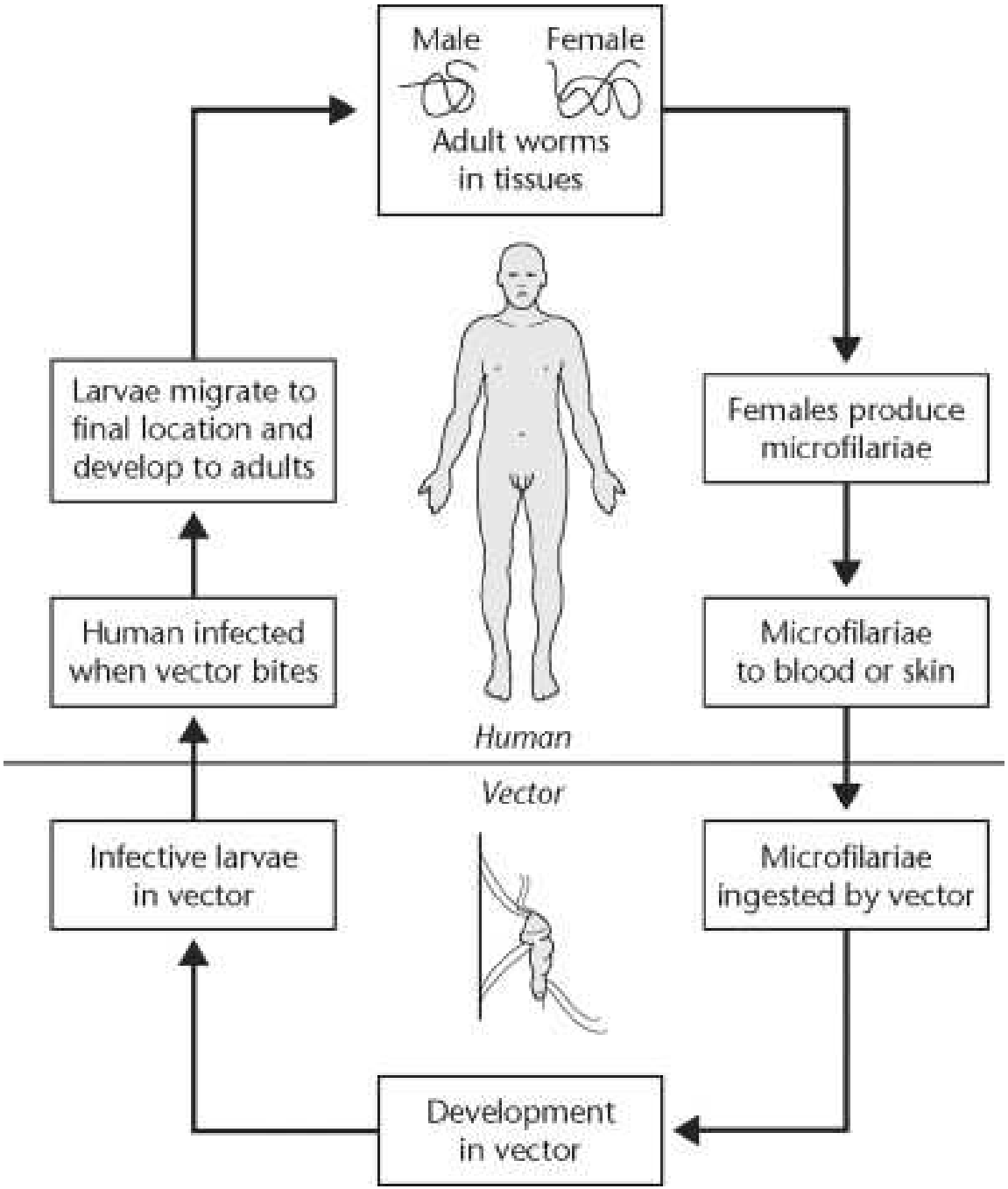
Filarial worms

Blood & tissues Nematodes

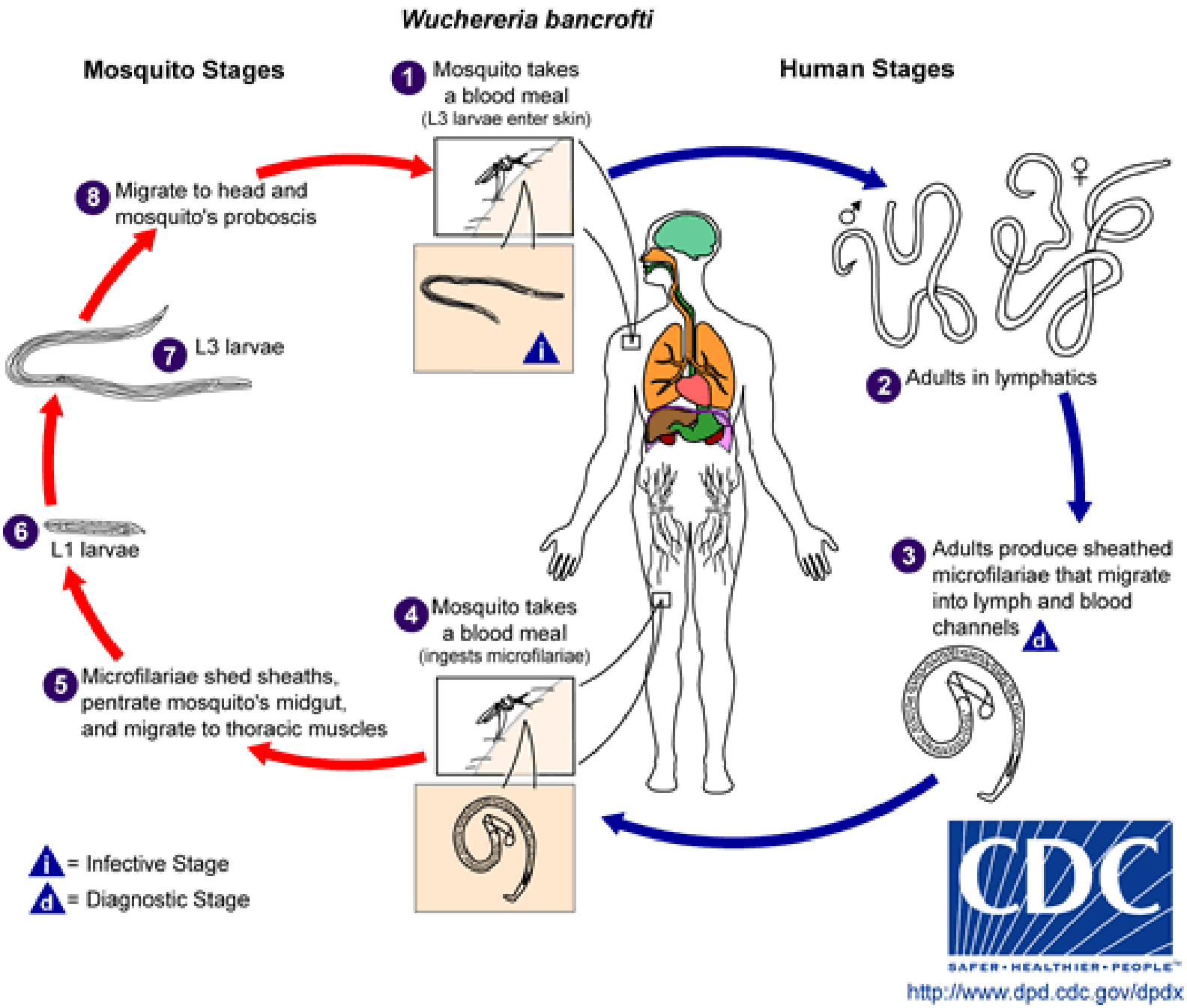
Blood & tissues filarial worms

- ***Wuchereria bancrofti***
- ***Brugia malayi & timori***
- ***Loa loa***
- ***Onchocerca volvulus***
- ***Mansonella spp***
- ***Dirofilaria immitis***



General life cycle of filariae

From Manson's Tropical Diseases, 22nd edition



Wuchereria bancrofti

Life cycle

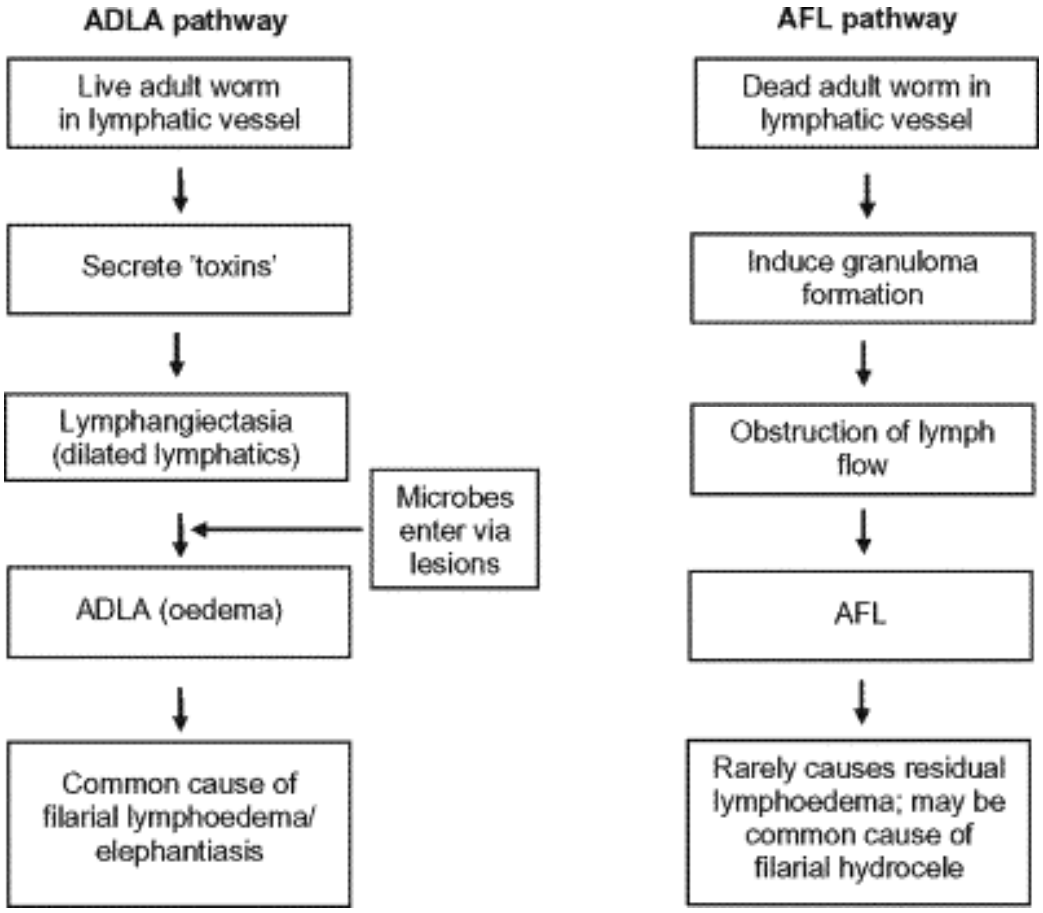
CDC
SAFER · HEALTHIER · PEOPLE™

http://www.dpd.cdc.gov/dpdx

Lymphatic filariasis Clinical manifestations

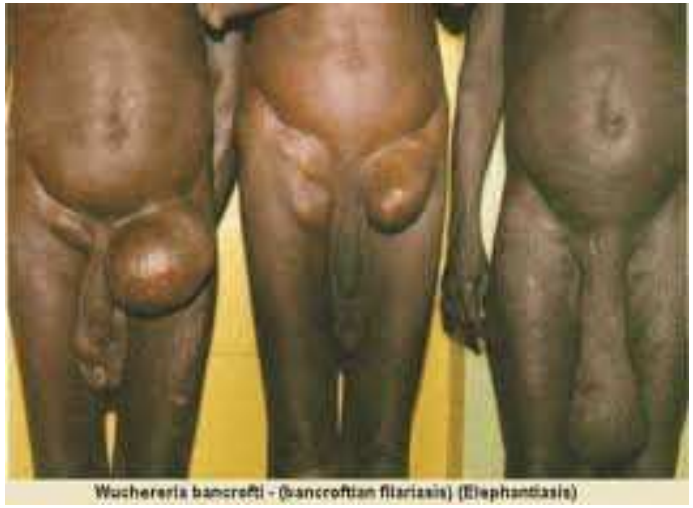
1. Acute adenolymphangitis (ADLA)
2. Hydrocoele
3. Lymphoedema
4. Elephantiasis
5. Chyluria
6. Tropical pulmonary eosinophilia (TPE)

Figure 84.10 Sequence of development of the two types of acute filarial syndromes, acute dermatolymphangioadenitis (ADLA) and acute filarial lymphangitis (AFL), and their possible relationship to chronic filarial disease.

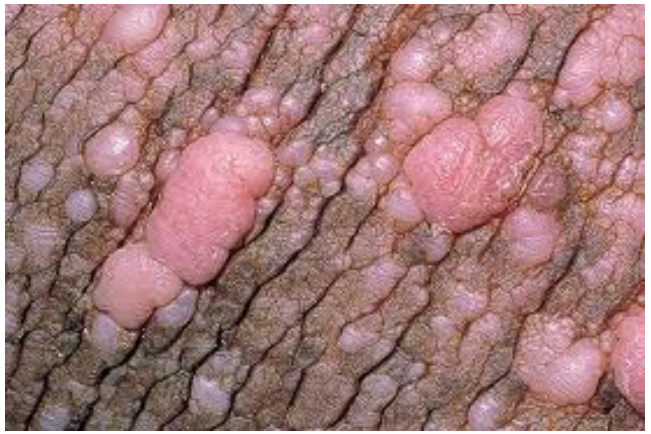


From Manson's tropical Diseases, 22nd edition

Bancroftian filariasis Pathology



Wuchereria bancrofti - (bancroftian filariasis) (Elephantiasis)



Lymphatic filariasis Parasitological Diagnosis

- **Usually diagnosis of microfilariae from blood but often negative (amicrofilaraemia does not exclude the disease!)**
- **No relationship between microfilarial density and severity of the disease**
- **Obtain a specimen at peak (9pm-3am for W.b)**
- **Counting chamber technique: 100 ml blood + 0.9 ml of 3% acetic acid ⟶ microscope. Species identification is difficult!**

Lymphatic filariasis Parasitological Diagnosis

- **Staining (Giemsa, haematoxylin) . Observe differences in size, shape, nuclei location, etc.**
- **Membrane filtration technique on venous blood (Nucleopore) and staining of filters (sensitive but costly)**
- **Knott concentration technique with saponin (highly sensitive) may be used**

The microfilaria of *Wuchereria bancrofti* are sheathed and measure 240-300 µm in stained blood smears and 275-320 µm in 2% formalin.

They have a gently curved body, and a tail that becomes thinner to a point.

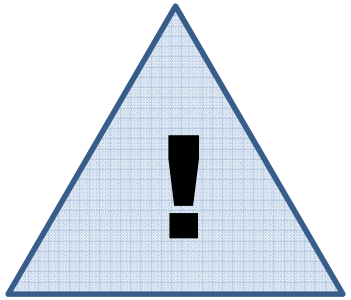
The nuclear column (the cells that constitute the body of the microfilaria) is loosely packed; the cells can be visualized individually and do not extend to the tip of the tail.

Microfilariae circulate in the blood.

Lymphatic filariasis Parasitological Diagnosis

DEC (diethylcarbamazine) provocative test:

- **Provoque by DEC (2mg/kg) the microfilariae to enter the peripheral blood in daytime**



In Onchocerciasis endemic areas, there is a risk of severe Mazzotti reaction

- **Ultrasonography : Adult worms can be detected in lymphatic vessels of scrotal area of infected males ⟶ Filaria dance sign (worms wriggling)**

Lymphatic filariasis Immunological Diagnosis

- Several techniques to detect filarial specific Ab but most people in endemic areas are + plus cross reactions!
- Detection of specific IgG4 Ab (markers of active infection)
- Highly specific & sensitive tests for detection of specific circulating filarial Ag (CFAs) exist for W.b. ⟶ TropBio test for serum/plasma
  ⟶ NOW Filariasis test (finger-prick blood (also for adult worms)
- PCR assays exist, based on DNA

Lymphatic filariasis Pathology & Immunology

- Most of the pathology is associated with adults & their location in lymphatics
- Wide range of manifestations form asymptomatic microfilariae carriers to fever to chronic lymphatic pathology
- Majority of people in endemic areas show an immunological response to the worm Ag
- Ab & T cell response: T helper cell (Th)-type 2 response in microfilaraemic people
- Th1-type response in people with chronic disease
- Protective immunity not proven

Lymphatic filariasis Pathology & Immunology

- **Effect of HIV on filariasis is unknown but some studies in endemic area (N-E Tanzania) have shown positive relation**
- **In TPE, strong immune response directed to microfilariae with sigh eosinophilia and high serum levels of filaria–specific IgG & IgE. Foci of inflammation in the lungs around the degenerating microfilariae**
- **Ab-mediated mechanisms of microfilariae destruction occur in the lungs**

Lymphatic filariasis Epidemiology

VECTORS:

Vectors	Geographical distribution
Culex quinquefasciatus **(night biter, endophilic)**	**For *W.b.*** **Urban/semi-urban** **S-E Asia, East Africa, America**
***Anopheles* spp (*A. gambiae, A. funestus*)**	**For *W.b.*** **Rural** **Asia, Africa**
***Mansonia* spp**	**Asia** ***Brugia malayi* endemic areas**

Filarial worms

Blood & tissues Nematodes

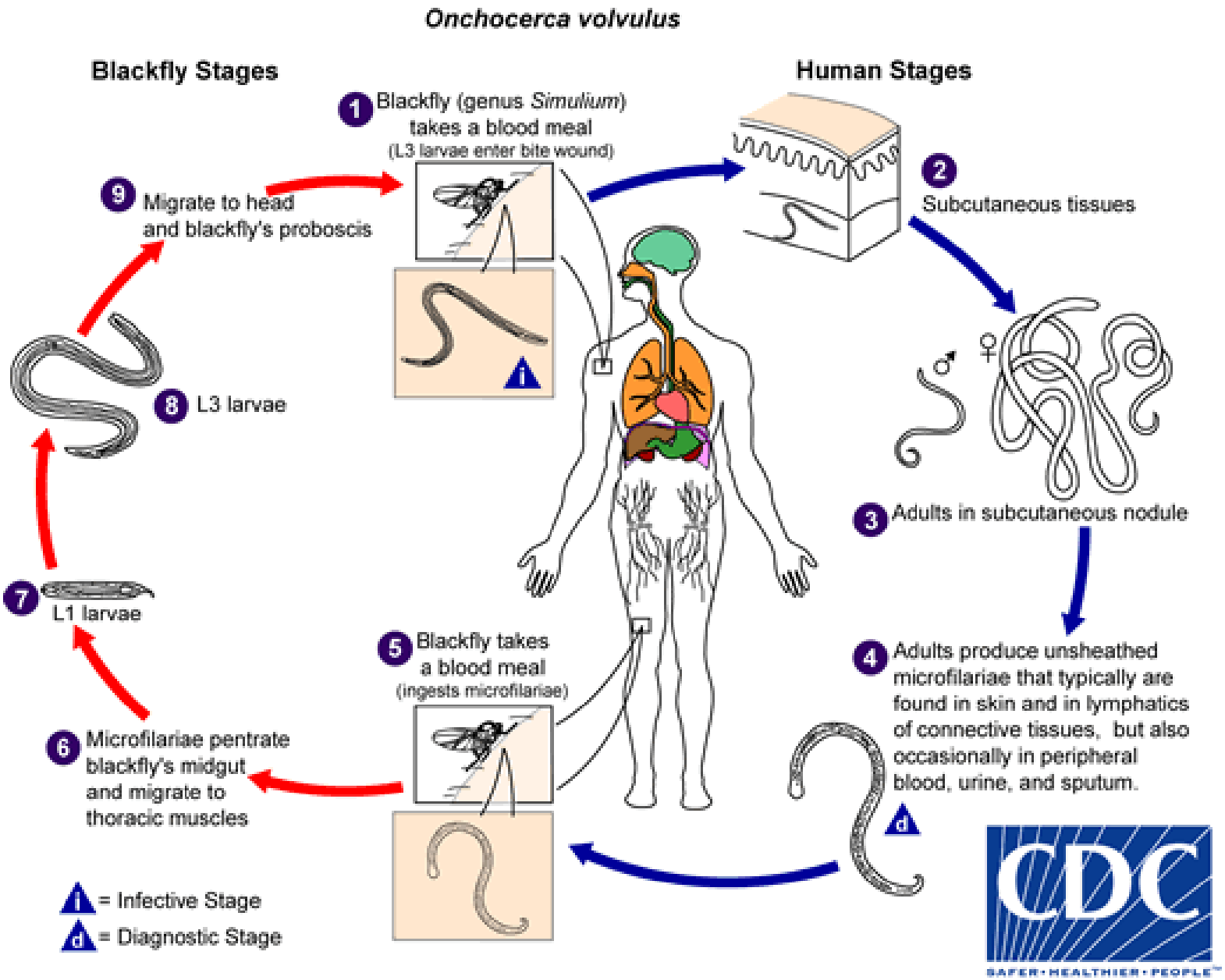
Blood & tissues filarial worms

- *Wuchereria bancrofti*
- *Brugia malayi & timori*
- ***Onchocerca volvulus***
- ***Loa loa***
- ***Mansonella spp***
- ***Dirofilaria immitis***

Filarial worms Onchocerciasis

- **Also called river blindness**
- **Agent: *Onchocerca volvulus***
- **Vector: blackflies (*Simulium* spp)**
- **Around 18 M people infected worldwide, of which 270'000 are blind and 500'000 visually disabled**
- **More than 99% cases are in Africa (tropical zone West to East)**
- **Few cases in central America**

Onchocerciasis Geographical distribution



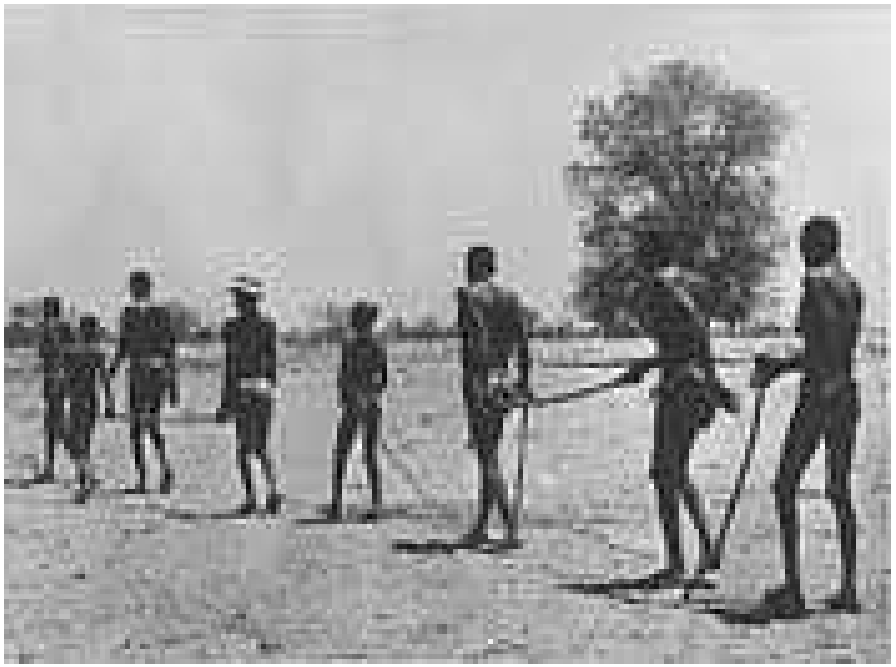
Onchocerca volvulus

Life cycle

Filarial worms Onchocerciasis

- **Male: 2-5 cm ⌀ 0.2 mm**
- **Female: 35-70 cm ⌀ 0.4 mm**
- **Longevity of female: 9-11 years**
- **Nb of larvae released each day per female: 500 – 1500**
- ***Simulium* breeds only in well oxygenated water (fast flowing rivers & streams, rapids)**
- **Transmission in utero of O.v. is possible but not viable**

River blindness



Onchocerciasis Clinical features

- Skin lesions, eye lesions & nodules formation
- Usually clinical signs develop after long exposure to infection & severity depends on the intensity of infection
- Many people are symptomless
- May be associated with growth arrest & delayed sexual development (Nakalanga syndrome in Uganda & Burundi)
- May be associated with weight loss, musculo-skeletal pain

Onchocerciasis Clinical features

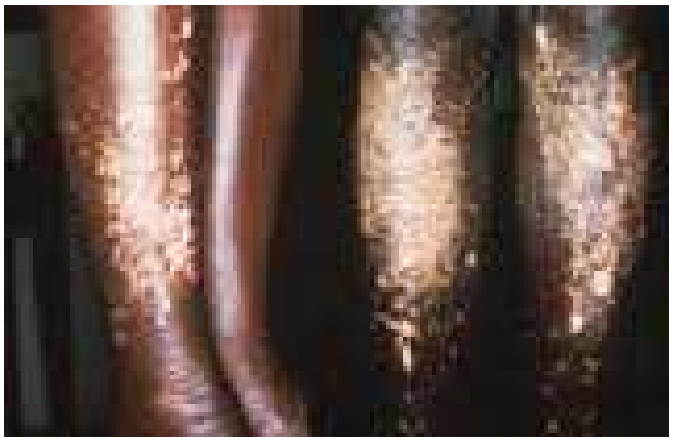
SKIN LESIONS:

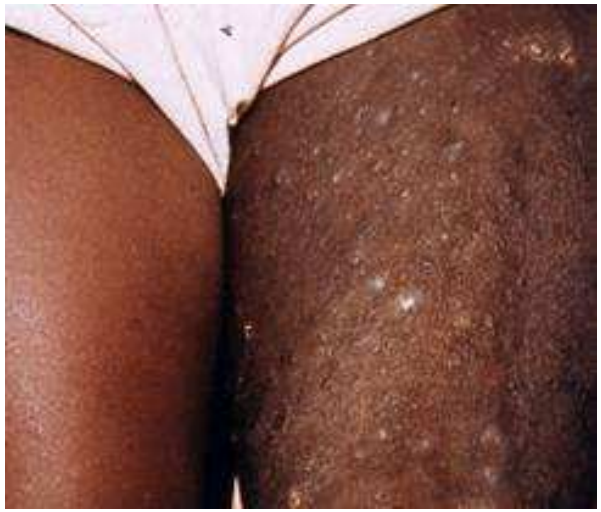
- Dermal changes when microfilariae undergo destruction in the skin:
  - Acute papular onchodermatitis
  - Chronic papular onchodermatitis
  - Lichenified onchodermatitis
  - Skin atrophy
  - Skin depigmentation
- A combination of those categories can exist in the same person
- In Africa, the skin lesions are mostly over the legs

Onchocerciasis Clinical features

- Early signs : itching & rash (micro abscesses)
- In later stages, heavy lichenification & thickening of skin (lizard skin)
- Chronic stages are related to repeated occurrence of local pathology around dying parasites
  - Skin atrophy with loss of elasticity (aged appearance: presbyderma)
  - Loss of elasticity of groin skin ⟹ hernia & hanging groin (inguinal/femoral glands in pendulous fold)
  - Leopard skin due to loss of pigment, degeneration of dermal collagen & thinning of epidermis, especially in pre-tibial regions

Onchocerciasis





Skin lesions

Onchocerciasis Clinical features

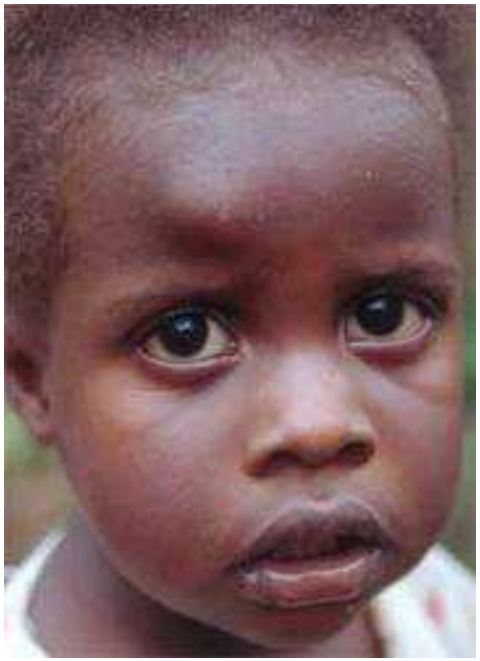
SOWDA (from Arabic: black): Localized oncho dermatitis due to strong immune response of host (usually one limb). Intense itching, the skin swells & darkens + scaly papules

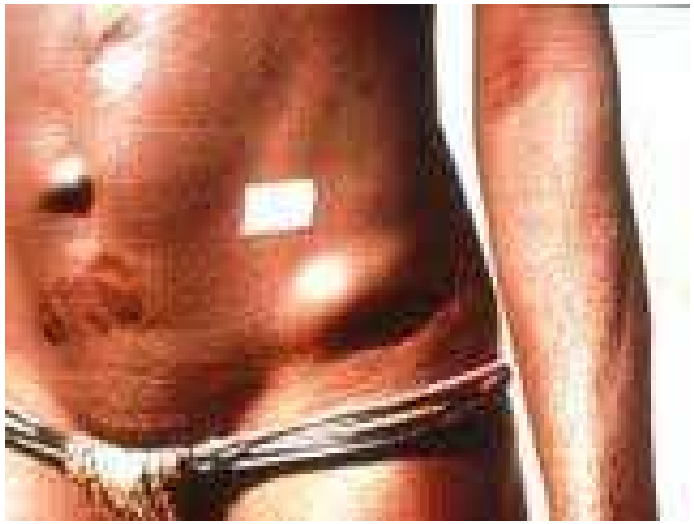
NODULES (Onchocercomata)

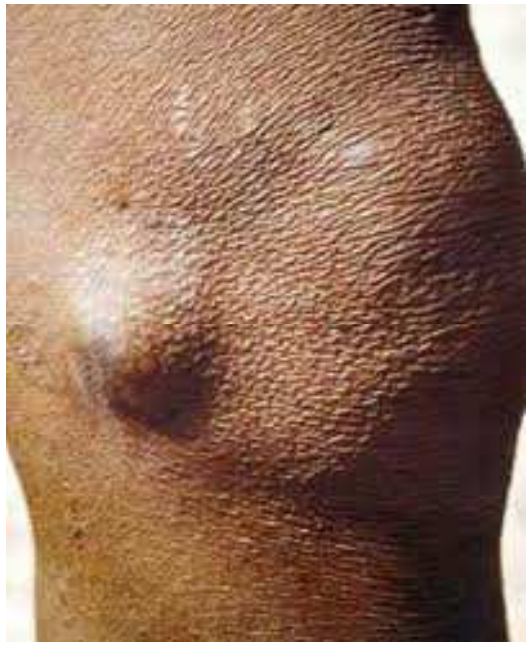
- **Granulomas due to tissue reaction around adult worms. Mostly in sub-cutaneous tissues. Painless round, oval firm, smooth, size varies**
- **In Africa, 80% of nodules are on the body prominences of pelvic girdle but also chest, head, abdomen**
- **Location of nodules may depend on biting habits of vector**
- **Usually not a medical problem**

Onchocerciasis

Nodules







Onchocerciasis Clinical features

EYE LESIONS:

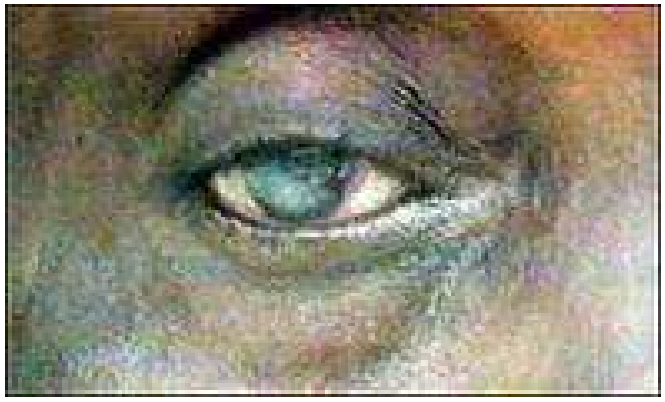
- **As an inflammatory reaction to microfilariae. Exacerbation associated with death of larvae after drug therapy**

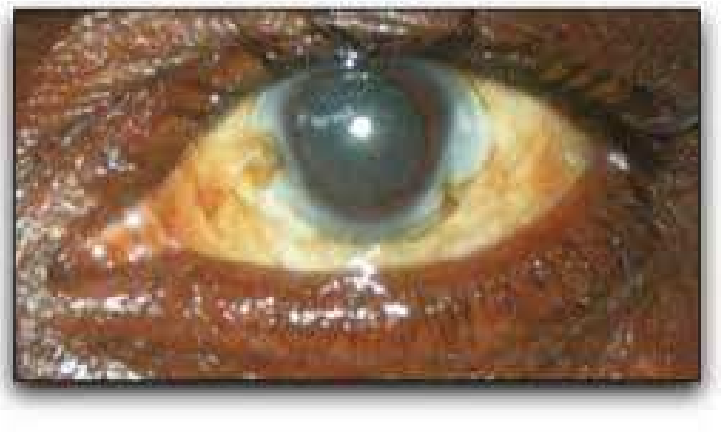
  NB. There is a geographical variation in the clinical picture. In East & Central Africa, the picture is usually less severe and eye lesions are rare. Skin lesions also differ widely in different endemic areas.

Onchocerciasis Clinical features

Anterior segment lesions	Posterior segment lesions
Punctate keratitis (snowflake opacity) in cornea : • Common in younger age groups • Lesions are reversible	Optic nerve atrophy & choroidoretinitis of posterior segment may lead to blindness
Sclerosing keratitis (excessive scarring of cornea) which causes blindness	Choroidoretinitis ranges from inflammatory processes to atrophic lesions
Iridocyclitis (formation of synechiae) due to microfilariae dying in the ciliary body	Optic nerve atrophy is the main cause of decreased visual acuity

Onchocerciasis





Eye lesions

Onchocerciasis Pathology & Immunology

- **Live microfilariae do not necessarily induce tissue reaction**
- **Pathology is caused mainly by dead/dying larvae**
- ***O.v.* contains endosymbiotic bacteria (genus Wolbachia) which products might cause pathology, especially in the eyes.**
- **Initial lesions: inflammatory reactions around degenerating microfilariae (eosinophils, neutrophils & macrophages)**
- **Later: dermal fibroblasts increase in numbers leading to fibrosis. Normal collagen & elastic fibers are replaced by hyalinized scar tissue +/- loss of pigment in the skin**

Onchocerciasis Pathology & Immunology

- Advanced cases: presbyderma and also damage due to scratching by toxins inoculated when the black fly take blood or from secondary infection.
- In Sowda: immunological hyperactivity ⟹ presence of extensive inflammatory cell infiltrate of upper dermis
- In eye: no visible tissue response to live larvae. Dead microfilariae cause foci of inflammation (snowflake keratitis) with opacities around each larva
- Adult worms may be free in subcutaneous tissues but most are in nodules, often in separate chambers with several adults. Thick fibrous walls + infiltration +/- macrophages. Calcification may occur (old nodules/ dead worms)

Onchocerciasis Pathology & Immunology

- **Specific humoral immune response marked in people in endemic area**
- **Role of immune response: contains/limits inflammation around dying/dead microfilariae**
- **Ab mediated cell killing of microfilariae observed in endemic area so immune elimination can occur in some infected people but protective immunity not proved**
- **In people from non-endemic areas, who become infected while travelling, infection is usually mild with occasional dermatitis, microfilaraemia low or none, nodules rare**
- **HIV+ patients infected with *O.v.* show significantly impaired Ab response to O.v. Ag & tend to loose their reactivity to these Ag over time**

Onchocerciasis Diagnosis

CLINICAL:

- **Skin lesions, eye lesions, nodules**
- **Pruritic onchodermatitis (filarial itch) must be differentiated from infection with *Mansonella streptocerca*, scabies, reactions to insect bites, prickly heat. It must be distinguished, in later stages, from yaws, mycoses, leprosy & chronic eczema**
- **Nodules: painless, firm, mobile. Distinguish from enlarged lymph glands, lipomas, dermal cysts, ganglia, neurofibromas**

Onchocerciasis Diagnosis

US:

- **Detection of deep nodules in tissues & assess drug effects on adult worms**

THE MAZZOTTI TEST:

- **Administration of small dose of DEC by mouth (50mg for adult) & observation of pruritus & skin rash (1-24h later). It is not a routine test, as complications may occur.**

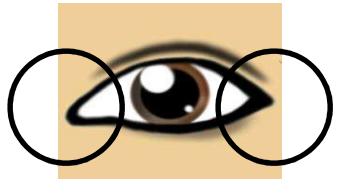
PARASITOLOGICAL:

- **Demonstration of microfilariae from skin snips (most people with clinical signs have + skin snips but not always!)**

Onchocerciasis Diagnosis

PARASITOLOGICAL: (Ctd)

- In Africa, skin snips of iliac crest or below
- 2-4 snips are taken
- For eye lesions, snips from outer canthus or use of slit lamp to see live microfilariae in the cornea



SNIP:

- Clean skin with spirit then dry
- Shave off some skin with razor blade or punch
- Immerse snip in isotonic saline & count larvae under microscope
- Microfilariae are 270-320 µm long, unsheathed, pointed tail

Onchocerciasis Diagnosis

IMMUNOLOGICAL & PCR:

- Development of specific & sensitive tests is a priority ⟹ ELISA with cocktail of IgG4 Ab
- Tests for detecting circulating Ag have given mixed results
- Dipsticks for detecting Ag in urine have been recently developped
- PCR (high specificity for *O.v.* DNA) can detect worm DNA in skin snips and distinguish between various strains of the parasite

Onchocerciasis Management

- DEC & Suramin are no longer recommended because of severe adverse reactions
- IVERMECTIN (Mectizan) is the drug of choice
  - Single oral dose 150µg/kg
  - Re-treatment might be necessary after 6-12 months
  - Not indicate for pregnant women, breastfeeding infant below 1 w, children ≤5y & people with serious illnesses
  - Disappearance of microfilariae from eye is more gradual but regression of lesions occurs, except chorioretinitis
- Benzimidazoles are under investigation
- Endosymbiotic bacteria (*Wolbachia* spp) are new targets with antibiotics
- Nodulectomy: only limited use, as worms are also outside nodules, restricted to head noduleles (eyes!)

Onchocerciasis Epidemiology

- **Many species of *Simulium* can act as vectors**
- **Geographical variations in pathogenicity but same morphology**
- **Different patterns of infection & disease associated with difference in abundance, vector competence, feeding patterns of *Simulium*, human hosts response, occupation, migration, socioeconomic factors, concurrent infections & racial groups**
- **Usually low in young children, increases with age**
- **Burden of disease is proportional to intensity of transmission**
- **Hyperendemicity with almost all people infected and having clinical disease. Same in ♀ and ♂**

Onchocerciasis Epidemiology

LEVELS OF ENDEMICITY:

Hypoendemic	Mesoendemic	Hyperendemic
Nodules Prevalence ≤ 20%	Nodules Prevalence ≤ 20-39%	Nodules Prevalence ≥ 40%
Microfilariae Prevalence ≤ 40%	Microfilariae Prevalence 40-59%	Microfilariae Prevalence ≥ 60%
Blindness rate ≤ 1%		Blindness rate ≥ 10%
Few social effects		Fertile lands are abandoned

AFRICAN ONCHOCERCIASIS:

- Vector : *Simulium damnosum* complex
- In East-Central Africa: Also *S. neavei* group
- In Tanzania: *S. woodi* is the most important

SIMULIUM DAMNOSUM complex :

- Flies breed in large rivers, small streams, often in rapids with rocks emerging
- Adequate velocity of water, food supply & attachment sites (rocks, sticks, vegetation)
- Females bite in proximity of breeding sites and feed also on bovines, horses, etc.

Onchocerciasis Control

- African Programme for Onchocerciasis Control (APOC)
- For control, endemicity should be mapped (usually nodules count in a sample of 50 males in a community)

VECTOR CONTROL:

- Aerial larviciding of breeding sites but emergence of resistance to larvicides & re-invasion of treated areas fron non-treated. High cost!

NODULECTOMY CAMPAIGNS:

- Especially in countries with head nodules

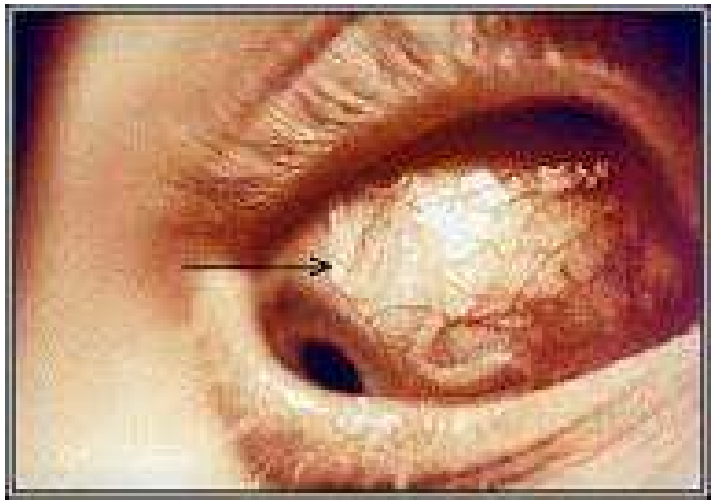
Onchocerciasis Control

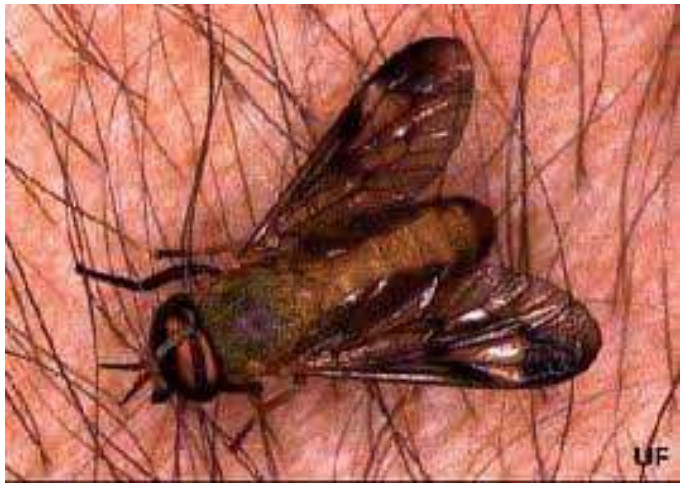
CHEMOTHERAPEUTIC CONTROL:

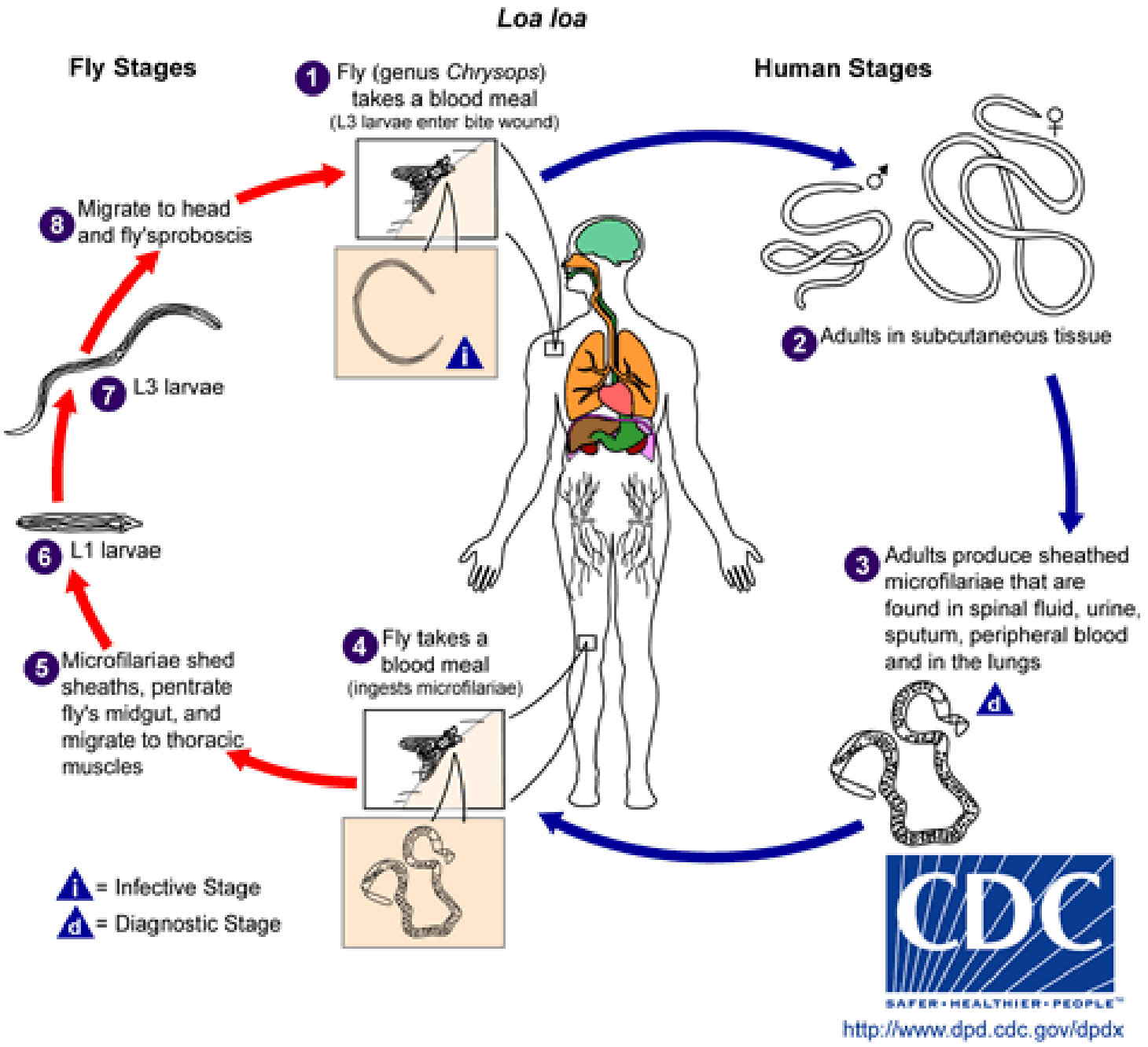
- Use of Ivermectin for annual mass treatment to reduce microfilaremia thus transmission
- Ivermectin if microfilaricidal only so the treatment has to continue for the whole reproductive lifespan of adult female worms
- Decrease of itching, eye and skin lesions
- Severe reaction/death have been reported in high intensity of loiasis after treatment, so caution!
- No resistance to date

Filarial worms Loiasis

- **Agent : *Loa loa***
- **Vector: Tabanid flies of genus *Chrysops***
- **West and Central Africa**
- **Also called eye worm (because adult worms are sometimes seen moving across the eye)**







Loa loa

Life cycle

Loiasis Cycle

- Adult female: 50-70 x 0.5 mm
- Adult male: 30-35 x 0.4 mm
- Sheathed microfilariae in blood: 230-300 x6-8µm
- Diurnal periodicity of microfilariae (peak at noon)
- Development in fat body of tabanid fly (8-12d)

  ⟹ infective larvae which go to proboscis and penetrate human host when fly is feeding
- Pre-patent period until appearance of micro filariae is 5-6 months
- Adults live for 17 years or more

Loiasis Clinical features

- **Most common: recurrent angio-oedema (Calabar swellings) & pruritus**
- **Adult worms sometimes seen as they pass under the eye conjunctiva**
- **Hypereosinophilia**
- **Calabar swellings mostly on hands, wrists, forearms. They are painless, not pitting, last for few hours to days. Recurrent for years.**
- **Usually one swelling at a time. Probably due to host immune reaction to *Loa loa* Ag at the site**
- **Fatigue, arthralgia**
- **Death of adult worms may cause abscess**

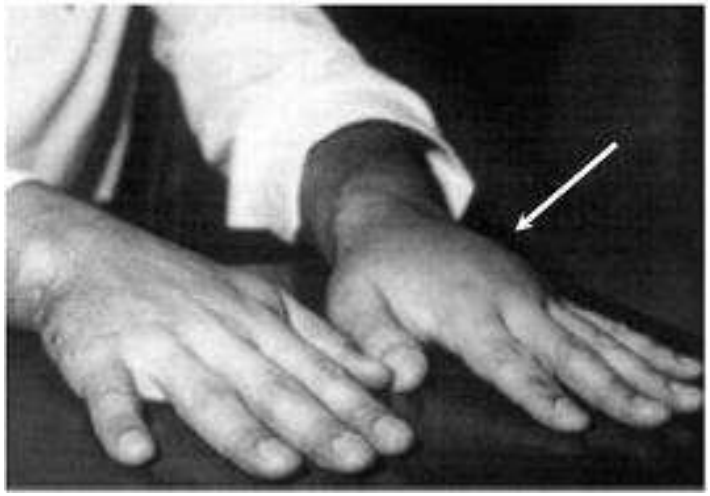
Loiasis — Clinical features

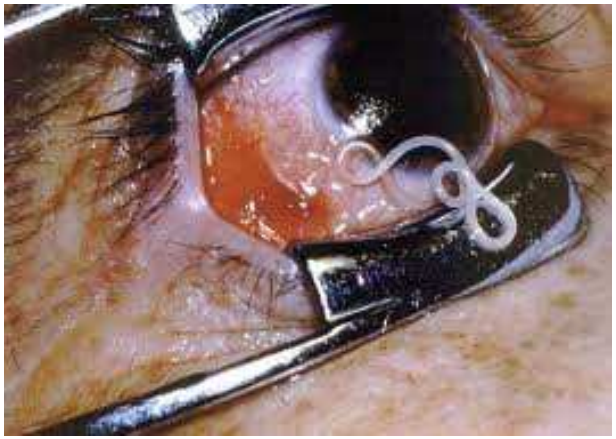
- **Complications when *Loa loa* invades the central nervous system or vital organs**
- **Correlation observed between loiasis & occurrence of endomyocardial fibrosis**
- **Nephropathy & encephalopathy may occur**
- **More trouble in expatriates than indigenous people**

Loiasis

Clinical features

Calabar swellings - Angio-oedema





Loiasis Diagnosis

CLINICAL:

- **Calabar swellings, worm crossing eyes**
- **Distinguish from *M.perstans*, cutaneous larva migrans (stronger reaction than loiasis)**
- **Distinguish from *Toxocara* in eye (*Loa* is larger)**

PARASITOLOGICAL:

- **Removal of adults from skin/eye**
- **Microfilariae in blood (take sample around noon) but also occult loiasis (no microfilariae)**
- **Same technique as for *W.b.* Sheath of *Loa* stains with haematoxylin but not with Giemsa**

IMMUNOLOGICAL:

- **Low sensitivity of tests & cross-reactions**
- **Detection of specicif IgG4 used when amicrofilaraemia**
- **PCR has been developped**

Loiasis Immunology

- **Most of the infected people have high Ab titres to filarial Ag**
- **People amicrofilaremic have Ab recognizing a surface Ag on *Loa loa* but people with microfilariae do not have those Ab**
- **Microfilaremic people have less cellular response**
- **Occult loiasis may result from the development of immune response specifically eliminating the microfilarial stage**

Loiasis Management

- **DEC (5-10 mg/kg) for 2-4 w. May require repeated treatment**
- **In people with high microfilaremia, there may be severe side effects with risk of CNS complications so start with small doses of DEC.**
- **IVERMECTIN (200 µg/kg) as microfilaricide. Watch side effects when onchocerciasis!**
- **MEBENDAZOLE (low doses) also uses as microfilaricide**

Loiasis Epidemiology

- Only in West Africa (rain forests/swamps) due to vector distribution
- Chrysops is day-biting, attracted by movement, dark colours, wood smoke.
- Eggs in swamps/river edges below forest trees
- Transmission in wet season
- Not a zoonosis. Other species in monkeys

- Microfilaremia is low in children, then increases with age. Higher in males than females

Loiasis Control

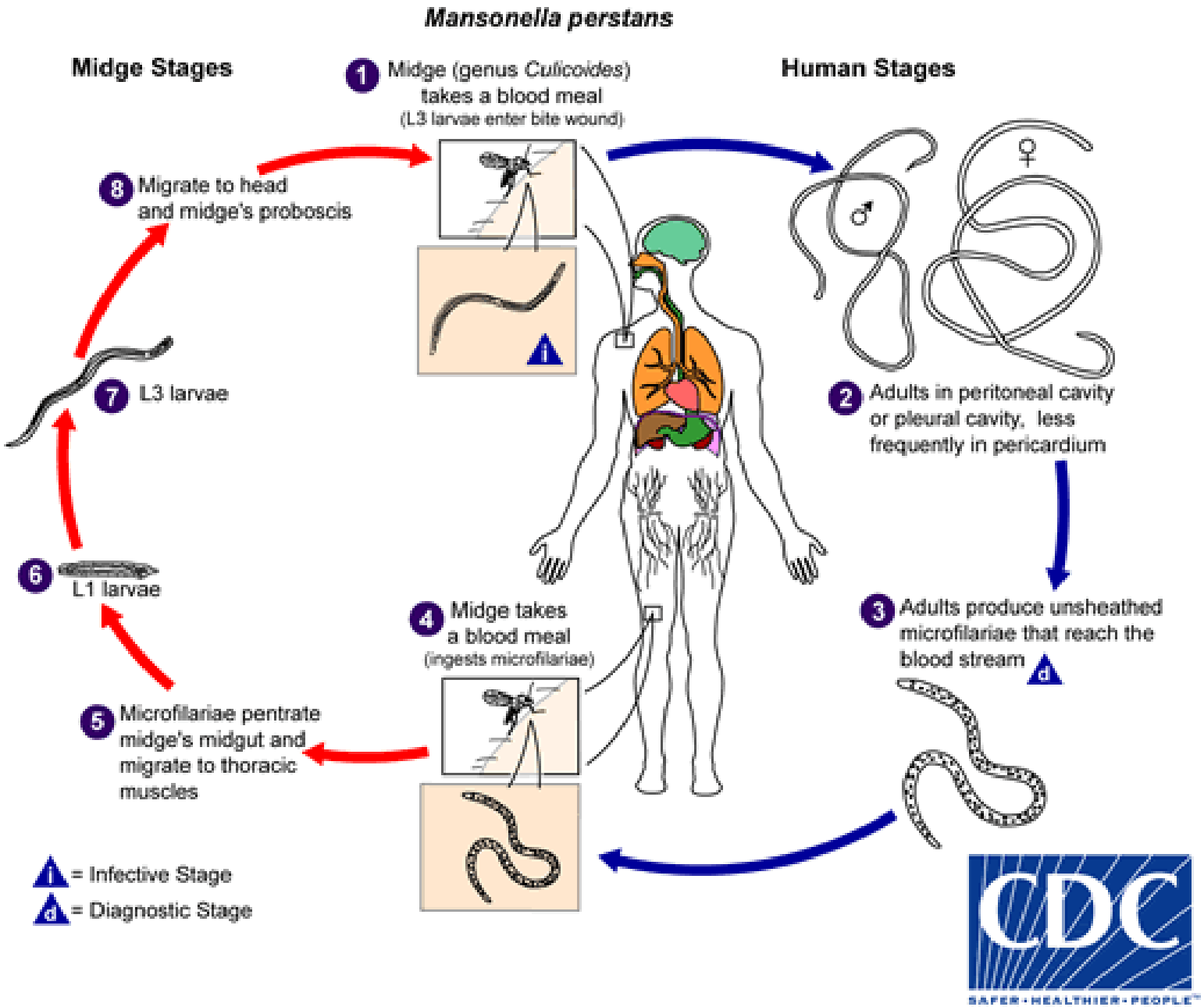
- Environmental modifications (set houses far from swamps)
- Personal protection (repellent)
- Vector control
- Prophylaxis (300mg DEC) once per week may be used

Filarial worms — *Mansonella* spp

- ***Mansonella perstans:*** **Africa, Central/S America**
- ***Mansonella streptocerca:*** **West Africa**
- ***Mansonella ozzardi:*** **Central/S America**
- **VECTOR: midges of the genus *Culicoides***

Filariae — *Mansonella perstans*

- **Adult worm in serous cavities (peritoneal cavity)**
- **May be found sub-cutaneously**
- **Adult female: 70-80 x 0.1 mm**
- **Adult male: 35-45 x 0.06 mm**
- **Microfilaria: 200 x 4.5 µm, unsheathed, non periodic in blood**
- **Usually asymptomatic**
- **Pre-patent period from infection to microfilarial stage unknown**



http://www.dpd.cdc.gov/dpdx

Mansonella perstans Pathology

- **Largely non pathogenic**
- **More frequent in expatriates**
- **In some people: transient swellings, pruritus, fever, pain, ache in bursae +/- joint synovia**
- **Severe abdominal pain may occur**
- **Nodules in conjonctiva, swelling of eyelids, proptosis**
- **Hypereosinophila has been reported**

Mansonella perstans Diagnosis & Management

- **Microfilariae in blood (same techniques as for lymphatic filariae but at any time of the day)**
- **Ivermectin has no effect**
- **DEC (200mg, twice daily for 3w)**
- **Mebendazole (100mg twice daily for 28d) is more effective**
- **The best is a combination of DEC & Mebendazole**
- **Albendazole (400mg twice daily for 10d) can also be used**

Mansonella perstans Epidemiology

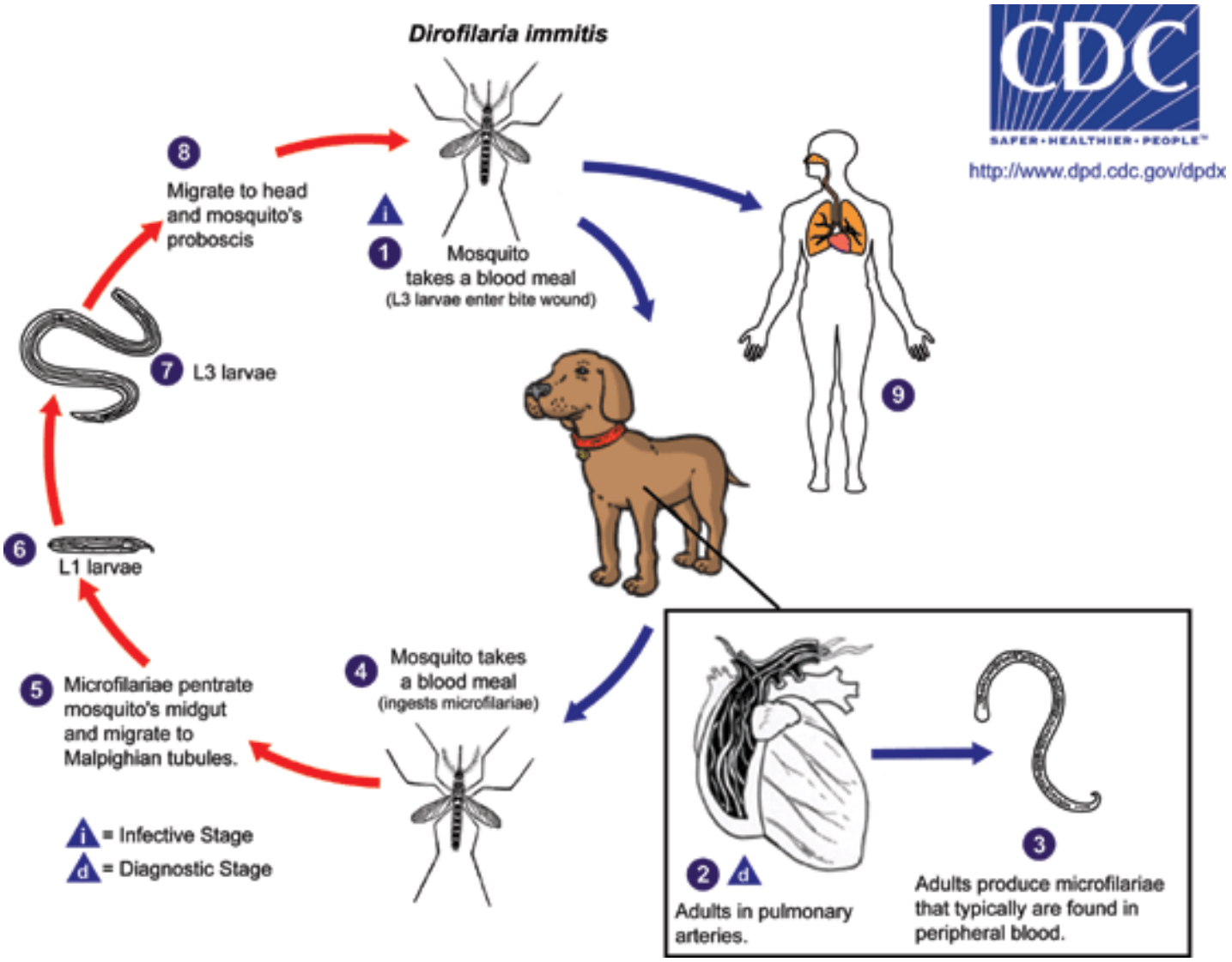
- **Few studies**
- **Microfilariae prevalence is higher in adults & males**
- **Vector in Africa are: *C. grahami* & *C. inornatipennis***
- **Also found in chimpanzees and gorillas**

- ***M. streptocerca :* Central & West Africa**
- ***M. ozzardi:* Central – South America**

Dirofilariasis

- **Zoonotic infection**
- **Dirofilaria spp. Are parasites of carnivores**
- **Microfilariae in blood**
- **Transmission by mosquitoes**
- **In humans, the development is impaired and no microfilariae are produced**
- **Two species may cause pathology in humans: *D. immitis* (heart worm) & *D. repens***

Dirofilaria immitis

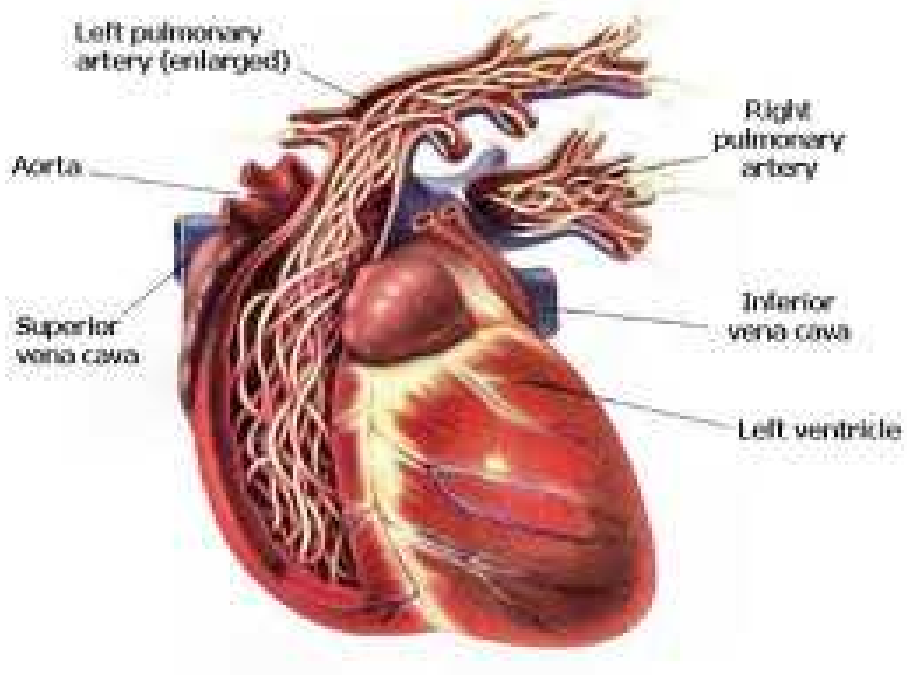


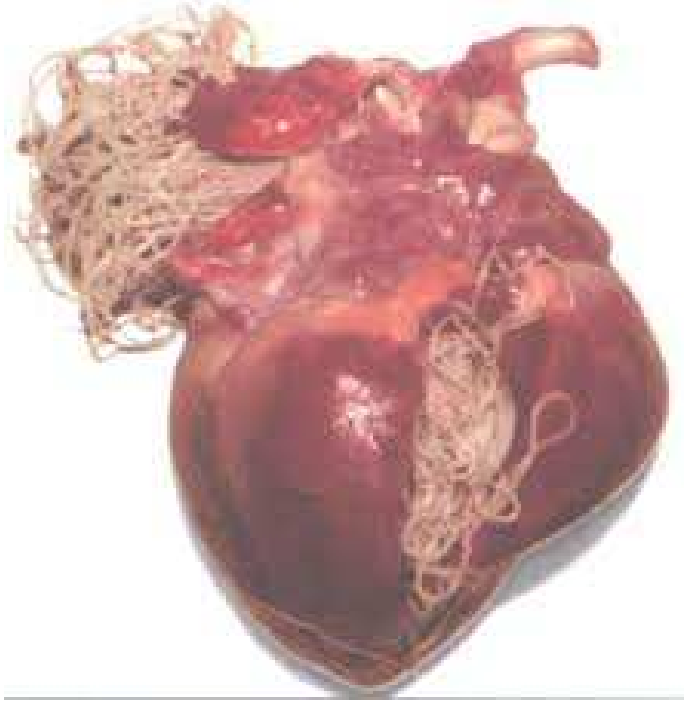
Dirofilariasis — Pathology

PULMONARY DIROFILARIASIS:

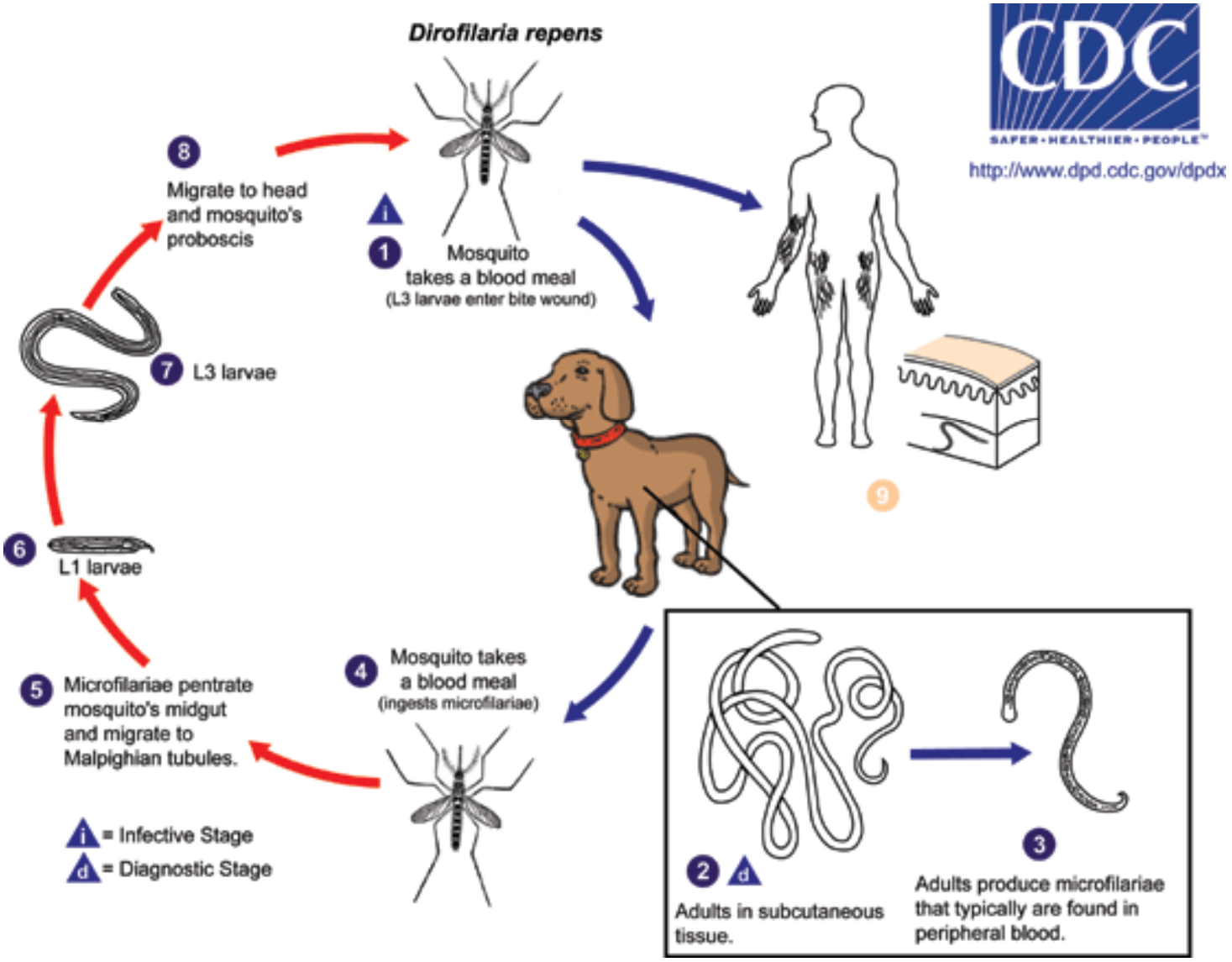
- Caused by *D. immitis*, parasite of dogs
- Worldwide, except cold climates
- In dogs, the adults live in pulmonary arteries & right ventricle of the heart (large coiled masses)
- In humans, the worm develops partially in the pulmonary arterial tree, where it then dies (inflammatory response ?)
- Spherical nodules (1-3 cm) is discovered in lungs on routine Xray or at autopsy
- A single necrotic worm in lumen of the artery
- Most patients are asymptomatic or cough, chest pain, haemoptysis, fever
  - Serological diagnosis not useful, only biopsy
  - Treatment is surgical excision

Dirofilaria immitis in the heart





Dirofilaria repens



SUBCUTANEOUS DIROFILARIASIS:

- Caused by *D. repens*, parasite of dogs/cats
- Old World
- Worms located in subcutaneous tissue
- In humans, occasional infection in form of nodules with degenerating immature worm + granulomatous tissue
- Nodules, esp. in breasts, arms, legs, scrotum, eyelid & conjunctiva
- Immunodiagnosis is not useful, only biopsy
- Treatment by surgical removal of nodules
- In North-America: *D. tenuis* (racoons) & *D. ursi* (bears) have been reported

Dirofilaria repens **Nodule in eyelid**