A. *Angiostrongylus cantonensis*—Rat Lungworm

- Infection in rats and bandicoots in the tropics and subtropics through traveling as stowaways on ships
- Endemic in Louisiana (USA) wildlife and kills zoo animals in Lafayette and New Orleans
- Causes *Eosinophilic Meningitis* in humans
  - Can also cause ocular infections

Geographical Distribution
- Southeast Asia
- Pacific basin
- Africa and Caribbean Island

Morphology
- Slender worm, up to 25mm long
- Sexes are separate:
  - Female worm
    - Anterior end
      - With barber-pole appearance
  - Male worm
    - Tail end
      - With:
        a. Copulatory Bursa
        b. Long spicules
        c. Gubernaculum

Life Cycle

Intermediate hosts—**Snails** and **Slugs**
Carrier/Paratenic hosts—**Prawns** and **Crabs**
Terminal/End hosts—**Humans**
Definitive Hosts—**Rats**

- In rats (Definitive Hosts)
  - 1—Larval stages develop in **slugs** and **land snails** (Intermediate hosts) to become 3rd stage larva
  - 2—When these intermediate hosts are eaten by rats, the larvae migrate to the meninges and develop in the brain for about a month
  - 3—Young adults then migrate to the pulmonary artery and attain maturity (which is why it is called the Rat Lungworm)
  - 4—Upon maturity of these worms within the lungs, they lay eggs that release 1st stage larva
  - 5—1st stage larva migrates to the upper trachea and is swallowed
6—The 1st stage larva passes through the GIT and is excreted in the feces

In humans (Terminal/End hosts)
- 1—3rd stage larvae are ingested (either larvae in Snails, Slugs, Prawns, and Crabs)
- 2—3rd stage larvae penetrate into the blood vessels in the intestinal tract and are carried to the meninges but are UNABLE to migrate to the lungs
- 3—in the meninges, they rarely mature, and soon die
- 4—Upon death of larvae or young adults in the meninges, the inflammatory reaction elicited by the dead worms cause characteristic signs and symptoms of human infection

Sources of Human Infection
- Slugs, snails and fresh-water prawns that are consumed in islands of the Pacific, Thailand, and Vietnam
- In Thailand and Malaysia, snails of the genus Pila are eaten raw, either mixed with vegetables or as a form of medication
- The giant African land snail, Achatina fulica, has spread throughout the Pacific islands and is apparently a common vector
- The contamination of fresh vegetables by carnivorous land planarians that have fed on infected snails appears to be another important means of infection

Diagnosis
- History of traveling to endemic areas
- History of eating habits
- Laboratory exam revealing Leukocytosis
- Blood and CSF exam revealing eosinophilia
- Use of computed tomography (CT scan) to reveal meningeal lesions
- Serologic confirmation of the infection by ELISA

Pathogenesis
- On autopsy, sections of immature A. cantonensis have been seen in the following organs with infiltrates of eosinophils, monocytes, and foreign-body giant cells:
  - Cerebrum
  - Cerebellum
  - Foreign-body giant cells
- Marked tissue necrosis has been seen in some areas in connection with dead worms
- Immature worms have been found in CSF obtained by lumbar puncture. The CSF obtained is characterized by:
  - Low glucose
  - High protein
50-70% eosinophilia

- Adult worms have been found in the:
  - Eye
  - Pulmonary Artery

**Symptoms**

- Incubation period of the disease can be as long as **47 days**
- Infection in man is usually benign and self-limited, although deaths have occurred
- Symptoms of **meningitis** and **meningoencephalitis** (due to the toxins released by the dead worms and is a main feature in the disease) during onset of disease:
  - Headache
  - Stiff neck and nuchal rigidity
  - Altered sensorium
- In the infected Korean fishermen (16 out of 21) who ate uncooked snail *Achatina fulica*, the following were observed:
  - Radiculomyeloencephalitis
  - Pain and Paresthesias of Lower Extremities
  - Bowel and Bladder Dysfunction
    - There were 5 fishermen who cooked *Achatina fulica* and seemed to be uninfected
- CSF pleocytosis of more than 500/microliter occurred in 80% of infected person and on autopsy, worms were found in the subarachnoid space of the lumbar cord, with invasion of the white and gray matter
- Other common symptoms include:
  - Nausea
  - Emesis
  - Fever
  - Abdominal Pain
  - Malaise
  - Constipation
  - Leukocytosis
  - Partial Facial Palsy
- Eye invasion is marked by:
  - Visual impairment
  - Ocular pain
  - Blepharospasm
  - Circumcorneal injection
  - Keratitis
  - Cells and flares in the anterior chamber and vitreous humor
  - Iritis
  - Retinal edema
Treatment

→ Specific therapy are still inconclusive
→ Thiabendazole is ineffective in human cases
→ Symptomatic treatment is needed in the majority of the infections but where specific antihelminthic therapy seems necessary, **Mebendazole 100mg x2 daily for five days** is recommended
→ Surgery when necessary

Prevention

→ Boiling of snails and prawns that are to be eaten for 2 minutes
→ Refrigerate food at **-15degC** for **24 hours**
→ Careful washing and cooking vegetables
→ Ensure safety of drinking water

**B. Angiostrongylus costaricensis**

→ The adult *A. costaricensis* inhabits the **mesenteric arteries** of the **cotton rat** (*Sigmodon hispidus*) and several other species of wild rodents
→ It has been encountered as a human parasite principally in **Costa Rica** (kaya siya *costaricensis*) although some cases have been reported from Central America: Mexico and Brazil
→ Most infections occur in children
→ Also called **Parastrongylus**

Morphology

→ Male worm has:
  - Copulatory Bursa
  - Gubernaculum
  - Long spicules

Hosts

Definitive Hosts—**Rats**
Intermediate Hosts—**Snails** (Physid snails) and **Slugs**
Accidental Hosts—**Humans**

In Rats

→ Adults worms reside in the **ileocecal area**
→ Egg laying takes place in arterioles of the intestinal wall of the rodent host
→ The eggs hatch to produce larvae which will migrate through the intestinal wall to appear in the feces
Life Cycle

- 1—Larvae excreted in the rat feces
- 2—1st stage larvae are ingested by the slug (*Vaginulus plebeius*)
- 3—The larvae within the slug undergo two molts after which, they become infective to rats and humans
- 4—Ingestion of the larvae by slugs continues the life cycle and the life cycle is completed as by a rodent swallowing infected slug or snail making ulit #1

In humans

- The larvae penetrate the wall of the intestine and first enter lymphatic vessels and then migrate to the ileoceocolic branches of the anterior mesenteric artery
  - They may be found in ectopic locations such as the spermatic arteries
    - When lodged here, the worm can cause:
      1. Obstruction and Necrosis to the organ supplied by the spermatic arteries
      2. Acute Testicular Pain
  - Ectopic migrations may in other instances place the worms where their eggs reach the liver
    - If the eggs and larvae reach the liver, the clinical picture may resemble the hepatic involvement seen in and can mimic symptomology of visceral larva migrans
- The presence of the adult worms provokes an inflammatory reaction that damages the endothelium of the occupied vessels causing localized thrombosis and necrosis of the tissues perfused by the thrombosed vessels
- An eosinophilic infiltrate and granuloma formation occur around the eggs and larvae
  - In the most common form, with localization of the worms in the cecal region, there is usually pain in the right flank and iliac fossa and tenderness to palpation
    - A tumor-like mass is often palpable and the x-ray picture on barium enema may mimic malignancy
- The intestinal wall may become thickened even to the point of intestinal obstruction
  - In most cases, there is a leukocytosis of 15,000–40,000 cells per microliter and 20-50% eosinophilia
- A skin test antigen has been prepared and is reported to give good results
  - A precipitin test has also been developed
    - However, neither of these test are generally available
- Usual clinical manifestation:
  - Intestinal eosinophilic granulomata
  - Intestinal obstruction
Diagnosis
➔ Usually made by surgery

Treatment
➔ Thiabendazole
➔ Mebendazole

NOTE: Eggs and Larva of Angiostrongylus costaricensis do NOT appear in human stool

C. Dracunculus medinensis
➔ Origin: Greek word—Drakontion—little dragon
➔ Universally recognized symbol of medicine—the Greek Asklepios (Roman: Aesclepius) which consist of one-headed snake wrapped around a stick
➔ Common names: Guinea worm, Medina worm, Serpent worm
➔ Parasitizes: Dogs, Mammalian carnivores, and Humans

Geographical Distribution
➔ In the early 1990s, 3-5 million cases of Dracunculiasis occurred worldwide each year
➔ By 1996, only 152,805 cases were reported, mostly from SUDAN
➔ Endemic countries: Sudan, India, Pakistan, Nigeria, Cameroon, and Ghana

Morphology
➔ Though usually classed with the filarial worms, the Dracunculus is NOT a true filarial
➔ The worms are elongate
➔ The sexes are separate:
  o Females
    ▪ Measuring up to a meter(!!!) or slightly more in length
    ▪ Diameter is less than 2mm
  o Male
    ▪ Only 2 cm long

Life Cycle
Intermediate host—Copepods
Definitive host—Humans

➔ 1—Free swimming larva liberated in water from skin lesion
➔ 2—Larva ingested by copepod (water flea) and develops to infective stage in about 2 weeks
➔ 3—Infective stage larva liberated from copepod are ingested in drinking water
➔ 4—Penetrates through the digestive tract of humans to mature in deeper tissues
5—Adults female worms localize in the subcutaneous tissue producing a skin lesion
   o Maturation to become an adult female worm takes about 1 year. After maturation, copulation takes place. After copulation, the male worms die and the females reside in the subcutaneous tissue

6—Ulit sa #1
   The larvae of Dracunculus, unlike other microfilariae, have a well-developed digestive tract and are never found in blood/tissues of the host, are discharged into water. In endemic areas, the immersion of the ulcerated skin lesions releases larvae and these larvae are ingested by appropriate copepods. Drinking of water containing copepods with infective stage larvae infects humans.

**Diagnosis**
   Diagnosis is made once the female worm emerges in the distal lower extremity because it causes an ulcer and ruptures exposing the female worm’s head at the ruptured hole of skin.

**Symptoms and Pathogenesis**
   One or many worms may be seen at one time, in any part of the body, but usually on the lower legs or feet.
   The majority of infections consist of a single worm, but in endemic areas, repeated reinfection is the rule.
   The presence of maturing worms may give rise to mild allergic symptoms such as urticarial—skin itching
   When the gravid female seeks a position close to the skin, there may be some localized erythema and tenderness in the area where the ulcer will form.
   o The patient frequently exhibits some generalized symptoms at this time:
     ▪ Pruritus
     ▪ Sometimes with:
       1 Nausea
       2 Emesis
       3 Diarrhea
       4 Asthma attacks
         a These symptoms usually disappear with:
           i The appearance of the skin ulcer
           ii The drainage of fluid that has formed around the female worm
           iii The initial discharge of larvae
         • Discharge is intermittent, usually only happens when the skin ulcer is immersed in water. Which is why patients dip it in water and the larvae is
released. When the larvae are ingested by a copepod, the life cycle continues.

- A localized reaction that is often painful persists around the site of the skin ulcer during the entire period while the worm continues to discharge its larvae.
- 40% of the patients experience severe disability, lasting an average of 6 weeks.
- About 1% of the patients suffer permanent damage from ankylosis of a joint.
- When the uterus of the gravid female worm is emptied, the worm may withdraw into the tissues and become resorbed or it may be expelled.
  - If the lesion does not become secondarily infected, healing is rapid after all larvae have been discharged.
    - However, it has been estimated that about 50% of the lesions become infected causing problems lasting for up to a year after the worms emerge.
    1. If the worms are removed surgically, the wound heals promptly.
    2. A rare complication of this infection is invasion of the extradural space by the guinea worm leading to abscess formation and paraplegia.
- The calcified remains of worms that have died in the subcutaneous tissues may be found on x-ray examination. They may appear as linear calcific densities up to 25 cm in length, as tightly coiled bodies, or as rather dense, usually elongate nodules.

Treatment
- Surgical removal of the worms by methods as primitive as twisting them around a stick has been practiced for centuries and may be quite successful if the worm is removed wholly.
  - If in the process of its removal, the worm is broken, secondary infection almost always develops.
- Metronidazole
- Thiabendazole
  - Side effects are more common with Thiabendazole than Metronidazole.
  - Both drugs will not kill the worm but will facilitate its removal.
- Mebendazole kills the worms.

Epidemiology and Control
- Control is simple.
  - Via the installation of filtration system that will filter out copepods.

THE FILARIAL WORMS

The filariae are long, thread-like nematodes, various species of which inhabit portion of the human lymphatic system, and others inhabit the subcutaneous and deep connective tissues. In addition to the eight species that commonly infect...
humans, a number of filariae that are primarily parasites of other animals are reported occasionally from humans.

The adults of all species of filariae are parasites of vertebrate hosts. The female worms produce eggs that, during their development, become elongate and worm-like in appearance, a modification that adapts them for life within the vascular system or for migration through the tissues. These highly modified eggs, referred to as microfilariae, are generally capable of living for a long period within the vertebrate host but not of developing further until ingested by their intermediate host and vector, an insect.

In the insect, the microfilariae molt and grow, transforming into infective larvae, which are deposited on the skin when the insect next takes blood from a suitable host.

The most important of the filarial disease of humans are the lymphatic filariases, so called because the adult worms are found in the lymphatic system. Agents of lymphatic filariasis are: Wuchereria bancrofti, Brugia malayi, and Brugia timori.

D. *Wuchereria bancrofti*

➔ 90% of lymphatic filariasis are caused by *Wuchereria bancrofti* (Bancroftian filariasis) Others, by *Brugia*.

➔ Occurs in:
- Central Africa
- Madagascar
- Nile delta
- Asia
- New World: Haiti, Dominican Republic, Guyana, Surinam, French Guiana, and coastal Brazil

➔ Thought to originate in Southeast Asia where its closest relative, the *W. kalimantani*, parasitized the Indonesian Leaf Monkey

➔ Humans are the exclusive/definitive host of *W. bancrofti*

Morphology

➔ The sexes are separate:
- Females—Bigger being 5 to 10 cm long
- Males—2.5 to 4 cm long

Life Cycle

➔ 1.—Microfilaria ingested by mosquito (from an infective) during blood meal develops into infective larva
- The microfilariae bore through the stomach wall of the mosquito to enter the body cavity (hemocoel), and migrate to the thoracic musculature for them to grow and molt.
After 10 days or so, the larvae become **infective**

1. During this period, they have increased in length and they enter the **proboscis** of the mosquito and when the next blood meal is taken, they escape from the proboscis to the human skin

2. Infective larva actively penetrates skin after being deposited there when the mosquito bites

3. It then migrates in the lymphatics where it matures
   - In here, they molt **twice** to become adults before they can enter **regional lymph nodes**

4. Adult worms live in lymph nodes
   - If females and males are present in here, they mate to produce **eggs/microfilariae**

5. Females produce worm-like sheathed eggs (microfilariae) which circulate in the bloodstream
   - The eggs are sheathed and the sheath is actually the **egg shell** which is very thin and delicate and surrounds the embryo as it circulates in the **blood**.
   - The **sheath** is not lost until it is digested away in the **mosquito’s stomach**

6. Ulit sa #1

**Microfilarial Morphology (W. bancrofti)**

- A large number of distinct **nuclei** can be seen in the body of a well-stained microfilariae—**nuclear columns**
  - Some nuclei are also found in the rudiments of some organs of the adult worm
  - Nuclei are NOT found in the tip of the tail

- **Length:** 245 to 300 microns
- **NO** alimentary canal
- **Stains with** hematoxylin
  - The sheath of microfilaria are only slightly stained by hematoxylin

- **Aspects:**
  - **Anterior:**
    - The cylindrical body is blunted at this end
  - **Posterior:**
    - Observed **tapering** of the posterior end

In some parts of the world where filariasis is endemic, the infection is seen in **filarial periodicity:**

- **Periodic form**
Microfilariae present in very small numbers in the circulating blood during the daytime hours and often virtually undetectable then, appear at their greatest density at night between the hours of **10pm and 2-4am**

**Subperiodic form**
- Persons infected with this strain exhibit **microfilaremia AT ALL TIMES**, but the organisms are present in greatest numbers between **noon and 8pm**
- Occurs in the **Pacific islands and Vietnam**

Factors Affecting Filarial Periodicity
- 24-hour rhythm of the host
- Increased pulmonary pO₂ and **exertion**
  - The same pulmonary phenomenon can also influence migration of microfilariae of the **periodic strain** of *W. bancrofti* to the lungs

*Note insect vectors of **periodic filariasis** take blood meals during the **night**. While insect vectors of **non-periodic filariasis** take blood meals during the day.

**Diagnosis**

**Gold standard:** Microfilaremia—presence of **microfilariae** in the circulating blood
- Examination of fresh blood film where their movements make them conspicuous
- If present in small numbers, it may be necessary to prepare a thick blood film or **concentrate** of a larger volume of **venous blood** to detect them
  - Concentration techniques used:
    - Nucleopore filtration
    - Knott concentration
- The “provocative” administration of **diethylcarbamazine** (a slow-acting **microfilaricidal drug**) may enable the examiner to detect the presence of **nocturnally periodic microfilariae** in blood samples taken during the day
  - Microfilariae can be demonstrated at about 1/3 of nocturnal number after **45-2 hours AFTER** drug the oral administration of **100mg diethylcarbamazine**
  - This microfilarial presentation by **diethylcarbamazine** is **NOT** applicable to **subperiodic/Pacific microfilariae**
- In areas where more than one kind of filarial disease occurs, well-stained slides are essential, as the different filarial infections are distinguished by differences in structure of the microfilariae
- A skin test using an extract of the **dog heartworms** (*Dirofilaria immitis*) is **group-specific** for filarial infections as are various serologic tests
- Radiographs can at times give evidence of infection—because worms die and become **calcified**—the calcification is evident on x-ray
- **Lymphangiography** may demonstrate characteristic changes in **filarial elephantiasis**
Ultrasound can detect the movements of the adult worms in the lymphatics showing the “Filarial Dance Sign” (FDS).

Some filarial infections can occur WITHOUT microfilaremia—amicrofilaremia

- Occurs in immunologically naïve persons coming from non-endemic areas
  - In such cases, patients show hyperreactivity to the microfilariae resulting in their rapid destruction by host’s immune mechanisms. Patients that are amicrofilaremic can present with:
    1. Tropical pulmonary eosinophilia
    2. Meyers and Kouwenaar’s syndrome
      - Lymphadenopathy with splenomegaly
      - Hypereosinophilia
      - Transient pulmonary infiltrates

Diagnosis by detection of circulating filarial antigens

- ELISA kit test
- ICT—A whole-blood antigen card test

Of all those infected with lymphatic filariasis worldwide, WHO review indicates that nearly 2/3s are microfilaremics without overt symptoms but with subclinical renal and lymphatic damage. Nearly ¼ of male have hydrocele, and a little over 1/8 of infected person have elephantiasis and/or lymphedema with accompanying attacks of lymphangitis of lymphadenitis

- Hydrocele—accumulation of fluid within the tunica vaginalis/spermatic cord
- Lymphangitis—inflammation of the lymphatic channels that occurs as a result of infection at a site distal to the channel
- Lymphedema—abnormal collection of protein-rich fluid in the interstitium resulting from obstruction of lymphatic draining
- Lymphadenitis—the inflammation or enlargement of a lymph node

Symptoms

Incubation Period

- There is an asymptomatic incubation period of at least 6 months that can last to 6 years
- As this may lead to difficulty in diagnosis, some have suggested routine post-travel serologic screening for those individuals with more than 1 year exposure in an endemic area

Risk to the Traveler

- Risk is low
  - However, risk is increased in the long-term traveler like missionaries, field scientists, and volunteers as disease usually requires repeated exposure to the particular infected vector over months to years
  - As the adult worm cannot multiply in the human host, disease manifestations will depend on the frequency of bites as well as the worm burden
Asymptomatic presentations
- Of all the patients with lymphatic filariasis, at least half appear **clinically asymptomatic**, though they have **microfilaremia** and hidden damage to their lymphatics as evidenced by **lymphoscintigraphy** and **subclinical hematuria/proteinuria**
- A second asymptomatic “presentation” exists in individuals previously termed as **endemic normal**
- No microfilaremia but parasite antigen is present in blood (that will disappear after appropriate treatment)

Expatriate Syndrome
- Individuals who have grown **outside** of the endemic regions and then moved to these regions and acquired a filarial infection manifest prominent signs and symptoms of inflammatory reactions (including allergy) to the mature or maturing parasites
- In bancroftian filariasis (when military personnel or other migrants to endemic areas have acquired these infections), they usually have **lymphangitis, lymphadenitis, genital pain**, along with **hives, rashes** and other **allergic-like** manifestations, including **blood eosinophilia**
- The reason for these different clinical presentations lies almost certainly in the different immunoregulatory responses to filarial antigens between those with long (including **prenatal**) exposure to these antigens and those meeting them for the first time.

Clinical manifestations of infection are variable and probably depend on constitutional factors in the host, numbers of infecting organisms, and possibly strain differences in the parasite itself.

- Some persons become heavily infected without showing any signs of disease other than microfilaremia
  - However, in these patients, there is **subclinical hematuria** and **proteinuria**

In asymptomatic microfilaremics:
- **Lymphangioscintigraphy** has allowed the visualization of the peripheral lymphatics revealing significant abnormalities in lymphatic structure and function
  - Renal and lymphatic disease in these “asymptomatic” individuals suggests the advisability of starting treatment

In some patients that are not from the endemic areas:
- There may be immune hyperreaction so much so that even in presence of few worms can provoke severe reactions
Early manifestations:

- **Fever**
- **Lymphangitis**
  - Usually with febrile attacks (but febrile attacks can happen in those patients without lymphangitis)
    - These attacks are called *filarial/elephantoid fever*
      1. The fever usually begins with a chill, and the fever remains high for 1-2 days and gradually subsides over the following 2-5 day period
    - Commonly affects the limbs but can occur in breast, scrotum, etc
      - When on the limbs, it develops centrifugally, starting in the region of a lymph node and progressing distally along the lymphatic channel
        1. The affected lymphatic vessel is distended and acutely tender, and the overlying skin is tense, erythematous, and hot.
        2. The surrounding area is edematous.
      - Attacks of lymphangitis occur periodically with occasional accompaniment by abscess formation, either along the course of the lymphatics or at a lymph node.
        - When such abscesses are drained or opened, remnants of adult worms are sometimes found in the drainage
- **Lymphadenitis**
  - Affects femoral and epitrochlear nodes which, once enlarged, remains so
    - The enlargement is firm, discrete, and somewhat tender
    - Enlargement of the epitrochlear lymph nodes occurs early in the subperiodic form of filariasis

The scrotal lymphatics appear to be a preferential site for localization of the adult worms.

- Ultrasound examination of the scrotal lymphatics can reveal the random movements of the adult filariae in the dilated lymphatics called—*Filarial Dance Sign (FDS)*
  - FDS can occur in amicrofilaremic patients
  - FDS is associated with higher microfilarial blood levels
  - FDS can disappear with oral treatment of *diethylcarbamazine*

**Orchitis** and inflammation of the spermatic cord are common, and some permanent thickening of the cord is seen in a large percentage of the cases that are asymptomatic.

- A lymph varix of the cord may appear and rupture into the scrotal sac causing lymphocele
  - Lymphocele is one type of *hydrocele*—a condition that may also develop gradually as a result of recurrent attacks of orchitis
  - Microfilariae can be found in the *hydrocele fluid* if it is wholly or partially made up of lymph
Rupture of **lymph varices** into any part of the **urinary tract** leads to the passage of **lymph in the urine (chyluria)**

- Chyluria usually comes on suddenly and lasts for a few days
- There may be repeated episodes, separated by long intervals
- Microfilariae may be found in the **chylous urine**

**Intraocular filariasis** is an extremely rare condition that can be treated with surgical intervention.

- Usually presents with:
  - Redness
  - Irritation
  - Diminished vision

- Since the eye has **NO** lymphatics, entry to the eye was presumed to be **hematogenous**
- Only 42 patients had intraocular filariasis out of the millions who have been infected

**Elephantiasis** is a relatively uncommon and late complication of filariasis

- Elephantiasis—Enlargement of one or more **limbs**, the **scrotum, breasts, or vulva**
  - with **dermal hypertrophy** and **verrucous changes**
- Elephantiasis does not always happen in patients with microfilariasis

**Pathogenesis**

Adult worms are found in lymph vessels throughout the body but principally in or around the:

- **Axillary**
- **Epitrochlear**
- **Inguinal**
- **Pelvic nodes**
- And the lymphatics **distal** to them
- **Testis**
- **Epididymis**
- **Spermatic cord**

Inflammatory changes in and around the lymphatic vessels comprise the basic reaction to infection, though the expression of this reaction may be variable.

Attacks of **lymphangitis** and **lymphadenitis** may begin before the worms mature.

- These attacks are marked by **retrograde lymphangitis** if a limb is involved
- **Funiculitis, epididymitis**, or **orchitis** may be seen if the worms are located in the scrotal lymphatics—fever and other constitutional symptoms without localizing signs are seen if the pelvic or abdominal lymphatics are the site of inflammation.
It is now recognized that the bacterial or fungal superinfection of the already compromised lymphatics may play an important role in the recurrent attacks of adenolymphangitis

Repeated attacks of inflammation lead to dilation and thickening of the affected lymphatic vessels, which may become incompetent and lead to lymphedema.
- Lymphedema may be intermittent early in the course of the disease, but lymphatic vessels tend to become fibrosed after repeated attack of lymphangitis.
  - With chronic lymphedema, there is hyperplasia of connective tissue, and infiltration of plasma cells, macrophages, and eosinophils.

Finally, woody induration of the tissues may take place, with thickening and verrucous changes of the skin—producing the condition known as elephantiasis.
- Elephantiasis may develop in any limb, scrotum, breasts and the vulva.
- Elephantiasis is a disfiguring and frequently disabling condition, and because circulation is badly impaired, an elephantoid limb/organ is in constant danger of secondary infection.

Involvement of the scrotal lymphatics may lead to hydrocele far earlier in the disease, and more commonly, than to scrotal elephantiasis.

Lymph varices may form in any affected vessels.
- If in the urinary tract, rupture of such varices may bring on attacks of chyluria and if near the surface of the scrotum, they may be readily seen and palpated through the skin and may rupture.
  - This rare condition is called lymph scrotum

Death of an adult worm generally leads to severe localized inflammation.
- Often, the worms are absorbed, sometimes, they calcify and can be identified on x-ray and at other times, an abscess forms around them.

Lymphangitis and its sequelae occur as a result of reactions to the products of developing, adult, or dying worms or from secondary bacterial/fungal infection.
- Microfilariae seem not to be directly responsible for any of the major manifestations of lymphatic filariasis.

Antifilarial antibodies—IgG, IgM, and IgE—have been identified in patients with bancroftian filariasis.
- Lowest antibody titer: Patients with asymptomatic microfilaremia.
- Intermediate antibody titer: Patients with filarial fever and chronic lymphatic disease.
- Highest antibody titer: Patients who are amicrofilaremic.
In the same patients, they exhibit the greatest response of **lymphocytic proliferation**

In the same patients, **antisheath antibodies** (reacting with surface antigens of microfilariae) have been detected

In the same patients, **opsonizing antibodies** promoting in vitro adherence of normal leukocytes to microfilariae were found

**Treatment**

- Attacks of **filarial lymphangitis** often respond to the administration of antihistamines/analgesics
  - In advanced cases where there is secondary infection, **antibiotic therapy** is appropriate
    - In such cases, **careful hygienic measures** help prevent **recurrent infection** and **lymphangitis**

- **Diethylcarbamazine (DEC)** is an effective **microfilaricidal drug** but it eliminates the adult worms more slowly.
  - In vitro, DEC has no microfilaricidal activity
    - Its effect is dependent on integrity of the **cellular** and **humoral immune mechanisms** of the host
  - Most of the microfilariae are destroyed by the **reticuloendothelial cells** of the **liver**

  - For a better long-term suppression of **microfilaremia** is obtained by the **concurrent administration** of **DEC + Ivermectin (Mectizan)**
    - Isolated from **Streptomyces avermitilis**
    - Mechanism of Ivermectin: Modifying release of GABA, resulting in the paralysis of the microfilariae

- Severe allergic reactions accompany the death of the worm including abscess formation
  - Administration of **corticosteroids** can help minimize adverse immune responses
    - But don’t use if the patient has secondary infections hehe

- **Scrotal elephantiasis** can be treated through surgery

**Epidemiology**

- **Night-biting Anopheles** (In rural Africa areas) and **Culex** (Urban and semi-urban areas) mosquitoes are vectors of the **nocturnally periodic** **W. bancrofti**

- **Daytime-biting Aedes polynesiensis** carries the **subperiodic Pacific strain**

- **Culex quinquefasciatus** is the principal vector of bancroftian filariasis in **India**

- Factors affecting decline of **bancroftian filariasis**:
Lecture 3: Nematodes 3—Blood & Tissue Nematodes #AsturiaNOTES

Parasitology: Angiostrongylus cantonensis to Loa loa

Decline of infected people
- Control of insect vectors and eradication of their breeding grounds

- Widely distributed in the **tropics/subtropics**
  - Transmission is restricted to the more **humid areas**
  - The **infective larvae** that are lodged from the mosquito’s proboscis onto the skin should find its way into the puncture wound left by the mosquito before it can enter the body.
    - Therefore, in less humid areas, the **minute drops of hemolymph** (from the mosquito) that protects these larvae from **desiccation** would be quickly lost resulting in failure to infect

E. *Brugia malayi*

- Causative agent for: **Brugian filariasis**
- Occurs in: South China, India, Indonesia, Thailand, Vietnam, Malaysia, Philippines, and South Korea
  - The distribution of these species obviously overlaps that of *W. bancrofti*
- The life cycle of *B. malayi* is almost similar to that of *W. bancrofti*—except that the principal mosquito vector belongs to the genus *Mansonina*
  - In some areas, the mosquito belonging to the genus *Anopheles* may be an important or the only vector for brugian filariasis
- Important reservoir hosts of *Brugia malayi*: *Macaques* and *Presbytis*—leaf monkeys
  - *B. malayi* can be transmitted to *cats* and *civet cats*
- In Indonesia, **zoophilic** and **anthropophilic strains** are recognized
  - The **zoophilic strain** can exhibit the following periodicity in human infection:
    - Aperiodic
    - Nocturnally subperiodic
    - Nocturnally periodic
  - The **zoophilic strain** exhibits **nocturnal subperiodicity** in experimental animals
  - The **anthropophilic strain**
    - Found in **rice-growing areas** of Indonesia (Sulawesi)
    - Transmitted by *Anopheles*
    - Always exhibits **nocturnal periodicity**
    - Cannot maintain infection in animals
  - Thus, both **anthropophilic** and **zoophilic** strains of *Brugia malayi* can be present in an individual with **Brugian filariasis**
    - The **zoophilic strain** is more difficult to control, in terms of epidemiology

**Morphology**
- The microfilariae are **sheathed**
- 200-275 microns in length
- Body nuclei extend almost to the tip of the tail—whereas the tail of *W. bancrofti* microfilariae contains NO nuclei
  - Two terminal nuclei are distinctly separate from the others in the tail
    - This characteristic is used to make a distinction from microfilariae of *Loa loa*
- Adults of *Brugia malayi* appear smaller than adults of *W. bancrofti*

**Life Cycle**
- 1—During a bloodmeal, an infected mosquito introduces 3rd stage filarial larvae onto the skin of the human host where they penetrate into the bite wound
- 2—Larvae develop into adults that commonly reside in the lymphatics
- 3—Adults produce microfilariae which are sheathed and have nocturnal periodicity
  - These microfilariae measure about 177-230 microns in length and 5-7 microns in width
- 4—Microfilariae migrate into lymph and enter the bloodstream reaching peripheral blood
- 5—The microfilariae in the peripheral blood are sucked by a new mosquito
  - In the mosquito, the microfilariae lose their sheaths and work their way through the wall of the proventriculus and cardiac portion of the midgut to reach the thoracic muscles
- 6—The microfilariae develop into 1st stage and 3rd stage larvae in the mosquito’s thoracic muscle
- 7—The 3rd stage larvae migrate through the hemocoel to the mosquito’s proboscis and this mosquito will bite another human making ulit the cycle at #1

**Diagnosis**
- Examination of blood films stained to demonstrate the differential morphologic features of the microfilariae
  - For examination of blood, hydrocele fluid, and articular effusions and urine:
    - Spread 20 microliters evenly over a clean slide and let dry
    - Stain with Giemsa
    - Wet smear: Dilute 20-40 microliters of anti-coagulated blood with water or 2% saponin
      1. Saponin will lyse the RBC but allow the microfilariae to remain motile and thus more readily identifiable
- Also, diagnostic modalities must be done in accordance to the parasite’s possible nocturnal periodicity
  - Thus, selectin the optimal blood drawing time (10pm-2am for most Brugian and even Bancroftian infections)
- Knott’s concentration technique:
1mL of anti-coagulated blood mixed with 10 mL of 2% formalin is centrifuged; examine the sediment either unstained or fixed and stained
The microfilariae are non-motile and generally straight and they can be easily missed if the viscous sediment is not searched diligently

→ Membrane filtration:
The most sensitive technique for quantifying microfilariae in the blood, urine, or other body fluids

→ Polycarbonate (Nuclepore):
Filters with a 3-micron pore size
Anti-coagulated blood or other fluid is passed through a Swinnex holder containing the filter followed by a 35-mL of pre-filtered water that lyses RBC
A volume of air then follows the water, and the filter is removed, placed on a slide, and stained

→ Immunoassay for antigen detection of circulating filarial antigens
Useful diagnostic approach because microfilaremia can be low and variable

→ Molecular diagnosis using PCR
Antibody detection is not very valuable in diagnosis of filariasis because it does not distinguish past and current infections

→ X-ray Diagnosis
Conventional x-rays are rarely helpful
Ultrasound exam of the lymphatics (especially scrotal lymphatics in men, and the breast and retroperitoneal lymphatics in women) can reveal moving adult worms
Lymphoscintigraphy can reveal functional and gross anatomical abnormalities of the lymphatics

Symptoms and Pathogenesis
Clinical features of Malay (Brugian) filariasis are generally similar to those seen in bancroftian infections

→ Lymphadenitis occurs most frequently in the inguinal area and may be followed by a retrograde lymphangitis, often accompanied by lymphedema of the foot and ankle
Occasionally (and more commonly than in bancroftian filariasis), there is ulceration of the affected lymph node

→ Involvement of the genital areas (funiculitis, orchitis, epididymitis, hydrocele) and chyluria are NOT characteristic of Brugian filariasis
When there is elephantiasis, it ONLY involves the leg below the knee
Less commonly, the arm below the elbow

→ Tropical Eosinophilia
Subacute or chronic form of Brugian and Bancroftian filariasis occurring in the tropics (India) with:
- Episodes of nocturnal wheezing and coughing
- Marked blood eosinophilia
- Interstitial thickening
Treatment

- Effective eradication of microfilariae by Diethylcarbamazine (eliminates adult worms slowly)
- Ivermectin single dose of 200-400 mg/kbw: NOT macrofilaricidal
- Corticosteroids for symptomatic relief
- Surgery

F. Brugia timori

- Discovered in the island of Timor in 1964
- Infections caused by B. timori closely resembles bancroftian filariasis in its clinical expression though the rate of abscess formation seems higher
  - Can cause elephantiasis

Morphology

- Microfilaria of B. timori is longer than that of B. malayi
  - 310 microns in length
- The cephalic space—part of the microfilaria that is anterior to the body nuclei has a length-width ratio of 3:1
  - In B. malayi, the ratio is only 2:1
    - Therefore, the cephalic space of B. timori is longer
- Microfilariae are ensheathed
  - Sheath stains deeply with Giemsa
    - In contrast, sheath of B. timori microfilaria DOES NOT
- The microfilariae exhibit a nocturnal periodicity and the vector is Anopheles barbirostris and humans are the only definitive host.

Diagnosis

- Almost similar with B. malayi

Treatment

- Treatment modalities are similar with B. malayi

Prevention of Filariasis

- The principal strategies for interrupting transmission of infection:
  - Identify endemic areas
  - Implement community-wide programmes to treat the entire population at risk
    - This breaks the cycle of transmission between mosquitoes and humans
- Community-wide prophylaxis
  - Once yearly for 4-6 years
  - Single dose of:
    - Albendazole + Ivermectin or Diethylcarbamazine
Individual prophylaxis
  o Prophylactic regimen of **Diethylcarbamazine**
    ▪ 6 mg DEC/kg per day 2x in one month
      1 This can prevent acquisition of infection

**G. Onchocerca volvulus**
  ➤ Widely distributed throughout Central Africa
    o Present in Saudi Arabia, Yemen, and in the Western Hemisphere in limited areas of Mexico, Guatemala, Venezuela, Colombia, Ecuador, and Brazil
  ➤ Thought to be introduced into the Americas via the slave trade
  ➤ Intermediate Host: *Simulium* (blackfly/buffalo gnat)
  ➤ The **only definitive host**: Man
  ➤ Causes: **River blindness/Onchocerciasis**

**Morphology**
  ➤ Sexes are separate:
    o Females are **bigger**:
      ▪ 40mm x 300 microns
      ▪ Wire-like and coiled
    o Males:
      ▪ 30mm x 150 microns

**Life Cycle**
  ➤ 1—Microfilaria are ingested by the blackfly during blood meal
    o The microfilariae within the blackfly develops into **infective larvae**
  ➤ 2—Infective larva **actively penetrates** the skin after being deposited there upon the blood meal bite by a blackfly harboring the infective larvae
  ➤ 3—The infective larva, now in the man, develops to maturity in the **subcutaneous tissue**
  ➤ 4—Adult female worms live in the **subcutaneous nodules** while male worms migrate in **subcutaneous tissues**
  ➤ 5—Female produces **worm-like unsheathed eggs** (microfilariae) which are found in skin which can be the site of the blackfly’s next blood meal making ulit #1
    o The nodules which are found on the skin:
      ▪ Develop **1 year after** infection
      ▪ Are **tumor-like masses** therefore can be called as **onchocercoma**
      ▪ Most usually occurring in the subcutaneous tissue but can also occur deep into the connective tissues
      ▪ Nodular lesions can be found on:
        1 Head, scalp
        2 Trunk
        3 Limbs
Lecture 3: Nematodes 3—Blood & Tissue Nematodes #AsturiaNOTES
Parasitology: Angiostrongylus cantonensis to Loa loa

Diagnosis

- Identification of microfilariae in skin snips either through:
  - Use of thumb and index finger squeezing on the dermal nodular lesion and cut with a razor blade/scalpel
  - Use of needle to raise the dermal nodular lesion and then cut with a scissor/razor blade
  - The sampled dermal nodular lesion (skin) is then incubated for 30-120 minutes in saline or culture medium and is then examined for microfilarial presence that have migrated from the tissue to the liquid specimen
  - It may be necessary to take multiple skin snips from patients with light infections
  - If skin snips reveal no microfilariae, further diagnosis can be made using Mazzotti Test
    - It consists of the oral administration of a single dose of 50mg Diethylcarbamazine which generally provokes intense pruritus within a few hours
      - Itching can be relieved by short-term administration of corticosteroids and subsides w/o corticosteroids in 2-3 days

- Ultrasound can detect onchocercal nodules in the deeper connective tissues
- NO microfilaremia

Symptoms

- Skin lesion seem disfiguring but are not painful and the importance of the infection lies not in the adult worms but in the effects their microfilariae may produce:
  - Skin lesions include:
    - Urticaria
    - Papules
    - Edema
    - Lichenified skin
    - Peau d’orange

- If the skin lesions cause an acute inflammatory reaction can make the skin hot, edematous, and sensitive to pain and there may be associated pruritus
  - The inflammation subsides slowly and may recur many times, eventually resulting in permanent thickening of the skin affected, which can assume a violaceous color
    - The repeatedly infected skin loses elasticity, becomes wrinkled, and atrophic
      - Heavy infections can be observed around the hip region through the presence of a “hanging groin”—a condition in which a sac of tissue forms in the inguinal region
        - It may contain inguinal or femoral lymph nodes and may hang down as far as the knees
i  It can cause actual herniation causing inguinal or femoral hernia

b  Lymphedema of the external genitalia and scrotal elephantiasis are seen in extreme complications

- The repeatedly infected skin can also exhibit depigmentation referred to as “leopard skin”
  - This reaction is associated with the death of microfilariae in the skin and liberation of antigenic materials from them
    - This reaction may result from the drugs known to kill microfilariae (DEC)
    - This reaction can be prevented by corticosteroids
  - Onchodermatitis
    - Can cause skin to exhibit “premature senility” and leonine facies

⇒ Eye lesions usually occur in areas with high Onchocerca endemicity:
  - Conjunctivitis (Lacrimation and photophobia)
  - Keratitis
    - When this develops, microfilariae can now be found in the:
      1  Cornea
      2  Anterior chamber
      - Keratitis-induced opacities may coalesce, usually in the lower portions of the cornea
  - Iritis
  - Iridocyclitis—appears after corneal pathology
    - The posterior synechiae frequently displace the pupil which becomes fixed or distorted
      1  And, an exudate may form and cover the pupillary area finally leading to blindness
  - Secondary glaucoma
  - Blindness

Pathogenesis
⇒ It has been found out that the bacteria Wolbachia contributes to the pathogenicity of onchocercal infections
  - Wolbachia are endosymbionts of filarial parasites:
    - W. bancrofti
    - B. malayi
    - O. volvulus
  - Wolbachia has a role in inflammation and possible blindness in concert with onchocercal infection
Treatment

- DEC is very effective in killing the microfilariae of *Onchocerca* but the rapidity of onset of its action can lead to severe side effects
  - Sudden death of enormous numbers of microfilariae
    - In the skin:
      1. May give rise to **intense pruritus** and **localized edema**
    - In the eye:
      1. **Chorioretinal damage** and **keratitis**
  - Other side effects of DEC:
    - Myalgia
    - Arthralgia
    - Headache
    - Dizziness
    - Sometimes, **hypotension**
- **Ivermectin** exerts its microfilaricidal effect more slowly
  - Therefore, pruritic reactions are **less severe** and ocular reactions are **minimal**
  - All side effects of DEC may occur in ivermectin use but are **milder**
- If there is microfilarial presence in the cornea or anterior chamber, pre-treat with steroids such as **Prednisone (1mg/kg daily)** for 2-3 days

Epidemiology

- African and American forms of onchocerciasis exhibit certain differences, some of which may be related to **vector-biting habits** (therefore, difference in the localization of the onchoceroma)
- The blackflies have larval stages that are **aquatic**, most of them requiring swiftly flowing streams in which the larvae and pupae attach to submerged rocks or vegetation
  - However, some species develop in quiet waters and certain African species attach themselves to **freshwater crabs**

**H. Loa loa**

- Causative agent for: **Loiaisis**
- Common name: **African eye worm**
- Location: **Sudan, Congo, and West Africa**
- Habitat: **Subcutaneous tissue**
  - However, it crosses the **conjunctiva** where it is **most conspicuous** and irritating
- Vector: **Chrysops**—the mango fly; has mouth parts that can produce a painful bite

Morphology

- Sexes are separate:
  - Females are **longer**
Lecture 3: Nematodes 3—Blood & Tissue Nematodes #AsturiaNOTES

Parasitology: Angiostrongylus cantonensis to Loa loa

- 5-7 cm
  - Males:
    - 2-3.5 cm
    - Both males and females are less than **0.5mm wide**

Microfilaria
- **250-300** microns long
- **Sheathed**
- Exhibits **diurnal periodicity**
  - Daytime—located in **peripheral blood**
  - Night time—located in the **lungs**
- Differs from microfilariae of *Wuchereria* and *Brugia* in having **body nuclei** that are **continuous to the tip of the tail**

Life Cycle
- **1**—Fly (from genus *Chrysops*) takes a blood meal from the human host and together with the bite is lodging of **infective stage larvae (L3 larvae)** onto the skin
- **2**—The larvae in the skin enter the human system through the wound bite
- **3**—The larvae locates itself in the **subcutaneous tissue** and there, it matures to become adults
- **4**—Adults produced **sheathed microfilariae** that are found in the **CSF, Urine, Sputum, Peripheral Blood, and Lungs**
- **5**—Another chrysopian fly takes a blood meal and as it does so, it ingests the sheathed microfilariae
- **6**—The microfilariae, now within the chrysopian flow, **shed the sheath**, penetrate the fly’s midgut, and migrate to the thoracic muscles where it matures
- **7**—The microfilariae mature to become **L1 larvae** and then become **L3 larvae**
- **8**—The chrysopian fly now with the mature **and infective L3 larvae** takes another blood meal and infects another human host making ulit the cycle at #1

Diagnosis
- Diagnosis of **loaisis** is most frequently made on the basis of a history of **Calabar swellings** (AKA **fugitive swellings**) or the **appearance of the worm in the conjunctivae**
- Microfilariae frequently do not appear in the blood until years after the worms or the result of their activities become apparent
  - Although early in the disease, sometimes, there can be microfilaremia

Symptoms
- Migration of the adult worms through the tissues is not painful and is seldom noticed unless they happen to pass over the **bridge of the nose** or through the **conjunctival tissue** across the eyeballs
While they migrate rapidly, they can often be immobilized with a few drops of 10% cocaine instilled into the eye and then be excised out of the conjunctiva.

There may be some edema of conjunctiva and lids when the worms are in that area.

Patches of localized subcutaneous edema—**Calabar swellings**—may appear anywhere on the body.

- The swellings are:
  - Several inches in diameter
  - Preceded by localized pain and pruritus
  - Present for several days to week and they subside slowly
  - A type of allergic reaction to the metabolic products of the worms or to dead worms

**Loa** worms can sometimes be located ectopically:

- In the tunica vaginalis or spermatic cord—causes hydrocele and orchitis
- In the intestinal wall—causes colonic lesion that causes intestinal obstruction
- In small vessels—causes membranous glomerulonephritis in patients who, after DEC therapy, developed local encephalitis and diffuse vascular obstruction as small vessels of all organs is with fibrin thrombi (thrombuses) surrounding degenerating microfilariae

In extreme cases, usually in patients coming from endemic areas, the following can be observed:

- Fibroblastic endocarditis
- Retinopathies
- Arthritis
- Peripheral neuropathy

**Expatriate Syndrome**

- In loiasis, these manifestations include primarily:
  - Calabar swellings
  - Hives
  - Rashes
  - And occasional asthma

**Pathogenesis**

- Eosinophilia of 50-70% is present especially when there are **Calabar swellings**
- IgE is elevated
- Hypersensitivity reactions to worms and microfilariae have been noted
- Lymphadenitis of a type considered to be characteristic of loiasis, marked by the distention of the subcapsular and medullary sinuses by histiocytes and eosinophils and by atrophy of lymphoid follicles, may also represent a local reaction to dead microfilariae
Tissue swellings are **hot** and **erythematous**
- Occurring in the **extremities** and **periorbital tissues**
- Rarely, adult parasite in the **CSF** can cause **meningoencephalitis**
- Amicrofilareic persons may have **high filarial antibody titers**

**Treatment**
- Surgical removal of conspicuously migrating worms
- DEC treatment is effective but can be risky
  - DEC penetrates the **blood-brain barrier** and in persons with heavy infections so much so that there are microfilariae in the brain parenchyma, sudden death of these worms can cause **fatal encephalitis**
  - DEC administration is also associated with **retinal hemorrhage** and possibly the exacerbation of the **renal lesions**
  - Use of DEC is **contraindicated** in microfilaremic patients with counts of 500 or more per 20 microliters of blood
  - Although, DEC is a good **prophylactic agent** against loiasis
- **Ivermectin** is an effective microfilaric in loiasis
  - Side effect: Pruritus

-**end**-

**References**

1. Markell and Voge’s Medical Parasitology (9th edition)
2. Lecture notes by RAsturiano from the lecturer

Downloadable for free at: [www.theelusivedoktora.wordpress.com](http://www.theelusivedoktora.wordpress.com)
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-THANKS-

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