Filaroidea: Filarial Nematodes

Tissue dwelling parasites

All species use arthropods as intermediate hosts

Many affect domestic animals or humans:

Lymphatic filariasis: *Brugia malayi*,
*Wuchereria bancrofti*

River Blindness:   *Onchocerca volvulus*
A. **Cyclopropagative Transmission**: The parasite undergoes cyclical changes and multiplies within the vector, i.e., there are both developmental changes and multiplication of the parasite.

B. **Cyclodevelopmental Transmission**: The parasite undergoes cyclical changes within the vector but does not multiply, i.e., there are only developmental changes of the parasite without multiplication.  
*Filarial nematodes*

C. **Propagative Transmission**: The parasite multiplies within the vector without any cyclical changes, i.e., the parasite increases in number within the vector but does not undergo any developmental changes.
The lymphatic filariases and onchocerciasis are among the most distressing of the helminth infections in humans.

They lead to gross disfigurement, irreversible changes in the skin, sexual dysfunction, and infected individuals are often ostracized by members of their society.

The WHO estimates that one fifth of the world’s population in 173 countries lives at risk for these infections, and that there are 120 million human infections at any one time.
Onchocerciasis (River Blindness) is distributed throughout much of the world, including parts of Africa, Arabia, Central America, northern South America, and Mexico. In Africa alone it is estimated that more than 30 million people are infected with this parasite.
Onchocerca volvulus

**Blackfly Stages**

1. Blackfly (genus Simulium) takes a blood meal (L3 larvae enter bite wound)

2. Subcutaneous tissues

3. Adults in subcutaneous nodule

4. Adults produce unsheathed microfilariae that typically are found in skin and in lymphatics of connective tissues, but also occasionally in peripheral blood, urine, and sputum.

5. Blackfly takes a blood meal (ingests microfilariae)

6. Microfilariae penetrate blackfly's midgut and migrate to thoracic muscles

7. L1 larvae

8. L3 larvae

9. Migrate to head and blackfly's proboscis

**Human Stages**

- = Infective Stage
- = Diagnostic Stage
Onchocerciasis is a major cause of blindness. Rarely life-threatening, the disease causes chronic suffering and severe disability. In Africa, it constitutes a serious obstacle to socioeconomic development. It is often called river blindness because of its most extreme manifestation and because the blackflies that transmit the disease abound in riverside areas, where they breed in fast-flowing waters. Fertile riverine areas are frequently abandoned for fear of the disease.

Adult *Onchocerca volvulus* may live in the human body for up to 15 years. Each adult female worm produces millions of microscopic larvae (microfilariae), that migrate throughout the body to cause a variety of symptoms. In Onchocerciasis the larval stages cause the damage to the human hosts.
The life cycle of this parasite is similar to that of other filarial parasites. The adult worms live in the skin of humans. The adults (which may be up to 50 cm long) are surrounded by fibrotic tissue (a result of the host's response to the parasite), and this fibrotic capsule often appears as a nodule under the skin. The female worms produce microfilariae. The vector for this parasite is a black fly (*Simulium* sp.), and the vector is infected when it feeds on an infected human. The microfilariae develop into infective larvae in the vector, and the disease is transmitted to another human via the infective larvae. Once the infective larvae are in the human they do not migrate; rather they develop to adults at the site of the vector's bite.
The major problems arise not from the reaction to the adults, but to the mf. Microfilariae that leave the nodule may be killed by components of the host’s immune response. Reactions to dead microfilariae around these nodules can lead to a destruction of the elastic tissues and the formation of redundant folds. There is also often a loss of pigmentation and the histological appearance of advanced cases often resembles the skin of very old normal subjects. The death of microfilariae in the skin can also result in a severe dermatitis accompanied by depigmentation, resulting in severe disfigurement.
Unlike many filarial infections in which the adult worms cause the problem (e.g., bancroftian filariasis), in infections with *O. volvulus* it is the microfilariae that cause most of the problems.

Microfilariae wander throughout the body, enter the eye and die, and this eventually results in blindness. In some areas of endemic disease, 30-40\% of the adult population is blind as a result of this disease. The microfilariae can also enter the eye by passing along the sheaths of the ciliary vessels and nerves from under the bulbar conjunctiva directly into the cornea, via the nutrient vessels into the optic nerve, and via the posterior perforating ciliary vessels into the choroid. Dead microfilariae in the eye lead to an inflammatory immune response and the eventual formation of secondary cataracts and ocular lesions. Because of this, heavy infections often lead to progressive blindness.
the larvae enter the host tissues, and develop to adults in subcutaneous nodules in about 1 year. Nodules are usually found in the upper part of the body in the american onchocerchiasis and in the pelvic region in the african form.
Onchocerca:
Parasites remain near bite site in nodules
Vectors are blackflies- require fast flowing water
Adults in nodules sometimes encapsulated by host tissues
Microfilariae move around in circulation- elicit little response
Problem is when large numbers of mf enter the eyes
Impaired vision-blindness. Eye lesions take many years to develop.
Some mf directly damage eyes.
When they die – lesions, chronic inflammation fibroblast proliferation,
chronic inflammatory infiltrates
Sclerotising keratitis- hardening inflammation of the cornea
Treatment: Nodule removal
Chemotherapy with ivermectin yearly treatment
Eliminates skin mf, suppresses release from females, kills females slowly
Lymphatic filariasis is a spectral disease. Massive elephantiasis as depicted here (in this case caused by *B. malayi*) is one of the common conditions associated with long-term lymphatic filarial infection. These gross and incapacitating deformities often require radical surgery to remove the surplus tissues and to provide a shunt around damaged lymphatics.
W. bancrofti is distributed throughout the tropical regions of Asia, Africa, China, the Pacific and isolated locations in the Americas. Current estimates (WHO, 1994) suggest that 100 million people are infected with lymphatic filariae of all types, and most of these cases are bancroftian filariasis. Nocturnally periodic forms occur indigenously in almost every tropical and subtropical country and are very widespread. However they show focal and periodic distribution patterns which are dependent on their vector of transmission. Culicine or anopheline mosquitoes are the main vectors of the nocturnally periodic forms of W. bancrofti, while day biting Aedes polynesiensis transmit the subperiodic form in various pacific islands.
Transmission takes place when an infected mosquito bites a human.

The nematodes are large and cannot live in the salivary glands: they live in the proboscis and the sheath area. When the mosquito bites, the nematodes recognize host signals and emerge from the mosquito.

The nematodes enter the bite site or other wounds. The nematodes enter the capillary beds and lymphatic system and are carried to the lymph nodes.

The worms reside in the lymphatics, molt and reach sexual maturity- 3-15 months. Adults may live and produce microfilariae for up to 15 years.
The symptoms of lymphatic filariasis begin within a month or less. Immune responses to the worms quickly lead to lymphoedema and swelling of the legs is a prominent early symptom. Bouts of fever and lymphangitis are common. Today gross elephantiasis is very uncommon. However, when it does occur it generally develops more quickly in Brugian (1 to 2 years) than the Bancroftian (3 or more years) filariasis.
Four stages:
Incubation- general swelling, itching
Symptomless, but patent, mf detectable
Acute, blockage of vessels, reaction of host to worms
Chronic, swelling, hypersensitivity

It takes years to develop the massive swelling and disfigurement. The sequence is:

1) blockage of lymphatics,
2) retention of fluids distal to the blockage,
3) immune response, allergic response around the adult worms which causes additional swelling.
The skin becomes stretched and loses its normal structure.
The role of protective immunity is unclear.

Some people never have symptoms nor are positive in all the tests-immune to infection.

Apart from this this is no real evidence for naturally occurring protective immunity.
Following infection with third stage larvae there is usually a period of vigorous immune response to the invading larvae. If the larvae are not cleared from the body during this period then the various pathologies associated with filarial infection can develop. Most of these conditions do not appear to arise from the effects of the nematodes themselves but from immune reactions to their presence. The most pronounced of these is the damage to the lymphatic vessels which is mediated by the immune system's response to the adult worms living in them. These immune responses are characterized by inflammation of the affected area (which are usually extremities) and fever.

Pathogenesis

Depends on inflammation and immune responses
From no symptoms to serious condition
May progress slowly from inflammation to obstructive disease

Inflammation response to female worm- affects lymph nodes, testes, hydrocele, fevers, abscesses around dead worms- bacterial infections
Diagnosis:

1) Clinical signs and symptoms
2) History of residing in endemic areas
3) Id of mf in the blood
4) Detection of circulating antigen shed by the parasite

Bancroftian filariasis. Lateral view of right outer aspect of leg of young man affected by gross elephantiasis secondary to *Wuchereria bancrofti* is shown. He was amicrofilaremic.
In infected people there is a circadian periodicity of infection.

During the daytime the microfilariae often are undetectable in peripheral blood- they are in the visceral organs, and lungs. During the evening they become detectable and reach highest densities from 10PM-2 AM, then decline again.

The timing coincides with the biting pattern of the vectors: the mf are present when suitable vectors bite the vertebrates. This periodicity to coincide with suitable vectors should increase the probability of transmission, but how do the mf tell time? Most evidence suggests it is related to blood oxygen levels.

Two types:

Periodic: defined periods of available mf

Sub periodic: 2-3 different peaks to coincide with different vectors

Can occur where W. bancrofti and B. malayi exist and are spread by mosquitoes with different biting behaviours.
Treatment / Control

1) Vector control:
   i) Blackfly control program in Africa (OCP) Millions of $ spent using BTi (a bacterial insecticide in the waters where blackfly larvae develop)
   ii) Mosquito control programs for malaria etc, helped reduce filariasis

2) Chemotherapy: reduce microfilaremias

3) Chemoprophylaxis to prevent infection

4) Integration of filariasis programs with other nematode control programs and vector control programs

Most common:

DEC salt in diet- reduces mf numbers in the blood, and sterilizes the adults
Used extensively in the Nile Delta

Ivermectin 2 x per year- reduces mf by 90%

Albendazole with ivermectin 99% reduction in mf
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Dirofilaria immitis  Life Cycle
Nematodes:

1) Mermithids: always kill their insect hosts, free living and parasitic stage, transmission via ingested eggs or penetration by juveniles

2) Ascarids have no free living stage. Eggs are released into environment. Immature stages go on migratory walks in the host before returning to the GI tract.

3) *Trichinella* sp. can kill hosts (density dependent), no free living stage, transmission via predation

4) Filarial nematodes are vector-borne, tissue dwelling parasites, that may cause disease reactions as adults, mf, or both.