Onchocerciasis (river blindness) occurs in 34 countries in Africa, Latin America, and the Arabian Peninsula (figure 1). An estimated 17.7 million persons are infected with the parasite *Onchocerca volvulus*, the vast majority of whom live in Africa. The infection has caused blindness in 270,000 and left another 500,000 with severe visual impairment. More than a blinding diseases, onchocerciasis is a chronic systemic illness, capable of causing extensive and disfiguring skin changes, musculoskeletal complaints, weight loss, changes in the immune system, and perhaps epilepsy and growth arrest as well. The disease, which is endemic in some of the world’s poorest areas, has had a major impact on the economic and social fabric of communities. Despite the damage done by the disease, a complex human-parasite tolerance allows people who host millions of parasites to continue daily existence.

Efforts to control onchocerciasis through suppression of its vector, the *Simulium* fly, have freed the Volta river basin of West Africa and adjacent areas from this scourge. The development of ivermectin and its donation by the manufacturer has been one of the signal events of international health. Mass distribution of this drug over the past decade has relieved misery, limited infection, and reduced transmission in many parts of Africa and Latin America.

**Epidemiology**

The microfilariae of *O. volvulus* were first observed by O’Neill in Ghana in 1875 in a case of “craw-craw”. Nearly 20 years later the adult worm was described by Leuckart from specimens sent by missionaries in Ghana. The final piece of the life cycle was discovered in 1923 when Blacklock in Sierra Leone showed the blackfly *S. damnosum* to be the vector. Hissette in the Congo, and Robles in Guatemala linked blindness with onchocerciasis. This blindness had probably caused the extensive depopulation of fertile river valleys in northern Ghana which so puzzled 19th century colonial administrators. But Ghanaians living along the Red Volta river had long associated the biting flies with skin lesions and blindness.

With the success of vector control in West Africa, the largest numbers of infected persons are now found in Nigeria, Cameroon, Ethiopia, Uganda, and the Congo. Most African foci are fairly stable, but in South America foci continue to enlarge and new ones are found. Within foci, prevalence of disease may be uneven due to differences in both distribution of flies and exposure to bites.

In Africa blindness was noted to be more common in savanna and woodland areas than in forest areas, but forest areas had more depigmented skin disease. The suspicion that various strains of parasites existed which differed in eye damage produced has been verified via DNA probes. Other factors such as population density, genetic factors, transmission patterns, and perhaps nutrition may also contribute to the risk of blindness.

Beyond the well-documented effects of blindness, onchocerciasis has other economic and social costs. Onchocercal skin disease may reduce marital prospects (and dowry size), influence the course of pregnancy, shorten length of breastfeeding, and disrupt social relationships. Among agricultural workers onchocerciasis has been associated with increased time away from work and reduced productivity, leading to lower income.

**Parasitology**

*Development of infection*

Larvae of *O. volvulus* enter the human during the blood meal of an infected female *Simulium* fly. Within a week the survivors from the invading L3 stage larvae will moult into L4 and by 1–3 months development into male or female adult worms will be complete. Larvae at some stage appear to be attracted by unknown signals to nodules which contain adult worms (macrofilariae). Nodules average 3 cm in diameter and are commonly located over bony prominences where they are easily palpable, but some nodules are deep, especially around the pelvis.

A female worm may release 1300–1900 microfilariae per day for 9–11 years. From the nodules, these microfilariae find their way mainly to the skin and eye. In the skin they are found predominantly in the lymphatics of the subepidermis. In the eye most are present in the anterior chamber, but microfilariae are also found in the retina and optic nerve. When an infected person is bitten, anticoagulants from *Simulium* fly create a pool of blood from which blood and microfilariae are ingested.

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Microfilariae which survive ingestion by the fly moult twice over the following 6–12 days to become infective (L3) larvae.

**Adult worms**

Adult worms lie inside thick fibrous nodules, being recognised but not seriously attacked by the host’s immune system. The worms probably elaborate substances which promote formation of a rich vascular network around the worm, providing nutrients. Nutrition may come from absorption through a highly convoluted cuticle, as well as from ingested blood. Immediately around the adult worm are macrophages and fibrous proteins. Eosinophils and lymphocytes predominate at the periphery of the nodule, where microfilariae migrating out of the nodule are often attacked. A typical nodule may contain two or three adult female worms (50 cm×0·4 mm), and about half as many males. Itinerant male worms (4 cm×0·20 mm) move from nodule to nodule inactivating the female worms, perhaps attracted by as yet unidentified pheromones.

The female worm produces oocytes in large numbers. In the absence of fertilisation, these degenerate within the uterus. When female worms are fertilised, microfilariae develop in 3–12 weeks. Many microfilariae do not successfully escape from the uterus and are reabsorbed.

**Microfilariae**

The interval between the bite of an infected fly and the appearance of microfilariae in a person’s skin is 10–20 months. Microfilariae are about 250–300 μm long and may live up to two years. They move easily through the skin and connective tissue, ordinarily provoking little reaction while alive and remaining within lymphatic vessels. Their presence has been noted in blood, urine, cerebrospinal fluid, and internal organs. In heavily infected persons 100 million or more microfilariae may be present.

**Vector**

The major species of *Simulium* are complexes of sibling species, identifiable through banding patterns of larval chromosomes. In Africa the main vectors are members of the *S damnosum* complex (or *S damnosum sensu lato*), which can travel long distances. The vectors in areas of Uganda, Tanzania, Ethiopia, and the Congo are members of the *S neavei* complex, and this fly is often restricted to localised areas. *S albivirgulatum* is a separate species which is a vector only in the Congo river basin. In the Americas complexes of *S ochraceum*, *S metallicum*, and *S exiguum* are the principal vectors. While in Africa onchocerciasis generally follows the distribution of the vector, there are many areas in the Americas where vectors exist in the absence of infection. Among the vector complexes, some will bite man almost exclusively while others are to varying degrees zoophilic.

The immature stages of *Simulium* develop in watercourses which vary from broad rivers to small streams, depending on the requirements of individual sibling species. Rapid-flowing water provides the oxygenation needed for development. Most larvae and pupae develop on rocks or vegetation just below the water surface but those of *S neavei* develop on amphibious *Potamonautes* crabs. Aquatic stages of the fly require about 10 days to complete development, depending on temperature and nutrients available. Deforestation, which has occurred in many foci both in Africa and the Americas, may have an important impact on the distribution of vectors and spread of disease.

When the adult fly bites an infected person, microfilariae which survive uptake and escape the peritropic membrane which forms around the blood meal, penetrate the midgut and move to the flight muscles. By 28 hours differentiation into L1 larvae has begun, and by 96 hours the first moult, to an L2 larva, has occurred. A second moult occurs by day 7, and the L3, or infective larva now moves to the insect head or sometimes wanders elsewhere within the fly. Ultimately the infective larva finds its way to the insect’s mouth parts to enter a person’s skin at the next blood meal.

Experimental studies suggested that the efficiency with which sibling species of *Simulium* flies transmitted forest and savanna strains of the parasite varied considerably. This has given rise to the concept of vector-parasite complexes in which forest strains of parasites are preferentially transmitted by forest species of flies and savanna strains by savanna species. Recently, studies with *O volvulus* larval DNA taken from savanna and forest flies has cast doubt on the present importance of transmission complexes.

**Symptoms**

The clinical manifestations of onchocerciasis are almost entirely due to localised host inflammatory responses to dead or dying microfilariae. In a heavily infected person 100 000 or more microfilariae die every day. The immune responses are predominantly antibody, but with an important cellular component. Inflammatory responses may vary considerably from person to person, depending on length of exposure to antigens and down-regulating activities by the host.

Eosinophils play a major role in the inflammatory responses which produce skin damage. Cellular proteins derived from eosinophils are deposited on connective tissues throughout the dermis and are attached to elastic fibres. Even when eosinophils are absent from tissues, their proteins are still found in connective tissue and circulating in the blood.

In the eye eosinophils are also present in the anterior segment; however, the predominant cells noted are lymphocytes and macrophages. In addition, there is an activation of vascular endothelium, pericytes, and fibroblasts in persons with chronic changes to the eye. Autoantibodies have been found to cells in the inner retina and to the retinal photoreceptors. The relationship of these antibodies to retinal damage is not certain. There is extensive evidence for a down-regulating of the immune response in chronically infected eye tissue by suppressor T cells and lymphocytes producing the cytokine interleukin-4.

Adult worms may elaborate substances which inhibit the normal immune response by the human host. Exposure to filarial antigens in utero and through breast milk may induce an immune tolerance in residents of endemic areas, which could explain the difference in disease patterns seen in people from non-endemic areas who become infected.

Among people coinfected with HIV there is a reduced reactivity to *O volvulus* antigens, but no difference in adverse reactions after ivermectin treatment.
Eye damage
The risks of visual impairment increase as prevalence and intensity of infection rises in a community. Microfilariae enter the cornea from the skin and conjunctiva, and a punctate keratitis develops around dead microfilariae which clears when inflammation settles. With exposure to years of heavy and prolonged infection, sclerosing keratitis and iridocyclitis are likely to develop, causing permanent visual impairment or blindness (figure 2).

The first sign of sclerosing keratitis is a haziness at the medial and lateral margins of the cornea. This is followed by a migration of pigment onto the cornea accompanied by a progressive in-growth of vessels. Gradually the cornea opacifies, the central and superior areas being the last to be affected.24 Although eye lesions can be found wherever onchocerciasis is present, in west Africa blindness is most common in savanna areas. Before control efforts began in Burkina Faso, 46% of men and 35% of women would eventually become blind.25 Today Chad, which has not benefited from sustained control efforts, has the largest number blind from onchocerciasis.

Posterior segments lesions, which can coexist with anterior eye lesions, may be caused by inflammation around microfilariae entering the retina along the posterior ciliary vessels.26 Chorioidoretinal lesions are commonly seen at the outer side of the macula or encircling the optic disc.27 Active optic neuritis is an important cause of blindness in Nigeria.28 Optic atrophy has been reported in 1–4% of persons with onchocerciasis in Cameroon and 6–9% in northern Nigeria.29 Loss of peripheral vision is well recognised in onchocerciasis but as yet lacks specific classification.30

Skin disease
Of all the consequences of onchocerciasis, skin lesions are the most pervasive. In surveys of seven endemic sites in five African countries between 40% and 50% of adults reported troublesome itching.31 In some cases itching is so intense that people have to sleep on their elbows and knees.

In its mildest cutaneous form, onchocerciasis presents as itching associated with a localised maculopapular rash. These reactive lesions and itching may be evanescent, clearing completely without treatment in a few months. In other instances the papular lesions become chronic and generalised, accompanied by severe itching. Oedema and excoriations can be associated, and lesions may heal with hyperpigmentation. Particularly distressing are lichenified, hyperkeratotic lesions which may be widespread and intensely itchy (figure 3). A localised form of chronic papular dermatitis, often confined to one extremity, is known as Sowdah (Arabic for “dark”). In this condition, first described from Yemen, there is an exceptionally strong IgG antibody response.32

After years of active infection, degenerative skin changes develop. Elastic fibres are destroyed, leaving the skin thinned with a wrinkled, cigarette-paper appearance. The atrophied skin begins to sag, the most extreme state being “hanging groin” with its apron-like folds.33 Depigmentation of the pretibial areas, or “leopard skin”, is a characteristic finding in older people living in endemic areas. This begins as discrete depigmented maculas sparing areas around hair follicles, and in time may become confluent, affecting much of the anterior area below the knee. Dermal lesions of onchocerciasis have been described for many years, but only recently was a standardised classification developed.34

Figure 2: Eye lesions
Upper: punctate keratitis.
Lower: far advanced sclerosing keratitis.

Other conditions
Several studies have shown that both men and women with onchocerciasis weigh less than an uninfected cohort. People with onchocerciasis also report more musculoskeletal pains. Evidence from Uganda has suggested a possible association with epilepsy.35 Similar conclusions were reached in a Burundi survey, but not in Burkina Faso.36,37

In the 1960s a peculiar of growth arrest beginning around age 6–10 was reported from an onchocerciasis focus near Jinja, Uganda, but it now seems to have disappeared following elimination of onchocerciasis. This growth arrest, called Nakalanga syndrome, has recently been described from an onchocerciasis focus in western Uganda, and may also be present in Burundi.38,39

Diagnosis
Diagnosis has traditionally been by taking small (3–5 mg) snips of skin from the iliac crest area and elsewhere. These snips are immersed in saline, and the emerging microfilariae counted microscopically. An alternative, when microfilariae cannot be demonstrated, is administration of 6 mg diethylcarbamazine (the Mazzotti test), which produces itching and sometimes intense inflammation where microfilariae are present. Highly sensitive tests based on polymerase chain amplification of parasite DNA and recombinant antigen-based enzyme-linked immunoassays have been developed which can be useful both for individual diagnoses and for surveillance, especially in control programmes. Onchocerciasis should be considered in persons from endemic areas or expatriate visitors who present with itching with or without a rash. Microfilariae may be
Onchocerciasis Control Programme (OCP) was formed by the Mabari forest of Uganda (1960s). In 1974 the rivers, onchocerciasis was eliminated from Kenya (1947) and there is no evidence to date of drug resistance in man.45 Ivermectin resistance has developed in animal parasites, of glutamate-gated chloride channels.44 Although some appears to be mediated by potentiation or direct opening neurotransmitters, producing paralysis. This action occur initially. The drug acts primarily on parasite reactions are less frequent or severe than those which subsequent annual ivermectin treatments adverse have also been seen occasionally. In heavily infected persons, and bullae reported rarely after treatment in increased. Hypotension has been the pace and intensity are often reducing release of microfilariae, except that microfilariae to 7% of the years reduced the number of microfilariae by adult worms it does not destroy the adults. In Ghana giving ivermectin once a year for five years reduced the number of microfilariae to 7% of the pretreatment baseline count.41 Limiting the numbers of microfilariae through annual treatment with ivermectin has improved early and advanced anterior segment eye lesions, halted development of optic nerve disease, and improved severe onchodermal skin lesions.42,43 Adverse reactions to ivermectin do not differ from usual responses to death of microfilariae, except that the pace and intensity are often increased. Hypotension has been reported rarely after treatment in heavily infected persons, and bullae have also been seen occasionally. In subsequent annual ivermectin treatments adverse reactions are less frequent or severe than those which occur initially. The drug acts primarily on parasite neurotransmitters, producing paralysis. This action appears to be mediated by potentiation or direct opening of glutamate-gated chloride channels.46 Although some ivermectin resistance has developed in animal parasites, there is no evidence to date of drug resistance in man.46 Vector control The first efforts to control onchocerciasis concentrated on elimination of the Simulium vector. Using DDT added to rivers, onchocerciasis was eliminated from Kenya (1947) and the Mabari forest of Uganda (1960s). In 1974 the Onchocerciasis Control Programme (OCP) was formed by four UN agencies and seven countries (now 11) in the Volta basin of West Africa to control Simulium by adding larvicides, such as temephos and later, where resistance developed, Bacillus thuringiensis, to rivers. This highly successful vector control programme, later supplemented with ivermectin distribution, now permits ten of millions of persons to live free of disease.46 Although vector control may still be preferable in some localised circumstances, particularly around dams or in S. neavei foci, mass distribution of ivermectin is now the principal method for onchocerciasis control. Ivermectin mass distribution After the efficacy of ivermectin had been demonstrated, its manufacturers, Merck & Co, established the Mectizan Donation Program to provide the drug free “for as long as necessary to as many as necessary”. By mid-1997 74 million ivermectin treatments had been given by 82 programmes in 33 of 34 endemic countries.47 The goal of a control programme may be either eradication of the parasite reservoir entirely or elimination of the public health and socioeconomic consequences of the continuing infection. In Guatemala, where high population coverage with six-monthly treatment has reduced parasite transmission by 80–100% after three years, eradication may ultimately be possible, and this could be true elsewhere in Latin America. But in Africa and many parts of Latin America elimination seems more feasible. A first step to control of onchocerciasis is to map foci and establish treatment priorities. The prevalence of nodules in 30–50% males over age 20 is measured on examination by a rapid assessment method. Simply asking people about the presence of nodules was found in the Congo to be nearly as accurate as physical examination.48 Where the prevalence of nodules is over 40% the risk of blinding disease is high. Multiplying nodule prevalence in males by 1–5 will give the approximate community prevalence of onchocerciasis. The simplest approach to mass treatment is a passive which makes one ivermectin available at clinics free of charge to all who come. This seldom reaches large numbers of those infected. Active distribution, with health workers moving through the community, can achieve much higher coverage but usually at a greater cost. Community-based programmes are generally the most effective but need formal links with the health system. In many places public sector health services have become dysfunctional, or never existed, and it is tempting to...
develop a direct distribution approach. But “onchocerciasis only” programmes may erode already fragile primary health care services and have an overall negative effect on services. On the other hand, programmes with heavy reliance on community volunteers can be difficult to maintain, especially in subsistence economies.

Because of the longevity of adult worms, ivermectin distribution programmes will achieve little in the long term if they are not sustainable for 15–20 years. In many places the duration may have to be even longer because of the difficulty in achieving and sustaining good coverage. The non-governmental organisations, which do the bulk of ivermectin distribution, frequently have had tenuous financial support. To promote sustainable and coordinated community-based control, the Onchocerciasis Elimination Program in the Americas (OEPA) and the African Programme for Onchocerciasis Control (APOC) have been formed, with support by the World Bank and three other UN agencies. Programme objectives are to eliminate the public consequences of infection through sustainable community-based ivermectin distribution, and in selected foci, through vector control.

**Nodulectomy**

A third form of onchocerciasis control has been the nodulectomy programmes of Mexico and Guatemala. For many years health workers have moved from village to village removing nodules, especially around the head. This approach may lessen numbers of microfilariae entering the eye, though the evidence for prevention of blindness is not strong. 40

**Future directions**

The immediate need is to extend ivermectin mass distribution to as many endemic areas as possible on a continuing basis. Implementation methods are needed which will ensure community “ownership” of such programmes, yet at the same time ensure support and incentives from the formal health sector. A critical need is for a drug that can destroy adult worms and be distributed via community-based schemes. In the end, this will be the most effective control method. Alas, progress in developing a drug active against adult worms has been slow.

Many gaps remain in our knowledge of *O. volvulus* and the disease it causes. These include a fuller understanding about the parasite and its relation with the host, the nature of the systemic effects of *O. volvulus* infection, the natural history of skin disease, and a better appreciation of the economic and social consequences of this disease which continues to affect millions worldwide.

**Acknowledgments**

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**References**

42 Dadzie KY, Remme J, DeSole G. Changes in ocular onchocerciasis.


Further reading

Background


Parasitology


Epidemiology


Immunology


Clinical manifestations


Treatment


Control measures


