Filariasis

Filariasis

Summary

Major filariasis

Lymphatic: *Wuchereria* (90%) and *Brugia* (10%)

- Lymphangitis + adenitis + superinfection
- Lymphatic obstruction with hydrocele, lymphoedema and elephantiasis
- Chyluria, intermittent fever and asthmatic syndrome.
- Microfilariae principally at night in blood
- Transmission via mosquitoes

Onchocerciasis: Onchocerca volvulus

- Skin nodules, pruritus, eye lesions, swollen lymph nodes, sometimes lymphoedema
- Microfilariae in skin samples (snip, scarification) and eye (anterior chamber)
- Transmission via simulids

Loiasis: Loa loa

- Calabar oedema, subconjunctival migration across the eye, subcutaneous migration
- Microfilariae in blood during the day
- Transmission via fly which bites during daylight

“Minor” filariasis

- Mansonellosis (M. perstans, streptocerca, ozzardi)
- Dirofilariasis (*D. immitis,…*)
- Dracunculiasis (*D. medinensis*)

Filariae are nematodes that live as adults in various human tissues. They do not lay eggs, but constantly produce enormous numbers of larvae (microfilariae) in humans. These are found in the skin or blood. Human-to-human transmission occurs via insects: the parasites are thus “arthropod-borne”. Animal reservoirs play no role of significance in most places, except in subperiodic Brugia

malayi. Filariasis only exist in warm climates because of the high temperature necessary for the development of the worm in the vector.

There are several species of filariae, but 6 are commonly pathogenic:

- *Wuchereria bancrofti*
- *Brugia malayi*
- *Brugia timori*
- *Loa loa*
- *Onchocerca volvulus*
- *(Mansonella streptocerca)*

There are 2 filariae that are often well tolerated by humans: *Mansonella perstans* and *Mansonella ozzardi*. The reason for this tolerance is not known; however it should be recognised that not all people infected with these filariae are asymptomatic. Insufficient is known about these parasites.

Dirofilariasis is for the most part only of anecdotal importance and no microfilariae are found in humans.

Dracunculiasis is traditionally included among the filariasis, although there are marked clinical differences between this parasite and the other filariae.

Lymphatic filariasis

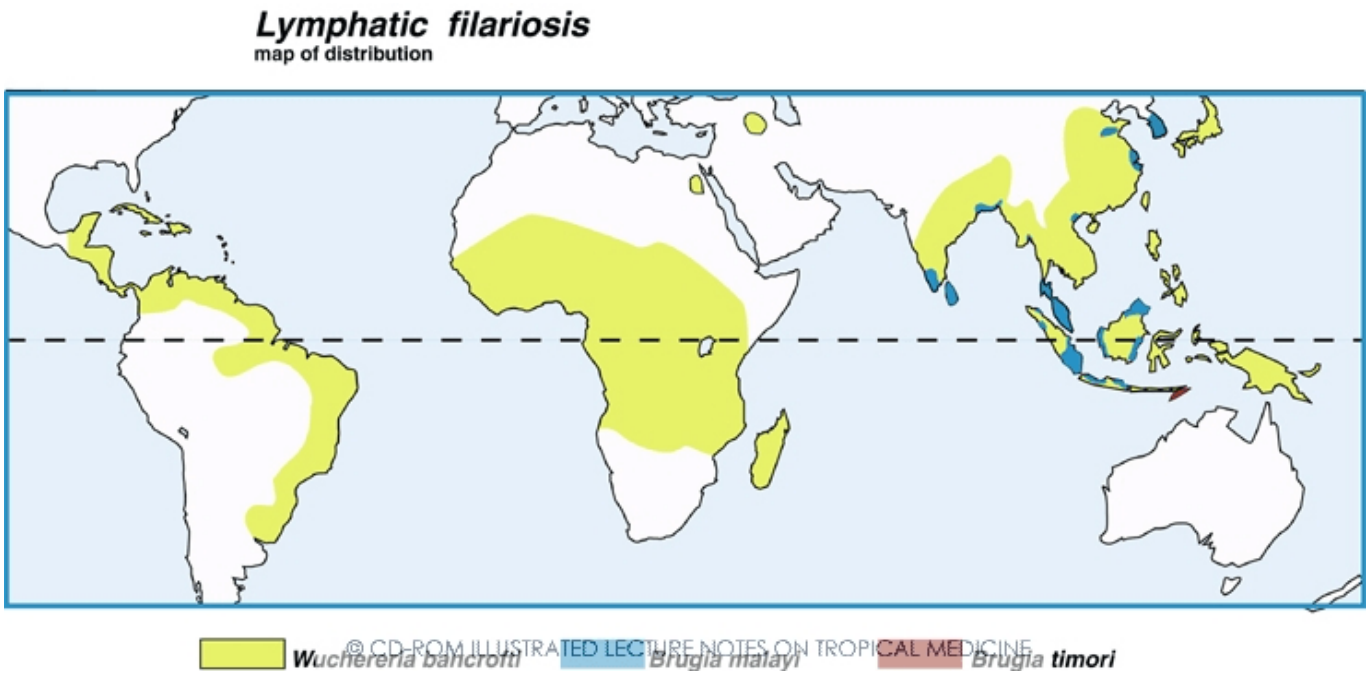
General

Wuchereria bancrofti, *Brugia malayi* and *Brugia timori* cause lymphatic disorders. *Wuchereria bancrofti* is the most widespread of the human filariae in the world. The majority of infections occur in Asia, but this parasite also causes considerable problems in Africa and the north-west of South America. There is a periodic and a subperiodic form.

B. malayi occurs in Southeast Asia. There are two forms: a periodically transmitted form (without animal reservoir) and a subperiodic form (animal reservoir in monkeys). Consequently, subperiodic *B. malayi* infection is a zoonosis.

Brugia timori is limited to a few islands around Timor.

Parasite	Rhythm	Reservoir	Main vector
W. bancrofti	Periodic	Humans	Culex, Anopheles
W. bancrofti	Subperiodic	Humans	Aedes
B. malayi	Periodic	Humans	Anopheles
B. malayi	Subperiodic	Humans, monkeys, cats	Mansonia
B. timori	Periodic	Humans	Anopheles



Lymphatic filariasis, geographical distribution

Transmission

It became clear that the parasites are transmitted via the bite of infected mosquitoes, primarily by the night-biting *Culex (quinquefaciatus)* and *Anopheles* mosquitoes. This biting behaviour is important as the numbers of microfilariae in the peripheral blood systematically fluctuate over a 24-hour period reaching their highest levels at night. There is a remarkable periodicity of the microfilariae. The density of parasites is greatest at the time when the chance of transmission is greatest (at night).

Wuchereria bancrofti becomes adult in human lymphatics and lymph nodes. The adult female worms are 0.2 mm wide and can be up to 10 cm long. The males are shorter (40 x 0,1 mm). *Brugia* adults are about half this size. They can survive for up to 20 years, but the average life time is 5 years. Approximately 8 months after infection *W. bancrofti* microfilariae appear in the circulation. For Brugia sp, this prepatent period is about 3 months.

Historical note

In 1866, the German doctor Otto Wucherer discovered numerous microfilariae in patients with haematuria and chyluria in Bahia, Brazil. In 1872 the Briton, Lewis, in Calcutta discovered that patients with elephantiasis were infected with filariae. Bancroft was the first to discover the adult worm in an abscess and later in fluid which he tapped from a hydrocele during his surgical practice. He was one of the first to suggest that disease was transmitted by mosquitoes, although it was Patrick Manson (1844-1922) who reported the development of filarial embryos in the mosquito. Because microfilariae were periodically detectable in the blood, the Scottish doctor Patrick Manson suspected that night-biting mosquitoes might be responsible for transmission.

Pathogenesis

The adult worm induces an immunological reaction in humans. The basic lesion is a sterile inflammation around the worm; in and around the lymph nodes and lymph vessels. In the case of lymphangitis, there is often retrograde inflammation (centrifugal spread). This inflammation leads to obstruction of lymph vessels, resulting in temporary lymphostasis and lymphoedema. Following repeated attacks, irreversible damage to the lymphatics occurs with permanent “non-pitting” lymphoedema. Sometimes abscesses occur at the site of dead adult worms. There is also evidence that indicates adult worms can themselves directly attack the lymphatics (irrespective of the immunological response).

In humans with severe symptoms, low or no microfilaraemia is often found, whereas humans with high microfilaraemia often have no symptoms. The reasons for this apparent paradox is, that the resulting pathology is caused by the patient’s own immunological response to the adult worms. If the reaction is violent, few adult worms and microfilariae survive but considerable inflammation will occur with sequelae. During infection with the filariae the immunological response evolves. Down-regulation can occur and some patients do not produce any interferon-gamma after exposure to parasitic antigen. This is currently the subject of intense study. It is likely that this influence on the immune system explains the many asymptomatic patients in endemic areas. Both infected amicrofilaemic and microfilaraemic patients display lymphangiectasis on ultrasound or scintigraphy. The adult worms

seem to induce multiplication of endothelial cells and dilatation of lymph vessels, even in the absence of inflammation. On the opposite side, when there is a violent immune reaction against the microfilariae, Weingarten syndrome appears (see below).

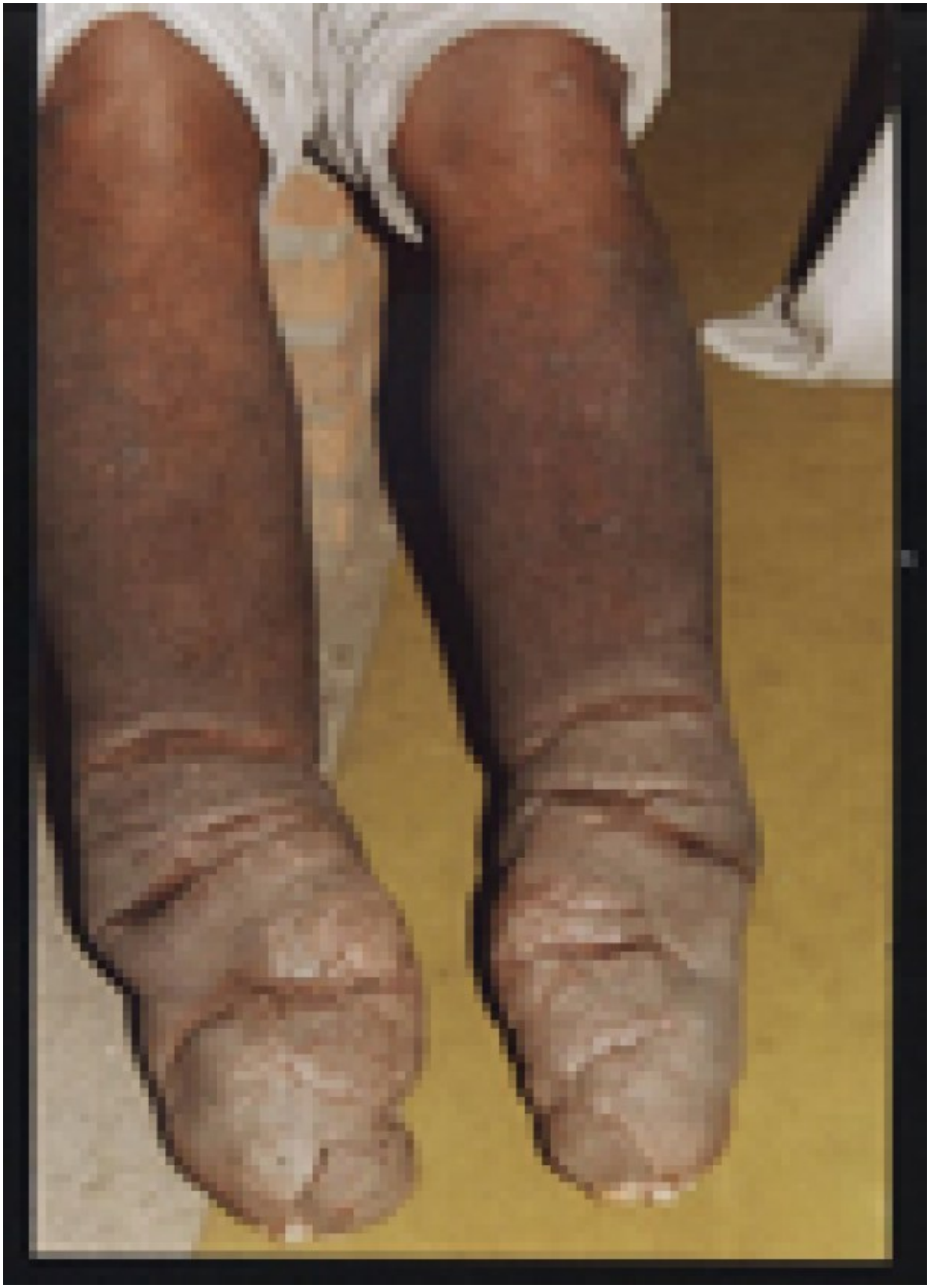
Worm load

There is no multiplication of adult parasites in humans so that the worm load and the degree of illness is proportional to the number of infective larvae transmitted by infected insects. The number of insect bites is directly proportional to the duration and intensity of exposure in a filariasis region. In most cases; severe disease is only seen in humans who have lived for a long time in an endemic area. The patient's individual immunological response has a significant role in the development of the various symptoms.

Endosymbiont

The intracellular *Wolbachia* endosymbiont is apparently an obligate parasite of these worms. These bacteria are related to *Rickettsiae*. Their presence appears to be favourable for the growth and fertility of the nematode. This has become a target for therapeutic intervention, after it was observed that *Wolbachia* is susceptible to tetracyclines.

Clinical aspects



Severe myxedema as complication of hyperthyroidism. This needs to be distinguished from lymphatic filariasis

The majority of infected people exhibit no or few obvious clinical signs even though they can have microfilariae in their peripheral blood. Although these people are asymptomatic or paucisymptomatic, almost all have subclinical disease with microscopic haematuria or proteinuria, dilated tortuous lymphatics and, in males, scrotal lymphangiectasia. Among the more obviously symptomatic the acute temporary signs and symptoms caused by inflammation should be distinguished from those resulting from chronic lymph tract obstruction.

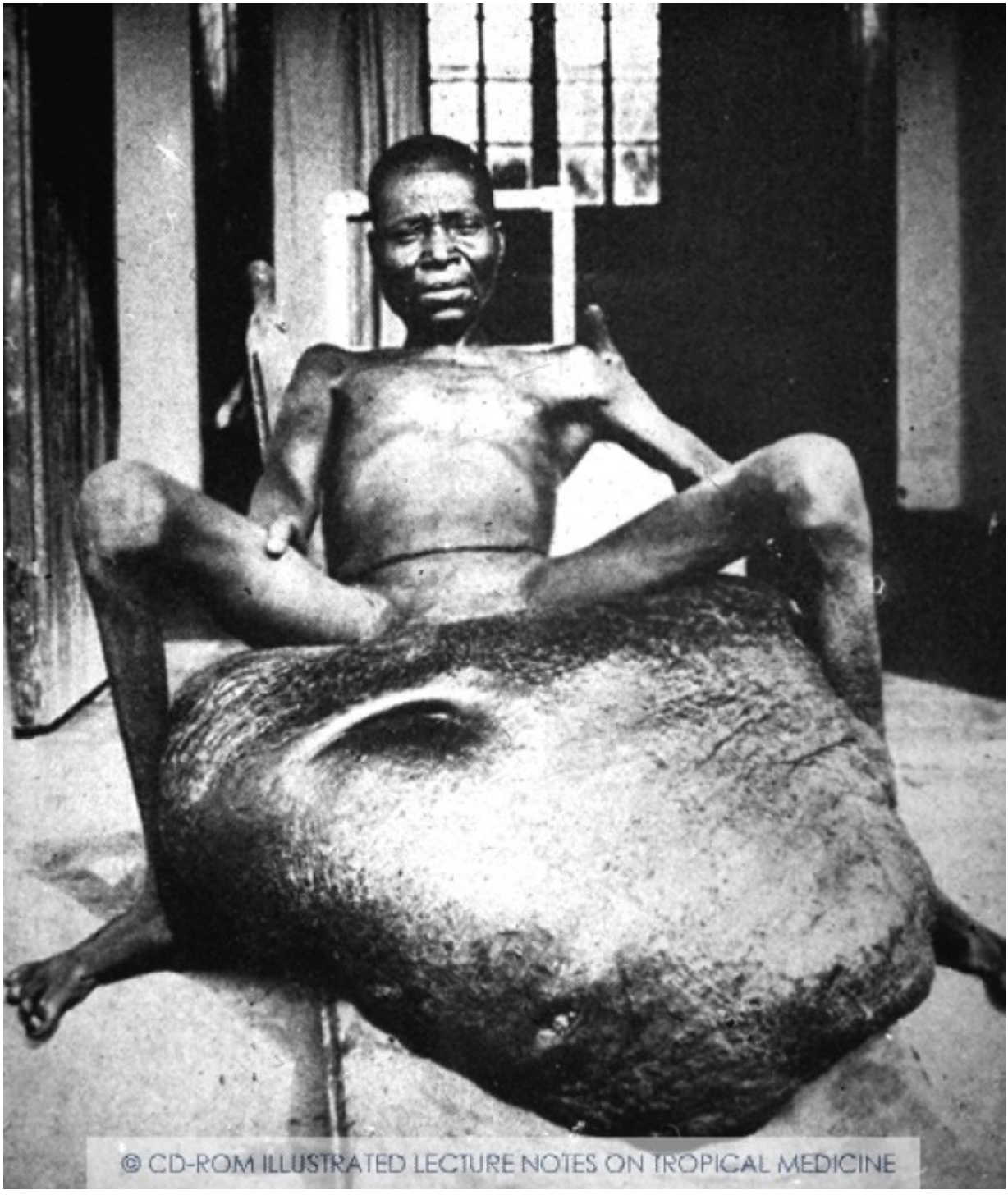
Signs of inflammation

Adenolymphangitis: Acute pain and inflammation in one or more lymph nodes (groin, axilla, elbow, neck). This is associated with fever and general malaise. Retrograde lymphangitis often occurs after 4 to 8 hours. There is centrifugal redness, pain and heat over the course of the lymph vessels. Pyogenic lymphangitis proceeds centripetal, not centrifugal. In most cases, the symptoms last 3-4 days. Each episode results in several days of incapacity for work.

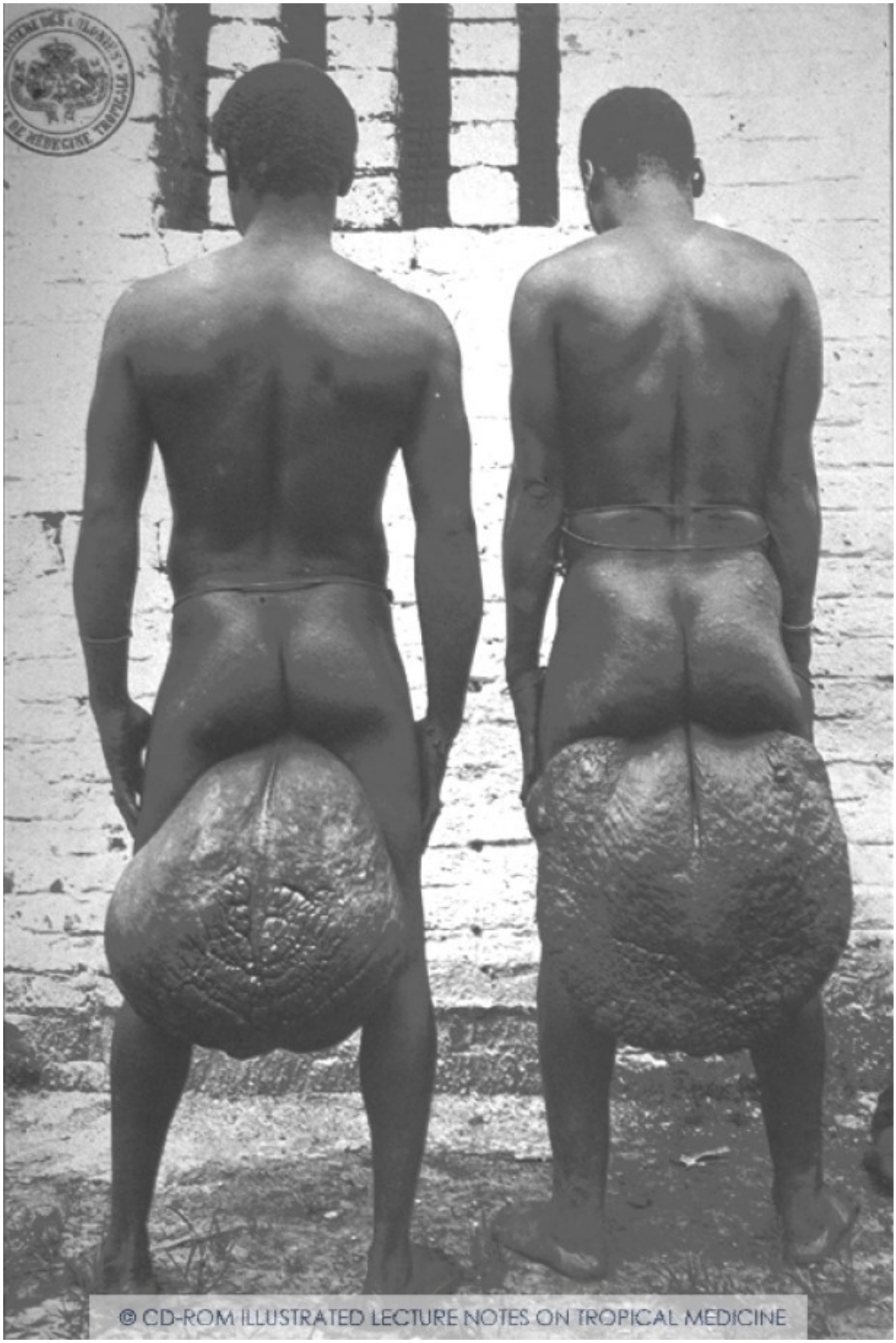
Inflammation of testis and spermatic cord: acute pain, swelling and fever. Repeated funiculitis (inflammation of the spermatic cord) results in thickening of this structure.

Filaria fever: Irregular fever often occurs without external lymph node inflammation, as a result of inflammation of the deeper lymphatics and lymph nodes. The fever may recur irregularly for months or years after the patient leaves an endemic region (observed in 20,000 American military personnel who fought in the South Pacific during the Second World War, an area endemic for *W. bancrofti*).

Signs of chronic obstruction



Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM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Wuchereria bancrofti filariasis, elephantiasis of the genitals. Copyright ITM

Hydrocoele: accumulation of fluid in the tunica vaginalis. Hydrocoele often occurs in orchitis (inflammation of the testis). This is very common in endemic regions. Microfilariae are often found in hydrocoele fluid. Large hydrocoeles can be very inconvenient. Sexual incapacity associated with genital filariasis is a major concern for those infected. Shame, anxiety, sexual problems and social stigmatisation are widespread. In the differential, inguinal hernia is important. Besides the fact that it can be reducible or irreducible (even obstructed), it is not possible to feel above the upper edge of the swelling. A testis tumour, tuberculosis of the epidydimis and chronic lymphogranuloma venereum and chronic schistosomiasis also need to be ruled out.

Lymphoedema and elephantiasis: Chronic lymphostasis can lead to lymphoedema. The first sign is the loss of contour around the ankles. Later, a reversible pitting oedema appears. After this has turned into non-pitting oedema, the skin will thicken. Lymphoedema is most striking in the legs, scrotum, breasts and arms. The labia and penis are somewhat less frequently affected. If the lymphoedema persists for a long time, elephantiasis can occur. The skin is then markedly thickened and can become wart-like. The oedema is “non-pitting” because there is also a proliferation of connective tissue. The tissue is fibrotic and hard. Recurrent erysipelas (bacterial superinfection) causes the elephantiasis to increase still further. Entry points for bacteria are; fissures caused by athlete’s foot, traditional scarifications, insect bites and small scratch wounds. *Brugia* infections mostly cause elephantiasis confined to lower legs and lower arms.

Lymph leakage: The rupture of swollen lymphatics into the renal pelvis can cause chyluria (milk-like pale pink urine). This can have an insidious or sudden onset. The prevalence is low. It is often recurrent. The chyluria is often more pronounced in the morning and after a heavy fatty meal. This sort of fistula can follow a very chronic course. Rupture of lymphatics in the abdominal cavity or thorax results in chylous ascites and chylothorax (chyle = lymph). A protein-rich white fluid is obtained on aspiration. Lymph leakage into the area of the tunica vaginalis results in chylocoele. Clumping of lymph proteins in the ureters can cause obstruction. Long-term extensive chyluria results in hypoproteinaemia. The rupture of numerous small skin lymphatics in the scrotum can lead to a constantly wet, sticky scrotum which is particularly unpleasant.

Tropical pulmonary eosinophilia, Weingarten’s syndrome.

Tropical pulmonary eosinophilia is particularly common in India and Southeast Asia. In other geographical areas it seems to be rare. Pulmonary symptoms are predominant: cough, dyspnoea,

asthmatic syndrome. Chest X-rays consistently show patchy infiltrates, in contrast to Loeffler's syndrome in which they are more fleeting. Microfilariae can be detected on lung biopsies. Sometimes the lymph nodes swell and splenomegaly occurs. The erythrocyte sedimentation rate increases and there is marked eosinophilia (usually >3000 cells/mm3). There are no microfilariae in the peripheral blood. Serological tests for filariae are strongly positive. This condition responds very well to therapy with DEC (in contrast to Loeffler's syndrome). Usually 6 mg/kg/day x 21 days is given. Steroids can be given if other diagnoses (e.g. strongyloidosis) can be excluded. If not treated it can lead to pulmonary fibrosis. Tropical pulmonary eosinophilia needs to be differentiated from classic astma, tuberculosis, chronic strongyloidosis, schistosomiasis (does not occur in India), repeated *Ascaris* migrations and toxocariosis.

Endomyocardial fibrosis

Chronic hypereosinophilia can cause cardiac lesions such as endomyocardial fibrosis or fibroplastic endocarditis. The contents of the eosinophilic granules (including major basic protein) are toxic to the endocardium and the adjacent myocardium. A restrictive cardiomyopathy develops.

Clinical difference between W. bancrofti and Brugia infections.
Brugia infections rarely lead to genital lesions or chyluria. The elephantiasis tends to be limited to below the knee. A filarial dance sign cannot be obtained on ultrasound.

Diagnosis

Microfilariae should be searched for in blood: thin smear, thick smear, concentration method (Knott's test, microfilter). Because of the periodicity, it is best to take the blood at night. A small dose of DEC can increase microfilaraemia during the day: the microfilariae are then expelled from the pulmonary vascular bed; it is optimal to sample 45 mins after administration of 100 mg of DEC (adult dose). This does not work for people who have a disturbed sleeping pattern. Do not use DEC in an onchocerciasis area (Mazotti reaction). Albendazole and ivermectin do not provoke a release of microfilariae into the peripheral blood. Microfilariae are sometimes detected in chylous urine, hydrocoele fluid and ascites fluid.

Indirect diagnosis can be made by serological detection of antibodies. Serological testing is of limited sensitivity and specificity.

Lymph node biopsies should be avoided as they obstruct lymph drainage still further.

Live adult *Wuchereria* worms can be detected by Doppler ultrasound of the scrotum. Dilated lymphatics are observed in which moving worms are found ("filarial dance sign"). This tool has however limited sensitivity; strangely enough adult *Brugia* malayi are almost never detected by ultrasound.

Circulating antigen of adult *W. bancrofti* can be detected with an antigen-capture ELISA but this is not practical in the field (although it is in a central laboratory). Several ICT tests have been developed which are very simple (like an ICT-test for malaria). There is no diurnal variation in the concentration of free circulating antigen so that nocturnal blood sampling is not necessary. It is a powerful test for studying the efficacy of chemotherapy. People who have no microfilariae in the blood but who do harbour live adult *W. bancrofti* test positive. People who recover no longer have circulating antigen in the blood. For population surveys, the previous standard parasitological techniques (nocturnal blood samples) were cumbersome, time-consuming, expensive and very intrusive. The use of rapid tests detecting circulating antigen has entered the clinical practice in endemic areas.

There is still no commercially available antigen test for detecting *Brugia* infections, which is a problem in *Brugia* endemic regions.

PCR tests have been developed that detect DNA of *W. bancrofti*, *Brugia malayi* and *B. timori*. They are used predominantly in epidemiological work and research settings.

Differential diagnosis lymphedema:

- Primary lymphedema: aplasia or hypoplasia lymphatics, tendency towards symmetrical lesions
- Lepromatous leprosy
- Chlamydia trachomatis, LGV
- Contact dermatitis with recurrent erysipelas
- Pretibial myxedema
- Chromomycosis
- Mycetoma
- Loiasis: Calabar swelling
- Onchocerciasis: hanging groin
- Kaposi sarcoma
- Lymphatic damage (surgery, radiation, burns, TB, malignancy)
- Podoconiosis

Podoconiosis

Podoconiosis (syn. lymphatic siderosilicosis or lymphoconiosis) is a chronic disorder characterised by the very slow onset of oedema, subsequent lymphoedema and later elephantiasis (mostly limited to below the knee). The disease is caused by immunological response to certain minerals (silicates, zirconium or beryllium-containing minerals). When walking barefoot on ground containing these minerals, dust particles can absorbed through the soles of the feet via small wounds. They are then transported via the lymphatics to the inguinal lymph nodes where they cause a local inflammatory reaction. Atrophy and fibrosis of the lymphatics occur subsequently (in contrast to bancroftiasis where dilatation occurs). The disorder occurs in well-defined areas (specific mineral composition of the soil!) in people who walk about barefoot, such as Ethiopia, Kenya, Rwanda, Uganda, West Africa and India. Whereas lymphatic filariases occur predominantly in lower-lying areas (vector biotope), podoconiosis is characteristic of higher-lying zones. This is not absolute. Other signs of bancroftiasis are absent (hydrocoele, eosinophilia, and nocturnal microfilaraemia). Confusion with mycetoma (“Madura foot”) or with classic Kaposi’s sarcoma is possible.

Treatment

General

Self-help groups in a community can play an important role. In an acute situation, pain relief, antipyretics and anti-inflammatories are indicated. In chronic lesions of the scrotum, surgery can be performed. Elephantiasis of the limbs is relatively treatment-resistant. Physical methods (lymph drainage by massage) should be continued for a long time and will not in any way alter the fibrotic component of the swelling. Permanent compressive bandages are not practical in a warm, moist environment. A firm, compressive dressing (elastic bandages) may be applied centripetally. These are then changed daily and relatively good results can be achieved in this way, particularly if elastic compressive stockings can be worn afterwards. Microsurgery with the creation of several lymphovenous anastomoses is difficult.

Hygiene and antibiotics

Good, enforced hygiene can dramatically reduce the number of complications. General cleanliness, washing with soap and disinfection of wounds are crucial. If bacterial superinfection is present, this should be treated appropriately. There is often a fungal infection between the toes (athlete’s foot),

which acts as a portal of entry for various bacteria. Simple hygiene is important and should be stressed:

- Washing the affected part of the body twice daily with soap and water
- Elevation of the affected limb at night
- Keeping nails clean
- Wearing shoes
- Disinfecting skin wounds rapidly and properly
- Systemic antibiotics for superinfection (erysipelas)
- Treating athlete's foot
- Daily physical exercise to improve lymph drainage
- Physiotherapy
- Diethylcarbamazine or DEC

Diethylcarbamazine (= DEC)

Was introduced in 1947. In 1967 Frank Hawking, father of the famous physicist Stephen Hawking, published the results of a study in Brazil of the effect of enriching cooking salt with DEC on lymphatic fialriasis. DEC (Notezine®, Hetrazan®, Banocide®) has a **rapid, but indirect microfilaricidal effect** on *Wuchereria* and *Brugia*. DEC somehow modifies the microfilariae so they can be destroyed by the immune cells. If it is taken for prolonged periods, there is also an incomplete macrofilaricidal effect. The dose conventionally given as monotherapy is 72 mg/kg (in total) over 10-14 days (e.g. 50 tablets of 100 mg), although often it will be stated that 3 divided doses after meals will be better. There is evidence to show that lower doses for shorter periods are as effective (e.g. single dose of 6 mg/kg). DEC in monotherapy has an efficacy of ± 90% (against microfilariae). Pregnancy is a contra-indication for the administration of DEC. This medication is fairly well tolerated, but systemic reactions can occur, caused by the massive and sudden death of microfilariae. Recent studies suggest that these reactions are due to the abrupt release of *Wolbachia* in the human tissues (substantial increase in Wolbachia DNA by pCR). Symptoms may include malaise, pruritus, urticaria, fever, headache, vomiting and asthmatic crisis (cf. Mazzotti reaction in onchocerciasis and the Jarish-Herxheimer reaction in spirochaetosis). This usually happens in the first 48 hours. For mild reactions antihistamines can be used, in severe reactions steroids are indicated. Local tissue reactions can also occur around dead macrofilariae (lymphangitis, abscess, funiculitis). Those local reactions can occur up to several weeks after therapy. Most microfilaraemic patients have a transient increase of haematuria and/or proteinuria after starting DEC. Because of these potential side effects, treatment is started with a low dose and increased progressively. It sometimes needs to be repeated. The microfilariae are not killed immediately by DEC, but their phagocytosis is facilitated. The indirect

effect of DEC means that microfilariae can remain alive in cavities (e.g. hydrocoele). This can give rise to confusion, but otherwise is not important as microfilariae are not pathogenic. If the adult worms are not killed, microfilariae reappear in the blood 3-6 months later.

Ivermectin (Mectizan®,Stromectol®)

This drug became available in 1984 for the treatment of onchocerciasis. It is also active as a microfilaricide against *W. bancrofti*. It has the enormous advantage that it can be given in one oral dose and has few side effects. It is not macrofilaricidal, even if repeated at high doses. It is useful in the control of bancroftiasis (suppressing microfilaraemia stops transmission to the vectors) but probably not in helping individual patients. The combination of single dose DEC with single dose ivermectin is much more effective (99% of decrease of microfilariae load at least for 12 months) than each medication alone.

Albendazole

Albendazole has a very limited macrofilaricidal effect. It has been shown however that the combination of single doses of ivermectin with albendazole suppresses microfilaraemia by 99% for at least 15 months. This combination is more effective than each medication used separately. This combination also has the great advantage of eliminating diverse intestinal worms and of treating scabies (ivermectin).

Tetracyclines

Tetracyclines are active against the endosymbiotic *Wolbachia,* and their eradication results in long-term sterility and eventual death of macrofilariae. This has become a new therapeutic point of attack, and this is the first effective macrofilaricidal treatment (although indirect and slow). Initial clinical studies showed a favourable effect of a 8-week course of tetracycline on the clinical symptoms and the number of adult worms as reflected by the decrease/suppression of worms detected by ultrasound, decrease/suppression of circulating antigen load. In addition, a much lower rate of adverse reaction was observed when compared to the classic DEC treatment. Subsequent studies showed that a 4-week course of doxycycline has a similar efficacy as a 8-week course, but treatments of shorter duration do not seem to provide the same clinical benefit (although a microfilaricidal effect was also observed). **Nowadays, a 4 to 6-week course of doxycycline (200 mg/day) is the first-line treatment for the patient diagnosed with acute or chronic lymphatic filariasis**.

Of note, azithromycin does not deplete the *Wolbachia,* so that there is still no therapeutic option for

children and pregnant women. A 2 to 4-week course of rifampicin (but not a 1-week course) has substantial anti-Wolbachia activity, but its therapeutic implications need to be further studied.

Combination therapy

Combination therapy (albendazole 400 mg + ivermectin 200µg/kg) or (albendazole 400 mg + DEC 6 mg/kg) is largely used in mass drug administration at present to stop transmission. The second regimen is not used in countries where onchocerciasis occurs (risk of Mazotti reaction with acute blindness).

For the individual symptomatic patient, some experts recommend to combine a 6-week course of doxycycline with 14 days DEC, although the clinical superiority of this combination over doxycycline monotherapy has not been demonstrated so far.

Prevention

At the end of the 20th Century, it was estimated that about 120 million people were infected and about 43 million were symptomatic. In May 1997, the WHO adopted a resolution to eliminate lymphatic filariasis as a public health problem. The programme “Global Programme to Eliminate Lymphatic Filariasis” or “Global Lymphatic Filariasis Initiative” was launched in the year 2000. It is based on two approaches:

- annual single dose, two-drug treatment allowing suppression of microfilaraemia for a year and which can be given as mass treatment for 5-6 successive years [albendazole + ivermectin in onchocerciasis areas; albendazole + DEC in other areas],
- simple diagnostic tests that can be performed by a finger prick at any time of the day.

An alternative used in some countries (China, Taiwan) is DEC 0,3% medicated salt x 12 months. It is hoped to eradicate lymphatic filariasis by about 2020. Good financial backing has been provided but this still needs to be extended. Technical training, logistics and management support should be organised. Continuous monitoring and evaluation should constitute an integral part of the programme.

Of note, a recent small study in Papua New Guinea suggests that a triple-drug therapy (DEC + albendazole + ivermectin) would suppress the microfilaremia for up to 2 years (and should be considered in heavily infected patients). This requires confirmation in larger trials.

The focus of disease control has been mass drug administration programs as described above. Vector control with insecticide-treated bed nets is useful where Anopheles (night biting mosquito) transmit the parasite. Repellents as personal protection tools prevent on an individual level. Currently, no vaccine exists.

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