systematic non-compliance. Treatment with amocarzine, requiring 3 days of dosing, and showing mild CNS effects, could give such non-compliance. If this proved a problem, one could reduce microfilarial loads in such patients by switching to treatment with ivermectin.

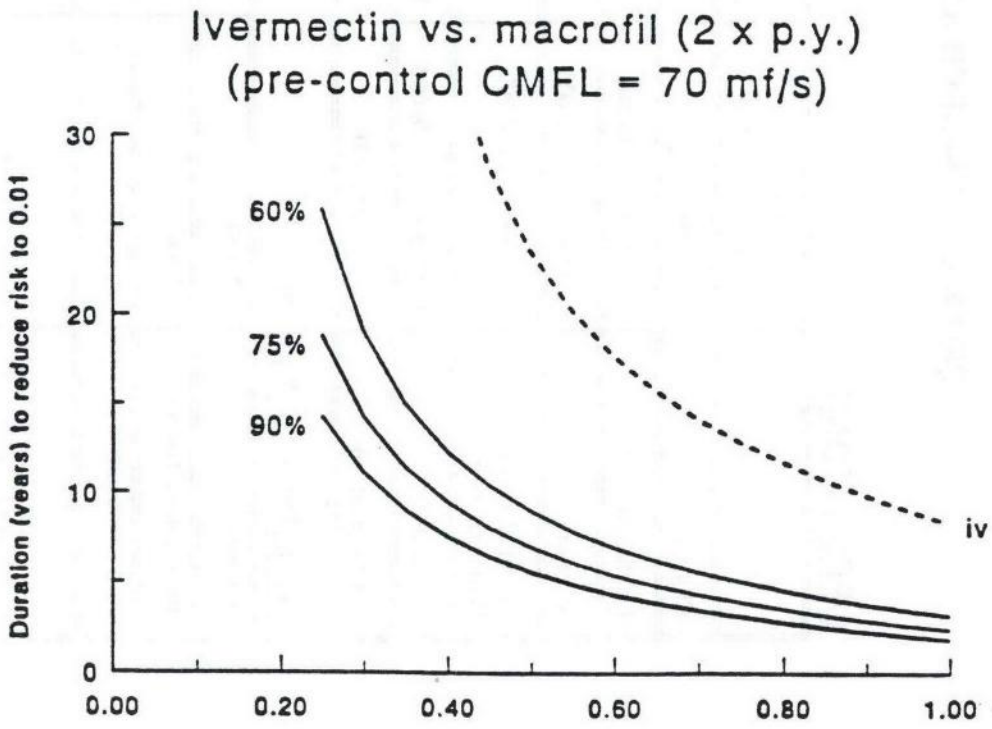


Figure 1.

Figure 2.

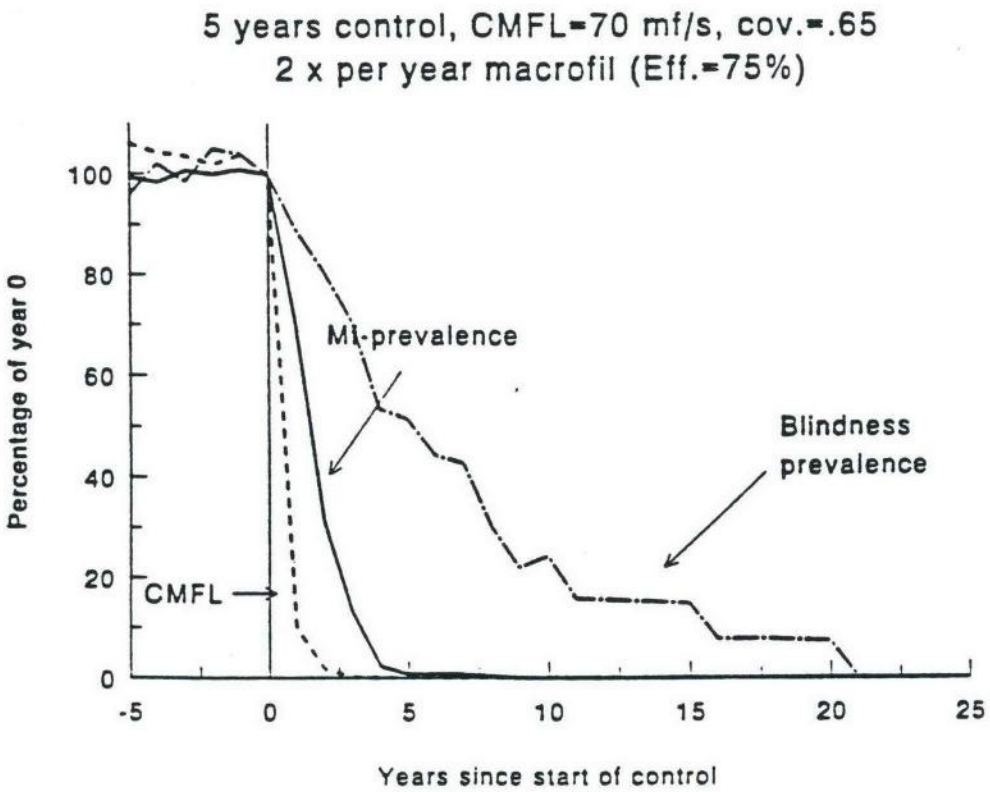
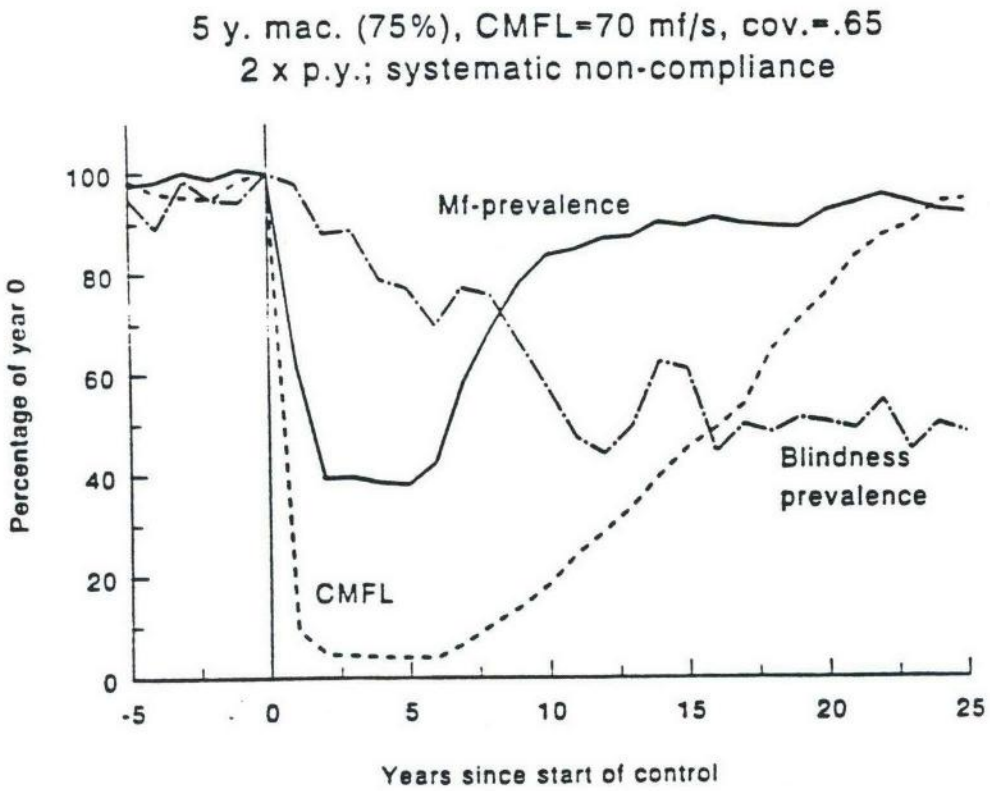


Figure 3.



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PROGRESS REPORT OF THE ONCHOCERCIASIS CHEMOTHERAPY PROJECT (OCT) FOR 1990

1. Introduction

1990 has been a year of consolidation and reorientation, rather than dramatic advance. CGI 18041 remains the most promising compound in preclinical development and a 10 kg batch of characterized material is expected at the end of the year, which will allow Ciba-Geigy to initiate preclinical toxicological studies. Additional efficacy studies of CGI 18041 in animal models will then be carried out by OCT investigators. Results of these studies should be available by the middle of 1991, when clinical trials in volunteers could be initiated.

While awaiting the initiation of clinical studies with CGI 18041 full use must be made of CGP 6140. Although having a narrow therapeutic index, and hence unsuitable for community therapy, preliminary reports from clinical trials in Latin America suggest that this compound does have macrofilaricidal activity when given as six oral doses over a three-day period. It may therefore have potential use by OCP as a control tool for disease recrudescence in localized foci.

Another promising lead, for which a preclinical development plan is being prepared, is the benzimidazole UMF 078 from the University of Michigan. In animals this compound is active only by intramuscular injection, and formulation studies by a commercial company may well be required to allow clinical trials to be initiated.

Legal agreements have now been signed, or are in the final stages of negotiation, with several international pharmaceutical companies, and increasing numbers of test compounds are entering the primary screening assays. However, in addition to such lead-directed work, OCT has been encouraged by the Expert Advisory Committee (EAC) to reinitiate some basic research work directed to the identification and exploitation of novel biochemical targets in filarial parasites.

The various committees governing OCP and the Special Programme for Research and Training in Tropical Diseases (TDR) activities have also agreed with the recommendations of the Directors of OCP and TDR, that OCT and the chemotherapy component of TDR-Filariasis (FIL) should be amalgamated to form a new programme "MACROFIL", devoted solely to the discovery and development of macrofilaricides for both onchocerciasis and lymphatic filariasis. Such a programme would be funded and managed jointly by OCP and TDR.

PART 1
CURRENT STATUS OF MACROFILARICIDE DEVELOPMENT

2. Compounds from Ciba-Geigy

2.1 CGP 6140. At the JPC meeting in 1989, it was reported that histopathological data were awaited from Ciba-Geigy relating to the macrofilaricidal effects of drug treatments with CGP 6140, carried out in the OCT-funded centres in Mali and Ghana. Interim reports made available from Ciba-Geigy relating to its own trials of CGP 6140 in Latin America indicate that multidose schedules of CGP 6140 (3 mg/kg twice a day on three consecutive days) kill 70-75% of adult female worms. While this dosing schedule, coupled with the low therapeutic ratio of the drug, make it unacceptable for routine community therapy, there is a possible role for the drug in control of disease recrudescence in isolated foci within OCP, and discussions with the company regarding further trials of this compound in West Africa have been initiated.

2.2 CGI 18041. The most promising new compound from Ciba-Geigy at present is the benzothiazole derivative, CGI 18041. Although related chemically to both the earlier compounds, CGP 6140 and CGP 20376, it is a more lipophilic compound with very different pharmacological properties to these latter compounds, and also does not give the same high levels of the potentially toxic isothiocyanate derivative. CGI 18041 has shown macrofilaricidal activity against Brugia malayi in the leaf monkey using single oral doses of 25 or 50 mg/kg. Some safety pharmacology for the compound has already been carried out by Hindustan Ciba-Geigy Limited (India), giving results which encourage further development. Accordingly, a clinical programme outline for CGI 18041 has been developed by OCT and Ciba-Geigy, Switzerland. The company has agreed to carry out all preclinical development work to allow the compound to enter Phase I trials in man, and is currently synthesizing 10 kg of compound to allow toxicological testing and the planned clinical trials. This material will be available by the end of 1990, and will then be used for toxicological testing. Reports of that testing should be available by the second half of 1991. If results are favourable, the compound will then be tested first in uninfected volunteers and then in lightly-infected onchocerciasis and lymphatic filariasis patients in the second half of 1991. Protocols for each of these clinical trials have been prepared. Further efficacy testing in secondary and tertiary screening models, including Onchocerca gibsoni in cattle, will be carried out when pure CGI 18041 is made available and these results should be available by the time the preclinical toxicology is completed.

2.3 "Back-up" benzothiazoles and benzoxazoles. Two compounds, CGP 20309 and 21833, related to CGP 6140 show good activity as macrofilaricides against O. gibsoni in cattle, and OCT requested Ciba-Geigy to carry out preliminary toxicological studies to allow consideration of the therapeutic index for each compound. These compounds will therefore be considered for toxicology, but with a low priority until more is known regarding CGI 18041. Both compounds may be made available for further secondary evaluations of antifilarial activity in the dog and leaf monkey models, and these activities will continue during 1991.

Development of analytical methodology for pharmacokinetic and metabolic studies of these Ciba-Geigy compounds in man and experimental animals is being carried out at the Universiti Sains Malaysia, Penang, Malaysia, with financial support from TDR/FIL.

OCT and TDR/FIL have concluded an agreement with Ciba-Geigy by which the company will supply compounds of current interest for testing in all diseases of interest to TDR. If antifilarial activity worthy of further development is discovered then Ciba-Geigy will carry out all non-clinical work required to allow trials to be initiated on company compounds. All efficacy testing and clinical trials will be carried out by WHO, and at the Organization's expense. Ciba-Geigy has recently introduced a "Risk Fund" within the company, from which finance is available to use in those projects which for economic or scientific reasons carry a greater degree of risk than usual, and funding has been made available from this Fund for collaborative work with OCT on development of macrofilaricides. Such an agreement makes best use of the complementary expertise of TDR/OCT and industry, and may be possible with other companies, although each collaboration with industry usually needs a different agreement.

3. Repeated standard doses of ivermectin, given at short time intervals

In the previous report to JPC10, a clinical study was noted from Liberia in which 30 onchocerciasis patients had been treated on six occasions with 150 ug/kg ivermectin, given orally at two-weekly intervals. Examination has now been completed of nodules removed from these patients four months after treatment, together with 30 control patients. Results indicated that there was no statistically significant increase in numbers of dead adult female worms in ivermectin-treated patients, even though there had obviously been a reversible inhibitory effect on microfilarial release and embryogenesis within the female. Thus, multiple ivermectin treatments are not clearly macrofilaricidal, although the examining laboratory (US Armed Forces Institute of Pathology, Washington, D.C.) did report slightly more dead worms in the ivermectin-treated patients, together with a reduction in the numbers of male worms found in the nodules. Thus, a slight effect on worm viability, behaviour and fecundity may be occurring with repeated ivermectin treatments.

4. Combination therapy: albendazole preceded by ivermectin

Previous clinical trials have shown that (a) ivermectin treatment can inhibit the release of microfilariae from the female worm uterus, and (b) benzimidazoles, e.g. mebendazole, can inhibit embryogenesis in O. volvulus females.

A clinical trial has been initiated at the Onchocerciasis Chemotherapy Research Centre (OCRC) in Hohoe, Ghana, in which a high, but clinically tolerated, dose of albendazole (the best absorbed of the benzimidazole drugs) will be given to patients one week after a standard oral dose (150 ug/kg) of ivermectin. It is hoped that these two drugs, both acting on the female reproductive system but by different mechanisms, might combine to give a macrofilaricidal or permanently sterilizing effect on the female worms.

Increasing, multiple-dose regimens of albendazole given alone have already been tested to find a clinically tolerated dose, giving maximum effect on female worm reproduction, which will then be used in the combination study with ivermectin. Doses already given (800 mg per day for three days, 1200 mg per day for three days and 800 mg per day for seven days) have produced severe disturbance of embryogenesis in female worms removed from patients 30 and 90 days post-treatment, without any severe adverse effects in the treated patients.

5. Suramin treatment: improvements in evaluation of macrofilaricidal action

Suramin is the only macrofilaricide recommended for treatment of onchocerciasis, and its use demands careful monitoring of clinical effects in a hospital environment. In a current trial conducted at the OCRC, 20 onchocerciasis patients have been treated with the standard multidose, intravenous regimen of suramin. The state of palpable nodules has been monitored by ultrasonic scanning and these nodules will be removed at intervals throughout the next year for histopathological examination. Simultaneously, blood and urine samples have been taken, to be stored in the TDR/FIL Serum Bank, and tested for antigen and/or antibody changes following therapy. Related experiments are planned in the O. gibsoni/O. gutturosa cattle model to allow sera and urine samples to be collected from known macro- and microfilaricidal drugs.

It is hoped that such physical or immunological parameters will allow quantitation of worm damage within the nodule, complementary to the time-consuming histopathological technique. Successful methodology will then be applied to evaluation of macrofilaricidal activity of experimental drugs.

6. Compounds under development as potential macrofilaricides

6.1 Benzimidazole and thiophanate analogues (University of Michigan, USA). Benzimidazoles generally show good macrofilaricidal activity in animal screening models, and partial activity has been demonstrated against O. volvulus in man by mebendazole and flubendazole. TDR/FIL has for several years supported a chemistry programme to synthesize analogues with either better bioavailability by the oral route, or providing a painless and efficient parenteral formulation. The most promising of these novel benzimidazoles (UMF 058, UMF 078 and UMF 173), and thiophanate-like prodrugs of benzimidazoles (UMF 135 and UMF 359), from primary screening in the rodent, have been resynthesized in sufficient amounts to allow secondary and tertiary screening against Brugia spp. in the dog, cat and leaf monkey, and to allow in vitro testing against Onchocerca species. Mebendazole and flubendazole were used as positive controls for comparative purposes.

Encouraging results from the University of Michigan series were seen against O. gutturosa adult worms either in vitro, or when implanted into mice within micropore chambers. In the latter system, UMF 359 given subcutaneously at 100 mg/kg/day x 5 days completely inhibited worm motility when assayed six weeks after drug treatment, while UMF 135 gave 72% inhibition. However, these non-motile worms still showed "viability" as measured by the dye-reduction assay.

Against B. pahangi in the dog, using subcutaneous dosing at 50 mg/kg/day x 3 days, flubendazole showed 88% efficacy as a macrofilaricide, with UMF 078 giving 76% macrofilaricidal activity. UMF 173 was apparently toxic and other benzimidazoles/thiophanates were much less effective. However, in the most recent series of experiments in the dog, UMF 078, given intramuscularly as a suspension in peanut oil, gave complete clearance of adult B. pahangi worms, and little tissue reaction was seen at the injection site.

Resynthesis of larger amounts of UMF 078 will be initiated to allow further testing in the dog, and also in the O. gibsoni cattle model. A development plan for this compound has been drawn up by the OCT/TDR-FIL Preclinical Drug Development Team (PDDT). For intramuscular injection in man, formulation studies will need to be carried out at an early stage, probably using a commercial company.

Drug assays for the University of Michigan compounds are under development at the Universiti Sains Malaysia (funded by TDR/FIL) and will permit drug and metabolite levels to be determined in the body fluids of treated animals, and give quantitative data on drug bioavailability and metabolism. Sufficient data should then be available to allow a final decision on termination or continuation of studies on this compound.

6.2 Walter Reed Army Institute of Research (WRAIR). Compounds continue to be selected and tested, based on previous activity in primary antifilarial screening. Activity, worthy of follow-up, has been detected both in primary rodent screens and against O. gutturosa adult worms in vitro. Some structures of active leads are unknown, but will be further developed if structures can be disclosed. Representatives of WRAIR will attend a PDDT meeting in the USA in November 1990.

6.3 Parke-Davis guanidines. Three guanidine compounds, originally shown to have in vivo macrofilaricidal activity against Litomosoides carinii, have shown good activity (65-90% inhibition) against O. volvulus adults in vitro when tested at 10 uM concentration. Retesting at 1 uM resulted in considerably reduced activity (14-40% inhibition), whereas the standard arsenical compound Mel W still showed good activity at this lower concentration. Compounds in this series are as active as CGP 6140 when tested in vitro against O. gutturosa adults, and additional analogues are being obtained for further testing, as activity against Onchocerca adults seems particularly good. Resynthesis of the original leads has been carried out to allow extended animal testing, and mode-of-action studies will be initiated.

An agreement with the parent company (Warner-Lambert) to allow access to other compounds is in the hands of the WHO Legal Counsel.

7. Summary: prospects for a usable macrofilaricide in the near future

If CGI 18041 passes successfully through the preclinical stages, volunteer testing may begin in 1991 and quickly proceed to trials in onchocerciasis patients, which will begin to provide clinical data in 1992. If its therapeutic index is superior to earlier Ciba-Geigy compounds, then clinical studies with increasing patient numbers could proceed. Related compounds, CGP 20309 and 21833, will continue development as "back-up" compounds. Meanwhile, limited use will be made of the only available modern macrofilaricide, CGP 6140, in areas where sophisticated medical care can be provided.

All other compounds are at a very early stage of development, i.e. prior to successful secondary testing in the B. pahangi/dog model, or against O. gibsoni in cattle, and neither preclinical development nor clinical trials can be predicted for such compounds at the present time.

PART 2

THE EXPERIENCES OF OCT AND TDR IN DRUG RESEARCH AND DEVELOPMENT: LESSONS LEARNED AND PLANS FOR THE FUTURE

8. Collaboration with the pharmaceutical industry

OCT now has in place a scientific and administrative structure which can take novel chemical compounds at any stage of development and test them efficiently, albeit with biological assays which are not fully predictive of macrofilaricidal activity in human onchocerciasis. Past experience has shown that drug development in collaboration with large pharmaceutical companies can be successful, e.g. Merck Sharp & Dohme, Ciba-Geigy, Wellcome. However, in the future OCT must become more

self sufficient in the drug development process. The pharmaceutical industry is currently rationalizing its own structure, with company mergers creating a few extremely large companies, capable of providing the high investment (about $100 million) for production of a single new drug. Such companies are unwilling to invest valuable resources in initiating research into tropical medicine where economic returns are poor, but they do seem willing to carry out specific work related to development of drugs for parasitic diseases, if it is in some way related to their own interests.

To allow OCT to engage in such an interactive dialogue with the pharmaceutical industry it is necessary to have as much specific knowledge as possible about the chemotherapeutic targets within the parasite of interest, in this case the adult filarial worm. The present "package" which OCT gives to a potential industrial collaborator, includes the screening pathways used to detect macrofilaricidal activity, the minimum weight of compound required in each biological assay, and most importantly the types of compounds requested for screening. These are made up of several types: (i) analogues of chemical structures known to show antifilarial activity; (ii) specific drug targets (enzymes, receptors, etc.) known to exist in filarial worms; and (iii) compounds of novel structure with biological activity in other areas, e.g. antitumour, insecticides.

Chemotherapeutic studies on specific drug targets in filarial worms was the subject of a paper presented by the OCT Project Manager at the Onchocerciasis-Now! Symposium in 1989. While such information on filarial biochemistry may appear spontaneously in the scientific literature, the only way to obtain information directly in the area of potential chemotherapeutic interest is to sponsor research focused on that target. In order to obtain compounds of interest from the pharmaceutical industry and elsewhere, there is a need to maintain some interest in fundamental research to generate information on novel chemotherapeutic targets, and to study the mode of action of active lead compounds, and such work is included in the proposal for funding in the next financial phase. This proposal was discussed at the EAC meeting in June 1990, and generally encouraged by the Committee.

9. Scientific Working Group: identification of novel drug targets

It is planned that a joint Scientific Working Group of TDR/FIL and OCT meet in 1991 to generate information on biological targets in filarial worms, and particularly to introduce new areas for which potential inhibitors can be solicited from industry, with invitations extended to workers outside the parasitology area, as well as experts in filarial biochemistry. Recent advances in molecular biology and genetic engineering have allowed chemotherapeutic target enzymes and receptors to be cloned from parasites and expressed in heterologous systems in an active form, in hitherto unavailable quantities. These techniques allow detailed *in vitro* studies of the interaction of target molecules and inhibitors, and have the potential to be adapted as routine high throughput screens for novel inhibitors, which could be run in academic or contract laboratories under OCT sponsorship.

10. Legal agreements with industry

During the past two years the OCT Project Manager, with the WHO Legal Counsel, has drawn up many collaborative agreements to cover drug development with pharmaceutical companies. Legal agreements used by other groups attempting drug development outside the pharmaceutical industry, e.g. WRAIR, National Cancer Institute, have been obtained for comparison, and the general problems discussed with both individual companies and the International Federation of Pharmaceutical Manufacturers. In general, if WHO tries to insist on ongoing commitment by a company at too early a stage then the company does not wish to become involved in

collaborative agreements. The best which one can achieve is a simple confidentiality agreement to allow initial testing of compounds, with a commitment to talk again "in good faith" on development once good antiparasitic activity has been indicated.

Agreements have either been completed or are in the process of negotiation with the following companies: Merck Sharp & Dohme, Glaxo, Rhône-Poulenc, Merrell-Dow, Wellcome and Warner-Lambert.

If a very promising lead is identified from an academic or non-company source, whose chances of success seem high, then collaboration with the pharmaceutical industry would be sought for a coordinated approach to its further development.

PART 3

RESPONSE OF OCT TO RECOMMENDATIONS FROM JPC10 AND EAC11 ON ITS FUTURE OBJECTIVES

11. Recommendations of EAC10 and JPC10

EAC at its meeting in June 1989 included the following recommendations after discussions on OCT:

- while noting that funding for OCT had been approved by the JPC until 1991, the Committee emphasized that the search for a macrofilaricide must be continued beyond that date, as its delivery even by the year 2010 would still be in time to deal with recrudescence of the disease within the Programme area; and

- in principle, the Committee was strongly in favour of the further integration of OCT into the TDR structure, and therefore requested that the Programme, in collaboration with TDR and Project Manager OCT, should prepare a plan for the continuation of research on macrofilaricides, for presentation to its eleventh session in 1990.

JPC10 agreed that high priority must be given to developing an operationally convenient macrofilaricide and there was a need to continue the search beyond the previously specified date of 1991, since even after termination of the Programme a proven macrofilaricide would still be needed to deal with any recrudescence of onchocerciasis. As requested by EAC and JPC, OCT submitted a scientific plan for macrofilaricide discovery and development to EAC at its eleventh session in June 1990, together with suggestions for financial support.

12. Future scientific programme, financing and administration of OCT in the next financial phase, 1992-1997

12.1 Research programme. The primary objective for OCT in the immediate future will be the development of the Ciba-Geigy compound CGI 18041 as a potential macrofilaricide for both onchocerciasis and lymphatic filariasis, and to carry out Phase I-III clinical trials on this compound as soon as possible.

The known macrofilaricidal properties of CGP 6140 will continue to be monitored for its potential in the control of disease recrudescence, and its possible combination with ivermectin. Similarly, other drug combinations with ivermectin will continue to be studied at the clinical level. *In vitro* studies, using adult *O. gutturosa*, indicate that the action of several drugs is cumulative with ivermectin but not synergistic. However, even the effect of removing microfilariae

with a minimal Mazzotti reaction, prior to treatment with a macrofilaricide, may make combinations with ivermectin a more acceptable treatment for onchocerciasis than use of the macrofilaricide alone.

Studies on the efficacy and safety of Ciba-Geigy compounds CGP 20309 and 21833 will continue, to allow for their continuing development if CGI 18041 fails at any stage of its development, and development of UMF 078 will proceed at the preclinical level. Beyond these identified leads, compounds will continue to be evaluated in primary, secondary and tertiary screening systems to identify candidates for preclinical development. The flubendazole analogue UMF 078 may be suitable for development, but only as an intramuscular formulation.

The difficulties of interpretation and time-consuming nature of histopathological studies to confirm macrofilaricidal activity following experimental chemotherapy in man and animals make it essential that alternative methods for assessing death of adult filarial worms be developed. The most convenient of these would seem to be the use of immunological techniques on patient body fluids, or biochemical assays of worm viability following drug treatment. TDR/FIL is pursuing this objective as part of its immunological development programme.

Although not available on a routine basis in endemic areas, there are more sophisticated approaches to the evaluation of worm death, which may be applicable at key points in drug development. Some of these are non-invasive, e.g. ultrasonography, Nuclear Magnetic Resonance (NMR) or methods needing only minor clinical procedures, e.g. lymphoscintography or videoscopy. OCT will stimulate research in these areas and make available suitable biological materials from treated animals and man to allow evaluation of alternative methods.

EAC has indicated the importance of development of an assay to monitor the sensitivity of O. volvulus to ivermectin which would allow early detection of ivermectin resistance, if and when it appears in treated patients. Projects already funded have taken a direct approach in which microfilariae are incubated in vitro with varying concentrations of ivermectin, and their viability estimated by infection into a blackfly vector. Contact is being maintained with Merck Sharp & Dohme and individual researchers in the hope that once the mechanism of ivermectin resistance is known in other nematode species a DNA or protein marker may become available to detect resistance in the Onchocerca population, using techniques of molecular biology or immunology.

12.2 Source of compounds and coordination of screening. At present, OCT and the chemotherapy component of TDR/FIL have collaborated informally and put in place a practical screening system for selection of antifilarial drugs, which is supervised by the Secretariat, the PDDT and the Steering Committees. The success of the PDDT management system in development of antifilarial agents has been used as a model for other TDR diseases. As indicated earlier, there is a need to identify novel biological/biochemical targets in filarial worms, and to obtain appropriate chemical compounds as potential inhibitors of these targets. As new areas are identified as good biochemical targets they will be supported by research funding, and collaboration sought with pharmaceutical companies or other sources of compounds to obtain compounds interacting with these defined targets.

A vital need for the antifilarial chemotherapy programme at the present time is to increase the number of compounds tested, and a major effort to obtain compounds for antifilarial screening has been made during the past year. An additional primary screening centre was established at the end of 1988, to cope with increased throughput of compounds, and facilities for resynthesis of active compounds are in place.

A decision will be made in the near future on the use of a contract laboratory to receive, store and transfer compounds to collaborating screening laboratories. Weighing and shipment of test compounds has previously been done at WHO/HQ under inadequate conditions, and with increased flow of compounds can no longer be undertaken by the OCT Project Manager.

12.3 Administration and budget (including the "MACROFIL" project proposal)

The Directors of OCP and TDR, having met with the professional staff responsible for the OCT and TDR filariasis programmes, recommended (see statement to EAC11 - Appendix 1) that all work related to the discovery and development of macrofilaricidal drugs, for both onchocerciasis and lymphatic filariasis, would best be carried out within a single programme, designated "MACROFIL".

It is suggested that an amalgamation of the OCT and TDR/FIL resources for research and development of macrofilaricides should formally be initiated in 1992, at the start of the OCT fourth financial phase (1992-97) and the TDR 1992-93 biennium. However, the system could be provisionally operated during 1991 to allow any required minor amendments in procedure to be identified.

The administration of MACROFIL would be carried out by OCP-appointed staff following current OCT procedures, and the same progress reports would be submitted to OCP and TDR review committees to avoid unnecessary duplication.

To extend the drug research and development programme to lymphatic filariasis, one would add the ongoing preclinical drug development projects of TDR/FIL (seven in number) to the existing OCT programme of work. These projects are currently funded by TDR at a total cost of US$355 707, and the Director of TDR has therefore agreed that a contribution of US$400 000 would be made to MACROFIL for such preclinical work. In addition there would be a separate fund for "operational research" from whch contributions for consultants, meetings, etc. could be made. Any potential macrofilaricidal drug emerging from the MACROFIL research and development programme would be eligible for professional and financial assistance from the newly created Product Development Unit (PDU) of TDR, if the product was considered suitable for further development by the Director of TDR and his advisers.

The current cost of support of drug testing for onchocerciasis in clinical trials centres is US$425 000 p.a. and Director TDR has agreed that funding up to a similar level would be provided by TDR if the potential macrofilaricide enters clinical trials for lymphatic filariasis.

A summary of the annual budget for the proposed MACROFIL Project for 1992-1997 forms Appendix 2 to this document, showing a maximum combined expenditure of just over US$3 million p.a. Any funds remaining unspent at the end of any year (or biennium) would be returned to the donor programme if expenditure could be specifically identified, or "pro rata" if such identification if such identification was not possible.

These proposals have been submitted to the Scientific and Technical Advisory Committee (STAC) and the Joint Coordinating Board (JCB) of TDR, and to EAC of OCP, and each of these Committees have recommended that the MACROFIL Project should be introduced following the format proposed by the Directors of OCP and TDR.

APPENDIX 1

ONCHOCERCIASIS CONTROL PROGRAMME IN WEST AFRICA

EXPERT ADVISORY COMMITTEE
Eleventh Session
Ouagadougou, 11-15 June 1990

Onchocerciasis Chemotherapy Project (OCT)

At its tenth session, EAC "was strongly in favour of the further integration of OCT into the TDR structure, and therefore requested that the Programme, in collaboration with TDR and the Manager of OCT, should prepare a plan for the continuation of research on macrofilaricides, for presentation to its eleventh session in 1990."

The scientific objectives and level of support required from OCP are given in the report of OCT to EAC (document OCP/EAC11.3). We would here like to focus on managerial aspects of a further OCT/TDR integration. In outlining our recommendations we have borne three aspects in mind:

1. The activity must be focused on the search for a macrofilaricide, and not be "diluted" by other activities.

2. That a streamlining gain must be achieved.

3. Unnecessary changes should be avoided.

On this basis, we recommend that:

1. A joint OCP/TDR project be established for the development of a macrofilaricidal drug. The activity of this project (OCP/TDR Macrofil Project) would include all research (identification of targets, screening, preclinical work and clinical trials if necessary) required to bring the drug to the point of registration. This proposal would streamline all macrofilaricide activities (for both onchocerciasis and filariasis) into one project management group.

2. The OCP/TDR Macrofil Project would be funded jointly by OCP and TDR, each making contributions which would be managed separately, i.e. no change in present financial reporting of OCT resources. TDR would establish a new budget line for OCP/TDR Macrofil. The OCP/TDR Macrofil Project would, as OCT, be under the technical supervision of Director TDR.

3. It is important that duplicative reporting and reviewing should be avoided as this is time consuming. Thus one report would be prepared yearly which would go to OCP/EAC and TDR/STAC. EAC and STAC would then report as appropriate to JPC and JCB.

4. The Manager (P5) and secretary (G4) of OCT would be transferred to OCP/TDR Macrofil but would remain as OCP staff.

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Appendix 1

We are satisfied that the arrangements outlined above will retain the flexibility of action required for rapid development of potential macrofilaricides, yet will give accountability for the OCP/TDR Macrofil to both TDR and OCP. In view of the operational importance attached to the development of a macrofilaricide for onchocerciasis by OCP and its governing committees, we hope that the EAC will be able to give support to these recommendations at its meeting next month. We look forward to your discussions on this matter.

Yours sincerely,

Ebrahim M. Samba
Director
Onchocerciasis Control Programme

Tore Godal, Director
Special Programme for Research
and Training in Tropical Diseases

APPENDIX 2

ANNUAL BUDGET FOR "MACROFIL" - DEVELOPMENT OF MACROFILARICIDES
1992-97

1. OCP costs for operation of "MACROFIL" (in collaboration with TDR)

		US$ (1991 figures)
A.	**Administration**	
	OCT personnel - Geneva	
	One P5 professional scientist)	226 000
	One G4 secretary)	
	Consultants	
	6 month (computerized drug data base)	36 000
	1 month (Chairman PDDT)	7 842[1]
	Operational travel (Secretariat)	20 000[2]
	Meetings (Steering Committee, PDDT, SWG)	120 000[2]
	Supplies, Operating Costs	15 000
	Administration sub-total	424 842
B.	**Research and development**	
	1. Drug screening (in vitro/in vivo)	700 000
	2. Basic research programme[3]	226 000
	3. Preclinical drug development (estimated)[3]	500 000
	4. Clinical trials centres (oncho)	425 000
	Research and development sub-total	1 851 000
	TOTAL	2 275 842

2. TDR contribution for "MACROFIL"

Based on current TDR-Filariasis funding for preclinical work in macrofilaricidal drug discovery and development (seven projects), TDR would contribute an additional US$400 000, together with an additional $425 000 p.a. for clinical trials in lymphatic filariasis when this is required. Thus maximum funding of "MACROFIL" would be $3 100 842 p.a.

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[1] Chairman PDDT - currently half of total costs ($15 685) paid by TDR. This should continue.

[2] TDR may make contribution to travel and meetings costs, if significant savings are made by removing chemotherapy component from the TDR-Filariasis programme.

[3] Not in the 1991 budget of OCT. For details, see document OCP/EAC11.3.

APPENDIX 3A

As at 25.9.90

RESEARCH PROJECTS CURRENTLY FUNDED BY OCT

Costs (US$)

1. CLINICAL TRIALS CENTRES

A. Novel macrofilaricides

AWADZI, Dr K.
Onchocerciasis Chemotherapy Research Centre (OCRC)
Hohoe Hospital
P.O. Box 144
Hohoe, Ghana

"Clinical trials of drugs for onchocerciasis" (RP: 85006) 352 146

"Setting up of in vitro laboratory" [1] 40 000

ORME, Professor M.C.L'E.
Dept of Pharmacology & Therapeutics
The University of Liverpool
P.O. Box 147
Liverpool, L69 3BX
United Kingdom

"The effect of albendazole when combined with ivermectin in the treatment of onchocerciasis" (RP: 89010) 21 899[2]

B. Continuing ivermectin work

RIVAS-ALCALA, Dr A.R.
Centro de Investigaciones Ecologicas del Sureste (CIES)
Carretera Panamericana y Periférico Sur
San Cristobal de Las Casas 29290
Chiapas, Mexico

"A study of the tolerability, safety and efficacy of successive single oral doses of ivermectin in adults with onchocerciasis" (RP: 86017) 8 000

(TERMINATED 30 JULY 1990)

2. DRUG SCREENING CENTRES

A. In vitro test systems

BUTTNER, Professor D.W.
Bernhard-Nocht-Institute
Bernhard-Nocht-Strasse 74
2000 Hamburg 4
Federal Republic of Germany

"In vitro and in vivo drug tests of adult and larval O. volvulus and electron microscopic study of drug effects" (RP: 88006) 125 300

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[1] Emergency funding to allow transfer of O. volvulus drug-screening work from Liberia to the OCRC (Professor D.W. Büttner and Dr K. Awadzi).

[2] Amount of funding requested at 11-12 October 1990 OCT Steering Committee meeting.

Appendix 3A

Costs (US$)

TOWNSON, Dr S.
CAB International Institute of Parasitology
395A Hatfield Road
St Albans, Herts AL4 0XU
United Kingdom

"Experimental chemotherapy and screening of drugs against Onchocerca in vitro and in vivo" (RP: 89001) — 142 300 / 7 355[1]

B. In vivo test systems

COPEMAN, Professor D.B.
Graduate School of Tropical Veterinary Science
James Cook University of North Queensland
Townsville, QLD 4811
Australia

"Bovine screen for Onchocerca gibsoni" (RP: 89003) — 87 000

LOWRIE, Dr R.C.
Tulane University Delta Regional Primate Research Centre
Parasitology Department
Three Rivers Road
Covington, Louisiana 70433
United States of America

"Suitability of the patas monkey (Erythrocebus patas) as a host for Onchocerca volvulus" (RP: 88003) — NIL

(TERMINATES 31 OCTOBER 1990)

MAK, Dr Joon Wah
Head, Malaria & Filariasis Division
Institute for Medical Research
Jalan Pahang
50588 Kuala Lumpur, Malaysia

"Screening potential filaricides against subperiodic B. malayi in Presbytis spp." (RP: 87013)

(TERMINATES 30 NOVEMBER 1990)

McCALL, Dr J.W.
Department of Parasitology
College of Veterinary Medicine
University of Georgia

"Drug screening utilizing Brugia pahangi in the dog" (RP: 88013) — 96 866[1]

[1] Amount of funding requested at 11-12 October 1990 OCT Steering Committee meeting.

Appendix 3A

Costs (US$)

TOWNSON, Dr S.
CAB International Institute of Parasitology
395A Hatfield Road
St Albans, Herts AL4 0XU
United Kingdom

"Discovery and development of new antifilarial drugs" (RP: 89012) 119 000
21 888[1]

ZAHNER, Dr H.
Institut für Parasitologie
Justus-Liebig-Universität Giessen
Rudolf-Buchheim-Strasse 2
6300 Giessen
Federal Republic of Germany

"Experimental chemotherapy and chemoprophylaxis of filariasis and screening of filaricides" (RP: 85011) 200 113[1]

C. Resistance to ivermectin

DAVIES, Dr J.B.
Liverpool School of Tropical Medicine
Pembroke Place
Liverpool, L3 5QA
United Kingdom

"To develop a bioassay for microfilaricidal drugs using intrathoracic inoculation of Simulium" (RP: 90001) 9 619

TOWNSON, Dr S.
CAB International Institute of Parasitology
395A Hatfield Road
St Albans, Herts AL4 0XU
United Kingdom

"Studies on the sensitivity of Onchocerca microfilariae to ivermectin" (RP: 89011) 10 000

"Studies on the sensitivity of O. volvulus microfilariae to ivermectin" (RP: 90003) 67 570[1]

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[1] Amount of funding requested at 11-12 October 1990 OCT Steering Committee meeting.

Appendix 3A

3. SUPPORTING WORK

	Costs (US$)
BAKER, Dr D.C. Department of Chemistry The University of Alabama P.O. Box 870336 Tuscaloosa, Alabama 35487-0336 United States of America	
"Resynthesis and evaluation of antifilarial compounds" (RP: 89009)	83 210
ELSLAGER, Dr E.F. Elslager Associates 4081 Thornoaks Drive Ann Arbor, Michigan 48104 United States of America	
Expenses - Chairmanship of PDDT	7 843
LOISEAU, Dr P. Faculté de Pharmacie Université Paris-Sud 92296 Chatenay-Malabry France	
"Evaluation de précurseurs biochimiques à tropisme lymphatique pour augmenter l'activité macrofilaricide de substances connues et d'inhibiteurs metaboliques potentiels" (RP: 90004)	104 630[1]

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[1] Amount of funding requested at 11-12 October 1990 OCT Steering Committee meeting. (Actual amount requested: FF 565 000, calculated at $1 = FF 5.40.)

APPENDIX 3B

TDR/FIL PRECLINICAL DRUG DEVELOPMENT PROJECTS
(to be added to existing OCT programme of work
if MACROFIL Project initiated)

(currently funded by TDR at a total of US$355 707)

BAIN, Dr O.
Laboratoire de Zoologie - Vers
Museum National d'Histoire Naturelle
75231 Paris Cedex 05
France

"Monanema martini: filariasis with dermal microfilariae: animal model for drug trials: biological and anatomopathological studies" (RP: 870128)

MAK, Dr J.W.
Head, Malaria & Filariasis Division
Institute for Medical Research
Jalan Pahang
Kuala Lumpur 50588
Malaysia

"Screening potential filaricides against B. malayi infection in Presbytis spp." (RP: 860304)

McCALL, Dr J.W.
Department of Parasitology
University of Georgia
Athens, GA 30602
United States of America

"Experimental chemotherapy of filariasis and screening of filaricides" (RP: 860043)

NAVARATNAM, Dr V.
Director, National Drug Research Centre
Universiti Sains Malaysia
Minden 11800
Penang
Malaysia

"Pharmacokinetics of antifilarial drugs" (RP: 880112)

RUKMONO, Professor B.
Head, Department of Parasitology
Faculty of Medicine
University of Indonesia
Jl Salemba Raya 6
Jakarta 10430
Indonesia

"Screening of potential filaricides against W. kalimantani in Presbytis spp." (RP: 860278)

Appendix 3b

TOWNSEND, Professor L.B.
College of Pharmacy
University of Michigan
Ann Arbor, MI 48109
United States of America

"Lead-directed synthesis of potential filaricides" (RP: 870387)

WALTER, Dr R.D.
Abteilung Biochemie
Bernhard-Nocht-Institut für Tropenmedizin
Bernhard-Nocht-Str. 74
2000 Hamburg 36
Federal Republic of Germany

"Neuroleptic receptors in O. volvulus and allied parasites" (RP: 880029)

APPENDIX 4

As at September 1990

LIST OF OCT STEERING COMMITTEE MEMBERS

Mr P. Acred, Chemotherapy Department, Glaxo Group Research Limited, Greenford Road, Greenford, Middlesex UB6 0HE, United Kingdom

Dr W.C. Campbell, Department of Biology, College of Liberal Arts, Drew University, Madison, New Jersey 07940-4037, United States of America

Dr E.F. Elslager, Elslager Associates, 4081 Thornoaks Drive, Ann Arbor Michigan 48104, United States of America

Professor P. Gayral, Faculté de Pharmacie, Université Paris-Sud, rue Jean-Baptiste Clément, 92290 Chatenay-Malabry, France

Professor B.M. Greene, Director Division of Geographic Medicine, School of Medicine/ Dept of Medicine, University of Alabama at Birmingham, University Station, Birmingham, Alabama 35294, United States of America

Dr G. Jollès, Directeur Scientifique, Rhône-Poulenc Santé 20, avenue Raymond-Aron, 92165 Antony, France

Dr K. Sachsse, RCC Research and Consulting Company Ltd, Zeigliweg 1, Postfach 4452 Itingen, Switzerland

Coopted members

Dr K. Awadzi, Director, Onchocerciasis Chemotherapy Research Centre (OCRC), Hohoe Hospital, P.O. Box 144, Hohoe, Ghana

Dr D.A. Denham, Department of Medical Parasitology, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom

Dr L.L. Fleckenstein, Acting Chief, Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, United States of America

Dr W.E. Gutteridge, Head, Antiparasite Chemotherapy Research, Wellcome Research Laboratories, Langley Court, Beckenham, Kent, BR3 3BS, United Kingdom

Observer

Representative of the Expert Advisory Committee (EAC) of the Onchocerciasis Control Programme in West Africa (OCP)

WHO Secretariat

Dr D.A.T. Baldry, Chief, OCP Liaison Office (OCP)
Dr J.F. Dunne, Director Division of Drug Management and Policies (DMP)
Dr C.D. Ginger, Project Manager, Onchocerciasis Chemotherapy Project (OCT)
Dr T. Godal, Director, Special Programme for Research and Training in Tropical Diseases (TDR)
Dr R. Le Berre, Chief, Filarial Infections (CTD/FIL)
Dr P. de Raadt, Associate Director, Operations, Division of Tropical Diseases Control (CTD)
Dr C.P. Ramachandran, Secretary, Steering Committee on Filariasis (TDR/FIL)
Dr B. Thylefors, Programme Manager, Programme for the Prevention of Blindness (PBL)

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Modified 1 December, 1995

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

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THE MACROFIL CHEMOTHERAPY PROJECT. 1996-99

BACKGROUND

The Independent Commission, reporting in 1981 on the long term prospects for the Onchocerciasis Central Programme in West Africa (OCP) recommended that the Onchocerciasis Chemotherapy Project (OCT) be set up to develop a safe and effective macrofilaricidal drug, which would both help OCP to bring its programme to an end within the allocated 20 year time period, and to maintain disease control thereafter. OCT began operations in 1982, and pursued a multidisciplinary drug discovery and development programme, initially with the collaboration of two multinational pharmaceutical companies (Wellcome and Upjohn). In these early years of OCT, Merck and Co initiated human clinical trials of ivermectin (Mectizan^{R}) as a microfilaricidal drug for onchocerciasis, and in collaboration with OCT, successfully registered Mectizan as a treatment for onchocerciasis in 1987. With a very safe drug available for control of morbidity, mainly in preventing blindness and skin changes, the OCT again turned its full resources towards development of a macrofilaricide to kill the long-lived adult Onchocerca worms (mean lifespan of a female worm is 10-12 years).

The OCT has always been based in Geneva, and has operated in the same way as Steering Committees of the Special Programme for Research and Training in Tropical Diseases (TDR), and scientific work has been under the day-to-day control of Director, TDR, although funding for the project came from the OCP budget. OCT always collaborated closely with the Filariasis Steering Committee of TDR, which also had a drug development component for both onchocerciasis and lymphatic filariasis, and it was suggested that all work on drug development for onchocerciasis should be carried out within one programme. Thus in 1991, OCT became the Macrofil Chemotherapy Project (MACROFIL) and the drug development projects of TDR-FIL were transferred to the new project.

The Fourth Financial Phase of OCP (1992 - 1997) comes to an end in 1997, and a Mid-Term Prospective Evaluation was carried out by the Expert Advisory Committee (EAC) of OCP in June 1994. Macrofil, as a component of OCP, was included in this review, and when the review was discussed by the Joint Programme Committee (JPC) of OCP later in the year, "the Chairman of EAC stressed that a field-applicable macrofilaricide was unlikely to materialize before the end of OCP operations in time to reduce the duration of vector control and that his Committee had therefore recommended the cessation of OCP funding of Macrofil by the end of 1997. Several delegations emphasized in this connection the importance of continuing the search for a field-applicable macrofilaricide beyond 1997."

JPC was informed that "Director, TDR, intended to support continued search for a macrofilaricide to control onchocerciasis and lymphatic filariasis. Proposals would be made in that respect to the TDR Governing Body within a 1996-1999 four-year plan."

Such a 4-year plan was produced by the Macrofil secretariat, and the document was considered during 1995 by both the Scientific and Technical Advisory Committee (STAC) and the Joint Coordinating Board (JCB) of TDR.

"STAC considered that an effective and affordable macrofilaricidal drug would be of potentially great importance in maintaining control in the OCP area after vector control efforts are discontinued and in the expanded African Programme for Onchocerciasis Control in which ivermectin will be employed with minimal vector control. STAC also considered that the availability of a macrofilaricide, in addition to ivermectin, can be expected to be a vital tool in future efforts to reduce morbidity in lymphatic filariasis." "STAC recommends the continued development of a candidate macrofilaricide by TDR after OCP funding is withdrawn. TDR will have to identify sources of new funds to support this activity." JCB endorsed this recommendation in 1995.

At an ad hoc meeting of TDR on "Prospects for eradication of some of the TDR target diseases" (September, 1995), it was suggested that onchocerciasis could be eliminated as a public health problem by the use of ivermectin, and lymphatic filariasis by the use of combinations of diethylcarbamazine, ivermectin and albendazole; in both cases complemented by local vector control, "but not without an investment of new funds for a finite period of time". For a further discussion of this topic, see Appendix I.

CURRENT OBJECTIVES AND WORKPLAN OF MACROFIL

The objectives of the Programme are to discover adulticidal (macrofilaricidal) drugs for onchocerciasis and lymphatic filariasis with the following profile:

- Effective (>70% Kill);
- Safe (for community use with limited medical supervision);
- Acceptable dosing regimen (oral dosing over no more than 3 days, or single intramuscular injection);
- Long shelf life (>2 years at ambient temperatures).

The value to the patient of such drugs would be:

- Permanent removal of the source of pathology (Microfilariae in onchocerciasis; adult worms in lymphatic filariasis);
- Removal of need to take ivermectin continuously.

The value to the community is:

- Control or elimination of transmission; sustaining and consolidating OCP's achievements to date in onchocerciasis control;
- Elimination of needs for, and costs of, continuous ivermectin treatment;
- Reduction in the likelihood of acquired resistance to ivermectin;
- An alternative to larviciding, which is no longer an affordable option;

- Providing a fully effective adulticidal drug to replace diethylcarbamazine in lymphatic filariasis.

Two complementary strategies are being followed to discover new lead molecules:

- Characterization and validation of potential drug targets in filariae, leading to both rational, computer-aided design, and identification of novel ligands by interaction with parasite enzymes/receptors;
- In vivo assays (against B. pahangi and A. viteae in the gerbil) of novel molecules obtained from as wide a range of novel compounds as possible. Two compound screening centres are currently supported for these activities.

Once active molecules are identified, chemical synthesis may be supported when analogues are not available, to optimize promising leads.

Details of how the Macrofil Project is carrying out work to achieve these objectives can be found in the current Macrofil Workplan (July, 1995).

During the period 1995-1997, MACROFIL will primarily pursue the objectives outlined by EAC of OCP, namely to bring to field use, as quickly as possible, the two drugs with identified macrofilaricidal activity, amocarzine and UMF 078, and to study the possibility of resistance to ivermectin in onchocerciasis and how it could be detected at an early stage.

AMOCARZINE - CLINICAL DEVELOPMENT

Ciba Geigy have now terminated all work on amocarzine (CGP 6140), and by formal legal agreement have transferred all documentation relating to the drug, and all available supplies of bulk drug and tabletted material to WHO. All future development of amocarzine will therefore need to be carried out by the Macrofil Project.

Ciba-generated preclinical data indicated that amocarzine could be given safely to patients at a level of 10mg/kg/day. Pregnant females should not be treated. However, existing clinical data from over 2000 patients with amocarzine in Africa and Latin America, showed that above a total dose of 20 mg/kg, reversible central nervous system effects became limiting, and the optimal dose schedule, developed in Ecuador, was 3mg/kg p.p., b.i.d., for 3 days, i.e. a total dose of 18mg/kg. Protocols for future clinical trials in onchocerciasis and lymphatic filariasis using this dose regimen, have been developed at Macrofil sponsored meetings.

The Onchocerciasis Chemotherapy Research Centre in Hohoe, Ghana has almost completed enrollment in a Phase II study in onchocerciasis patients to examine the safety and efficacy of the optimum dosing schedule on a "forest" strain of O. volvulus. In order to separate the adverse effects of the Mazzotti reaction from any intrinsic toxicity of amocarzine, a subgroup of patients has been pretreated with the standard dose of ivermectin (150 μg/kg) one week prior to dosing with amocarzine, to remove macrofilariae.

If reasonable efficacy (70% kill of adult worms) is shown in the trial, (which will be reviewed at the February, 1996, meeting of MACROFIL), then further development will proceed by way of a pivotal, possibly multicentre, Phase III trial during 1996-97. Key issues with amocarzine relate to its efficacy against African strains of onchocerciasis, and its narrow therapeutic index. If all items of safety and efficacy are resolved in the multicentre clinical trials then a registration dossier will be prepared during 1997-98, for submission, and hopefully approval during 1998.

For lymphatic filariasis, where optimal dosing schedules are unknown, a Phase I safety, tolerance and pharmacokinetic study is being carried out in India, prior to Phase II studies against Brugian and Bancroftian filariasis in the same country. The Phase I study will begin soon, and a report could be available early in 1996. Phase II studies in infected patients would begin in early 1996 (dependant upon Indian government approval). Multi-centre trials would then take place during 1997 and the first half of 1998. If good clinical results are available by the end of 1998, preparation of the registration dossier could begin, and a submission made during 1999. Thus the earliest approval of amocarzine use for lymphatic filariasis would be the end of 1999.

UMF 078 - PRECLINICAL DEVELOPMENT

UMF 078, which came from a TDR-Supported programme of research, is a derivative of flubendazole which in animals, unlike the parent compound, is significantly bio-available via the oral route, and is not an irritant when given by the parenteral route. Recent assays have shown that, unlike most benzimidazole carbamates, it is not mutagenic in the Ames test. Work during 1996 will concentrate on preclinical toxicological studies such as the acute toxicity in rats to augment that already obtained from mice, and the muscle irritancy study to allow a final decision to be made on preferred routes of administration. Efficacy and dosing regimens of UMF 078 were worked out in the Brugia/dog model, and thus during 1995, the efficiency against Onchocerca ochengi is being studied in the cattle model.

If all studies have a successful outcome, chronic toxicity studies in rat and dog will be initiated in 1996, and plans made for a Phase I study in man. The earliest date for clinical trials would be late 1996, continuing into 1997. Phase II studies in infected patients (onchocerciasis and lymphatic filariasis) could then take place in 1997 and Phase III in 1998. Analysis of clinical data and assembly of a registration dossier would then take place in 1998 and 1999, giving 2000 as the earliest possible time for approval.

THE POSSIBILITY OF IVERMECTIN RESISTANCE IN ONCHOCERCIASIS

As ivermectin is the only drug currently used for control of onchocerciasis, appearance of resistance would be a major problem both for OCP, and the recently created African Programme for Onchocerciasis Control, which is based on the widespread use of ivermectin.

Ivermectin resistance has already occurred in several gastrointestinal parasitic nematodes in the veterinary field, where ivermectin has been in widespread use since 1981, and in insects. Macrofil was therefore asked by EAC of OCP, to study the mechanism by which nematodes became resistant to ivermectin, and if possible to develop

a diagnostic method by which resistance genes could be identified in Onchocerca before resistance had become a problem in the field.

Initial work has utilized resistant mutants of the free-living nematode Caenorhabditis elegans, and the animal parasite of sheep Haemonchus contortus. Several resistance genes have now been cloned and sequenced from these parasites, and the mechanisms of mutation studied. Genetic studies are now being extended to other parasitic nematodes and to O. volvulus itself. Additionally, support has been given to the Rotterdam group who have developed the robust and predictive model of onchocerciasis in man - ONCHOSIM. Computer simulations over a 50 year time span have been developed to model the spread of dominant or recessive resistance genes through the worm population under various programmes of ivermectin distribution. A MACROFIL-sponsored meeting on ivermectin resistance took place in 1995, to determine the most productive way to continue these investigations, and the recommendations which emerged were brought into action at the September, 1995 meeting of the Macrofil Steering Committee.

DRUG DISCOVERY

MACROFIL, as part of the TDR Product Development Unit, collaborates with the two major chemotherapy programmes (CHEMAL and I-CHEM) via the in-house CHEMCORE group. The same strategy is followed; i.e. potentially lethal molecular targets are identified in parasites, and then the genes for these are cloned and expressed, with the objective of generating a robotic screening assay capable of high-throughput screening of molecules to be done in collaboration with pharmaceutical companies.

Additionally, compounds obtained from pharmaceutical companies and elsewhere are tested in the various in vivo models available to Macrofil:

Primary testing against	B. pahangi and A. viteae in gerbils,
Secondary testing against	B. pahangi in dogs, and
	O. ochengi in cattle.
In vitro testing against	O. volvulus adult worms.

Successful compounds from such assays go on to preclinical development involving scale-up chemistry, assay development, metabolism, toxicology, pharmacokinetics, formulation, etc., as appropriate, in laboratories identified able to carry out such work to international recognized GLP standards. Four such lead compounds have been identified, and are under development.

FINANCIAL SUPPORT FOR MACROFIL 1996-99

Prior to 1991, OCT/MACROFIL was fully funded by OCP, and funds were earmarked for the full cost of the project i.e. salaries of personnel, cost of meetings, duty travel etc were all to be paid from the funds allocated, in addition to the operational costs of the research and development of macrofilaricidal drugs. In 1986, just prior to registration of ivermectin for onchocerciasis, OCT costs peaked to just over US$ 3 million. In the late 1980's with structural changes taking place within the project annual costs fell to about US$ 1.5 million. In the 1990's JPC requested an acceleration

the Fourth financial phase of OCP budgets were planned to peak in 1993-4 and to fall steadily thereafter to the termination of OCT/OCP in 1997.

Since 1991, TDR has contributed to the operations budget at a level of approximately US$ 400,000 per annum. STAC-17 has recommended that this be increased to US$500,000 per annum for the biennium 1996-97. Thus (see Table 1 - MACROFIL PROJECT - FUNDING 1995-99) the total budget of MACROFIL for 1995 is just below US$ 3 million, but will fall to about US$ 2.3 million by 1997. If TDR wishes to continue to operate the Macrofil Chemotherapy Project beyond 1997 at even that minimal level, it will need to meet the total annual costs of $2.2-2.3 million. This allows for approximately $0.5 million per annum for administrative costs, and gives an operational budget of $1.7-1.8 million broken down as indicated in the budget table. Note that TDR funding for MACROFIL during the 1996-97 biennium is set at US$500,000 per annum. To date, TDR has not needed to supply funds for clinical trials of new drugs in lymphatic filariasis, but this year amocarzine will enter into such clinical trials in India and specific funds need to be earmarked for this purpose in the next biennium.

Thus it can be seen that the Macrofil Chemotherapy Project has a balanced programme of work with identified clinical and preclinical candidates, which will carry it to 1999 and beyond. It is therefore hoped that as recommended by participating and donor countries at JPC-15 and JCB-18, TDR can continue to support a programme of macrofilaricide development, for both onchocerciasis and lymphatic filariasis, within its overall chemotherapy programme.

Table 1.

PRODUCT RESEARCH AND DEVELOPMENT MACROFIL PROJECT - FUNDING 1995-99
ANNUAL BUDGET IN US$

OPERATIONS

	1995 OCP	1995 TDR	1996 OCP	1996 TDR	1997 OCP	1997 TDR	1998 TDR	1999 TDR
Clinical	603 500	-	654 925	75 000	485 671	50 000	1 000 000	1 000 000
Preclinical	700 000	18 000	800 000	50 000	550 000	100 000	200 000	300 000
Screening	300 000	150 000	150 000	200 000	100 000	200 000	300 000	300 000
Target Identification IVM resistance	300 000	210 000	100 000	175 000	75 000	150 000	200 000	200 000
Sub-totals	1 903 500	378 000	1 704 925	500 000	1 210 671	500 000	-	-
Total Operations	2 281 500		2 204 925		1,710,671		1 700 000	1 800 000

ADMINISTRATION

Personnel	271 500	-	285 075	-	299 329	-	270 000	280 000
Meetings/Duty Travel etc.	335 000	-	305 000	-	275 000	-	230 000	220 000
Total Administration	606 500	-	590 075	-	574 329	-	500 000	500 000
Total Costs Macrofil	2 888 000		2 795 000		2 285 000		2 200 000	2 300 000

At a recent (September 1995) "**Ad hoc meeting on prospects for eradication of some of the TDR target diseases. Modelling the tools and time frame required.**", Professor Habbema (Rotterdam) summarized results of computer simulations which examined the "macrofilaricidal" properties of ivermectin, and also of a theoretical macrofilaricide (parameters used were based on data from Suramin and amocarzine).

Originally, when ivermectin was considered to have only microfilaricidal activity, ONCHOSIM modelling predicted that even after 25 years of annual treatment recrudescence would still occur if drug treatment was then stopped (Habbema JDF et al. Parasitology Today 8 99, 1992). Then, when data from a detailed study of 5 years of annual ivermectin treatment in Asubende Ghana, were modelled, it was shown that during a period of about 10 months following each drug treatment, the rate of microfilarial production increased, but at one year post treatment, this rate was still about 35% less than that prior to the last treatment. The most acceptable hypothesis was that all adult females had suffered an irreversible loss in fecundity due to ivermectin treatment. (Plaisier, A.P. et al. Journal of Infectious Diseases 172, 204, 1995).

Taking this finding into account, with relatively low community microfilarial loads (20mf/snip) and 65% coverage of the population, modelling predicted that after 15 years of annual treatment with ivermectin, the risk of recrudescence would be slightly less than 1%. If biannual treatments were to be given, the risk of recrudescence, after even 10 years, was negligible. If the community microfilarial loads were higher (60mf/snip), then the risk of recrudescence is high even after 20 years of annual ivermectin treatments.

Professor Habbema also presented previously unpublished simulations comparing biannual ivermectin treatments with a hypothetical macrofilaricide at high community microfilarial levels (70mf/snip). These simulations (see Fig. 1) indicate that if drug coverage is maintained at the levels possible with ivermectin, i.e., 65%, even a relatively ineffective macrofilaricidal drug (60% or 75% adulticidal activity) would reduce the risk of recrudescence to less than 1% within a 5 to 10-year period, while ivermectin would require 10 - 20 years of treatment. Fig. 2 demonstrates that a macrofilaricide with 75% efficacy could control the parasite population in five years if given twice a year.

One important factor which could greatly influence the success of drug treatment when coverage is incomplete is systematic non-compliance of certain persons requiring treatment, rather than assuming random non-compliance, and the former situation is shown in Fig. 3. Five years of treatment with a macrofilaricide showing unacceptable adverse effects could then result in treatment failure due to systematic non-compliance. Treatment with amocarzine, requiring 3 days of dosing, and showing mild CNS effects, could give such non-compliance. If this proved a problem, one could reduce microfilarial loads in such patients by switching to treatment with ivermectin.

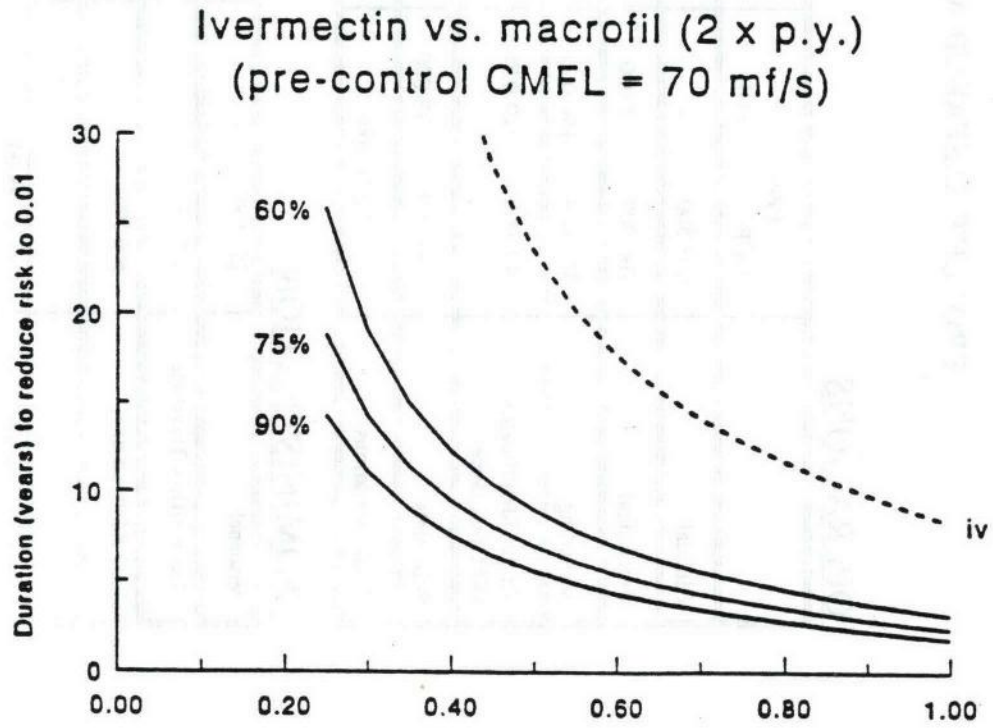


Figure 2.

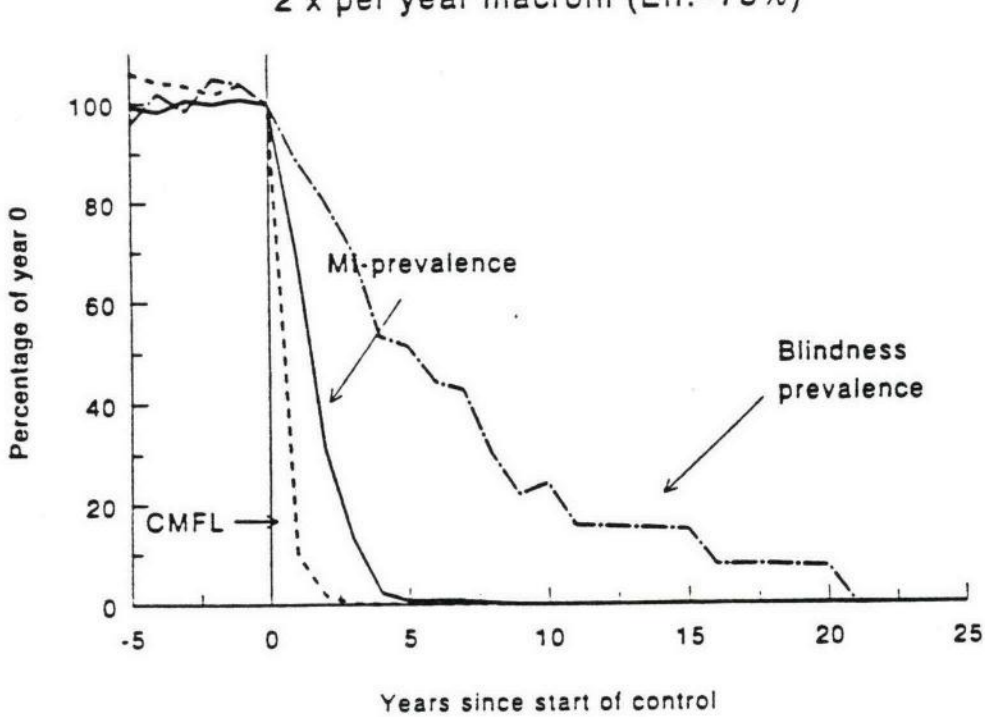
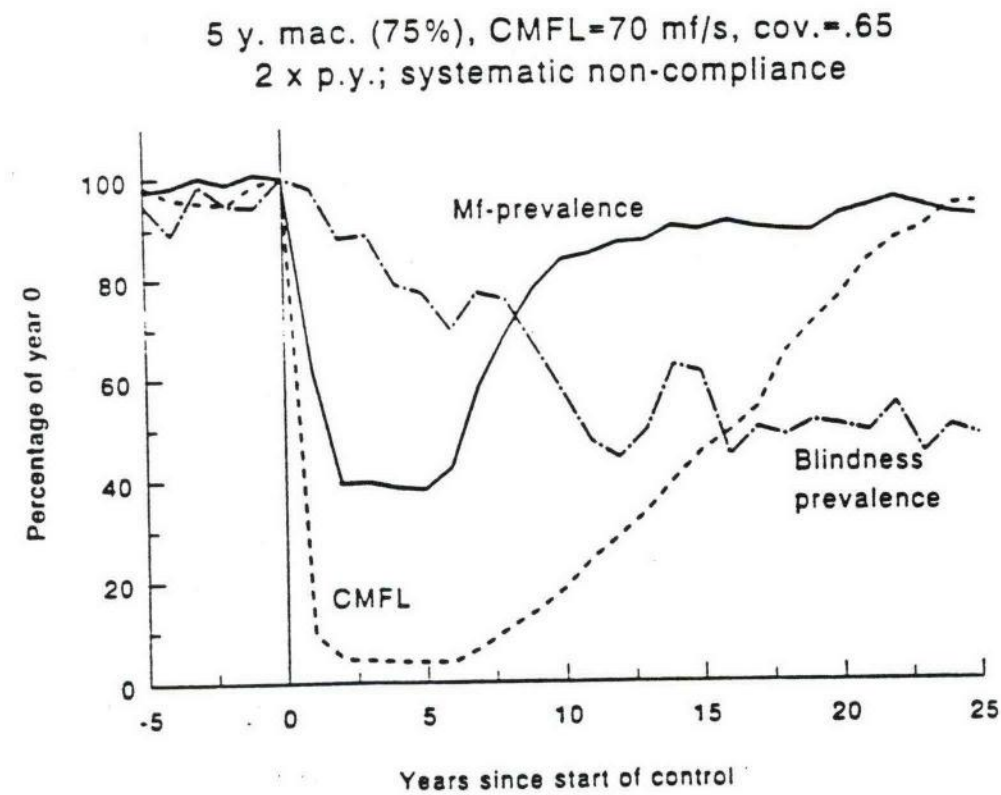


Figure 3.



brief – CSA –
Macrofilaricide

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(FAX 44-1524-388-942)

18 June 1996

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Dear Mr Benton,

You may remember that last February Dr Donald Hopkins, in his then capacity as President of the River Blindness Foundation (RBF), handed you an outline protocol *cum* progress report and future budget of the research project to investigate the macrofilaricidal potential against *Onchocerca vovlulus* of higher and more frequent doses of ivermectin. This project, which is being carried out in Cameroon by research workers from ORSTOM under my supervision, has now been running successfully for two and a half years and should be completed within another two years. So far it has been funded entirely by the RBF.

It was requested of you to consider whether APOC would be in a position to provide any funds to help support the budget for the estimated running costs (excluding salaries of personnel) of the project during 1997 (US$121'000) and 1998 (US$51'600). As a result, I believe you consulted with various research-oriented persons in WHO and said that our request would be considered by the CSA of the APOC.

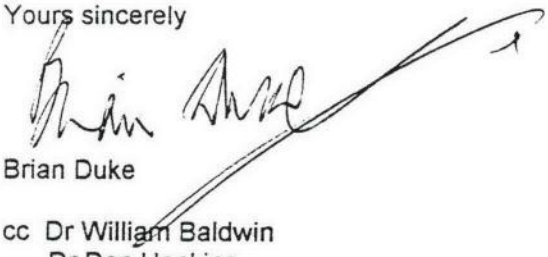
On 30 April 1996, RBF transferred the greater part of its programmes and assets to the Carter Center's Global 2000 River Blindness Program (GRBP) Dr Hopkins resigned as President of the RBF at that time in order to concentrate on his responsibilities as Director of the GRBP. Because of technical arrangements in their affiliations with other organizations, the Carter Center elected not to manage the macrofilaricide research project in Cameroon. RBF, which will continue in existence for three years, retained the responsibility for carrying out the macrofilaricide research project through ORSTOM, including its administration, supervision and financing. The oversight of the project, therefore, remains as my responsibility under review of the RBF Board.

I should be most grateful if you could let me know whether the CSA of APOC has yet been able to consider the RBF's request for assistance with the funding of the Cameroon macrofilaricide project in 1997 and 1998 or, if the matter has not yet been discussed, if you could give me some idea as to when we might learn of APOC's decision. As has previously been emphasised by a number of knowledgeable persons, it is really of vital importance to know whether more intense treatment with ivermectin (the drug on which the whole strategy of APOC is based) has or has not a macrofilaricidal action on *O. volvulus*. If the present trial gives a positive result, it could change completely the present tactics of APOC distribution and could bring the end-point of the programme into much clearer and more satisfactory focus than it is at present.

I shall look forward to hearing from you.

With kindest regards

Yours sincerely



Brian Duke

cc Dr William Baldwin
Dr Don Hopkins

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