Fourth meeting
Geneva, 2-4 November 1976
Agenda item 5.(c)

DRUG DEVELOPMENT

There is no chemoprophylactic suitable for practical use against Onchocerca volvulus infections and with the drugs at present available, namely diethylcarbamazine and suramin, the chemotherapeutic treatment of onchocerciasis patients is difficult. Of more importance for OCP, is the fact that neither diethylcarbamazine nor suramin can be safely used for mass drug administration campaigns due to the very severe and dangerous side reactions associated with the drugs, especially when they are given to heavily infected patients, a condition which prevails in the Onchocerciasis Control Programme area.

The Scientific and Technical Advisory Committee, realizing that there is a pressing need to improve chemotherapeutic treatment for onchocerciasis patients, made a series of recommendations at its previous sessions. Some of these recommendations have been implemented, some have been duly considered by the Organization. The present document summarizes the action which has been taken so far and briefly details the initiatives which have been considered for future implementation.

Three different approaches have been followed:

- to improve the use of existing drugs;
- to test other drugs already released for use in human medicine, for action against O. volvulus;
- to establish a screening programme for new filaricides.

(a) To improve the use of existing drugs. Steps are being taken to increase our understanding on the mode of action of diethylcarbamazine and suramin in onchocerciasis patients, so as to develop optimal dosage schedules for treatment. In this regard, UNDP project funds allocated to OCP have been utilized to finance the following activities:

(i) a thorough study of the literature on suramin and diethylcarbamazine, with special reference to pharmaco-dynamics and toxicity has been accomplished;
(ii) the Ghana Government has established a Chemotherapeutic Research Centre at Tamale where a well-equipped and staffed hospital-cum-laboratory is available. At this Centre, with the cooperation of the Ghana Government and with technical and professional assistance from the Liverpool School of Tropical Medicine, UK, thorough clinical, biological and pharmacological investigations will be made on onchocerciasis patients under treatment with diethylcarbamazine and suramin. The protocols for these investigations are being prepared by the various parties concerned;

(iii) investigations have been undertaken by the Unité d'Enseignement et de Recherche de Médecine et de Santé Tropicales, Marseille, France, into the effect on *O. volvulus* of various low-total-dose of suramin.

(b) Testing other drugs already released for the treatment of other parasitic diseases

A variety of anthelminthic and trypanocidal compounds which are already considered safe for human use, need to be tested, or tested further, for possible action against *O. volvulus*. Possible candidate compounds include: levamisole, mebendazole, trichlorophone, nifurtimox and Berenil; as well as various combinations of these drugs, with or without diethylcarbamazine. Trials on these lines, organized and financed by OCP out of UNDP funds for research are being carried out at present under the auspices of OCCGE at Centre Muraz in Bobo-Dioulasso, Upper Volta, and by the British Medical Research Council team in Cameroon. Additional trials will soon be started by the Chemotherapeutic Research Centre at Tamale.

(c) Screening programme for new filaricides. The search for entirely new groups of filaricidal compounds, or basic variants of existing compounds, involves going back to the primary screening of chemicals for filaricidal action. This is a long-term research project involving much work in those few laboratories where filaricide screening can be done, and demanding also the cooperation of the pharmaceutical industry, of synthetic chemists, and perhaps of biochemists. Financial support on a very small scale is already given to some laboratories carrying out this work under agreements concluded with the WHO Division of Malaria and other Parasitic Diseases (see Annex I).

Greatly increased financial support for such a programme of research is envisaged from the WHO Special Programme for Research and Training in Tropical Diseases. Under the Filarialasis section of this programme, plans for which have been drawn up in close consultation with OCP, it is proposed as follows:
(i) Additional support will be given to a number of academic centres where primary and secondary filaricidal screening is already going on. This will enable those centres to increase the number of compounds screened annually, and will include screening for action against infective larvae (chemoprophylactics), adult worms (macrofilaricides), and microfilariae (microfilaricides). Several suitable centres have already been approached, and specific costed programmes of research have been worked out.

(ii) Attempts will be made to obtain a large variety of selected compounds for screening. It is hoped that these will be derived from:

- pharmaceutical companies;
- the United States Army bank of compounds synthesized in the search for anti-malarials (250,000 compounds);
- intelligent synthesis of new compounds by chemists;
- leads obtained from basic studies on the biochemistry of filarial parasites.

All these lines are at present being explored.

(iii) A tertiary screening centre will be set up, where new potential filaricides revealed by the primary and secondary screening can be investigated for action against *O.gibsoni* and *O.gutturosa* in cattle.

In view of the fact that the WHO Special Programme is unlikely to receive adequate funding or to get truly under way until mid-1977, consideration may be given to the use of OCP research funds to initiate this programme of research.
ANNEX I

Research agreements relating to onchocerciasis entered into by MPD in 1976

1. Dr D. Denham, Dept. of Helminthology, London School of Hygiene and Tropical Medicine
   $4,000 for development of screening methods for filaricides using Brugia pahangi in vitro and in vivo in jirds and cats, and for testing of new compounds obtained from industry.

2. Dr W. Kozek, California Primate Research Centre, University of California, Davis, California
   $4,000 for attempts to transmit Onchocerca volvulus to a variety of monkey species, and for investigations into the nature of Chlamydia-like organisms (CLO) found in Onchocerca worms.

3. Dr P. Wenk, Institute of Tropical Medicine, Tubingen, Germany
   $2,000 for investigations into the occurrence of natural infections with Onchocerca spp in tame fallow deer and possible transmission of Onchocerca spp to dwarf goats.

4. Prof. G. Lämmer, Institut für Parasitologie, Justus Liebig-Universität, Giessen, Federal Republic of Germany
   $2,000 for studies on the chemotherapeutic and chemoprophylactic action of new compounds on Litomosoides carinii in Mastomys.

5. Dr R. Grasbeck, Minerva Institute for Medical Research, Helsinki, Finland
   $4,000 for work on the preparation and purification of O. volvulus antigens.

6. Dr A. Rougemont, Université d’Aix-Marseille, Marseille, France
   $3,000 for studies in rabbits to assess the blood-level of suramin resulting from a number of different low-total-dose schedules, as well as from standard schedules. These investigations are a preliminary adjunct to work to be carried out on human patients in Mali with the aid of a grant from OCP.

7. Dr D.H. Connor, Department of Infectious and Parasitic Disease Pathology, Armed Forces Institute of Pathology, Washington, USA
   $2,000 to assist in the development, preparation and dispatch of kits for the collection of autopsy material from onchocerciasis cases, and for the establishment of an Onchocerciasis Pathology Registry for recording and examining tissues collected.

8. Dr O. Bain, Muséum national d’Histoire naturelle, Laboratoire de Zoologie, Paris, France
   $1,500 for histological studies of the phenomenon of limitation of microfilarial passage through the stomach wall of insect vectors and allied phenomenon in a number of filaria-vector couples, including Onchocerca volvulus/Simulium.

9. Prof. J. Ngu, University of Cameroon, Yaoundé
   $3,000 for studies of the humoral and cellular profiles of onchocerciasis patients exhibiting various skin and eye lesions.