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are mosquito-borne lymphatic-dwelling nematode parasites that are important causes of morbidity, disability, and social stigma in tropical and subtropical countries. Bancroftian filariasis due to W. bancrofti, which has no animal reservoir, accounts for 90% of human infections worldwide. Clinical features Acute lymphatic filariasis—(1) lymphadenitis and lymphangitis—most common in the inguinal and femoral nodes; (2) acute genital— usually tender fusiform or cylindrical swelling of the spermatic cord; (3) abscess and fever—affected nodes may break down to produce an open ulcer. Chronic lymphatic filariasis—(1) lymphoedema and elephantiasis— initially transient pitting oedema occurs during acute inflammatory episodes in proximal nodes; eventually brawny, nonpitting oedema becomes permanent; (2) chronic genital—most commonly hydro- cele; (3) chronic lymphadenitis and lymphangitis; (4) chyluria and lymphuria; (5) nonlymphatic pathology—including tropical pul- monary eosinophilia, filarial arthritis, and filarial glomerulonephritis. Diagnosis, treatment, and control Diagnosis—microfilariae are typically found in Giemsa-stained blood films; the sample is best taken at night (22.00–02.00), except in Oceania and parts of Southeast Asia. Microfilariae are also some- times found in aspirates from lymph varix, hydrocele, lymphocele of the cord, or in urine. A rapid antigen detection test allows the mapping of prevalence and assessment of the impact of mass drug distribution. Individual treatment—diethylcarbamazine, which may provoke both local and systemic reactions, or doxycycline are needed in some situations, including infected visitors, people leaving infected areas, and those with tropical pulmonary eosinophilia or other clinical features where elimination of adult worms is a priority. Concurrent bacterial infection requires prompt treatment with antibiotics, and supportive bandaging can reduce chronic oedema. Community wide treatment and control—The Global Programme for the Elimination of Lymphatic Filariasis usually involves four or six annual rounds using two-drug combinations of ivermectin, albendazole, or diethylcarbamazine to all eligible persons to interrupt transmission by reducing the numbers of circulating micro- filariae, together with (in appropriate circumstances) vector control. This regimen will eliminate acute disease episodes and significantly reduce chronic morbidity. Introduction Wuchereria bancrofti, Brugia malayi, and B. timori are mosquito- borne nematode parasites. They are important causes of morbidity, disability, and social stigma in tropical and subtropical countries (Fig. 8.9.2.1). The total population at risk is estimated to be 856 mil- lion in some 52 countries where these infections are endemic. In 2000 bancroftian filariasis due to W. bancrofti infected 120 million people of whom about 40 million had clinical disease and some 80 million had hidden lymphatic damage; it was introduced into the Americas from Africa by the Atlantic slave trade. The two Brugia species in- fected about 13 million people in South and Southeast Asia. B. timori has a localized distribution in a few islands in eastern Indonesia. Lymphatic filariasis ranks second as a cause of disability worldwide.

section 8 Infectious diseases 1488 Fig. 8.9.2.1 Lymphatic filariasis endemic countries and territories by mass drug administration (MDA), 2013. Reproduced from WHO Weekly Epidemiological Record No. 38, 2014, 89, 409–420, with kind permission of the World Health Organization.

8.9.2 Lymphatic filariasis 1489 Aetiology: The biology of the parasite The adult worms live in the larger lymphatic vessels and lymph nodes; many live as ‘worm nests’ within dilated lymphatics of the limbs and male genitals. The worms are smooth, creamy-white, and threadlike; females measure 8 to 10 cm in length and males 4 cm. Their lifespan is estimated to be 4 to 6 years, but may be longer—a critical issue for planning, implementation, and duration of elimin- ation

programmes. Mated females produce numerous microfilariae throughout their life; these actively motile embryonic worms are sheathed by the remnants of the egg shell. They are 180–290 µm in length and 7–10 µm in diameter, with diagnostic species morpholo- gies in stained blood films. Microfilariae migrate via the lymphatic system to the blood, where they have an estimated lifespan of up to 12 months. Their numbers in the peripheral blood vary during the day and night, a phenomenon known as periodicity, and when not circulating they are sequestered in lung and reticuloendothelial capillaries. Maximum counts in the blood coincide with the biting cycle of the vector. The species and strain of parasite determine the periodicity. Most common is the nocturnally periodic form, with maximum microfilarial counts found between 22.00 and 02.00, and virtual absence during the day. Alternatively, microfilariae may be pre- sent throughout the 24-h cycle, with prominent peaks during the day or the night; referred to as diurnal or nocturnal subperiodicity, respectively. After ingestion by the mosquito, microfilariae penetrate the midgut and migrate to the thoracic muscles, where they mature over 9 to 15 days to infective third-stage larvae. These then migrate to the head of the mosquito and escape through the arthrodial membranes around the proboscis during a blood meal. Larval worms enter the puncture wound made by the vector, enter the peripheral lymphatic system, and most eventually reach the lymph vessels of the prox- imal limb and male genitalia. Sexual maturity and the appearance of microfilariae in the blood usually take 8 to 18 months, but some- times only 3 months. Both adult worms and microfilariae harbour Wolbachia bacterial endosymbionts that are essential for the repro- duction and survival of the parasite. Epidemiology and transmission In endemic areas microfilaria prevalence rates increase steadily from early childhood and often reach a maximum in early adult life, when a prevalence of 10–30% is not unusual in highly endemic areas. However, a recent meta-analysis suggests that prevalence, in the absence of a decline in transmission, may often continue to rise with age. Prevalence in males is generally higher, perhaps as a result of greater vector exposure. The cord blood of some infants shows microfilariae. Recent studies using an immunochromatographic card test to detect adult worm antigen showed that in a population of Haitian children prevalence reached 25% by the age of 4 years. The test is used to map the distribution of Wuchereria bancrofti and gives a prevalence of approximately double that detected by night blood films. Detailed mapping, using districts, assists in defining pro- gramme implementation units for the purposes of planning mass drug distribution. W. bancrofti has no animal reservoir. Brugia malayi, however, is a zoonosis in some areas of its distribution (southern Thailand, Indonesia, and Malaysia), with a reservoir in cats and leaf monkeys, although their importance in terms of maintaining the cycle in hu- mans is not known; elsewhere it is an anthroponosis with only a human source of infection. Mosquito vectors and geographical distribution W. bancrofti infection Culex spp. transmission This vector, mainly C. quinquefasciatus, breeds mostly in organic- ally polluted water, usually in urban and suburban areas, but also villages where there are suitable latrine and cesspit habitats. Culex is the most widely distributed vector and is increasing with urban- ization; it occurs in India, Sri Lanka, Central and South America, some Caribbean islands, urban and coastal villages in East Africa and Egypt, and formerly in parts of China, where transmission has been eliminated. Culex bites at night; the microfilariae are noctur- nally periodic. Culex is the most efficient vector and can maintain transmission at low microfilarial densities, making control difficult. Anopheles spp. transmission The same species of Anopheles, notably An. gambiae sensu lato and An. funestus, commonly transmit both filariasis and malaria in East and West Africa. In Papua New Guinea and Vanuatu, the vectors are Anopheles of the punctulatus complex. Anopheles bites at night, mainly on the legs; microfilariae are nocturnally periodic. Aedes spp. transmission This is limited to southern Oceania, especially Fiji, Samoa, Tonga,

the Cook Islands, and New Caledonia; but also patchily in Thailand, the Philippines, Vietnam, and the Nicobar islands. Aedes feeds throughout the 24-h cycle, but predominantly with a daytime biting peak, and bites all over the body; the microfilariae are diurnally subperiodic. Ochlerotatus spp. transmission This genus of mosquito transmits subperiodic and aperiodic strains of W. bancrofti in Asian forest habitats and in the Philippines, Samoa, and New Caledonia. Until recently this genus was classified in the genus Aedes. B. malayi infection Zoonotic Mansonia spp. transmission in swamp forests This occurs in Malaysia, Indonesia, and southern Thailand. Mansonia bites mainly by night, but also during the day, usually on the legs below the knee; the microfilariae are nocturnally subperiodic. Transmission in agricultural areas In parts of Malaysia, Buru in Indonesia, and southern Thailand a mixed anthroponosis and zoonosis occurs in transitional zones, with monkeys and cats as reservoirs, and both Anopheles and Mansonia as vectors. Microfilariae have periodicities intermediate between nocturnally periodic and nocturnally subperiodic.

section 8 Infectious diseases 1490 In India (mainly Kerala), Malaysia, Sulawesi, southern Thailand, and Vietnam infection involves humans only, with Anopheles as the main vector and Mansonia as an accessory vector; the microfilariae are nocturnally periodic. B. timori infection This is confined to Timor Leste and islands in the Lesser Sundas group in eastern Indonesia. Anopheles barbirostris is the vector, and the microfilariae are nocturnally periodic. Pathogenesis Local immunological reactions to worm antigens provoke acute and subacute responses, with dilatation of lymphatics and infiltra- tion of tissues with eosinophils and monocytes. The antigens derive from the moulting fluids of developing worms, excretory products, microfilariae trapped within the lymphatic system, and also dying worms, including those killed by chemotherapy. Wolbachia lipopro- teins from living and dying worms also provoke inflammation; thus, living worms can create lymph vessel dilatation and stasis. Several immunological mechanisms and cytokines are involved including vascular endothelial growth factors. Living worms also induce sup- pressive immunomodulatory responses that facilitate worm survival so that subjects with high blood microfilaraemias may have no evi- dent clinical disease. Dead and disintegrating worms become surrounded by granula- tion tissue with giant cells and epithelioid cells. Stasis and blockage of lymph vessels leads to distal dilatation, with varicosities and valve incompetence. Prolonged or recurrent lymph stasis leads to the ac- cumulation of protein-rich interstitial tissue fluid, fibroblast prolif- eration, dilated dermal lymphatics, and epithelial acanthosis and hyperkeratosis. Determinants of pathology include the duration of exposure, in- tensity of transmission, anatomical sites of infective mosquito bites, human genetic factors, and the species and strain of parasite. Prenatal exposure to filarial antigen is of great importance and induces im- munological tolerance. Residents in high-transmission areas often show patent microfilaraemia, but little immunopathology. However, in some adults a later decline in microfilarial prevalence parallels in- creased host immunological reactivity and pathology. New residents and visitors show marked local reactivity to worms, and often no blood microfilariae; the latter situation was well documented among American troops in the Pacific in the Second World War, and French troops in former Indochina. Clinical manifestations Acute lymphatic filariasis In endemic areas acute episodes are recurrent from the age of 10 years, and most frequent 4 to 8 months after the peak of seasonal transmission. Episodes last several days or weeks; fever and malaise are common, but blood eosinophilia is not marked. Persons leaving endemic areas cease to have acute episodes after 1 year, although they may experience recurrent pain in previously affected tissues, especially after unusual exercise. Filarial lymphadenitis and lymphangitis Tender lymphadenopathy is most common in the inguinal and fem- oral nodes, but axillary and epitrochlear nodes are also affected. Tender retrograde lymphangitis typically spreads

peripherally below the node. Acute genital filariasis This is uncommon in boys before puberty, but common thereafter. The typical lesion is funiculitis, with a tender fusiform or cylindrical swelling of the spermatic cord; epididymitis and orchitis are less common. Filarial abscess and filarial fever Affected nodes in the groin or elsewhere may break down producing an open ulcer that heals slowly leaving characteristic scars. Pelvic and retroperitoneal lymphadenitis can produce a febrile illness that is difficult to diagnose. Chronic lymphatic filariasis Lymphoedema and elephantiasis Initially, transient pitting oedema occurs during acute inflamma- tory episodes in proximal nodes. Bacterial infection, often caused by Streptococcus pyogenes, is common in those with compromised lymphatics, especially when the skin is fissured, breached in an inter- digital cleft, or when there is minor injury, an ulcer, or insect bite; this presents as cellulitis and ascending lymphangitis. Later, oedema persists between episodes, becoming distally nonpitting. Eventually, brawny nonpitting oedema becomes permanent (Fig. 8.9.2.2). In patients with leg involvement, epidermal thickening, papillomatosis, and fissuring are common (Fig. 8.9.2.3). Fig. 8.9.2.2 Chronic elephantiasis in a man in Belém, northern Brazil. Note the scars of unsuccessful surgery. Copyright Pedro Pardal.

8.9.2 Lymphatic filariasis 1491 Chronic genital filariasis Hydrocele (Fig. 8.9.2.4) is the most common lesion, and preva- lence rates may reach 30% in men over 35 years in highly en- demic areas; many patients give a history of preceding episodes of funiculitis or epididymitis. Hydrocele fluid is usually a transudate, but lymph or blood may be present. The tunica vaginalis is often thickened. Nodular lesions of the spermatic cord and epididymis are common, and the testis itself may become enlarged and indur- ated. Lymphoceles occur on the cord. Dilated dermal lymphatics in the scrotal wall associated with atrophic epidermis produce ‘lymph scrotum’, the skin having a velvety appearance. Rupture of these lymphatics leads to weeping skin lesions and often secondary in- fection, occasionally complicated by Fournier’s gangrene caused by anaerobic bacterial sepsis. Lymphoedema of the scrotum is a late sequel; often the testes are unaffected, and penile lesions are rare. Vulval lymphoedema is underrecognized; it is associated with dilated retroperitoneal lymph- atics, and must be distinguished from lymphogranuloma venereum. Chronic lymphadenitis and lymphangitis Recurrent episodes of acute inflammation lead to persisting and sometimes massive lymph node enlargement. Thickened lymph- atic cords may be palpable connecting the axillary and epitrochlear, or the femoral and popliteal nodes. Varicose lymph vessels may be visible in these areas. ‘Lymph varices’ are fluctuant sacs of lymph- atic tissue derived usually from the capsule of a node, hence the alternative term ‘lymphadenocele’. They partially empty when the part is raised, and aspiration reveals lymph or occasionally chyle. They occur in the medial thigh, groin, axilla, and sometimes even the neck. Chyluria and lymphuria Dilated pelvic and retroperitoneal lymphatics may rupture into the urinary tract in the renal pelvis, ureter, or bladder. When there is lymph stasis above the cisterna chyli then small-bowel chyle may re- flux into the urine postprandially. Chyluria is often intermittent and blood stained (Fig. 8.9.2.5). Continued loss of protein and lipids in the urine may lead to weight loss and cachexia. Chyluria may even- tually be self-limiting. Nonlymphatic pathology Tropical pulmonary eosinophilia This presents as a subacute or chronic illness with cough, wheezing, and reticular or miliary pulmonary shadowing. Microfilariae are absent from the blood, but eosinophilia is marked, and titres of filarial antibody are very high. Some patients have features of lymphadenopathic or genital filariasis, but many do not. The defect in of lung function is restrictive. The response to antifilarial treat- ment is good, but untreated the condition can lead to pulmonary fibrosis and pulmonary hypertension. The syndrome is the result of a heightened immunological response to dead microfilariae, which may

be found in biopsies of lung and other tissue, surrounded by eosinophilic microabscesses. It occurs in most endemic areas, but is rare in Africa. It is more common in men, and rare in children, and many patients are not long-term residents. Filarial arthritis Joint involvement is subacute, and often recurrent with effusion; it usually affects the knee. Fig. 8.9.2.4 Gross hydrocele in a patient with chronic filariasis. Courtesy of the late P. E. C. Manson-Bahr. Fig. 8.9.2.3 Chronic elephantiasis with epidermal thickening, fissuring, and papillomatosis in a man in north-east Nigeria. Copyright D. A. Warrell.

section 8 Infectious diseases 1492 Filarial glomerulonephritis This results from filarial and streptococcal immune-complex deposition on the glomerular basement membrane, but there is also tubular damage. Clinical findings include proteinuria and haematuria, which usually respond to chemotherapy. The incidence of clinically significant disease and its prognosis are uncertain. Diagnosis Clinical Many patients will have several clinical features that, together with a history of preceding acute episodes, will be strongly suggestive diagnostically—manifestations such as varicose lymphatics, lymphadenocele, retrograde lymphangitis, and lymph scrotum are highly specific to filariasis. Genital lesions are rare in Brugia infec- tions, which usually present with lymphoedema below the knee. In B. timori infection lymph node pathology in the legs is often severe, sometimes with skin ulceration. Upper limb and breast le- sions are common in diurnally subperiodic W. bancrofti infections in the Pacific, but they do occur elsewhere with other strains of this parasite. Parasitological Microfilariae (Fig. 8.9.2.6) are typically found in Giemsa-stained blood films, but also in aspirates from a lymph varix, hydrocele, or lymphocele of the cord, or in urine in chyluria patients. Blood should be taken to coincide with the expected microfilarial peri- odicity. For quantitative studies, measured 10- or 20-µl volumes are used to prepare thick blood films. For measuring changes in intensity, larger measured quantities of blood (60 microlitres) should be used to increase the sensitivity and accuracy of a key parameter. Counting chambers taking 100 microlitres of lysed blood can be used, or larger volumes may be lysed and the spun de- posit examined. A sensitive method which allows quantitation of parasite density is filtration of 1–5 ml of heparinized venous blood through a nucleopore filter of pore size 5 microns; microfilariae on the filters can then be stained. Nocturnally periodic W. ban crofti microfilariae appear transiently in the blood 30 to 60 min after a 100-mg dose of diethylcarbamazine, which forms the basis of the provocation test. Species diagnosis of stained microfilariae is made by their sheath characteristics and the arrangement of caudal nuclei. The microfilariae of Loa loa, the tropical eye worm (found only in West and Central Africa) are diurnally periodic and also have a sheath; they must be distinguished from those of lymphatic filariasis. Immunodiagnosis Positive filarial antibody and skin tests are common in those ex- posed to infection, and may be of value in visitors to an endemic area. Several tests are now available for W. bancrofti antigen in serum, including a card test for field use. A positive test indicates persisting adult worms; antigen may be present in the absence of microfilaraemia. For Brugia infections, techniques for DNA detec- tion by polymerase chain reaction are available, and also specific IgG4 antibody tests. Imaging of lymphatic vessels Lymphangiography will delineate the anatomical details of ab- normal lymphatic tissues, such as lymph varices and lymphatic connections to the urinary tract in chyluria. They are not usually diagnostic for filariasis. Scrotal ultrasonography can show nests of live worms—the ‘filarial dance’ sign; this can be used to assess the impact of chemotherapy on adult worms. Lymphoscintigraphy using technetium-labelled dextran or al- bumin is a less invasive technique for demonstrating lymphatic pathology. Abnormal dermal lymphatics occur in many asymptom- atic infected persons in endemic areas. Fig. 8.9.2.5 Chyluria and haematuria in a patient with chronic filariasis. Courtesy

of the late P. E. C. Manson-Bahr. Fig. 8.9.2.6 Microfilaria of W. bancrofti on a Giemsa-stained blood film showing sheath and row of terminal nuclei (right).

8.9.2 Lymphatic filariasis 1493 Drugs for the control and treatment
of lymphatic filariasis Filaricides may act against adult worms (macrofilaricides), against microfilariae (microfilaricides), or both. They often also act against other filarial infections such as Onchocercaa volvulus and L. loa; this may cause severe reactions in patients coinfected with these para- sites. Side effects of filaricides are mainly due to immunological re- actions to dying worms and the release of Wolbachia lipoproteins. Diethylcarbamazine Diethylcarbamazine was first introduced for treatment of lymphatic filariasis in 1948 and until 25 years ago it was the only drug available. It acts against both adult worms and microfilariae, but predominantly the latter; its mode of action is poorly understood but involves the arachi- donic pathway. The resulting damage to the worm surface leads to vig- orous immunological reactions that may be dangerous. A single dose of 6 mg/kg body weight greatly reduces the level of blood microfilariae for a year and kills some adult worms. In communities with low and declining endemicity many of the remaining adult worms are near the end of their lifespan and more easily killed with diethylcarbamazine. Ivermectin Ivermectin has a broad spectrum of antiparasitic activity. In lymph- atic filariasis it acts only against microfilariae, and a dose of 100– 200 µg/kg will clear microfilariae as well as diethylcarbamazine. Its action is rapid and side effects correlate with microfilaria load. Ivermectin immobilizes microfilariae by hyperpolarization of glutamate-sensitive channels. Albendazole Albendazole is a broad spectrum anthelminthic and is widely used to treat intestinal nematodes. It acts by inhibiting polymerization of β-tubulin and microtubules. A 400 mg dose will clear most intestinal nematode infections and will reduce microfilaria levels in lymphatic fil- ariasis progressively over 6–12 months; greater reductions occur when it is given with either diethylcarbamazine or ivermectin, with which it acts synergistically against microfilariae. It does not kill adult worms. Doxycycline Doxycycline is a broad spectrum antibiotic that kills the Wolbachia endosymbionts. A 100 mg or 200 mg dose given daily for 3 to 8 weeks will kill both adult worms and microfilarariae; its action is slow over 12 months and this greatly reduces the severity of side effects that occur in response to the rapidly dying worms and Wolbachia with other filaricides. Treated patients show a significant improvement of their hydrocele, lymphoedema, and other clinical manifestations of lymphatic filariasis. Unfortunately, the drug is contraindicated in children under 9 years of age and in pregnant women. Filariasis at the community level The Global Programme to Eliminate
Lymphatic Filariasis A World Health Assembly Resolution in 1997 launched a pro- gramme to eliminate lymphatic filariasis as a public health problem by 2020. This resolution was based on new evidence of the impact of two-drug combinations on microfilaraemia, and the availability of a rapid antigen test, the immunochromatographic card test, that allows mapping of the prevalence of disease and assessment of the impact of mass drug administration (MDA). Clinical studies had demonstrated that the annual distribution of diethylcarbamazine and albendazole, or albendazole and ivermectin, for 4 or 6 years re- duced microfilaraemia levels by about 95%. Mathematical models suggested that this would interrupt transmission, provided that an- nual coverage exceeded 65%. The programme was backed by generous commitments by the manufacturers to donate albendazole and ivermectin. A global public–private partnership was formed in 2000, the Global Alliance to Eliminate Lymphatic Filariasis (GAELF). The extensive geo- graphic distribution of lymphatic filariasis required a regional ap- proach to programme management and planning with detailed mapping, baseline data collection, and the establishment of evalu- ation and monitoring

based on sentinel-site selection. Training drug distributors; selecting appropriate drug distribution systems; infor- mation, education, and communication; social mobilization needs; and reporting systems were recognized as being of great importance. By 2015, having reviewed the global situation, the World Health Organization (WHO) reported that 73 countries were endemic and 63 of these had implemented mass drug distribution to stop trans- mission; 18 countries that were previously included in the list of endemic countries were deemed to be free of endemic disease. In 2015, a total of 698 million people were targeted for MDA, of whom 556 million received the recommended WHO two-drug combin- ation of albendazole plus either ivermectin or diethylcarbamazine, an average coverage of 80%. The estimated numbers of cumulative treatments since the programme began in 2000 is around 6.7 billion treatments. An important advantage in using albendazole is the re- duction of the burden of soil-transmitted helminths such as hook- worm, Trichuris, and Ascaris. To assess the impact of MDA WHO has provided guidelines for Transmission Assessment Surveys which are based on using immunochromatographic tests in cohorts of children aged 6 to 10 years who were born shortly after the annual drug distributions began. Additional assessment of transmission or the existence of microfilarial parasites in the population can be achieved by a technique known as xenomonitoring when mosqui- toes are caught and examined for the presence of filarial DNA. Drug coverage in an MDA programme may be misleading as compliance, actual ingestion of the tablets, may be lower; in an extensive review of the programme in India it was 22% lower. Compliance varies be- tween households and relate to absences, lack of perceived need, drug contraindications, or fears of toxicity. The programmes are not yet including all those who need it; In the African Region 395 mil- lion were estimated to need MDA but only 44% were covered, the respective figures in the Southeast Asian Region were 501 million and 72%. The needs of patients already afflicted with lymphoedema and hydrocele must also be addressed. To this end WHO has issued guidelines for home-based care, whereby lymphoedema patients and their families are taught how to treat lymphatic filariasis-related lymphoedema and prevent acute attacks. WHO also aims to increase access to hydrocele surgery that uses new reconstructive techniques. Despite resource constraints, particularly in sub-Saharan Africa, there are encouraging signs that the programme is reducing the

section 8 Infectious diseases 1494 prevalence of the disease. Egypt has reported the elimination of transmission in formerly endemic areas of the Nile Delta. China has been certified by WHO as free of transmission in a population of some 350 million who were previously at risk. The Republic of Korea has also eliminated a focus of Brugia malayi and certified free of transmission. Several smaller countries previously demonstrated disease elimination following a range of different interventions. These are Suriname, Costa Rica, Trinidad and Tobago, and also the Solomon Islands, where vector control for malaria, using indoor re- sidual spraying with dichlorodiphenyltrichloroethane (DDT) in the 1970s, appears to have been effective. Population-based chemotherapy In the past, different dosage regimens of diethylcarbamazine alone were used in many endemic areas. Drugs were given annually or 6 monthly, either to the whole population or to those found to be infected; medicated salt being the alternative. The main aim was to eliminate microfilaraemia and hence transmission, but with re- peated doses many adult worms are eventually killed. The availability of ivermectin offered an effective alternative for reducing microfilaraemia, but does not kill adult worms. A single dose of 200 μg/kg of ivermectin is as effective as a 6 mg/kg dose of diethylcarbamazine. Both will virtually eliminate microfilaraemia for 6 or 12 months, adverse reactions are probably equally common with both drugs. Albendazole is also effective as a microfilaricide, and probably has some activity against adult worms. A 400 mg dose given annually can replace either diethylcarbamazine or ivermectin in a two-drug annual

regimen. Annual dosage with either of these two-drug combinations, continued for 4 to 6 years (the lifespan of nearly all adult worms), will interrupt transmission. It is not recommended that diethylcarbamazine be given in areas where onchocerciasis or loiasis are endemic to avoid dangerous reactions. Loa-associated encephalopathy occurs especially in people with Loa microfilarial loads of more than 8000/ml of blood. Similarly, extreme caution needs to be exercised when community treatment with ivermectin and albendazole is implemented in areas where Loa is endemic; in such areas twice yearly albendazole 400 mg should be given alone. As there are few areas in sub-Saharan Africa where Loa and Onchocerca do not have potential overlap with W. bancrofti, the use of diethylcarbamazine has been discouraged or abandoned there in recent years. As there are many areas of Africa where W. bancrofti and Onchocerca are coendemic there is urgent need to integrate the two previously separate MDA programmes for these infections, which both employ ivermectin, more closely. In areas where population-based annual chemotherapy is in pro- gress there is a reduced incidence of worm-related acute manifest- ations, and often reductions in hydrocele size. In Brugia areas recent studies have shown that that mass drug administration programmes can reverse the subclinical lymphatic damage in children. In most areas the MDA also provides what is termed ‘beyond LF benefits’ because the drugs have a wide spectrum of antihelminthic benefits as well as the impact of ivermectin on scabies. In addition, there is stabilization or regression in lymphoedema when this is managed by health education, skin hygiene, and antibiotics. Vector control The vector control method used depends on the habits of the local vector to be targeted: Aedes breeding sites, such discarded tins, tyres, or coconut shells, can be removed; Culex numbers can be reduced by improved sanitation, larvicides, and polystyrene beads applied to the water surface of latrines and cesspits. Bed nets and repellents are universally applicable. However, vector control as part of the GAELF must be planned ac- cording to the cost of MDA, the collateral benefits from annual inter- vention with broad spectrum drugs, and the costs of vector control itself. Thus, vector control targeted specifically at the transmission of lymphatic filariasis itself has not been a major part of the global elimination programme. This is because a lymphatic filariasis spe- cific vector control activity, while it may reduce the number of rounds of MDA, is not likely to be a sustainable or cost-effective exercise. WHO promotes the principles of integrated vector management (IVM); hence in any country the vector control capacity must be as- sessed and opportunities for synergy and optimization of resources taken into account in initiating vector control. There is no doubt, however, that where there is vector control in Anopheles transmis- sion areas to control malaria (i.e. bed nets, particularly long-lasting impregnated nets (LLINs) and indoor residual spraying), there will be an impact on the transmission of W. bancrofti which will likely re- duce the number of rounds of MDA required. Evidence is emerging that LLINs alone at full coverage can arrest transmission, this has now happened in The Gambia. This strategy could be applied where L. loa is coendemic with W. bancrofti to reduce the risks of severe adverse reactions if ivermectin is used. There is also a case for imple- mentation of vector control in settings where MDA has not achieved the required reduction in prevalence (<1%) and intensity to reduce transmission below the threshold for parasite elimination. The risk of parasite re-emergence after MDA depends on the vectorial capacity or ‘force of infection through the mosquito population’. The vectorial capacity is the average number of new infections generated by the vector population during the lifetime of one mated female worm, if this remains below unity the infection will be eradicated. Management of patients in clinics and hospitals Chemotherapy Individual chemotherapy with diethylcarbamazine or doxycycline is needed in some situations, including infected visitors, people leaving infected areas, and those with tropical pulmonary eosino- philia or other clinical features where elimination of adult worms is a priority. Doxycycline has the advantage that side effects are much fewer because of its much slower mode

of action; it also has a signifi- cant morbidity reducing effect on both hydrocele and lymphoedema. Treatment with diethylcarbamazine may provoke both local and sys- temic reactions, and thus requires care and supervision in the initial stages, especially in Brugia infections. Coinfection with L. loa must be treated with great care as both ivermectin and diethylcarbamazine can cause encephalopathy when Loa microfilaria counts are high; patients coinfected with Onchocera volvulus should not be given diethylcarbamazine as serious ocular damage or systemic reactions may develop (see Chapter 8.9.1). Diethylcarbamazine treatment should be started at 1 mg/kg on the first day, increasing over 3 days or more to 6 mg/kg daily. In the standard regimen 6 mg/kg is continued for 12 days; alterna- tively, this dose is given weekly for 12 weeks. These regimens are poorly evidence based. Ultrasonography reveals the variable killing

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