



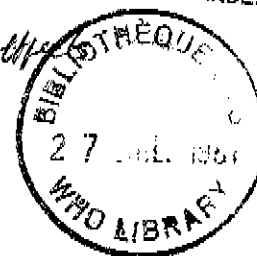
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CURRENT VIEWS ON THE TREATMENT OF ONCHOCERCIASIS
WITH DIETHYLCARBAMAZINE CITRATE AND SURAMIN *- adv eff*

by

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1. INTRODUCTION

Although an active search is in progress to find improved drugs for the treatment of onchocerciasis, it is likely to be at least five to 10 years before any successful new candidate compounds can become available for general use. In the meantime, the combination of diethylcarbamazine citrate (DEC-C) and suramin, coupled where appropriate with removal of nodules from the head, remains the best treatment for this disease.

Research over the past five years has improved understanding of the potential dangers of these two drugs and of the way in which they should best be used, particularly in the treatment of ocular onchocerciasis. On the assumption that DEC-C and suramin will still be the main form of treatment for some years to come, a review of currently recommended therapy in the light of recent advances may be helpful.

2. DEFINITIVE TREATMENT OF ONCHOCERCIASIS

When considering the treatment of onchocerciasis it is advisable to bear in mind the approximate life span of the various stages of the parasite. These may be recapitulated as follows:

- (i) pre-patent interval of infection (from introduction of infective larvae to first detection of microfilariae): 9-20 months (most commonly 12-15 months);
- (ii) adult worms: life span up to 15 years;
- (iii) development from egg to microfilariae: about 10 days;
- (iv) microfilariae: life span of 6-30 months;
- (v) development from microfilariae to infective larvae in Simulium: 6-8 days.

At present the definitive treatment of onchocerciasis depends in the main on chemotherapy with DEC-C and suramin, but, since nodulectomy may also play a subsidiary role, this subject will be dealt with first.

2.1 Nodules

Surgical removal of nodules is often a popular procedure for the patient can see that something is being done for him, and an unsightly lump is removed. Unfortunately, the only nodules that can be removed are those which can be palpated from the surface; these generally represent but a relatively small proportion of the total load of adult worms in the body, and hence only a small proportion of the total source of microfilariae. The remainder lie, usually as rather loosely encapsulated worm bundles (Duke, 1980) deep in the tissues, between the muscles, in deep fascial planes, against the shafts of bones and adpressed close to the capsules of joints, especially the hip joint (Duke, 1970a). In these sites they cannot, using present methods, be located for removal during life.

Even the removal of all palpable nodules often represents a considerable task. In patients with many nodules (up to 40 or 50 may be found in an individual) several sessions of minor surgery will be required. This, combined with the need for adequate after-care to remove stitches and to deal with possible haematomata or wound infections, raises considerable problems of logistics and cost if the method is to be applied on a large scale.

As a control method nodulectomy appears to have little or no effect on the microfilarial reservoir available for transmission, and the clinical benefits resulting are probably limited to the degree of prevention of ocular onchocerciasis which may follow early removal of nodules from the head.

2.1.1 Removal of head nodules

Nodules on the head should always be excised because of the danger that microfilariae stemming from them will enter the eye (Anderson et al., 1975). Unfortunately, severe damage to the eye may already have been done before a palpable nodule is formed around a worm or worms present on the head (Fuglsang & Anderson, 1978). A more valuable simple prognostic sign of danger to the eye may be the concentration of microfilariae at the outer canthus (Fuglsang & Anderson, 1977); and recent opinion suggests that five or more microfilariae in a skin snip from this area may be taken as an indication that the patient is at high risk of serious ocular damage.

A careful search is needed to find nodules on the head. The patient should be asked to help in locating them, and it may be necessary to shave the head in order to find them. Often they are very small and, especially in Africa, they may be tucked away behind the ear.

In the African context it is almost never safe to rely solely on removal of head nodules to prevent further development of ocular onchocerciasis, and it is usually essential to follow up nodulectomy with adequate chemotherapy. In Guatemala and Mexico, where head nodules are very common, regular and repeated nodulectomy campaigns have probably been of some value in preventing the onset of severe eye lesions and blindness. Unfortunately, published figures in support of this belief are not available, and almost certainly the nodulectomy campaigns have not effectively reduced transmission (De León & Duke, 1966).

Removal of nodules elsewhere in the body may be regarded as optional. It may prove a popular measure and as such it may be encouraged, but it is unlikely to be of much direct benefit to the patient's ocular condition.

2.1.2 Examination of excised nodules

Nodules are often excised at intervals after treatment with new drugs in order to assess directly their effects on the adult worms. Nodules are also being excised at intervals from groups of patients residing in the area of the Onchocerciasis Control Programme in the Volta River Basin in order to determine the changes that occur in the adult worms over the years after transmission has ceased (Dr D. Büttner, in preparation). Such studies demand a thorough basic knowledge of the "normal" condition of worms removed from untreated subjects living in zones where transmission continues.

Knowledge on this subject has been greatly advanced by the recent discovery that excised nodules can be digested with collagenase so as to obtain the adult worms in a fresh, and often in a living condition (Schulz-Key et al., 1977). This provides a means of assessing the condition of each worm, its viability and its embryonic potential along the whole length of its body. The method has also proved useful in assessing the effects of drugs on adult Onchocerca volvulus worms (Schulz-Key et al., 1980), thus providing a valuable supplement to the use of impression smears made from dissected nodules and to the straightforward histological assessment of the contained worms (Copeman, 1979).

2.2 Chemotherapy

In view of the limitations of nodulectomy, the definitive treatment of onchocerciasis relies heavily on chemotherapy and, with the drugs currently available, namely DEC-C and suramin, this raises a number of problems.

2.2.1 The patient's general state and well-being during treatment

Before resorting to chemotherapy in onchocerciasis, the patient's need of therapy must be ascertained and be found to outweigh the risks and inconvenience involved in treatment. For example, it may well be better to leave untreated a lightly- to moderately-infected subject who has no symptoms resulting from his infection and whose eyes are not at risk.

Among patients who do present with signs or symptoms of onchocerciasis indicating that treatment is needed, the risks and difficulties involved will vary with the general condition of the patient and with the intensity of the infection. For example, a well-nourished expatriate, with a light infection chiefly manifest as an itching rash, is likely to support chemotherapy much better than a heavily-infected, undernourished person, who has been born and bred in the endemic area, who may be harbouring many other parasites besides O. volvulus, and whose eyes may also be seriously affected. The present paper concentrates mainly on the treatment of patients living in endemic areas, especially those who are heavily infected and are at risk of ocular complications.

Particularly in heavily-infected patients, who are living in rural endemic areas and who may be in poor general health or undernourished, treatment should not start until their general condition has been improved so that they may be expected to surmount the anticipated reactions to chemotherapy. Old and infirm patients, or those with severe disease of the liver or kidneys may simply not be strong enough to undergo treatment, especially with suramin. Treatment of pregnant women should be delayed until after delivery.

Steps must be taken to ensure that patients receive adequate food and drink during treatment (Duke & Anderson, 1975). Often this means that the physician himself will have to arrange for the supply and preparation of victuals. If this is not done, the patients may stop eating during the course of treatment, take too little fluid, and go into a decline. It follows that treatment needs to be undertaken, if not in hospital, then in some sort of treatment camp where staff and facilities are available for this purpose.

In order to assess the effects of treatment or its complications, it is also necessary to have access to certain basic laboratory facilities during the course of chemotherapy, as well as be able to provide ophthalmic care for patients with ocular complications.

Furthermore, if it is anticipated that corticosteroids may have to be used in order to reduce reactions to the death of O. volvulus parasites, it is important to exclude, or to treat beforehand, any conditions which contraindicate the use of these drugs, especially pulmonary tuberculosis. For example, a wasted patient who has a heavy infection with O. volvulus and intraocular microfilariae and is thus at high risk of blindness, but who is also suffering from pulmonary tuberculosis, represents a real challenge to the skill of the physician.

In general, totally blind persons having no perception of light should not be subjected to specific treatment for onchocerciasis for it is impossible to restore their sight. However, if they are suffering from severe itching skin lesions, treatment may be given on these grounds. Likewise, patients with painful blind eyes may require specialized ophthalmological intervention. On the other hand, patients who still have perception of light, but who are classed as economically blind (unable to count fingers at 3 m with the better eye), may be considered for treatment in order to avoid further deterioration in their sight or the development of painful self-perpetuating lesions. With patients in this category the decision whether or not to treat must depend on the assessment of the individual case made by the ophthalmologist.

A final factor entering into the decision whether or not to treat any particular patient, especially those threatened by severe ocular onchocerciasis, is the degree of exposure to reinfection to which the patient is likely to be submitted upon returning to his home environment. This aspect of the problem is considered in 2.2.4.4.

2.2.2 Treatment with DEC-C

DEC-C is at present the standard drug used in the treatment of onchocerciasis to bring about the death of the microfilariae of *O. volvulus*. In this respect it is preferred to either metrifonate (Awadzi & Gilles, 1980b) or levamisole (Duke, 1975), both of which are more toxic in their own right and have a less certain microfilaricidal action.

Unfortunately, DEC-C has virtually no lethal or sterilizing action on the adult worms of *O. volvulus*, as has been confirmed by studies on collagenase-digested nodules from patients treated with DEC-C (Taylor et al., 1980a). However, it is possible that prolonged treatment with this drug may increase the proportion of pathologically altered eggs and embryos in the uteri of the female worms (Schulz-Key et al., 1979).

Although apparent clinical cure has been reported in about half of a series of 100 lightly-infected patients treated with a single three-week course of DEC-C at 4 mg/kg body weight daily (Réé, 1977), it is not known how many of the infections in such patients would have died out or become asymptomatic without any treatment. While it is possible that DEC-C may sometimes have a macrofilaricidal effect in early, lightly-infected cases, as a general rule in patients who are permanently residing in endemic areas, it is wise to consider DEC-C as a purely microfilaricidal drug.

2.2.2.1 Reactions to DEC-C in patients with onchocerciasis (the Mazzotti reaction)

In almost all onchocerciasis patients, particularly those who are heavily infected, DEC-C gives rise to a reaction, known as the Mazzotti reaction (Mazzotti, 1948), which is usually localized to the skin but which may also be associated with systemic reactions.

Systemic reactions, which may be severe and alarming, come on rapidly and may last for some days. They include postural hypotension, collapse, respiratory distress, vertigo, fever, joint pains, muscular aches and headache (Bryceson et al., 1977; Duke et al., 1976a; Fuglsang & Anderson, 1974; Duke & Anderson, 1972, 1975; Rougemont et al., 1976).

Local reactions to the death of microfilariae in the skin may come on within 15 minutes to 24 hours of the first dose. They usually start with intense itching, followed by the development of an urticopapular rash or, in heavily-infected patients, by a generalized dermatitis and a feeling that the skin is "on fire". Depending on the distribution of the microfilariae the local reaction may be confined (to one limb for example) or may extend over the skin of the whole body. The lymph glands draining the affected areas of skin become swollen, tender and painful.

Patients with many microfilariae in the anterior segment of the eye suffer from an acute (but usually short-lived) exacerbation of watering and photophobia, with hyperaemia of the conjunctiva and sometimes with signs of iridocyclitis (Anderson et al., 1976a). Reactions

may also occur in the posterior segment of the eye, but in their early stages these are relatively silent clinically and are not usually recognizable by ordinary direct or indirect ophthalmoscopy (Anderson et al., 1976a). Their onset is usually only detectable by examination of the visual fields using the confrontation test or the tangent screen test, when they are manifest as a gradual loss of the peripheral visual field. In the early stages the loss will be partial but may develop into a severe constriction of the visual fields leading to tunnel vision. If fluoresceine angiography can be performed, leakage of dye from the optic disc and disturbances of the retinal pigment epithelium may be observed to develop (Bird et al., 1980). These findings will be further discussed under 2.2.4.2 and 2.2.4.3.

Oral DEC-C also has a marked effect in "mobilizing" microfilariae of *O. volvulus*. In the first 24-72 hours after the first dose, considerable numbers may invade the bloodstream, the urine, the sputum, the cerebrospinal fluid (CSF) and the tears (Duke et al., 1976a). They may even enter hydrocoele fluid (Kale, 1979).

The possible immunological mechanisms underlying the reaction to DEC-C and the possible role of pharmacological mediators secreted by inflammatory cells have been discussed at some length by Henson et al. (1979), and need to be further investigated. More recently, Greene et al. (1980) have suggested that circulating immune complexes may be involved in some aspects of the reaction; but Guerra-Caceres et al. (1980) could find no evidence for this and suggest that the clinical features may be due to release of mediators secreted from inflammatory cells, including eosinophils, in sites where microfilariae are destroyed.

2.2.2.2 Means of reducing the Mazzotti reaction to DEC-C in onchocerciasis

The various elements of the host's clinical response to death of microfilariae under the influence of DEC-C can be roughly quantified and a system has recently been developed for measuring the intensity of the Mazzotti reaction (Awadzi & Gilles, 1980a).

The clinical severity of the Mazzotti reaction can be reduced to some extent in two ways: (a) by the use of anti-inflammatory drugs, and (b) by starting DEC-C treatment with very low doses which are then gradually increased.

(a) Anti-inflammatory and other palliative drugs

Recent trials (Awadzi et al., in preparation) have shown that both cyproheptadine (as representative of the antihistamines) and indomethacin are without effect on any of the elements of the Mazzotti reaction. Of the drugs so far tested in double-blind trials, only corticosteroids have a beneficial action. They greatly reduce all elements of the reaction except the pruritis, which is usually most intense during the first few hours after the first dose of DEC-C, and the rash.

The steroid used should be one with minimal mineral and corticoid effects but with maximal anti-inflammatory action. Probably the best is betamethasone (Duke & Anderson, 1972). Treatment should start 24-48 hours before the first dose of DEC-C is given, the betamethasone being prescribed at 1.0-2.0 mg three times a day for an adult. This dosage should continue until the patient is through the worst of the reaction and most of the microfilariae have disappeared from the skin. The dosage should then be tailed off over a period of four days. If another corticosteroid is used the dosage should be such that it provides a similar anti-inflammatory action. The protective corticosteroid umbrella may be combined with the initial low dosage DEC-C schedule described in (b) below, but in the opinion of Awadzi (1980), provided the corticosteroids are given for 24 hours in advance, it is best to start DEC-C dosage as a single 200 mg daily dose and to continue this for 14 days.

As well as damping down the Mazzotti reaction, corticosteroids may slightly delay the destruction of microfilariae by DEC-C but the extent of this delay is not sufficient to represent any serious drawback (Duke et al., 1976b; Awadzi, 1980).

Aspirin and codeine may also help to reduce pain (in skin, lymph glands and joints), fever and headache during the first days of DEC-C therapy.

(b) Low initial and gradually increasing dosage with DEC-C

The use of low doses of DEC-C at the start of the treatment may also help to reduce the Mazzotti reaction. The course of oral DEC-C should start at 25 mg on the first day for an adult and the dose gradually increased, according to patient response, to perhaps 25 mg morning and evening on the second day, 50 mg morning and evening on the third day, and 100 mg morning and evening on the fourth day. From then on treatment may continue at 200 mg once a day until the microfilarial load in the skin has been reduced to near zero, a process which normally takes seven to 14 days. Higher or more frequent daily dosage is unnecessary (Awadzi & Gilles, 1980b).

Although this is an example of a currently recommended schedule, there is still room for investigation of non-pulsed, steady, low-dose delivery of DEC-C as a possible means of reducing the violence of the Mazzotti reaction.

2.2.3 Treatment with suramin

Suramin is used for its macrofilaricidal action. Unfortunately it is a somewhat toxic drug in its own right and it also has a slow microfilaricidal action against O. volvulus which can cause unpleasant reactions during treatment.

2.2.3.1 Toxic effects of suramin and reactions to treatment

The toxic effects of suramin are varied and upon occasion, they may even be fatal. They are briefly reviewed below.

Collapse has been recorded very occasionally during the first injection of the drug. To avoid this, the first test dose (i.e. 0.1-0.2 g in 1-2 ml water) should be given slowly according to the following schedule:

- (a) inject a few microlitres and wait one minute; if there are no manifestations of collapse
- (b) inject half a millilitre and wait again one minute; if no manifestation of collapse
- (c) inject the rest within one minute; total time of injection = three minutes.

Subsequent mild toxic manifestations, thought to be due to the pharmacological effects of the drug itself, have to be accepted as the price of successful treatment. These include:

- (i) mild albuminuria and a few granular casts in the urine;
- (ii) tenderness of the soles and palms;
- (iii) polyuria and increased thirst;
- (iv) slight tiredness, anorexia and malaise.

More severe toxic manifestations, indicating that treatment should be stopped, are:

- (v) heavy albuminuria with a heavy deposit of granular casts;
- (vi) ulceration of the mouth and tongue;
- (vii) exfoliative dermatitis;
- (viii) diarrhoea lasting more than three days;
- (ix) severe prostration;
- (x) prolonged high fever, sometimes with bronchitis developing.

Reactions, attributable to the effect of the drug on the parasites, are:

- (xi) urticaria and swelling of the parts of the body where adult parasites are located, developing within an hour of the first injection;
- (xii) later, gradually developing tenderness and swelling around nodules or impalpable worms as these are killed by the drug;
- (xiii) deep abscesses centred on deep-lying adult worms;
- (xiv) painful immobilization of the hip joint in a semi-flexed position due to reaction around worm bundles against the capsule of the hip joint;
- (xv) itching, swelling, and inflammation of the skin, with papular and vesicular eruptions, usually followed by desquamation, all associated with death of microfilariae;
- (xvi) swelling, pain and limitation of the joints of the fingers, toes, wrists, ankles, and other limb joints (may be due to the formation of immune complexes as a result of death of parasites).

To these may be added the reactions caused by the drug's effect on intraocular microfilariae. These include:

- (xvii) exacerbation of keratitic lesions;
- (xviii) development of iridocyclitis with threat of anterior and posterior synechiae forming; and
- (xix) possible excitation of optic neuritis or choroidoretinal lesions leading on to post-neuritic optic atrophy and associated loss of the peripheral visual field.

Despite this lengthy list of possible complications, many onchocerciasis patients take suramin well. But in order to reduce or avoid the development of toxic manifestations and other reactions, it now appears that certain principles should be followed during treatment, all of which are discussed in greater detail elsewhere in this paper.

First, an adequate supply of nourishing food and drink should be ensured throughout the course (Duke & Anderson, 1975; see 2.2.1). Second, it is wise to reduce the microfilarial load by means of DEC-C before starting suramin treatment (Anderson & Fuglsang, 1978; see 2.2.3.2). Third, only the lowest effective dosage of suramin should be used, increasing the weekly dose gradually (Rougemont et al., 1980; see 2.2.3.2). Fourth, dangerous systemic toxic reactions must be watched for and treated, as necessary, with corticosteroids (Duke & Anderson, 1972; see 2.2.3.2). Fifth, the possible onset of iridocyclitis must be watched for and, if the patient develops a red eye, immediate symptomatic treatment must be given (see 2.2.4.1(a)).

The exact pathogenesis of the toxic manifestations of suramin is not well understood, owing in part to the lack of autopsy studies from fatal cases. However, one detailed study on a chimpanzee which died while under heavy dosage with suramin has been published (Gibson et al., 1977). In this animal, the primary target organs involved in suramin toxicity included the intestine, kidney, spleen and peripheral blood. There was no degeneration of the adrenal cortex. The toxicity was thought to be related to the known biochemical and pharmacological properties of the drug, which binds to albumin, haemoglobin and other plasma proteins, is an autocoagulant and anticomplement, and inhibits a variety of enzymes including proteases and ATPases.

Little is known about the metabolism, pharmacokinetics or pharmacodynamics of suramin or DEC-C, but studies on this subject, using C^{14} radiolabelled drugs in onchocerciasis patients, are at present in progress and the results should be available soon.¹

¹ These are being carried out at the Onchocerciasis Chemotherapeutic Research Centre in Tamale, Ghana, by Dr K. Awadzi in cooperation with Professor A. Breckenridge at the Department of Clinical Pharmacology, Liverpool University, United Kingdom.

2.2.3.2 Treatment schedules with suramin used either in conjunction with DEC-C or alone

For the definitive treatment of onchocerciasis, especially in individual treatment, a microfilaricidal course of oral DEC-C (as described in 2.2.2.2) is best given as a prelude to treatment with suramin, using the latter drug as far as possible solely to kill the adult worms and bring about a radical cure. In heavily-infected patients suramin is better tolerated, and particularly the dangers associated with its own slow microfilaricidal action (Anderson et al., 1976b) can be reduced if the original load of microfilariae is first greatly reduced or eliminated by DEC-C treatment (Anderson & Fuglsang, 1978). However, in lightly-infected patients, especially in relatively large-scale campaigns, pretreatment with DEC-C may not be practicable, and suramin may have to be used alone.

Recent work on suramin treatment in the context of heavily-infected African patients (especially those whose eyes are at risk) has tended to concentrate on low-total-dose schedules, such as were first used in the Sudan by Dr M. Sherif Dawood. In such patients, a 100% parasitological cure is not usually essential and, rather than run excessive risks of toxic reactions from higher dosage schedules, it is often better to be content with a lower and less toxic schedule provided that it reduces the parasite load sufficiently to prevent the development of serious ocular lesions.

On the other hand, in patients with acute pruritic onchocerciasis (who are usually relatively lightly infected), a 100% parasitological cure may be essential if clinical relief is to be obtained. Such persons may benefit more from the standard course, or from an extension of the low-dose course by one or two more full doses so as to ensure killing all the adult worms.

A typical low-dose schedule for an adult weighing 60 kg or more would be successive weekly doses of 0.2 g, 0.4 g, 0.6 g, 0.8 g, 0.8-1.0 g, 0.8-1.0 g, i.e. a total of 3.6-4.0 g (or 60-67 mg/kg). Courses of this magnitude appear to be effective in killing or permanently sterilizing at least 80% of the adult worms and, by comparison with the previously accepted standard suramin courses (i.e. for a 60 kg adult a test dose of 0.1 g followed by 1.0 g weekly to a total of 5-7 g¹ or 83-117 mg/kg), they appear to produce fewer adverse reactions to early doses, are better tolerated by heavily-infected patients and, when used without previous DEC-C, have a less marked immediate microfilaricidal action (Rougemont et al., 1980, 1981).

Nevertheless, even at this reduced dosage, which appears to be the minimum that is capable of producing an acceptable microfilaricidal action, the microfilaricidal effect of suramin can be sufficient to cause dangerous iridocyclitis with formation of anterior or posterior synechiae; and, as far as the posterior segment of the eye is concerned, it is not yet known whether such low-dose schedules are associated with the subsequent development of optic atrophy (see 2.2.4.2(b)) as can occur with the standard course of suramin (Thylefors & Rolland, 1979). Furthermore, this low-total-dose suramin schedule, although apparently safer than the standard regimen in heavily endemic areas, still cannot be administered indiscriminately to all infected persons, still requires repeated attendance of the patients over at least six weeks, and still does not avoid the difficulties associated with intravenous injections under field conditions or the need for medical supervision.

Following a course of suramin, even if this has been preceded by oral DEC-C, there are usually some microfilariae remaining in the skin and eye. These have emerged from the adult worms before they were killed, and some may even have emerged alive from the uteri of moribund or dead female worms. In the treatment of the individual, it may be desirable to get rid of these microfilariae by further short courses of DEC-C. It is wise to wait until the patient has quite overcome any debilitating effects of suramin before more DEC-C is given, and this may involve waiting for some weeks. When the post-suramin DEC-C is given, betamethasone coverage and a low initial DEC-C dosage are not usually necessary, for the microfilarial concentrations remaining at this stage will probably be low. Dosage at 200 mg DEC-C daily for three days

¹ It should be noted that the manufacturers' "instructions for use" leaflets enclosed with suramin vials often still recommend treatment with 10 weekly doses of 1.0 g for onchocerciasis. Such prolonged and high dosage is unnecessary and greatly increases the risk of toxic reactions.

should suffice, and this course can be repeated monthly until ingestion of the first dose of DEC-C given after the lapse of a month produces no further reaction (i.e. the Mazzotti test is negative). At this stage the infection can be said to have been eliminated.

If suramin has been used without prior DEC-C treatment, the microfilarial concentrations at the end of the course may still be considerable. Full precautions against reactions may then have to be taken if DEC-C is given.

2.2.4 Benefits and risks of DEC-C and suramin treatment in ocular onchocerciasis

2.2.4.1 Effects on the anterior segment

(a) DEC-C

Oral DEC-C has a rapid action on microfilariae in the eye. Those in the cornea and conjunctiva are killed within 24-48 hours and, after an initial period of excessive watering and photophobia, the patient usually experiences a great symptomatic improvement.

Similar rapid death of microfilariae occurs in the anterior uveal tissues, and this may be associated with a red eye, flare, and cells in the anterior chamber - the signs of iridocyclitis. When this happens there is grave danger of synechiae developing, unless symptomatic treatment is promptly given. Atropine drops (1%) should be instilled (having due regard to the risk of glaucoma); local or systemic corticosteroids may be needed; and acetazolamide may be very useful to reduce ocular pressure (Duke & Anderson, 1972, 1975).

Although DEC-C penetrates into the aqueous humor, microfilariae in the anterior chamber are not normally directly affected by the drug. Only when there are many cells in the aqueous humor, as a result of previous inflammation, will the microfilariae be attacked in this site. Nevertheless, the numbers of microfilariae in the anterior chamber decline slowly over one to three weeks of oral DEC-C treatment as the source of supply from the anterior uveal tissues is cut off and those present move out of the chamber (Duke, 1976; Duke et al., 1976b).

The net result of oral DEC-C treatment given under proper supervision is thus usually an immediate benefit to the anterior segment of the eye (Anderson et al., 1976a), and this benefit will be maintained if subsequent suramin treatment kills the adult worms from which further invading microfilariae would come; or if suppressive oral DEC-C treatment is continued regularly thereafter.

(b) Suramin

The beneficial effects of suramin on the anterior segment are essentially long-term and result from the drug killing the adult worms and stopping the further production of microfilariae. On the other hand, the microfilaricidal action of suramin in its own right tends to be dangerous in its effects both on the cornea and the anterior uvea.

The microfilaricidal action of suramin may start after the first or second dose of the course when 1 g is given weekly but it is more likely to come on after the third or fourth dose. Far from being a rapid action such as is seen with oral DEC-C, the microfilaricidal action of suramin is slow and drawn out, lasting for several weeks. During the whole of this period the patient may suffer from an acute or sub-acute kerato-conjunctivitis and/or an iridocyclitis, which can be painful and distressing. The iridocyclitis, if not adequately controlled by symptomatic (see (a) above) or preventive treatment, can produce lasting damage to the eye, especially from formation of synechiae and subsequent secondary glaucoma. It is to help avoid this catastrophe that the pre-suramin DEC-C treatment is recommended and that the low-total-dose suramin schedules, which help to reduce the microfilaricidal action of this drug, have been developed.

2.2.4.2 Effects on the posterior segment

(a) DEC-C

The beneficial effect of oral DEC-C in preventing the development of lesions of the posterior segment of the eye is much less certain and such evidence as there is indicates that any immediate effects of treatment are more likely to be detrimental than beneficial. Lesions of the retina and optic disc have appeared and developed in children with onchocerciasis while on prolonged low dosage treatment with oral DEC-C at 12.5-25 mg daily (Sowa & Sowa, 1978). Furthermore, in a proportion of heavily-infected patients showing microfilariae at the outer canthus and/or with intraocular microfilariae, oral DEC-C treatment appears to provoke the development of inflammatory changes in the optic disc or the retinal pigment epithelium (Bird et al., 1980). In the early stages, these changes are only revealed as arcuate losses of the peripheral visual field or by leakage of dye from the disc or retinal tissues during fluoresceine angiography. Such changes may later develop into the post-neuritic optic atrophy or onchocercal choroidoretinal lesions described by Anderson et al. (1976a) as following on DEC-C treatment.

(b) Suramin

No perimetric or fluoresceine angiography studies have yet been reported on onchocerciasis patients being treated with suramin. However, the development of optic atrophy some months after suramin treatment has been reported in onchocerciasis patients with intraocular microfilariae (Anderson et al., 1976b; Thylefors & Rolland, 1979). The pathogenesis of these lesions may be similar to that following DEC-C.

2.2.4.3 The pathogenesis and further investigation of posterior segment lesions developing during and after chemotherapeutic treatment of ocular onchocerciasis

It seems highly unlikely that either DEC-C or suramin *per se* has any direct toxic action on the tissues of the posterior ocular segment. DEC-C has been used to treat millions of persons with lymphatic filariasis without any reports of eye trouble developing. Similarly suramin has been widely used in the treatment of African trypanosomiasis without reports of such lesions.

The damage to the posterior segment appears to be associated with microfilaricidal treatment but its exact pathogenesis requires further careful investigation. For the time being, it is postulated that drug-induced death of microfilariae in the posterior segment of the eye is the basic cause of these lesions, but whether they result from local inflammatory reactions around dying microfilariae or from a more generalized process, perhaps involving circulating immune complexes (Greene et al., 1980), remains to be established.

It is not yet known how many of the field defects and optic disc leakages of fluoresceine provoked by DEC-C or suramin are transient and how many lead on to permanent damage. Nor is it known whether the development of these lesions can be prevented or reduced by the use of corticosteroids. Nor is it yet possible with any degree of certainty to recognize in advance those in whom such lesions will develop.

The effects of suppressive DEC-C and of low-dose suramin schedules on the posterior segment in onchocerciasis patients with different intensities of infection also need to be investigated both in areas of continuing transmission and in areas where transmission has been interrupted by means of vector control. In the latter environment the length of the interval between interruption of transmission and the giving of treatment may also have to be taken into account.

2.2.4.4 Benefits and adverse effects of chemotherapy on the eye in relation to the natural evolution of ocular onchocerciasis

An important factor to be taken into account when assessing the potential dangers of systemic microfilaricidal treatment, whether with oral DEC-C or with suramin, in ocular onchocerciasis is the expected natural evolution of the untreated disease.

Under conditions of continuing transmission, untreated patients with more than minimal numbers of intraocular microfilariae are at high risk of developing pathology of the anterior or posterior ocular segments, or both, in the natural course of development of the disease (Anderson et al., 1978; Rolland et al., 1978). The considerable potential benefits of treatment, especially to the anterior segment, almost certainly outweigh the possible risks that any drug-induced death of microfilariae in the posterior segment may accelerate damage to the optic nerve head or to the choroidoretinal tissue. This applies particularly to regions, such as the West African savannas where anterior segment disease in the form of sclerosing keratitis is very prevalent, or to Guatemala where most of the blindness is probably due to sequelae of anterior uveitis. Despite the continuing risk of reinfection after treatment, which in the West African forest zone may re-establish infections at their original level within four to nine years (Duke, 1968b), suramin-treated patients from the West African Sudan savanna have been shown to derive considerable benefit, as far as the development of ocular lesions is concerned, over a period as long as 15 years after chemotherapy (Budden, 1976).

Where transmission of O. volvulus has been successfully interrupted by Simulium control, observations from the former onchocerciasis focus in the Kadera valley in Kenya, where the vector S. neavei was eradicated, indicate that eye lesions in infected persons may continue to progress for many years (Roberts et al., 1967). On the other hand, recent thorough sequential ocular examinations in the area of the Onchocerciasis Control Programme in the Volta River Basin indicate that eye lesions in most of those persons already affected do not progress significantly during the first three years following the interruption of transmission (Rolland & Thylefors, 1979; Thylefors and Tonjum, 1980). In such circumstances the potential danger to the posterior segment of giving microfilaricidal treatment may have to be weighed more seriously.

2.2.5 Suppressive treatment with DEC-C

2.2.5.1 Oral treatment

From time to time it has been suggested that DEC-C could be used as a microfilarial suppressant for O. volvulus in order to prevent the development of ocular onchocerciasis, to control the acute skin lesions, and to prevent chronic skin and gland lesions from developing.

First of all, virtually the whole of the patient's initial load of microfilariae has to be cleared from the skin. This can be accomplished either by giving a seven to 14 day course of DEC-C as described in 2.2.2.2 or by giving a weekly dose of DEC-C in the 50-200 mg range for a number of weeks. Once this has been done it is usually possible, by means of a weekly dose of 50-200 mg, to keep the skin and eyes almost free of microfilariae for long periods, despite the continued presence in the body of many fertile adult female worms.

This treatment has been used in individual patients to prevent the development of anterior segment lesions (Anderson et al., 1976a; Sowa & Sowa, 1978). On a larger scale, it could in theory be used to reduce the microfilarial reservoir in man, thus helping to control transmission of the parasite (Duke, 1968a). Unfortunately, in practice, suppressive DEC-C has scarcely ever proved acceptable to infected persons. The pruritic reaction, albeit relatively mild, which normally occurs for two to three days after each dose, is so unpleasant that all but the most highly-motivated patients fail to follow the schedule for long (Anderson et al., 1976b; Sowa & Sowa, 1978). A trial by Rougemont et al. (1976) showed that after one year of self-treatment at a weekly dose of 50 mg more than one-half of the 137 persons treated exhibited a highly significant decrease in microfilarial densities. Unfortunately, a

subsequent examination made after 36 months revealed that the microfilarial loads of all subjects had returned to their original level, indicating an interruption of the self-treatment (Rougemont, A., unpublished data). Only with the most careful supervision is it possible to maintain regular suppressive treatment for several months and this only in small groups of patients (Taylor et al., 1980a).

When considering the possible use of suppressive DEC-C therapy on a large scale to reduce the human microfilarial reservoir and thus to help control transmission, it must also be remembered that the Simulium/O. volvulus transmission relationship in the West African savannas, where blindness is most common, is characterized by the phenomenon of "limitation" (Bain, 1971, 1976; Pichon et al., 1974; Philippon, 1978). This implies that increased intake of microfilariae by the vector above a certain low level does not result in an increased production of infective larvae for transmission. From this it follows, conversely, that microfilarial suppression by means of DEC-C would have to be extremely thorough and widespread if it were effectively to reduce transmission in the absence of vector control. It would almost certainly be very difficult to achieve a sufficiently regular and large-scale coverage with DEC-C in most of the rural communities where onchocerciasis is endemic.

2.2.5.2 The possibility of transepidermal treatment

As an alternative to oral DEC-C, transepidermal DEC-C (as 1-2% lotion) has recently been advocated for microfilarial suppression. In lightly-infected (5-6 mf/skin snip) Liberian patients, seven daily applications of the lotion cleared almost all microfilariae from treated areas of skin but had no action on those in adjacent untreated skin. Skin reactions were reported to be minimal, and it was suggested that DEC-C lotion could provide a new and practical therapy for onchocerciasis (Langham et al., 1978). However, when the lotion was tested on heavily-infected (about 150 mf/skin snip) patients in Sudan, very severe local and systemic reactions resulted, although the reduction in microfilarial counts was less than with oral DEC-C (Hutchinson et al., 1979). These variable results led to the setting-up of two double-blind trials, one comparing DEC-C lotion with oral tablets in Liberia (Taylor et al., 1980a), the other comparing DEC-C lotion with a placebo lotion in Guatemala (Taylor et al., 1980b).

From the results of all these trials, it appears that: (i) DEC-C is absorbed systemically after topical application, albeit at very much reduced levels compared to conventional oral dosage (Hutchinson et al., in preparation); (ii) DEC-C lotion, like oral DEC-C, does not kill or sterilize the adult worms of O. volvulus (Taylor et al., 1980a; Schulz-Key et al., 1979); (iii) the lotion is less effective and slower than the tablets in reducing microfilarial concentrations in the skin (Hutchinson et al., 1979; Taylor et al., 1980a); (iv) the local and systemic side-effects of the lotion are as severe or worse than those of the tablets (Hutchinson et al., 1979; Taylor et al., 1980a); (v) the lotion, in marked contrast to the tablets, has little or no immediate action on microfilariae in the cornea or, apparently, in other ocular tissues even when it is applied to the face (Hutchinson et al., 1979; Taylor et al., 1980a); and (vi) regular use of the lotion over several months may be associated with an increase in intraocular microfilariae and the development of uveitis (Taylor et al., 1980a).

It seems, therefore, that there is no reason to use the lotion, as opposed to oral DEC-C, for suppression of skin microfilariae, unless the psychological appeal of a skin lotion should lead to a greater acceptability of DEC-C in this form. This might be so in some lightly-infected communities where onchocerciasis is predominantly a skin disease. Likewise there is no reason to use the lotion for the treatment and prevention of onchocerciasis in the anterior segment of the eye, which usually responds well, and much more rapidly, to oral treatment with DEC-C given, if necessary, under corticosteroid cover (Anderson et al., 1976a).

There remains only the question of whether DEC-C lotion would be beneficial for the treatment of patients who have considerable numbers of intraocular microfilariae and who may therefore be at risk of developing uveitis or posterior segment lesions including optic neuritis when they are treated with oral DEC-C and/or suramin. The possibility exists that

DEC-C lotion could bring about a decline in the numbers of microfilariae in the posterior segment without directly killing any of those present in the choroid retina or optic nerve; and thus a preliminary course of DEC-C lotion applied for a few weeks might lower the numbers of intraocular microfilariae sufficiently to permit standard treatment with oral DEC-C and suramin to be undertaken subsequently without running such a high risk of developing microfilaricide-induced lesions of the posterior segment. This therapeutic strategy needs to be tested in a controlled clinical trial, which could well be combined with some of the investigations mentioned in 2.2.4.3; but, before this can be done, further controlled data are required to show whether or not DEC-C lotion produces adverse effects on the posterior segment of the eye.

3. CHARACTERISTICS OF THE IDEAL DRUG FOR ONCHOCERCIASIS

The imperfections of DEC-C and suramin centre around the microfilaricidal action of both drugs and the intrinsic toxicity of the second.

The ideal drug for treatment of onchocerciasis would appear to be one with a purely macrofilaricidal action, and effective as a short (preferably one day) course of treatment either by injection or by mouth. Because of the long prepatent interval of O. volvulus, which is normally about 15 months (Duke, 1980), such a drug given once a year for two to three years could probably, by itself and without vector control, bring about the elimination of the parasite from the population. Furthermore, in all except a few of the most severe cases of ocular onchocerciasis, it would suffice, once the adult worms have been killed, to leave the microfilarial load to decline naturally from old age without treatment with a microfilaricide; while for those few patients whose eyes are in immediate danger from the existing load of microfilariae, careful use could be made of DEC-C under corticosteroid cover.

The nearest approach to a drug with an almost entirely macrofilaricidal action was the organic arsenical, melarsonyl potassium, otherwise known as Mel W or Trimelarsan (Friedheim, 1962). Unfortunately, the use of this preparation, which at first appeared very promising for the treatment of onchocerciasis on a large scale (Duke, 1970b), had to be abandoned because of the unpredictable risk of arsenical encephalopathy (Duke, 1966, 1970b). What is now needed is a non-toxic compound having a similar action on O. volvulus.

RESUME

Cette communication expose les idées qui ont cours aujourd'hui concernant le traitement de l'onchocercose par le citrate de diéthylcarbamazine (C-DEC) et la suramine. Les recherches des cinq dernières années ont enrichi nos connaissances sur les dangers que peuvent présenter ces deux médicaments et sur la meilleure façon de les utiliser, notamment contre l'onchocercose oculaire. Dans le texte, les thérapeutiques actuellement recommandées sont passées en revue à la lumière des plus récents progrès scientifiques.

Le traitement définitif de l'onchocercose repose principalement sur la chimiothérapie au moyen du C-DEC et de la suramine, mais la nodulectomie peut jouer un rôle auxiliaire. En tant que méthode de lutte, elle n'a apparemment guère d'effets, ou même n'en a aucun, sur le réservoir de microfilaries entretenant la transmission; quant à ses avantages cliniques, ils se bornent probablement à la protection plus ou moins grande que l'ablation précoce des nodules siégeant au niveau de la tête peut conférer contre l'onchocercose oculaire. Cependant, l'examen des nodules excisés, en tant que moyen d'évaluer l'action des médicaments sur les vers adultes, a acquis beaucoup d'intérêt depuis qu'on a découvert que ces nodules peuvent être digérés dans la collagénase et fournir ainsi des vers adultes en bon état, voire parfois vivants.

En chimiothérapie de l'onchocercose, l'emploi du C-DEC et de la suramine soulève un certain nombre de questions liées à l'action microfilaricide des deux médicaments et à la toxicité intrinsèque du second. Le bon état général et le bien-être du malade durant le traitement présentent une importance capitale, car les risques et difficultés varient selon l'état du patient et selon l'intensité de l'infection.

Avec le C-DEC, produit couramment employé aujourd'hui pour tuer les microfilaries d'Onchocerca volvulus, se pose le problème de la réaction de Mazzotti. Cette dernière, habituellement localisée à la peau mais éventuellement associée à des réactions générales, résulte de la mort des microfilaries. Elle peut être si grave que, pour la limiter, il est hautement souhaitable d'administrer des anti-inflammatoires ou de commencer le traitement par de très faibles doses de C-DEC qui seront progressivement augmentées.

Quant à la suramine, microfilaricide exerçant une action microfilaricide lente contre O. volvulus, elle peut avoir divers effets toxiques susceptibles à l'occasion de se révéler mortels. En outre, l'action microfilaricide risque de provoquer des réactions déplaisantes au cours du traitement.

La communication résumée ici examine les avantages et les inconvénients des deux médicaments susmentionnés contre l'onchocercose oculaire, notamment en ce qui concerne les segments antérieur et postérieur de l'oeil et compte tenu de l'évolution naturelle de la maladie.

On parle ensuite du traitement suppressif au moyen de C-DEC administré par voie orale ou sous forme de lotion à 1-2 % agissant à travers l'épiderme.

La conclusion est que l'idéal serait un médicament à action purement microfilaricide qui se montrerait efficace en traitement de brève durée (un jour de préférence) par injection ou par voie orale. Etant donné la longue période de prépatence d'O. volvulus (d'habitude, environ 15 mois), l'administration une fois par an pendant deux ou trois ans d'un produit de ce genre pourrait vraisemblablement à elle seule, et sans opérations de lutte antivectorielle, amener l'élimination du parasite dans une population. En outre, dans tous les cas d'onchocercose oculaire, sauf quelques-uns des plus graves, il suffirait, une fois les vers adultes tués, de laisser la charge microfilarienne diminuer naturellement sans recourir à un microfilaricide; quant aux malades peu nombreux pour les yeux desquels la charge existante de microfilaries représenterait un danger immédiat, ils pourraient être traités, avec prudence, au C-DEC sous couvert de corticostéroïdes.

REFERENCES

- Anderson, J. & Fuglsang, H. (1978) Further studies on the treatment of ocular onchocerciasis with diethylcarbamazine and suramin. British Journal of Ophthalmology, 62: 450-457
- Anderson, J., Fuglsang, H., Hamilton, P. J. S. & Marshall, T. F. de C. (1975) The prognostic value of head nodules and microfilariae in the skin in relation to ocular onchocerciasis. Tropenmedizin und Parasitologie, 26: 191-195
- Anderson, J., Fuglsang, H. & Marshall, T. F. (1976a) Effects of diethylcarbamazine on ocular onchocerciasis. Tropenmedizin und Parasitologie, 27: 263-275
- Anderson, J., Fuglsang, H. & Marshall, T. F. (1976b) Effects of suramin on ocular onchocerciasis. Tropenmedizin und Parasitologie, 27: 279-296
- Anderson, J., Fuglsang, H., Marshall, T. F. de C., Radolowicz, A. & Vaughan, J. P. (1978) Studies on onchocerciasis in the United Cameroon Republic. IV. A four-year follow-up of six rain-forest and six savanna villages. The incidence of ocular lesions. Transactions of the Royal Society of Tropical Medicine and Hygiene, 72: 513-515
- Awadzi, K. (1980) Chemotherapy of onchocerciasis: clinical trials at Tamale (Unpublished WHO document TDR/FIL/SWG(5)/80 Working Paper No. 13)
- Awadzi, K. & Gilles, H. M. (1980a) The chemotherapy of onchocerciasis. II. Quantitation of the clinical reaction to microfilaricides. Annals of Tropical Medicine and Parasitology, 74: 189-197
- Awadzi, K. & Gilles, H. M. (1980b) The chemotherapy of onchocerciasis. III. A comparative study of diethylcarbamazine (DEC) and metrifonate. Annals of Tropical Medicine and Parasitology, 74: 199-210
- Bain, O. (1971) Transmission des filarioses. Limitation des passages des microfilaries ingérées vers l'hémocèle du vecteur, interprétation. Annales de Parasitologie Humaine et Comparée, 46: 613-631
- Bain, O. (1976) Traversée de la paroi stomacale du vecteur par les microfilaries: techniques d'étude utilisées, importance épidémiologique. Bulletin of the World Health Organization, 54: 397-401
- Bird, A. C., El-Sheikh, H., Anderson, J. & Fuglsang, H. (1980) Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate. British Journal of Ophthalmology, 64: 191-200
- Bryceson, A. D. M., Warrell, D. A. & Pope, H. M. (1977) Dangerous reaction to treatment of onchocerciasis with diethylcarbamazine. British Medical Journal, 1: 742-744
- Budden, F. H. (1976) The natural history of ocular onchocerciasis over a period of 14-15 years and the effect on this of a single course of suramin. Transactions of the Royal Society of Tropical Medicine and Hygiene, 70: 484-491
- Copeman, D. B. (1979) An evaluation of the bovine - Onchocerca gibsoni, Onchocerca gutturosa model as a tertiary screen for drugs against Onchocerca volvulus in man. Tropenmedizin und Parasitologie, 30: 469-474
- De León, J. R. & Duke, B. O. L. (1966) Experimental studies on the transmission of Guatemalan and West African strains of Onchocerca volvulus by Simulium ochraceum, S. metallicum and S. callidum. Transactions of the Royal Society of Tropical Medicine and Hygiene, 60: 735-752

- Duke, B. O. L. (1966) A fatality during treatment of onchocerciasis with Mel W. Transactions of the Royal Society of Tropical Medicine and Hygiene, 60: 691-692
- Duke, B. O. L. (1968a) The intake and transmissibility of Onchocerca volvulus microfilariae by Simulium damnosum fed on patients treated with diethylcarbamazine, suramin or Mel W. Bulletin of the World Health Organization, 39: 169-178
- Duke, B. O. L. (1968b) Reinfections with Onchocerca volvulus in cured patients exposed to continuing transmission. Bulletin of the World Health Organization, 39: 307-309
- Duke, B. O. L. (1970a) Onchocerciasis; deep worm bundles close to the hip joints. Transactions of the Royal Society of Tropical Medicine and Hygiene, 64: 791-792
- Duke, B. O. L. (1970b) The effects of drugs on Onchocerca volvulus. 4. Trials of melarsonyl potassium. Bulletin of the World Health Organization, 42: 115-127
- Duke, B. O. L. (1975) Further trial of levamisole against Onchocerca volvulus. Transactions of the Royal Society of Tropical Medicine and Hygiene, 69: 287-288
- Duke, B. O. L. (1976) Route of entry of Onchocerca volvulus microfilariae into the eye. Transactions of the Royal Society of Tropical Medicine and Hygiene, 70: 90-91
- Duke, B. O. L. (1980) Observations on Onchocerca volvulus in experimentally infected chimpanzees. Tropenmedizin und Parasitologie, 31: 41-54
- Duke, B. O. L. & Anderson, J. (1972) Onchocerciasis and its treatment. Tropical Doctor, 2: 107-114
- Duke, B. O. L. & Anderson, J. (1975) Onchocerciasis. Tropical Doctor, 5: 141-142
- Duke, B. O. L., Vincelette, J. & Moore, P. J. (1976a) Microfilariae in the cerebrospinal fluid, and neurological complications during treatment of onchocerciasis with diethylcarbamazine. Tropenmedizin und Parasitologie, 27: 123-132
- Duke, B. O. L., Moore, P. J. & Vincelette, J. (1976b) The population dynamics of Onchocerca volvulus microfilariae during treatment with suramin and diethylcarbamazine. Tropenmedizin und Parasitologie, 27: 133-144
- Friedheim, E. A. H. (1962) Mel W in the treatment of filariasis due to Wuchereria bancrofti; results in 35 cases observed for 10-12 months after treatment. Annals of Tropical Medicine and Parasitology, 56: 343-342
- Fuglsang, H. & Anderson, J. (1974) Collapse during treatment of onchocerciasis with diethylcarbamazine. Transactions of the Royal Society of Tropical Medicine and Hygiene, 68: 72-73
- Fuglsang, H. & Anderson, J. (1977) The concentration of microfilariae in the skin near the eye as a simple measure of the severity of onchocerciasis in a community and as an indicator of danger to the eye. Tropenmedizin und Parasitologie, 28: 63-67
- Fuglsang, H. & Anderson, J. (1978) Further observations on the relationship between ocular onchocerciasis and the head nodule, and on the possible benefit of nodulectomy. British Journal of Ophthalmology, 62: 445-449
- Gibson, D. W., Duke, B. O. L. & Connor, D. H. (1977) Histopathological studies on suramin toxicity in a chimpanzee, Tropenmedizin und Parasitologie, 28: 387-405
- Greene, B. M., Taylor, H. R., Humphrey, R. L. & Lawley, T. J. (1980) Circulating immune complexes in onchocerciasis: significance and influence of diethylcarbamazine therapy. Clinical Research, 28: 370A

- Guerra-Caceres, J. G., Bryceson, A. D. M., Quakyi, I. & Spry, C. J. F. (1980) Studies on the mechanisms of adverse reactions produced by diethylcarbamazine in patients with onchocerciasis - Mazzotti reaction. Parasite Immunology, 2: 121-131
- Henson, P. M., Mackenzie, C. D. & Spector, W. G. (1979) Inflammatory reactions in onchocerciasis: a report on current knowledge and recommendations for further study. Bulletin of the World Health Organization, 57: 667-682
- Hutchinson, D. B. A., El-Sheikh, H., Jones, B. R., Anderson, J., Fuglsang, H. & Mackenzie, C. D. (1979) Adverse reactions to cutaneous diethylcarbamazine in onchocerciasis. Lancet, 2: 46
- Kale, O. O. (1979) Effect of diethylcarbamazine on the concentration of Onchocerca volvulus microfilariae in hydrocoele fluid and urine. Journal of Helminthology, 53: 169-174
- Langham, M. E., Traub, R. & Richardson, R. (1978) A transepidermal chemotherapy of onchocerciasis. Tropenmedizin und Parasitologie, 29: 156-162
- Mazzotti, L. (1948) Posibilidad de utilizar como medico diagnostico en la oncocercosis las reacciones alergicas consecutivas a la administracion de Hetrazan. Revista del Instituto de Salubridad y Enfermedades Tropicales (Mexico), 9: 235-237
- Philippon, B. (1978) L'onchocercose humaine en Afrique de l'Ouest - vecteurs, agent pathogene, epidemiologie, lutte. Documentations techniques No. 37, ORSTOM, Paris
- Pichon, G., Perrault, G. & Laigret, J. (1974) Rendement parasitaire chez les vecteurs de filarioses. Bulletin of the World Health Organization, 51: 517-524
- Rée, C. H. (1977) Onchocerciasis treated with diethylcarbamazine. British Journal of Dermatology, 97: 551-554
- Roberts, J. M. D., Neumann, E., Goeckel, C. W. & Highton, R. B. (1967) Onchocerciasis in Kenya 9, 11 and 18 years after elimination of the vector. Bulletin of the World Health Organization, 37: 195-212
- Rolland, A. & Thylefors, B. (1979) Aspects évolutifs de l'onchocercose oculaire en Afrique occidentale, après trois ans de lutte antismulidienne. Tropenmedizin und Parasitologie, 30: 409-552
- Rolland, A., Thylefors, B. & Pairault, C. (1978) Evolution sur neuf ans de l'onchocercose oculaire dans une communauté villageoise d'Afrique occidentale. Bulletin of the World Health Organization, 56: 805-810
- Rougemont, A., Boisson, M. E., Borges da Silva, G. & Zander, N. (1976) Un essai de traitement collectif par la diéthylcarbamazine dans un village d'hyperendémie onchocerquienne de la région de Bamako (Mali). Bulletin of the World Health Organization, 54: 403-410
- Rougemont, A., Thylefors, B., Ducan, M., Prost, A., Ranque, Ph. & Delmont, J. (1980) Traitement de l'onchocercose par la suramine à faibles doses progressives dans les collectivités hyperendémiques d'Afrique de l'ouest. I. Résultats parasitologiques et surveillance ophthalmologique en zone de transmission non interrompue. Bulletin of the World Health Organization, 58: 917-922
- Rougemont, A., Hien, M., Thylefors, B., Prost, A., Schulz-Key, H. & Rolland, A. (1981) Traitement de l'onchocercose par la suramine à faibles doses progressives dans les collectivités hyperendémiques d'Afrique occidentale. II. Résultats cliniques, parasitologiques et ophthalmologiques en zone de transmission interrompue. Bulletin of the World Health Organization (In press)

- Schulz-Key, H., Albiez, E. J. & Buettner, D. W. (1977) Isolation of adult Onchocerca volvulus from nodules. Tropenmedizin und Parasitologie, 28: 428-430
- Schulz-Key, H., Taylor, H. R. & Greene, B. M. (1979) Investigations on adult Onchocerca volvulus for the evaluation of a trial with oral and topical diethylcarbamazine (DEC). In: Annual report of the Liberia Research Institute of the Tropical Institute Hamburg for the year 1979, pp. 9-12
- Schulz-Key, H., Jean, B. & Albiez, E. J. (1980) Investigations on female Onchocerca volvulus for the evaluation of drug trials. Tropenmedizin und Parasitologie, 31: 34-40
- Sowa, J. & Sowa, S. C. I. (1978) Long-term treatment of onchocerciasis in children with low doses of diethylcarbamazine. Annals of Tropical Medicine and Parasitology, 72: 79-85
- Taylor, H. R., Greene, B. M. & Langham, M. E. (1980a) Controlled clinical trial of oral and topical diethylcarbamazine in treatment of onchocerciasis. Lancet, 1: 943-946
- Taylor, H. R., Langham, M. E., Stahl, E. M. de, Figueroa, L.-N. & Beltranena, F. (1980b) Chemotherapy of onchocerciasis: a controlled clinical trial of topical diethylcarbamazine (DEC) in Guatemala. Tropenmedizin und Parasitologie, 31: 357-364
- Thylefors, B. & Rolland, A. (1979) The risk of optic atrophy following suramin treatment of ocular onchocerciasis. Bulletin of the World Health Organization, 57: 479-480
- Thylefors, B. & Tonjum, A. M. (1980) A three-year follow-up of ocular onchocerciasis in an area of vector control. Bulletin of the World Health Organization, 58: 107-112
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