PART II

CHEMOTHERAPY OF FILARIASIS
Chapter I
General Introduction
Filariasis is a general term covering a variety of infections caused by nematode parasites (worms) belonging to the super-family Filarioidea. There are six closely related species of filarial organisms that infest man—Wuchereria bancrofti, Wuchereria malayi, Onchocerca volvulus, Loa loa, Mansonella ozzardi and Acanthocheilonema perstans—of which the first four are more common. Besides these, Dracunculus medinensis or the guinea worm is also commonly included among the causative organisms of filariasis. Filariasis is known to occur also in horses, cattle, goats, cotton rats, dogs, birds, swine, frogs and many other vertebrates.

The worms are transmitted by vectors and invade the lymphatics, the subcutaneous tissues and the serous cavities; the vector and the site of the pathological lesion are different in different types of filariasis. For example, W. bancrofti and W. malayi are transmitted by mosquitoes and affect primarily the lymphatics, whereas infection of Onchocerca volvulus is transmitted by the less common gnat, Simulium damnosum, and the worms are found in the numerous subcutaneous nodules or fibrous tumours which form a characteristic feature of this infection. This parasite also exhibits a localization in the eye where it penetrates the eye-ball and invades the optic nerve. Similarly the Loa loa worm, after migrating through the subcutaneous tissues, lodges itself usually under the conjunctiva of the eye, causing considerable irritation and swelling.
Table I summarises the names of the infecting organisms, the related vectors, routes of entry, sites of infection and the names of the individual pathological states classed under the general heading of filariasis.

The present discussion is restricted to the infections caused by *W. bancrofti* and *W. malayi*, as these are the ones most prevalent in India.

**Prevalence and geographical distribution of the disease**

Filariasis is strictly a disease of the tropics and most of the countries of Europe, North America and Northern Asia are practically free from this infection. The distribution of each filarial infection is fairly restricted and specific and is dependent upon (a) the availability of the specific vector, (b) the suitability of climatic conditions both for the parasite during its exogenous phase and for the intermediate host, and (c) on the living conditions of the people. It is estimated, there are more than 20 lacs infected individuals in the world.

Filariasis due to *W. bancrofti* and *W. malayi* is prevalent all over Asia, Africa, Middle East, East Indies and the Pacific Islands. Onchocerciasis and Loaiasis are endemic mostly in the African continent, while Dracontiasis or guinea worm disease is found in Africa, Middle East, India, Burma, and in West Indies.
### Table I
The various Filarial infections in human beings.

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<tr>
<th>Phylum</th>
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<td>Class</td>
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<thead>
<tr>
<th>Super-family</th>
<th>WORMS</th>
<th>INTERMEDIATE HOSTS</th>
<th>Routes of entry</th>
<th>Sites of pathogenic processes</th>
<th>Name of the disease induced</th>
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<tr>
<td>Llarioidae</td>
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<tr>
<td>Wuchereria</td>
<td>bancrofti</td>
<td>Various species of Culex, Aedes, and Anopheles</td>
<td>Mosquito</td>
<td>Cutaneous</td>
<td>Skin, lungs, lymphatics and scrotum</td>
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<tr>
<td>Wuchereria</td>
<td>malayi</td>
<td>Various species of genus Mansonoides and Anopheles</td>
<td>Mosquito</td>
<td>Cutaneous</td>
<td>Lymphatics, skin</td>
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<td>Onchocerca</td>
<td>volvulus</td>
<td>Simulium damnosum</td>
<td>Gnat</td>
<td>Cutaneous</td>
<td>Subcuticle, cornea, optic nerve</td>
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<td>Loa</td>
<td>loa</td>
<td>Crysops dimidiata</td>
<td>Mangrove fly</td>
<td>Cutaneous</td>
<td>Subcuticle, conjunctiva</td>
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<tr>
<td>Acanthocheilonema perstans</td>
<td>Culicoides austeni &amp; C. grahami</td>
<td>Midge</td>
<td>Cutaneous</td>
<td>Mesentery, peritoneum, pericardium and other serous cavities</td>
<td>FILARIASIS due to A. perstans</td>
</tr>
<tr>
<td>Mansonela</td>
<td>ozzardi</td>
<td>Culicoides furans</td>
<td>Midge</td>
<td>Cutaneous</td>
<td>Mesentery, peritoneum and other serous cavities</td>
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<tr>
<td>Dracunculus</td>
<td>medinensis</td>
<td>Cyclop quadricornis</td>
<td>Water flea</td>
<td>Mouth</td>
<td>Subcuticle, skin</td>
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Of the three main filarial types, *W. bancrofti*, *W. malayi* and *Dracunculus medinensis* prevalent in India, the incidence of Bancroftian filariasis is the highest. Infection due to *W. bancrofti* is particularly heavy in Bengal, Orissa, Travancore, Cochin and Malabar and moderate in the states of Assam, Uttar Pradesh, Bihar, Madhya Pradesh, Hyderabad and Bombay. *W. malayi* infection is found only in a few places in north Travancore, Orissa, Madhya Pradesh, Bengal and Assam. Dracontiasis or guinea worm disease occurs extensively in the states of Bombay, Hyderabad, Madras, Rajputana, Madhya Pradesh, Kashmir and Punjab.

**Life-cycle and morphology of *W. bancrofti* and *W. malayi***

There are two phases in the life-cycle of the filarial worms—the microfilaria or the embryonic form and the macrofilaria or the adult worm.

The adult worm is a white hair-like translucent organism having a smooth cuticle. The adult male measures anywhere from 2.5 to 5.0 cm. in length and about 0.1 mm. in breadth, whereas the female is twice as large. The microfilaria has a transparent sheath and measures about 360 μ by 7 μ.

In the human host the adult worms are usually found coiled together in the larger lymphatics near the aorta, in
the pelvis, in the genitalia and in the lymphatic glands, where they have been known to live for 12 years or more. The microfilariae appear in the peripheral blood in large numbers at night but disappear from this site during the day.

As in malaria, man acts as the reservoir and the mosquito as the carrier of infection. When a susceptible mosquito bites an infected individual, the microfilariae are ingested along with the blood-meal and are taken to the stomach. With the progress of digestion in the stomach, the blood plasma becomes thickened. This change in the viscosity of blood induces the microfilariae to wriggle out of their protective sheath and within a few minutes they make their way into the thorax and lie between the thoracic muscle fibres of the mosquito. Two days after its entry, the parasite begins its metamorphosis which lasts for 15 days, during which it develops a mouth, a body cavity, an alimentary canal and a tail. The larval filariae now leave the thorax and migrate to the proboscis and eventually reach the labium. At this stage the larvae are not sexually mature although they move about in pairs. When the infected mosquito bites a normal individual, the larvae escape from the proboscis and enter the puncture wound or penetrate the unbroken skin. Once in the human body, the larvae find their way into the peripheral lymphatics and subsequently into the larger lymphatics and glands where they attain sexual maturity in 5 to 18 months. Mating
takes place, and the female rapidly develops a large uterus filled with embryonic forms, the microfilariae, which are discharged into the lymphatic fluid and are carried to the different parts of the body. For the completion of its life-cycle, it is necessary for the filarial worm to spend a part of its life in the vector and the rest in the human body.

Filarial Periodicity. — The most remarkable feature in the life of the microfilariae is their "nocturnal periodicity" in the peripheral blood. In the normal human host the microfilariae are rarely seen in the blood during the day, but towards the evening (usually after sunset) they begin to appear in the blood stream in gradually increasing numbers. The swarm goes on increasing until at about midnight they reach a concentration of 300 to 600 organisms per drop of blood. This periodicity can, however, be reversed by making the filarial subject sleep during the day and keep awake at night. It may, however, be pointed out that the time of ingress and egress of the microfilariae into and from the blood does not strictly coincide with the period of sleep. From time to time, theories have been put forward to explain this singular phenomenon, but none has proved to be entirely satisfactory. It is well known that several functions of the body show cyclic fluctuations during the course of the day, e.g., the temperature, the tension of carbon dioxide in the lungs, the alkalinity of the body, etc. Nocturnal periodicity may be a response of
the microfilariae to the stimulus supplied by any one of these cycles.\textsuperscript{4}

**Pathogenesis of filariasis due to \textit{W. bancrofti} and \textit{W. malayi}**

Pathological changes are induced by one or more of the three main factors, viz., (1) destruction of the microfilariae in the lymphatic glands, (2) liberation of some toxic factor by the living worm or by the degeneration of dead worms, and (3) tissue reactions due to the presence of living or dead worms.

**The role of the microfilariae.**— Opinions are divided regarding the part played by the microfilariae. Manson,\textsuperscript{5} in 1900, ruled out the role of microfilariae in bringing about pathological changes in tissues. This assertion was contradicted by O'Connor and Hulse,\textsuperscript{6} in 1932, who showed that microfilariae are destroyed in the substance of the lymphatic glands and are responsible, to some extent, for the pathological changes found in these structures. This was further confirmed by the histo-pathological studies of Lane,\textsuperscript{7} who showed that the microfilariae in the lymphatic system initiate pathogenesis. When the mature worm in the lymphatics liberates microfilariae, new reticulo-endothelial cells are formed around the adult worms as well as the microfilariae. When the latter appear in the cortical sinuses of the lymph nodes, the lymph is blocked due to accumulation
of the reticulo-endothelial cells and some of the microfilariae are broken up and destroyed; new lymph channels are formed which carry the microfilariae to the next lymph node where the process repeats itself until the last node on the way to the blood stream is bypassed. By accumulating around the microfilariae, the reticulo-endothelial cells gradually develop into fibroblasts with further increase in lymphatic obstruction. Inspite of these observations some of the modern authors like Napier (1946) and Adams and Maegraith (1953) still maintain that the microfilariae do not contribute pathogenesis.

Reaction due to toxins. — When an adult female worm discharges its embryos the uterine fluid which is simultaneously expelled is supposed to contain highly irritating toxins. Toxic substances are also liberated from the degenerating worms in the tissues. The absorption of these toxins gives rise to sensitivity reactions. Most of the early and minor manifestations of the disease such as filarioid or elephantoid fever, fleeting tissue, oedemas, erythemas and urticaria are the allergic expressions of toxin-sensitivity. The febrile and inflammatory attacks correspond in frequency with the periodic liberation of toxins by the worms. The activation of endothelial cells, which follows, is also initiated to some extent by the toxins.

Tissue reaction to the presence of adult worms. — Pathological changes occur principally in the lymphatics,
the glands and connective tissues. The most marked reactions occur around adult worms lying in the lymphatics, especially when the worm dies and begins to degenerate.

The characteristic lesion is a granulomatous lymph-angitis, usually slowly progressive but subject to acute exacerbations. The granulomatous development takes place both outside and within the lymph vessels; the former tends to narrow the lumen of the vessels while the latter obstructs them. The tissues surrounding the lymphatic vessels become infiltrated with lymphatic cells, plasma cells, and eosinophils. When the adult worm is dead the reticulo-endothelial cells are mobilized and a process of extensive proliferation sets in in the endothelium. This leads to the formation of epithelioid nests and giant cells. The local blood vessels are dilated and usually show some cuffing with round cells. In this way nodules of cellular granular tissue are formed which press upon the lumen of the lymphatic vessel and tend to occlude it. The vessel is eventually occluded by the endothelial hyperplasia or as a result of lymph thrombosis. Sometimes the process goes on to necrosis and pus formation. Abscesses may discharge to the surface and lead to the development of persistent sinuses. By this time the blood supply is considerably cut off, as a result of which the granulomatous tissues and occluded vessels are replaced by fibrous tissue. Drinker and coworkers have shown that the enclosed
Lymph in the occluded vessels has a higher content of plasma protein than ordinary lymph. Lymph with high protein content forms an ideal medium for proliferating cells, thereby further stimulating lymphous hyperplasia and the fibroblastic activity of the tissues. The irregular development of granulomatous tissue gives the affected part a lobulated feel and appearance. Similar granulomatous and fibrotic lesions also develop in and around the lymphatic glands when the worms are lodged in the sinuses of the glands. The worm is now completely encapsulated and is calcified in the long run.

The blockage of the lymphatics interferes with the local lymphatic drainage and circulation and consequently leads to the accumulation of lymphatic fluid within the vessels and in the interstitial tissues. The affected vessels now show clinical signs of obstruction, dilatation and distortion and are tense with lymph. The symptoms of filariasis which now follow are either of inflammatory or obstructive nature or both.

When the obstruction is restricted to the vessels, it leads to varicosity of the superficial lymphatics, especially those of the femoral, inguinal and testicular regions. The skin in the affected region becomes oedematous and erythematous, and finally the entire limb becomes oedematous. Varicose vessels may become inextricably mingled with local enlarged lymph glands forming an irregu-
lar mass of tissue known as "varicose glands". If the vessels of the spermatic chord and testis are affected, the organs become enlarged usually resulting in orchitis, funiculitis or epididymitis, associated with hydrocele. When the varicosity of the abdominal lymphatics is acute the dilated vessel usually ruptures and the chyle or lymph may drain into the urinary tract, giving rise to chyluria or lymphuria respectively. When both the lymphatic vessels and the glands are blocked, as is usually the case in chronic infections, further complications set in. Obstruction and enlargement of the inguinal glands prevent the lymphatic drainage of the scrotal area. The scrotal skin becomes erythematous and covered with small vesicles containing clear or milky fluid in which microfilariae are present. The condition is called lymph scrotum and usually develops into hydrocele.

As the infection advances, the tissues involved gradually undergo elephantoid changes, which eventually lead to elephantiasis.

Elephantiasis.—Granulomatous lymphangitis and lymph stasis is followed by a gradual increase in thickness of all the tissues—the epithelial, the connective and the muscular. The epithelium thickens irregularly in all layers; in some areas hypertrophy exceeds that in others and warty excrescences develop. Secondary infection may lead to abscess formation and fibrosis. In the limbs, the muscles at first show hypertrophy but are later atrophied.
The thickened tissue tends to hang in folds. Affected limbs thicken enormously. The scrotum may become so large as to weigh more than the patient. When the trunk is affected, elephantoid areas of the skin tend to hang on pedicles of normal skin. In the folds of the skin secondary infections may invade the deeper tissues and lead to acute inflammation, necrosis, and abscess formation followed eventually by fibrosis. This completes the picture of elephantiasis.

Metabolism of the filarial worms

Our present knowledge regarding the metabolism of filarial worms is very meagre and whatever investigations have been carried out, are confined mainly to Litomosoides carinii, the filarial worm which infests cotton rats. It has been shown that this organism has predominantly aerobic metabolism and is capable of metabolising large quantities of glucose, which is stored mainly as glycogen. Under normal aerobic conditions the ultimate end products of carbohydrate metabolism are lactic acid (30 to 40% of utilized glucose), acetic acid and acetyl methyl carbinol (AMC), and the respiratory cycle proceeds according to the Embden-Meyerhof scheme of phosphorylating glycolysis. No information is yet available concerning the intermediate reactions and the necessary enzyme systems, except that in the respiratory metabolism the cytochrome system is not involved.
and the hydrogen transfer mechanism is probably mediated by a heavy metal containing flavin enzyme. The production of AMC from acetaldehyde is shown to require cocarboxylase and manganese, and is stimulated by pyruvate.

With the inhibition of the above described respiratory metabolism, there is a compensatory increase in the glycolytic fermentation cycle with increased production of lactic acid. It has been shown that under anaerobic conditions as much as 80% of the utilized carbohydrate is converted into lactic acid. The worms cannot live under these conditions and ultimately they die.

The only significant fact which has emerged from this study is that the respiratory metabolism of the worms is inhibited by the cyanine dyes. But the activity of the cyanine dyes is confined only to Litosomoides carinii and that also mainly to the adult worms.

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