8.9.1 Cutaneous filariasis 1478

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8.9 Nematodes (roundworms) CONTENTS 8.9.1 Cutaneous filariasis 1478 Gilbert Burnham 8.9.2 Lymphatic filariasis 1487 Richard Knight 8.9.3 Guinea worm disease (dracunculiasis) 1495 Richard Knight 8.9.4 Strongyloidiasis, hookworm, and other gut strongyloid nematodes 1500 Michael Brown 8.9.5 Gut and tissue nematode infections acquired by ingestion 1506 Peter L. Chiodini 8.9.6 Angiostrongyliasis 1516 Richard Knight 8.9.1 Cutaneous filariasis Gilbert Burnham ESSENTIALS The cutaneous filariae are transmitted by biting insects. Some, such as Onchocerca volvulus, are transmitted by Simulium flies and can cause debilitating conditions such as visual impairment and disfiguring skin conditions. The Mansonella infections are transmitted either by Simulium flies or biting midges (genus Culicoides), but consequences of infections are general mild. Loa loa is transmitted by the bite of the Chrysops fly. Loaisis is manifest by adult worms periodically passing beneath the sclera and by subcutaneous swellings, usually of the forearm. Onchocerciasis Onchocerciasis (river blindness), caused by O. volvulus, infects per- haps 18 million people, once in six countries in the Americas, but now almost entirely in Africa. Clinical features—the larvae are introduced into the body when the Simulium vector takes a blood meal, they then develop into male or female adult worms within palpable nodules, commonly located over bony prominences. Adults give rise to microfilariae which are responsible for clinical manifestations. Most important are: (1) Eye damage—microfilariae enter the cornea from the skin and con- junctiva; manifestations include sclerosing keratitis, iridocyclitis and (sometimes) choroidoretinal lesions; without treatment, permanent visual impairment or blindness are common. (2) Skin disease—which ranges from itching with a localized maculopapular rash, to in- tense itching with a chronic generalized papular rash, or lichenified hyperkeratotic lesions. Diagnosis, treatment, and prevention—diagnosis is usually made by finding microfilariae in skin snips. Treatment is with ivermectin (Mectizan®), often given as a single or twice annual dose. Ivermectin has dramatically reduced the eye and skin lesions that ravaged many communities in Africa and Latin America. Methods of disease pre- vention include adding insecticides to rivers to interrupt Simulium breeding and the regular mass distribution of ivermectin. Loa loa Loiasis, for which humans are the only host, is transmitted by the Chrysops fly in West and Central Africa. Clinical manifestations in- clude transient localized inflammatory oedema (Calabar swellings), the

appearance of a migrating worm under the skin or (most dra- matically) crossing the conjunctiva, and (rarely) meningoencephal- itis. Diagnosis is based on typical clinical findings, or traditionally by finding microfilariae in a daytime blood sample. Treatment is usu- ally with diethylcarbamazine, although ivermectin is effective, and albendazole less so. All treatments risk serious adverse reactions in the heavily affected persons. The best prevention is avoidance of Chrysops fly bites.
Mansonellas The Mansonellas are filarial infections is transmitted by Culicoides midges and is common to many countries, but of negligible clinical importance under most circumstances. Only Mansonella streptocerca produces clear-cut manifestations, most typically a mild chronic papular skin lesions. Diagnosis is by finding characteristic micro- filariae in the blood or skin. People who are asymptomatic do not require treatment, but M. streptocerca responds well to ivermectin.
M. perstans and M. ozzardi are widespread in tropical countries, with few specific symptoms.

8.9.1 Cutaneous filariasis 1479 Onchocerciasis Onchocerciasis, or river blindness, historically occurred in 34 coun- tries in Africa, Yemen, and Latin America (Fig. 8.9.1.1). It is esti- mated that 18 million people are infected, and 87 million at risk of infection. Most are in Africa. In 1995, it was estimated that in- fection with Onchocerca volvulus had caused blindness in 270 000 people, and left another 500 000 with severe visual impairment. Mass treatment with ivermectin has now greatly lessened the ocular burden of infection. Besides eye changes, onchocerciasis has chronic systemic effects, causing extensive and disfiguring skin changes, musculoskeletal complaints, weight loss, changes to the immune system, and perhaps also epilepsy and growth arrest. Skin lesions are the most common manifestation of onchocerciasis. Changes in- clude acute and chronic itchy papular disease, and intensely prur- itic lichenification. Lesions can be localized or widespread. In the later stages, severe degenerative skin disease develops, with a loss of elastic tissue, and extensive pigmentary changes. The disease, endemic to some of the world’s poorest areas, has a great impact on the economic and social fabric of communities. A complex (a) (b)
Fig. 8.9.1.1 Distribution of onchocerciasis in Africa, Yemen, and Latin America, where transmission is now largely interrupted.

section 8 Infectious diseases 1480 human–parasite tolerance allows people who host millions of para- sites to continue daily existence. Mass treatment with ivermectin (Mectizan®) has interrupted or eliminated transmission in almost all foci in the Americas and has controlled the public health consequences of this disease in Africa. A goal of control of onchocerciasis by 2020 was set by the London Declaration on Neglected Tropical Diseases in 2012. The elimination of transmission in Africa, long thought not feasible, is now accepted as possible in many locations.
Epidemiology The microfilariae of O. volvulus were first observed by O’Neill in Ghana in 1875 in an intensely pruritic chronic skin condition called ‘craw-craw’. Leuckart described the adult worm 20 years later, and in 1923 Blacklock in Sierra Leone showed the blackfly Simulium damnosum to be the vector. Hissette in the Congo and Robles in Guatemala linked blindness with onchocerciasis. Long before, Ghanaians along the Red Volta River had associated the biting flies with skin lesions and blindness. The Onchocerciasis Control Programme suppressed vector breeding in West Africa’s Volta basin between 1974 and 2002, and is thought to have prevented 600 000 cases of blindness. Today, the largest numbers of infected people live in Nigeria, Cameroon, Chad, Ethiopia, Uganda, Angola, and the Democratic Republic of the Congo. In the Americas, aggressive treatment with ivermectin has eliminated or interrupted onchocerciasis transmission in Guatemala, Mexico, Colombia, and Ecuador. A small focus remains among the Yanomami Indians on the Brazil-Venezuela border. In Africa, blindness had been noted to be more common in sa- vannah and

woodland than rainforest areas, but people in forest areas had more depigmented skin disease. Different strains or forms of the parasite were shown to be present in savannah and woodland areas, particularly in West Africa. Environmental changes and mi- grations have now lessened these distinctions. Pathology The larvae of O. volvulus enter the human during a blood meal taken by an infected female Simulium fly. Within 1 to 3 months, larvae develop into male or female adult worms within palpable nodules commonly located over the bony prominences of the thorax, pelvic girdle, or knees (Fig. 8.9.1.2). Nodules can also be found on the head, particularly among chil- dren. These average 3 cm in diameter and are easily palpable, but some are deep, particularly around the pelvis. A female worm might release 1300–1900 microfilariae per day for 9 to 11 years. From the nodules, these microfilariae find their way mainly to the skin and eyes. In the skin they are found predominantly in the subepidermal lymphatics. In the eye, most microfilariae are in the anterior chamber, but are also found in the retina and optic nerve. When an infected human is bitten, anticoagulants from the Simulium fly create a pool of blood from which blood and microfilariae are in- gested. Within the fly, those microfilariae that survive moult twice over the following 6 to 12 days to become infective larvae. Microfilariae are about 250–300 µm in length and may live for up to 2 years. They move easily through the skin and connective tissue, ordinarily remaining within lymphatic vessels and provoking little reaction while alive. They have been found in blood, urine, cerebro- spinal fluid, and internal organs. Millions of microfilariae can be present in a heavily infected person. Although live microfilariae are tolerated by their human hosts, dead and dying microfilariae can evoke intense inflammatory reactions, which are mainly responsible for the eye and skin damage. Important Simulium spp. are complexes made up of sibling spe- cies, identifiable through the banding patterns of their larval chromo- somes. In Africa, the main vectors are members of the S. damnosum complex or sensu lato (s.l.), which can fly long distances. The vectors in areas of Uganda, Tanzania, Ethiopia, and the Congo are members of the S. neavei complex. In the Americas, complexes of S. ochraceum, S. metallicum, and S. exiguum are the principal vectors; these cover shorter distances. Some Simulium flies will bite humans almost exclu- sively, whereas other species are to varying degrees zoophilic. Simulium breed in water courses varying in size from broad rivers to small streams, depending on the individual sibling species. Rapidly flowing water provides the oxygenation needed for the development of the immature stages. Most larvae and pupae develop on rocks or vegetation just below the water surface, but those of S. neavei develop on amphibious Potamonautes crabs. During this developmental period the larvae are susceptible to insecticides. These breeding pat- terns have made the larviciding of water sources an effective con- trol approach. Unique relationships have developed between the Simulium fly and local parasites, so that flies from one geographical area do not efficiently transmit parasites from other areas. Clinical features The manifestations of onchocerciasis are almost entirely caused by localized host inflammatory responses to dead or dying microfil- ariae. In a heavily infected person, 100 000 or more microfilariae die every day. The predominant immune response in onchocerciasis is antibody mediated, but with an important cellular component. Inflammatory responses might vary considerably between groups of people, depending on the length of exposure to antigens and the down-regulating activities of the host’s immune system. Eosinophils play an important role in the inflammatory re- sponse. Cellular proteins derived from eosinophils are deposited in connective tissues throughout the dermis, and bind to elastic fibres causing their destruction and, thereby, skin damage (see ‘Skin disease’, next).

Fig. 8.9.1.2 A 3-cm subcutaneous nodule.

8.9.1 Cutaneous filariasis 1481 An important discovery was that filarial parasites host endosymbiotic Wolbachia bacteria. The inflammatory response to onchocerciasis seems associated with the Wolbachia rather than to the parasite itself. When the parasites were depleted of their Wolbachia by doxycycline they did not induce corneal lesions. Further studies showed that in- flammatory changes in the cornea in response to Wolbachia were de- pendent on the expression of myeloid differentiation factor 88. Exposure of the fetus to antigens associated with the parasite in utero and later through breast milk might induce immune tolerance in residents of endemic areas. This could explain the difference in the disease patterns seen in people from nonendemic areas who become infected. Eye damage The risk of visual impairment increases as the prevalence and in- tensity of infection rises in a community. Microfilariae enter the cornea from the skin and conjunctiva. Punctate keratitis develops around dead microfilariae, and clears when inflammation settles. In those exposed to years of heavy infection, sclerosing keratitis and iridocyclitis are likely to develop, causing permanent visual impair- ment or blindness. The first sign of sclerosing keratitis (Fig. 8.9.1.3a) is haziness at the medial and lateral margins of the cornea. This is followed by the migration of pigment onto the cornea, accompanied by a progres- sive ingrowth of vessels. Gradually the cornea becomes opacified. The central and superior areas are the last involved. Although eye lesions can be found wherever onchocerciasis occurs, blindness is most common in the West African savannah. Before control efforts began in Burkina Faso, 46% of men and 35% of women would even- tually become blind. Posterior segment lesions, which can coexist with anterior eye lesions, might be caused by inflammation around microfilariae entering the retina along the posterior ciliary vessels (Fig. 8.9.1.3b). Chorioretinal lesions are commonly seen at the outer side of the macula, or encircling the optic disc. Posterior segment changes have been an important cause of loss of vision in some countries. Loss of peripheral vision is well recognized in onchocerciasis. Skin disease Of all the consequences of onchocerciasis, skin lesions are the most pervasive. Surveys of seven endemic sites in five African countries found that between 40 and 50% of adults had troublesome itching, which was so intense in some cases that those affected slept on their elbows and knees to minimize the symptom. In its mildest form, onchocerciasis presents as itching with a lo- calized maculopapular rash (Fig. 8.9.1.4). These reactive lesions and itching may be evanescent, clearing completely without treat- ment in a few months. In other instances, the papular lesions may become chronic, generalized, and accompanied by severe itching (Fig. 8.9.1.5). Oedema and excoriations can be associated, and le- sions may heal with hyperpigmentation. Particularly distressing are lichenified hyperkeratotic lesions, which can be widespread and intensely itchy (Fig. 8.9.1.6). A localized form of chronic papular dermatitis, often confined to one extremity, is known as ‘sowda’, Arabic for dark. In this condition, first described from Yemen, there is an exceptionally strong IgG antibody response. Light-skinned expatriates infected while visiting an endemic area might present a year or more later with intensely itchy and red macular, or maculopapular, lesions. These might be confined to one (a) (b) Fig. 8.9.1.3 (a) Bilateral sclerosing keratitis in a man blinded by onchocerciasis in Nigeria and (b) onchocerciasis producing a Hissette– Ridley fundus and optic atrophy in a person with central keyhole vision remaining. (a) Courtesy of Professor A. D. M. Bryceson; (b) courtesy of the Royal Tropical Institute, Amsterdam. Fig. 8.9.1.4 Maculopapular rash. Courtesy of Mauricio Sauerbrey.

section 8 Infectious diseases 1482 area of the body or be more generalized, and can be associated with fever, muscle and joint pain, and sometimes oedema. The rash can sometimes persist for several months following ivermectin treatment. In endemic areas, degenerative skin changes might develop in some people with long-standing infection. Elastic fibres are des- troyed, leaving the skin

thinned with a wrinkled cigarette-paper ap- pearance. The atrophied skin begins to sag, the most extreme state being ‘hanging groin’ with its apron-like skin folds (Fig. 8.9.1.7). Depigmentation of the pretibial areas, or ‘leopard skin’, is a charac- teristic finding in older people living in endemic areas (Fig. 8.9.1.8). Onchocercal skin disease reduces marital prospects (and dowry size), disrupts social relationships, and decreases the productivity of agricultural workers. As mass treatment with ivermectin has controlled onchocerciasis in many areas, appearance of these condi- tions is becoming increasingly rare. Other conditions associated with onchocerciasis Both men and women with onchocerciasis weigh less than unin- fected people and report more musculoskeletal pains. Evidence, first from Uganda and more recently from other African countries, has suggested an association between epilepsy and onchocerciasis. There is also evidence for an association between an increasing microfilarial load and excess mortality. Fig. 8.9.1.5 Excoriated papular lesions of onchocerciasis with hyperpigmentation. Fig. 8.9.1.6 Lichenified skin lesions with atrophy. Fig. 8.9.1.7 ‘Hanging groin’. Courtesy of the late Dr B. O. L. Duke. Fig. 8.9.1.8 Depigmented ‘leopard skin’.

8.9.1 Cutaneous filariasis 1483 A peculiar pattern of growth arrest beginning around the age of 6–10 years was reported from a Ugandan onchocerciasis focus near Jinja in 1951. This Nakalanga syndrome now seems to have disap- peared from the area following the elimination of onchocerciasis, but has been noted in western Uganda, and might be present in Burundi.
A condition of children in South Sudan, known as ‘nodding disease’, occurs in areas of onchocerciasis endemicity. ‘Nodding disease’ has also affected small areas of Uganda and Tanzania. Clinical features include head nodding, mental retardation, stunted growth, blind- ness, body stiffness, endless running nose and saliva, and faecal and urinary incontinence. This condition is still poorly understood, though infection with onchocerciasis might play some role. In nor- thern Uganda there have been no new cases in areas receiving twice yearly ivermectin distribution, augmented by insecticide application to rivers. Diagnosis Finding visible microfilariae in skin snips has been the time-honoured method of diagnosis. Microfilariae lie close to the surface, and are most plentiful in the iliac crest area, except in Latin America, where they were previously more common in the shoulder and scapular areas. This remains a common method for detection in both indi- vidual diagnosis and to assess interruption of transmission in a popu- lation. Using polymerase chain reaction (PCR) analysis of skin snips for microfilaria greatly improves diagnosis where parasite counts are low. The examination of excised onchocercal nodules shows sections of adult worms. Immunoassay detecting the IgG4 antibody response to parasite Ov.16 antigen is an available method of diagnosing a cur- rent or previous infection and has a high degree of sensitivity and spe- cificity. Eosinophilia is common in onchocerciasis. The Mazzotti test, in which people with onchocerciasis react with itching and a skin rash to 50 mg of oral diethylcarbamazine (DEC), is seldom needed for diagnosis, and can be dangerous in heavy infec- tions. However, DEC patch tests, evoking a skin response at 24/30hr are accurate and tolerated. Treatment The introduction of ivermectin for onchocerciasis in 1987 was one of the milestones of tropical disease treatment. Its discovery and de- velopment earned the 2016 Noble Prize in medicine. The symptoms of onchocerciasis can be effectively controlled by the treatment of individuals attending clinics, or through the mass treatment of en- demic communities. Ivermectin is derived from Streptomyces avermitilis. A single dose of 150–200 μg/kg clears microfilariae from the skin for sev- eral months through the killing of microfilariae as well as blocking embryogenesis among adult female worms. Annual treatment con- trols microfilarial counts, and prevents the progression of clinical findings, although increasingly it is given twice yearly, with the in- tention of interrupting

transmission. Treatment can be repeated if itching returns before the next dose is due. In the absence of reinfec- tion, individual treatment should probably be continued annually for 10 years or more, or until microfilariae are no longer detectable. In Nigeria, after 8 years of treatment, gross visual impairment de- creased from 16% to 1%, nodule prevalence fell from 59% to 18%, and papular skin dermatitis reduced from 15% to 2%. Treatment during pregnancy and under the age of 5 years is not recommended, although there has been no clear evidence of harm (increased risk of malformations or abortions) where treatment has been given inad- vertently in mass treatment programmes. Limiting the numbers of microfilariae through annual ivermectin treatment improves early and advanced anterior segment eye lesions, halts the development of optic nerve disease, and improves severe onchocercal skin lesions. Adverse reactions to ivermectin commonly consist of increased itching, swelling of the face or extremities, and headache and body pains. Hypotension has been reported rarely after treatment in heavily infected people. Bullae have been seen occasion- ally. The most pronounced adverse reactions occur after the first ivermectin treatment, decreasing after subsequent treatment cycles. Ivermectin has no adverse effects in uninfected people. Although ivermectin temporarily reduces the release of microfilariae by adult worms, it does not destroy the adults. Those coinfected with Loa loa, are at risk of developing potentially fatal central nervous system events after treatment with ivermectin. Although most severe reac- tions occur with L. loa counts more than 30 000 microfilariae/ml, great caution should be observed when treating anyone with counts greater than 8000 microfilariae/ml. Pretreatment with six weeks of Abendazole reduces levels of L. loa but levels might still put patients at risk of severe reactions after ivermectin. Ivermectin appears to have several separate actions against the parasite. In microfilariae it acts primarily on parasite neurotrans- mitters, producing paralysis. This action appears to be mediated by the potentiation or direct opening of glutamate-gated chloride channels. The prolonged disappearance of microfilariae after a single treatment is the result of the drug’s effect on embryogenesis in the adult female worm. Treatment with ivermectin does not prevent the development of new infections by additional larvae introduced by bites of infected flies. Resistance to ivermectin has been reported where animal para- sites have been exposed to high and prolonged drug selection pres- sures. In 2007, a suboptimal response to ivermectin was noted among some persons in an area in Ghana who received annual mass treatment for many years. In several areas of Africa, twice annual treatment has now been implemented as standard. Through its ac- tion against Wolbachia bacteria, doxycycline given for six weeks has been shown to be effective in clearing microfilariae and killing some adult worms. A new medicine, moxidectin, has recently shown an excellent pattern of clearing microfilariae after a single treatment. Its role in mass treatment for onchocerciasis is not yet clear. Prevention and control Treatment and prevention methods have included insecticides added to rivers to interrupt Simulium breeding, mass distribution of ivermectin, and nodulectomy in an attempt to prevent blindness. Vector control Killing Simulium larvae by adding the insecticide dichlorodiphenyltrichloroethane (DDT) to rivers eliminated on- chocerciasis in Kenya and the Mabari forest of Uganda. In 1974, the Onchocerciasis Control Programme was formed to control Simulium by larviciding rivers in the Volta basin of West Africa using ecologic- ally suitable compounds. This highly successful vector control pro- gramme, later supplemented with ivermectin distribution, helped eliminate onchocerciasis as a public health problem from most foci in West Africa. Vector control continues to be appropriate in some locations, especially where transmission is with S. naevi.

section 8 Infectious diseases 1484 Ivermectin mass distribution After the effectiveness of ivermectin had been shown, its manufac- turer, Merck & Co., established the Mectizan Donation

Program to provide the drug free ‘for as long as necessary to as many as ne- cessary’. Between 1988 and 2016, 2 billion ivermectin treatments had been provided for endemic countries through the Mectizan Donation Program which oversees drug approvals. This has in- volved the treatment of some 146 000 communities. The goal of a control programme in Latin America has been the elimination of disease transmission through twice yearly treatment. In all locations but two, there are no new infections or no evidence of disease transmission. The remaining ongoing transmission is among a small number of the Yanomami Indians who move back and forth across the Brazil-Venezuela border in difficult-to-reach circumstances. In Africa, the 20-year African Programme for Onchocerciasis Control oversaw mass distribution of annual ivermectin treatment which has eliminated the public health consequences of onchocer- ciasis in 20 countries. This has been accomplished using community selected distributors whose goal is to treat 85% of the eligible popu- lation each year. In several foci in several African countries the evi- dence suggests transmission has already been interrupted, but the final evidence is still awaited on elimination of transmission. The movement from control to elimination of transmission requires new public health approaches involving post-treatment methods to verify the end of vector transmission and postelimination surveillance to verify the absence of new human infections. Some countries such as Uganda, Ethiopia, and Nigeria are embarking on these, of which twice annual treatment might play an important part. Treatment has so far been largely confined to meso- and hyperendemic areas. An elimination strategy would need to encompass the larger area where infection is hypoendemic (so previously excluded from mass treat- ment) and where transmission can still occur. Modelling suggests that elimination, with an accelerated strategy, is achievable in many countries by 2025, though some in countries this might be protracted, especially those with extensive Loa infections, and those with weak infrastructure. Countries such as the Democratic Republic of the Congo, Cameroon, and Angola have presented particular challenges. Conflict has retarded mass distribution in several areas. Population migration has changed the distribution of the disease in some loca- tions. Treatment of onchocerciasis in urban areas, such as in Congo (Brazzaville), present unique challenges. With the closure of the African Programme for Onchocercias Control in 2015, onchocerciasis mass treatment is now combined with mass drug distribution for the control or elimination of four other diseases in most African countries. Onchocerciasis control in Africa is now coordinated by the World Health Organiation’s Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN). 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, es- pecially around the head. Evidence for this approach in preventing blindness is not strong. Eliminating infection Although ivermectin brings great relief to the individual, and has a clear impact on the disease in mass distribution programmes for affected populations, it does not kill adult worms. While symptoms and risks are controlled through annual ivermectin treatment, the disease itself is not eliminated, and the potential for the development of drug resistance remains. Several macrofilaricidal drugs capable of eliminating the disease through the killing of adult worms have been tested, but none has so far proved suitable for either individual or mass treatment. Treatment with doxycycline combined with ivermectin does show promise as do early trials with flubendazole. The filarial endosymbiont Wolbachia is a target for further drug development. Loiasis Loa loa is a filaria transmitted by Chrysops spp. flies in West and Central Africa. The adult worm migrates beneath the skin, and some- times across the eye, moving at about 1 cm per minute. Periodically, the infection causes sudden but transient localized inflammatory oedema known as Calabar swellings. Parasitology The larvae of L. loa burrow into human skin during feeding of the Chrysops

or mangrove fly (C. silacea or C. dimidiata). In hu- mans, the parasites mature and live in the fascial layers. After 1 year or more, microfilariae are produced. Microfilariae are most heavily present in the blood in the daytime, between 10.00 and 15.00, when the Chrysops fly bites. Once taken up by the fly, microfilariae go through developmental stages in the fly's thoracic muscles. After 10 days the fly is able to infect a human, and can do so for another 5 days. Epidemiology Infection is most commonly reported from around the Gulf of Guinea, particularly in Cameroon, Gabon, Congo (Brazzaville), Equatorial Guinea, Central African Republic, and Democratic Republic of the Congo. With continuing deforestation in some areas, infections are less common than in the past (Fig. 8.9.1.9). Humans are the only host, although a similar parasite is found in monkeys in the same areas. The fly lives in the rainforest canopy, and descends to bite humans, attracted perhaps by movement. Transmission may be most intense during the rainy season, when flies are breeding on the muddy banks of forest streams. Clinical features The first clinical symptoms of loiasis can appear as soon as 5 months after infection, or as late as 13 years. Calabar swellings appear sud- denly, most commonly on the forearms or wrists, and sometimes following heavy exercise or exposure to heat. These oedematous le- sions are red and itchy, and might be associated with fever and irrit- ability, but are generally nontender. After several days the affected part returns to normal. However, recurrence is common at irregular intervals. Swellings are not confined to the arms, but can be present in the face, breasts, or legs. Calabar swellings are a hypersensitivity reaction to worm antigens which might be released in the process of migration or perhaps during the maturation of the worm. A high proportion of eosinophils are seen in peripheral blood smears, often exceeding 70%.

8.9.1 Cutaneous filariasis 1485 A second common feature is the appearance of a migrating worm (Fig. 8.9.1.10). This can be under the skin in any location, but is most dramatic when it crosses the eye ('eye worm'; Fig. 8.9.1.11). Other than local irritation of the conjunctiva while the worm is passing, and the obvious concern of the host, there are no serious consequences. The time of passage can last from 30 min to more than 1 day. Rare but potentially serious consequences of L. loa are meningo- encephalitis, renal disease, and endomyocardial fibrosis. Arthralgias have also been noted. The meningoencephalitis can occur spontan- eously, although usually after treatment with diethylcarbamazine or Fig. 8.9.1.9 Map of the reported instances of Loa loa eyeworms using RAPLOA observations. From Zouré HGM et al. (2011). The geographic distribution of Loa loa in Africa: results of large-scale implementation of the rapid assessment procedure for loiasis (RAPLOA). PLoS Negl Trop Dis 5(6), e1210, © 2011 Zouré et al. Fig. 8.9.1.10 Migrating adult Loa loa. Fig. 8.9.1.11 Loa loa crossing the bulbar conjunctiva.

section 8 Infectious diseases 1486 ivermectin. Fatalities have been reported following treatment. The renal and endocardial complications of loiasis are likely due to the deposition of immune complexes. Laboratory diagnosis Diagnosis has traditionally been by the finding of microfilariae in a daytime blood sample, or by a history of typical clinical findings. The use of more sensitive PCR methods has shown that many people, even perhaps most, of those infected do not have microfilariae in their peripheral blood. Treatment The standard treatment has been diethylcarbamazine, which kills microfilariae and many adult worms. The treatment is commonly given in doses of 8–10 mg/kg orally in three divided doses daily for 21 days. Fever, arthralgia, and itching can occur during treat- ment. Ivermectin at 200 µg/kg dramatically decreases the number of microfilariae and some of the loiasis symptoms, but has little macrofilaricidal effect. Two courses of treatment may be required. As with diethylcarbamazine, there is a high risk of potentially fatal meningoencephalitis in persons with microfilarial counts over 30 000 microfilariae/ml. Caution

should be observed in the treat- ment of all persons with over 8000 microfilariae/ml. Albendazole given in six doses substantially reduced high Loa microfilarial counts in some patients but not all. Treatment with small doses of iver- mectin does not offer any advantages. As L. loa does not harbour Wolbachia, treatment with doxycycline is ineffective. Since many people with loiasis also have onchocerciasis, careful monitoring for severe eye and skin inflammation is important when giving diethylcarbamazine. Blood films for microfilariae or PCR tests should be followed to indicate the need for retreatment. Prevention The best prevention is avoiding Chrysops fly bites. Having window screens on dwellings, wearing clothing to protect the legs and fore- arms, and avoiding areas where biting is frequent can reduce the risk. Chemoprophylaxis with diethylcarbamazine has been sug- gested, using either 5 mg/kg on three consecutive days in a month, or a weekly dose of 300 mg while living in an area of transmission. Mansonellosis Mansonella spp. are a group of filarial species common to many countries, but are of negligible clinical importance under most circumstances. Infection is transmitted by Culicoides spp. biting midges. Epidemiology Mansonella (formerly Dipetalonema) perstans is found widely in sub-Saharan Africa, as well as Trinidad and several parts of South America. The adult worms live free in the abdominal cavity, and microfilariae are found in the blood and skin. Mansonella ozzardi is found in the West Indies and Central and South America. In addition to Culicoides, Simulium flies have been reported to transmit M. ozzardi in the Amazon basin. Mansonella streptocerca is a common infection in West and Central Africa, extending into western Uganda. Both microfilariae and adult worms are found in the skin, but without the nodules seen in onchocerciasis. Unless M. streptocerca microfilariae are differentiated parasitologically from those of O. volvulus, inappropriate mass onchocerciasis treat- ment programmes could inadvertently be implemented. Clinical manifestations Of the Mansonellas, only M. streptocerca produces clear-cut symp- toms, although even these can be confused with those of O. volvulus, and which might be a coinfection. Chronic papular lesions are com- monly present, often associated with postinflammatory hyperpig- mentation. Lichenification occurs less commonly. Hypopigmentation has been noted in areas of skin overlying the location of adult worms in the skin. In general, these findings are not easily distinguishable from those of onchocerciasis. Eosinophilia is common. M. perstans has been reported to produce Calabar-like swellings, pruritus, fever, and headache. M. ozzardi infections are generally asymptomatic, although vague complaints of fever, arthralgia, head- ache, and itching have been associated with infection. There have been reports of ocular lesions in Brazil. Diagnosis Diagnosis is by finding characteristic microfilariae in the blood or skin. The tails of the microfilariae have a distinctive walking-stick shape, and contain four prominent nuclei, distinguishing them from microfilariae of O. volvulus. A PCR assssay has been described for M. streptocerca, and both quantitative buffy coat fluorescent staining and enzyme immunoassay methods for M. perstans. Eosinophilia is a characteristic finding. Treatment In asymptomatic people no treatment is required. M. streptocerca re- sponds well to ivermectin, producing prolonged suppression of circu- lating microfilariae. Mild reactions similar to those in onchocerciasis may be seen. The treatment of M. perstans with doxycycline is ef- fective, consistent with the effect of the drug on Wolbachia endosym- bionts. A combination of both diethylcarbamazine and mebendazole is highly effective against M. perstans, while ivermectin has little effect. For M. ozzardi infections, a single ivermectin dose of 0.14-0.2 mg/kg has been found to be highly effective, though the risks of Mazzotti-like reactions are well described in persons with high parasite loads. FURTHER READING Onchocerciasis African Programme for Onchocerciasis Control (2015). African Pro gramme for Onchocerciasis Control: progress report, 2014–2015. Wkly Epidemiol Rec, 90, 661–80. Coffeng LE, et al. (2013). African Programme for Onchocerciasis Control 1995–2015: model-estimated health impact and cost. PLoS Negl Trop Dis, 13, e2032. Colebunders R, et al. (2015). Nodding syndrome since 2012: recent progress, challenges and

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