Current Practice

MEDICINE IN THE TROPICS

Onchocerciasis

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Brit. med. J., 1968, 4, 301–307

The term onchocerciasis includes all morbid conditions resulting from infection with the filarial worm *Onchocerca volvulus*. The parasite is transmitted by "black-flies" of the genus *Simulium* and is confined to parts of tropical Africa and America. In Africa the disease may be contracted over a wide belt between Senegal and Angola in the west across to Abyssinia and Tanzania in the east. Within this area foci of transmission are restricted to the neighbourhood of fast-flowing stretches of rivers and streams which provide suitable breeding sites for the vectors *S. damnosum* and *S. neavei*. In the Americas there are foci of the disease in the mountainous coffee-growing areas of Guatemala and Mexico, where the main vector is *S. ochraceum*, and in lower-lying country in Venezuela and Columbia, where the vector is *S. metallicum*. A small focus is thought to exist in the Yemen.

Life Cycle of Parasite

The life cycle of the parasite and the duration of the various stages must be understood in order to appreciate the development of the disease in the patient. When an infective female *Simulium* bites man, a number of infective larvae (700μ in length) are inoculated. These larvae do not multiply in the human host, but each remains a single worm which grows and matures over a period of about a year. The mature males (2–4 cm.) and females (40–50 cm.) collect in tangled balls, bound together by fibrous tissue to produce the nodules which are typical of the disease. Each fertilized female worm produces large numbers of viviparous embryos or microfilariae (200–300μ), which invade the skin and remain there until they die or are ingested by a feeding *Simulium*. Only in the fly do they undergo development (again without any multiplication), so that some of them eventually reach the infective larval stage in the proboscis.

The time between the inoculation of infective larvae into the human host and the first appearance of microfilariae producing symptoms in the skin (i.e., the pre-patent interval) is commonly 15 to 18 months, with extremes of 10 to 20 months. The time needed for the passage of microfilariae from the nodules to the skin is probably four to six weeks. The life-span of the microfilariae in the skin may be as long as 30 months, and the fecund female worms can live for up to 15 years. The development from microfilaria to infective larva in *Simulium* depends largely on the external temperature, but is usually within the range of 6–10 days.

The fact that there is no multiplication of the parasite during development in man means that heavy infections can build up only from repeated inoculation of infective larvae following prolonged exposure to transmission.

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Pathological Changes

The microfilariae are responsible for most of the pathological lesions in onchocerciasis. They invade the skin, and from there enter the eye. Although in many persons they may be well tolerated, their death in the tissues is always associated with a minute foreign body reaction and the formation of fibrous tissue. The severity of these reactions, and the amount of damage done, vary with the individual.

The adult worms produce nodules, which when subcutaneous are visible and palpable and are usually situated over bony prominences. Over the scalp they may erode the bone. Many other adult worms lie encapsulated deep between the muscles and are impalpable. Their death may lead to abscess formation.

The production of toxins by adult worms or microfilariae has never been demonstrated, but their existence has been suspected at various times to account for certain lesions, notably those of the posterior segment of the eye.

Clinical Picture and Diagnosis

Broadly speaking, patients presenting with clinical onchocerciasis fall into two categories, which will be considered separately.

(1) Those with recently acquired, relatively light but "acute" infections presenting with an intensely pruritic skin rash, sometimes known as the "filarial itch." The chief sufferers in this group are children living in areas where onchocerciasis is endemic, and adults (including expatriates) who come to live therein without having had any previous exposure to infection.

(2) Those with heavy infections of long duration who present with deteriorating vision or gross skin manifestations. They are usually adult natives of heavily endemic areas.

Light, Recently Acquired Infections

Patients in this group are usually experiencing their first infection, and an adult female worm or worms (usually impalpable) are assumed to be present between the muscles or in the subcutaneous tissues around the limb girdle on the affected side. Microfilariae from these worms then invade the skin of the anatomical quarter concerned and produce the characteristic lesions.

The usual picture is of a persistent and intensely itchy rash, mainly confined to one anatomical quarter of the body. The area affected is typically lop-sided, comprising the buttock, thigh, and leg on one side with minor extensions on to the other buttock and thigh and up the back; or it comprises the shoulder and arm on one side with minor extensions across the back

and up the side of the neck. The rash is composed of numerous small circular, raised, discrete papules, 1–3 mm. in diameter, which are usually red when seen on a white skin. There are often urticarial overtones, together with scratch marks and excoriations, which may become secondarily infected, producing ulcers and boils. Less often the patient presents with thickening and lichenification of the skin of the affected part, and pruritus is minimal. There may be a deep-seated ache in the limb concerned.

The eyes are not commonly affected in these early cases unless the infection stems from a nodule on the head. Occasional microfilariae may invade the eyes, but lesions are unlikely to be severe. A few small, fluffy opacities may be found in the cornea which clear with treatment of the parasitic infection, and occasionally a phlyctenular conjunctivitis is seen.

Diagnosis can be confirmed by finding microfilariae in shavings of skin, known as "snips," taken from the affected part. After cleaning the skin with spirit and allowing to dry, an entomological pin mounted in a holder is inserted into the epidermis, thereby raising a small, cone-shaped fold of skin. The base of this cone is then sliced off with a safety razor blade, removing a small piece of skin 2–3 mm. in diameter and 0.5–1.0 mm. deep. The snip itself should be bloodless, but blood will well up into the tissue bed from which it was taken. The snip is placed in physiological saline, torn to shreds with stout needles, and examined in a wet state under the microscope (×25 or ×50) at intervals over the ensuing 10 minutes for the presence of microfilariae. The microfilariae of *O. volvulus* are relatively large and sturdy, 200–300μ in length; they have no sheath, the head is bulbous, the tail pointed, and they exhibit active lashing and wriggling movements. In practice, they have to be distinguished only from the other skin-dwelling microfilariae of *Dipetalonema streptocerca*, which are thinner, have shepherd's crook tails, and make shivering and stretching movements. Distinction is easy once both have been seen. If there is any doubt, the specimen can be dried, fixed in methyl alcohol, and stained for expert examination and comparison with textbook figures.

Microfilariae may also be seen in the anterior chamber of the eye using a slit lamp; or they may be viewed with an opthalmoscope, using a plus 20–32 lens, when they appear as dark, wriggling threads against the light reflected from the optic disc.

Skin snips are painful and unpopular with the patient and in many early cases microfilariae are very hard to find. If 2–4 snips from different areas of affected skin have proved negative, then Mazzotti's test should be performed. This consists in observing the reaction to a test dose of 50 mg. diethylcarbamazine given by mouth. From 2 to 24 hours later, if the test is positive, there will be an acute exacerbation of itching and of the rash, mainly over the affected area but often spreading more widely still. The reaction is due to the drug "unmasking" live microfilariae, which are suddenly recognized by the tissues as foreign bodies to be attacked and destroyed.

In general practice the diagnosis of onchocerciasis must depend on the clinical picture, the finding of microfilariae, and the result of Mazzotti's test. Although eosinophilia in the region of 700–1,500/cu. mm. is also suggestive it is of little aid in diagnosis, for it can be associated with many other tropical parasites. Complement-fixation tests and skin tests are not at present specific, for they depend on *Dirofilaria* antigens. They are suitable only for specialist hospital use.

Differential Diagnosis of "Filarial Itch"

The acute pruritic onchocercal rash has to be distinguished from the following:

Streptocerciasis.—Infections with the filarial parasite *D. streptocerca*, which is transmitted by *Culicoides grahamii*, are usually asymptomatic, but they may produce an itching "microfilarial" rash almost exactly like that of *O. volvulus*. The distribution may well be asymmetrical, but is most likely to be over the back, shoulders, and arms. The lower limbs are rarely affected. Diagnosis rests on the patient coming from an area where the parasite is common (for example, Ghana, Cameroon), on the finding of *D. streptocerca* microfilariae in skin snips, and the fact that the positive Mazzotti test is unlikely to be elicited with doses of less than 200 mg. of diethylcarbamazine. The infection can be eliminated by treatment with this drug alone.

Scabies.—The distribution of the eruption is more symmetrical. Typical burrows and the mite itself should be looked for between the fingers and at the umbilicus, and the response to application of 25% monosulphiram will be dramatic. In Africa, scabies and onchocerciasis are frequently found in the same patient, and it is not uncommon to find the *Sarcoptes* in a skin snip.

Insect Bites.—The bites of *Culicoides* or other insects, when numerous, may produce widespread itching eruptions, superficially similar to those of onchocerciasis, especially when they are obscured by scratching and secondary infection. This condition can be distinguished from onchocerciasis by the fact that the rash is found on the exposed parts of the body and generally occurs only during the first two to three months of sojourn in a new area (that is, long before locally acquired onchocerciasis could develop). Thereafter it improves as the patient becomes desensitized to the local biting flies. The condition is often mistaken by nervous, newly arrived expatriates for an attack of "the filaria."

Prickly Heat.—The eruption is usually much finer, the distribution more symmetrical, and especially marked on pressure areas. Asymmetrical lesions may cause difficulty, but Mazzotti's test is negative, and there is a response to cooler conditions, calamine, and dusting powders.

Contact Dermatitis.—This may be a source of confusion if the area of contact mimics a typical onchocercal distribution. Careful history and examination, the "sore" as opposed to itchy character of the rash, the absence of microfilariae, and the negative Mazzotti response should lead to accurate diagnosis.

Sycosis Cruris.—This indolent, probably bacterial infection, confined to the skin of the lower legs in Africans, is not related to onchocerciasis. The eruption is mainly over the shins, but may extend laterally to reach the posterior surface of the leg below. The lesions are confluent with a fairly sharp edge, no microfilariae can be found, and the response to treatment, even with antibiotics, is poor.

Heavy Infections of Long Standing

Patients in this group are indigenous to areas of heavy endemicity. They have built up heavy loads of adult worms and microfilariae as a result of long-standing and intense transmission, and they exhibit gross scarring of the tissues.

Skin Lesions.—In Africa the skin lesions are commonest over the lower limbs, but may cover the whole body. There is heavy lichenification and thickening of the skin, so that it comes to resemble that of a lizard or crocodile, or atrophic changes may supervene, producing a skin like tissue-paper over the legs, which becomes increasingly susceptible to tropical ulceration following minor abrasions. Mottled depigmentation, especially over the shins, is common. Enlargement of the femoral and inguinal lymph glands is seen, sometimes to the extent that they come to lie in pockets of skin, giving the condition known as "hanging groin," which in turn predisposes to herniae. Elephantiasis of the lower limbs, or of the scrotum with associated hydrocele, sometimes develops.

All these gross conditions are sufficiently characteristic to be easily recognized in a population where the disease abounds,

and in such persons the microfilariae can readily be demonstrated, often in enormous numbers, in skin snips taken from the lateral side of the calf or from the buttocks.

In the Central American form of the disease, gross skin changes are less marked even when microfilariae are abundant, but heavily infected persons, especially children, may show peculiar angry, reddish-mauve lesions on the face known as *erisipela de la costa*. Diagnostic snips are best taken from the scapular, buttock, or face regions.

Eye Lesions.—The lesions that may be produced in the eye from long-standing onchocerciasis are manifold. Most of them result from the invasion of microfilariae, which subsequently die and damage the delicate and specialized tissues, but the pathogenesis of the posterior segment lesions remains a subject of vehement discussion among opthalmologists.

Severe eye lesions are usually found in persons who have been heavily infected for a long period of time (20–40 years), but the presence of one or more nodules on the head is likely to give rise to eye lesions much more rapidly, owing to the increased ease with which microfilariae can invade that organ. Blinding lesions are most commonly encountered (*a*) in Central America, where nodules on the head are frequent, and (*b*) in the hot northern savanna regions of Africa. In forest areas of Africa onchocercal blindness is rare.

The eye lesions in onchocerciasis are steadily progressive, and the manifestations most often seen in heavily infected persons are as follows. (1) Photophobia and a chronic conjunctival inflammation. (2) Sclerosing keratitis with tongues of vascularized fibrous tissue invading the cornea from the limbus, typically at 4 o'clock and 8 o'clock, and eventually forming a pannus over the lower half of the cornea. This is virtually the only sign which is pathognomonic of onchocerciasis. (3) Chronic iridocyclitis, subject to acute or subacute exacerbations with a red eye, producing ultimately a pummice-stone iris and posterior synechiae. The extreme case shows typically a pear-shaped pupil pulled downwards, and there is a cellular and microfilarial exudate at the bottom of the anterior chamber. Secondary glaucoma and cataract often ensue and cause blindness. (4) Lesions of the posterior segment, which may be localized or generalized. Subjectively they begin with a characteristic difficulty in twilight vision. The basic pathological change appears to be a choroidal sclerosis, with associated derangement of the retinal tissues and pigment, and thinning and sheathing of the retinal vessels. Ultimately there is a degeneration of the retina so that the sclerosed choroidal vessels are visible against a background of white sclera and dark choroidal pigment, giving a "cracked mud" appearance. Consecutive optic atrophy follows.

The detection of eye lesions requires careful examination with lens and loupe, with a slit lamp if available, and with the ophthalmoscope. The differential diagnosis may be difficult in advanced cases and is from a multitude of conditions, some of which may coexist in the same patient. Among them must be considered leprosy, syphilis, alcohol poisoning, trachoma, and hereditary abiotrophies of the retina. In patients with onchocerciasis the parasite should always be considered first as a possible cause of any eye lesion.

Treatment

In areas of light to moderate endemicity a great number of persons carrying infections with *O. volvulus* live in asymptomatic harmony with their parasites and are not in need of treatment. If they are treated the natural host–parasite balance established over a lifetime will be upset, and subsequent reinfections, which are often inevitable, will probably be symptomatic and require further courses of treatment as often as they arise.

When treatment is undertaken the aim should be to eliminate the parasites which are the root cause of the lesions, leaving the tissues to heal themselves as far as possible. If fibrosis and scarring are already advanced, these processes can only be arrested, and little but symptomatic improvement can be expected.

The elimination of the parasites can be achieved by nodulectomy, or, more commonly, by chemotherapy.

Nodulectomy.—Nodulectomy is performed under local anaesthesia with procaine and adrenaline, using curved blunt-pointed scissors to open up the cleavage plane between the fibrous capsule of the nodule and the subcutaneous connective tissue in which it lies. It is most effective when palpable nodules are situated on the head and neck and microfilarial invasion of the eye is a serious risk, and in Central America regular annual nodulectomy campaigns have greatly reduced the incidence of blindness. It is also of use when it is believed that a single palpable nodule is the sole origin of the infection, especially if chemotherapy is contraindicated for some reason.

In the majority of cases, however, nodulectomy is of limited application because many of the adult worms lie deep in the tissues and cannot be located for excision.

Chemotherapy.—Only two drugs are to be recommended for use against *O. volvulus*: diethylcarbamazine, which kills the microfilariae but has little or no effect on the adult worms, and suramin, which kills the adult worms and many, but not all, of the microfilariae.

Antimonial and arsenical preparations should not be used. The former are generally ineffective and toxic to the patient. Of the latter, melarsonyl had a recent vogue as a macrofilaricide, but is now known to give rise to fatal arsenical encephalopathies in a quite unpredictable manner in a small but significant proportion of cases. This being so, there can be no justification for its use in a non-fatal disease.

Lightly Infected Patients

In lightly infected patients with the "filarial itch" it is usual to give a course of diethylcarbamazine, which kills the microfilariae and after an initial exacerbation of symptoms brings about their temporary relief.

Dosage for an adult should be given after meals, as follows: day one, 50 mg.; day two, 50 mg. t.i.d.; day three, 100 mg. t.i.d.; days four to ten, 200 mg. t.i.d. The intrinsic toxicity of the drug is very low, and in patients not harbouring filariae no more than slight dizziness, nausea, and sleepiness follow doses double the maximum recommended here. The reactions attending its use in onchocerciasis are due to the destruction of microfilariae in the tissues, and include intense itching, dermatitis, oedema of the skin followed by desquamation, fever, headache, and malaise. If microfilariae are present in the eyes there may be conjunctivitis and iridocyclitis. Temporarily incapacitating and distressing though it may be, the reaction seldom lasts more than four days. The patient should be encouraged to endure it with fortitude, and some relief may be obtained from antihistamines and analgesics. If the reaction is very severe more effective control can be achieved, without loss of microfilaricidal action, by a short course of betamethazone (1 mg. t.i.d. for two days; 0.5 mg. t.i.d. for two days; 0.25 mg. t.i.d. for two days). However, this drug should not be given routinely, for in tropical conditions facilities may not exist to exclude tuberculosis, peptic ulceration, or other contraindications to its use. Local application of cortisone and of mydriatics to the eye may be needed if a flare-up of iridocyclitis occurs. Secondary sepsis of the skin resulting from scratching must be treated on general lines.

When the initial load of microfilariae has been eliminated by diethylcarbamazine, a course of suramin injections should

be given to kill the adult worms. Suramin is a cumulative drug, slowly excreted via the kidney over two to three months. An initial test dose of 0.1 g. is given to test for a rare idiosyncrasy, and thereafter an adult of 60 kg. or over should receive 1.0 g. weekly to a total of 6 g. Suramin powder must be stored in a dry place and away from light. Each gramme of powder must be freshly dissolved in 10 ml. sterile, pyrogen-free distilled water, without heating, and the solution must be injected intravenously not more than 30 minutes after preparation, taking one to two minutes over the injection. Before each injection the urine must be examined for albumin and granular casts. Slight albuminuria and occasional casts frequently appear as the course proceeds, but these are not necessarily indications to stop treatment. If, however, the albuminuria exceeds the grade loosely termed "one plus" (+), that is, 20–30 mg./100 ml., and if many casts appear, treatment should be stopped or the next injection should be postponed. The albuminuria clears completely in about six weeks as the drug is excreted, and no permanent kidney damage has been reported.

To avoid toxic manifestations clinical judgement must be relied upon when considering whether to proceed with suramin treatment. Stomatitis, persistent diarrhoea, or severe lassitude and weakness are danger signs associated with the drug itself, and, rarely, an exfoliative dermatitis and prolonged fever result. Tenderness of the soles and palms is common but unimportant; the death of adult worms may be indicated by pain and swelling in nodules, and towards the end of the course destruction of microfilariae may cause itching and desquamation of the skin over the lower legs. A total of 6 g. is desirable for effective treatment, but in many patients who cannot take this amount 5 g. or even 4 g. suffice to kill all the adult worms.

Three to four weeks after the last suramin injection a second course of diethylcarbamazine (similar to the first) should be given to destroy any remaining microfilariae which may have emerged before the adult worms were killed. The reaction to this course will be much less severe, and after it the patient should be parasite-free. Some itching of the erstwhile affected parts may continue for as long as two to three months while the dead helminthic products are being absorbed from the tissues. This should be treated symptomatically, and if required a third course of diethylcarbamazine can be given at the end of this period.

If patients in this group cannot tolerate suramin they may be treated with repeated intensive courses of diethylcarbamazine (Banocide 2–3 mg./kg. t.i.d. for three weeks). Occasionally this is successful in killing the adult worms.

Heavily Infected Patients

In heavily infected patients with infections of long standing, in whom very severe reactions to diethylcarbamazine are to be expected, treatment may begin with suramin. This drug itself will kill many of the microfilariae in a gradual manner, and when, one month after the last injection, diethylcarbamazine is given to kill the residual microfilariae the reaction will be less severe than it would otherwise have been.

Suppressive Treatment

When it is impractical to undertake a complete filaricidal course of treatment, either because the individual cannot tolerate suramin or because early reinfection is inevitable, weekly suppressive doses of microfilaricidal diethylcarbamazine (50 mg. Banocide) may be given. The patient undergoes a series of reactions, decreasing in severity at each succeeding weekly dose, until his initial load of microfilariae has been eliminated. After the first six weeks the dosage can be increased to 200 mg. and can be tolerated with almost no inconvenience. Suppressive treatment can be continued as long as desired, and during this period the skin can be kept almost free from microfilariae, microfilarial invasion of the eye is prevented, and the patient is eliminated as a source of microfilariae transmissible by *Simulium*. However, the adult worms are not affected by the treatment.

Eye Lesions

The grosser manifestations in the eyes, which result from scarring of the tissues, cannot be expected to improve after effective filaricidal treatment. At best they will not get worse; at worst they may progress of their own accord to blindness. In a few cases, notably those with secondary glaucoma or cataract, surgical intervention may provide relief and amelioration of vision, provided that the posterior segment has not been damaged.

At present no causal chemoprophylactic is known. Diethylcarbamazine, which is effective against *Loa loa,* does not appear to have any action against the infective larvae of *O. volvulus*.

Lesions of the posterior segment may progress to consecutive optic atrophy and blindness despite complete parasitological cure. Unfortunately little is known of their pathogenesis, and treatment is unsatisfactory. It is worth while trying large doses of vitamin A and of the B complex.

If serious eye lesions are to be avoided in persons who are especially at risk, treatment to eliminate the parasites must be given early, before the eyes have suffered much damage. In areas of heavy endemicity *Simulium* control should also be undertaken whenever possible so as to reduce the risk of reinfection.

Personal Prophylaxis

Personal prophylaxis is possible to a limited extent by avoiding the places where biting *Simulium* are numerous, by wearing long trousers (for *S. damnosum*) or light gloves and a veil (for *S. ochraceum*), and by screening houses and verandas where the insects are known to invade these places. Repellents may be effective for short periods but are not practical for continued use in the tropics.