3- Leishmaniasis and Trypanosomiasis

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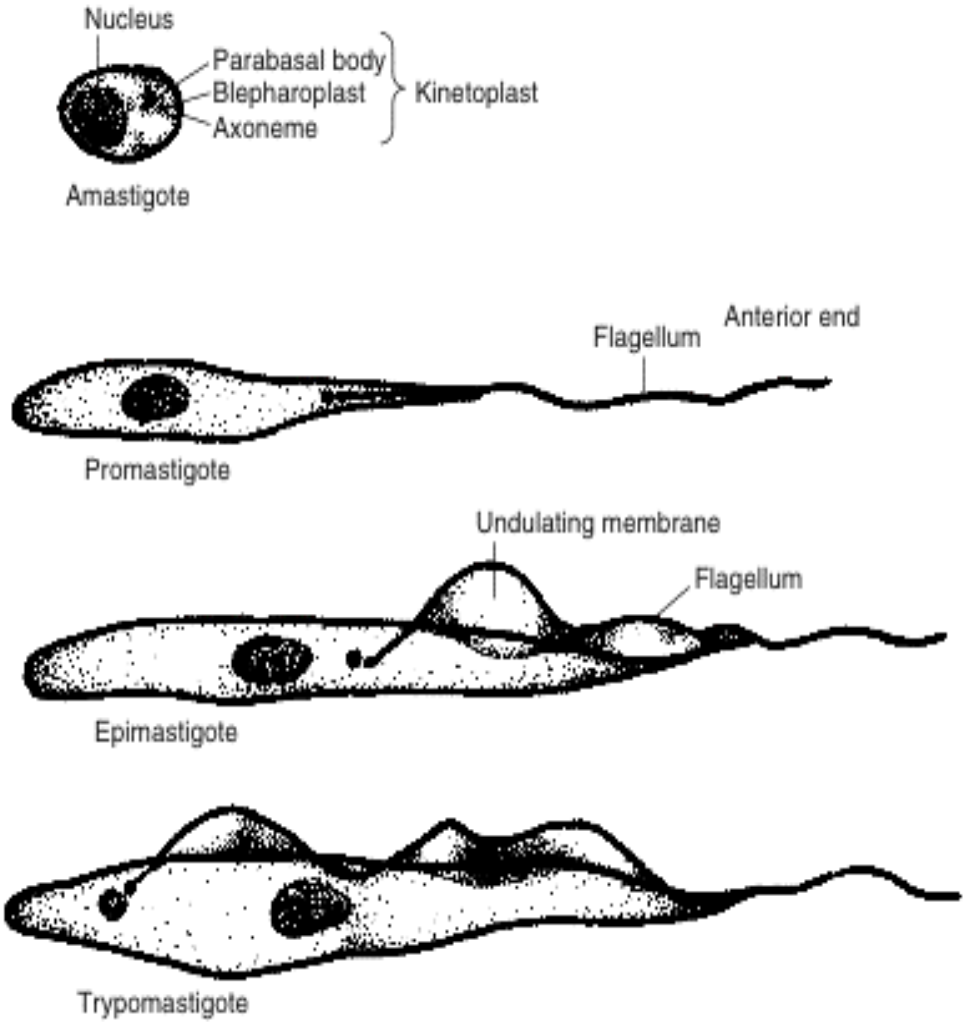
Objectives

- Describe the general characteristics, epidemiology, pathogenesis, clinical presentation and management of leishmania
- Describe the general characteristics, epidemiology, pathogenesis, clinical presentation and management of Trypanosomia

Introduction

- Two of the many genera of hemoflagellates are pathogenic to humans, Leishmania and Trypanosoma.
- They reside and reproduce within the gut of specific insect hosts. The life cycle is completed when a second insect ingests the infected mammalian blood
- During the course of their passage through insect and vertebrate hosts, flagellates undergo developmental change

Stages in the life cycle of the hemoflagellates



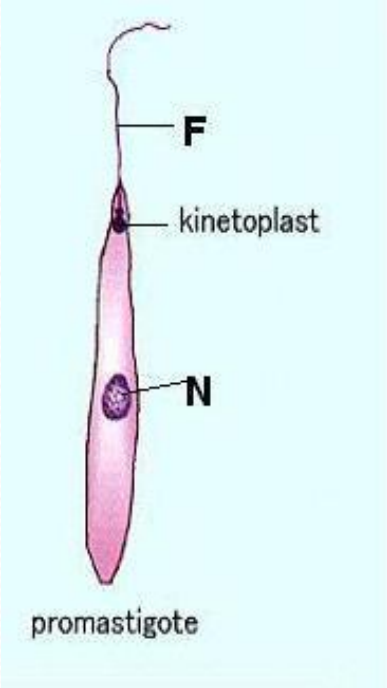
Leishmania
(Kala Azar)

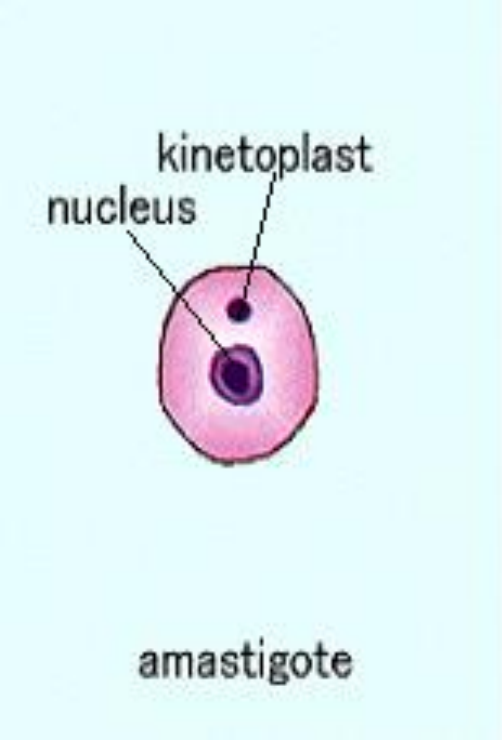
Species

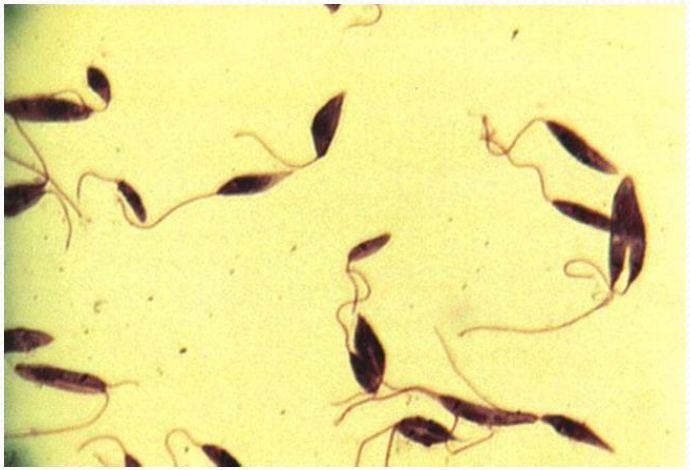
- The many strains can be more simply placed in four major groups based on their serologic, biochemical, cultural, and behavioral characteristics
  - *Leishmania tropica* and *L. mexicana* produce a localized cutaneous lesion or ulcer, known popularly as oriental sore
  - *L. braziliensis* is the cause of American mucocutaneous leishmaniasis
  - *L. donovani* is the etiologic agent of kala azar

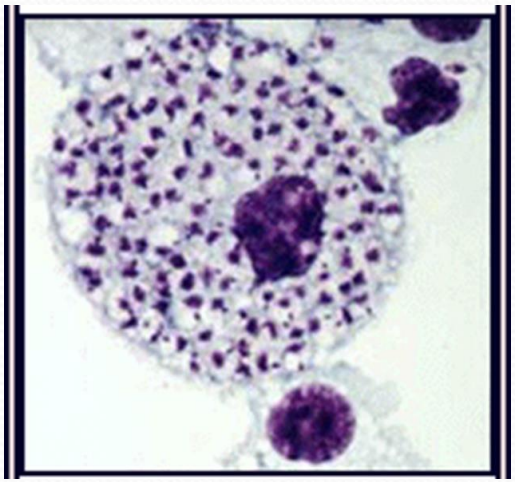
Morphology

- Promasitogte
- Amastigote





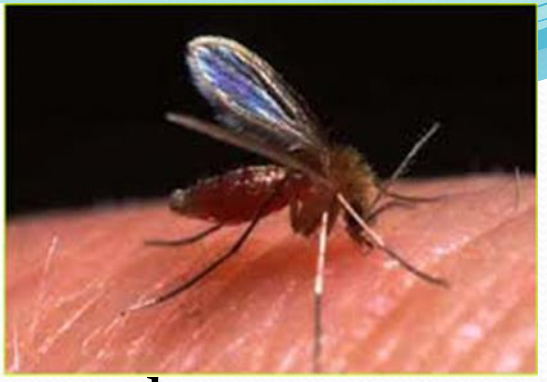




Epidemiology

- Endemic in 88 countries
- It is estimated that over 20 million people worldwide suffer from leishmaniasis and 1 to 2 million additional individuals acquire the infection annually.
- More than 90% of C.L. cases occur in; Iran, Algeria Afghanistan, Brazil, Peru, Saudi Arabia, and Syria
- More than 90% of V.L. Cases occur in 5 countries; Bangladesh, India , Nepal, Sudan, and Brazil
- Annual death due to V.L. is 59,000 cases

Life Cycle



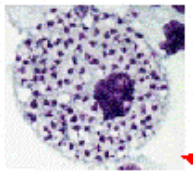
- Amastigotes ingested in the course of a meal assume the flagellated promastigote form, multiply within the gut, and eventually migrate to the buccal cavity of phlebotomine sandfly
- When the fly next feeds on a human or animal host, the buccal promastigotes are injected into the skin of the new host together with salivary peptides capable of inactivating host macrophages
- Amastogotes invade macrophage and divides until the infected cell ruptures
- The sandfly acquires the organisms during the blood meal

THE LIFE CYCLE OF *LEISHMANIA* SPP.
(VARIOUS FORMS OF LEISHMANIASIS)

The vertebrate host is infected with promastigotes when bitten by the vector.

The amastigotes are released in the vector's gut, and the parasite reproduces as promastigotes.

The promastigotes enter circulating macrophages and reproduce as asmastigotes.



The vector (a sand fly) ingests macrophages when it ingests blood.

The macrophage dies, the amastigotes are released, and they infect more circulating or fixed macrophages.

The "type" of leishmaniasis (i.e., cutaneous, visceral, etc.) is determined by the primary location of the macrophages that are infected.

(Parasites and Parasitological Resources)

Pathogenesis

- After the host is bitten by an infected sandfly, the parasites disseminate in the bloodstream and are taken up by the macrophages of the spleen, liver, bone marrow, lymph nodes, skin, and small intestine
- Histiocytic proliferation in these organs produces enlargement with atrophy or replacement of the normal tissue

Disseminated Intravascular Leishmeniasis (Kala azar)

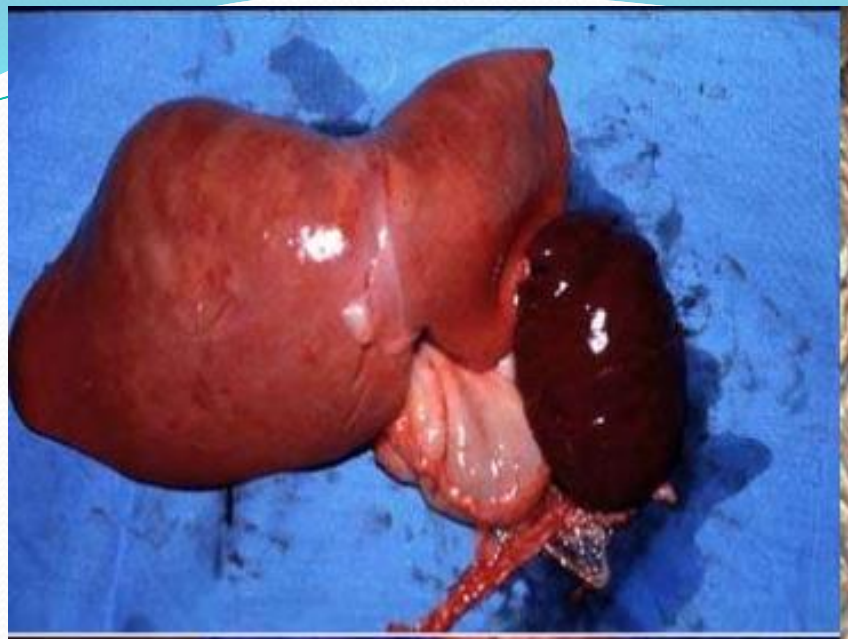
- Kala azar, which is caused by L. donovani, occurs in the tropical and subtropical areas of every continent except Australia
- In Africa, rodents serve as the primary reservoir. Human cases occur sporadically, and the disease is often acute and highly lethal. In Eurasia and Latin America, the domestic dog is the most common reservoir
- Human disease is endemic, primarily involves children, and runs a subacute to chronic course
- In India, the human is the only known reservoir, and transmission is carried out by sandflies. The disease recurs in epidemic form at 20year intervals, when a new nonimmune children and young adults appears in the community
- There appears to be a high incidence of visceral leishmaniasis in patients with HIV infection

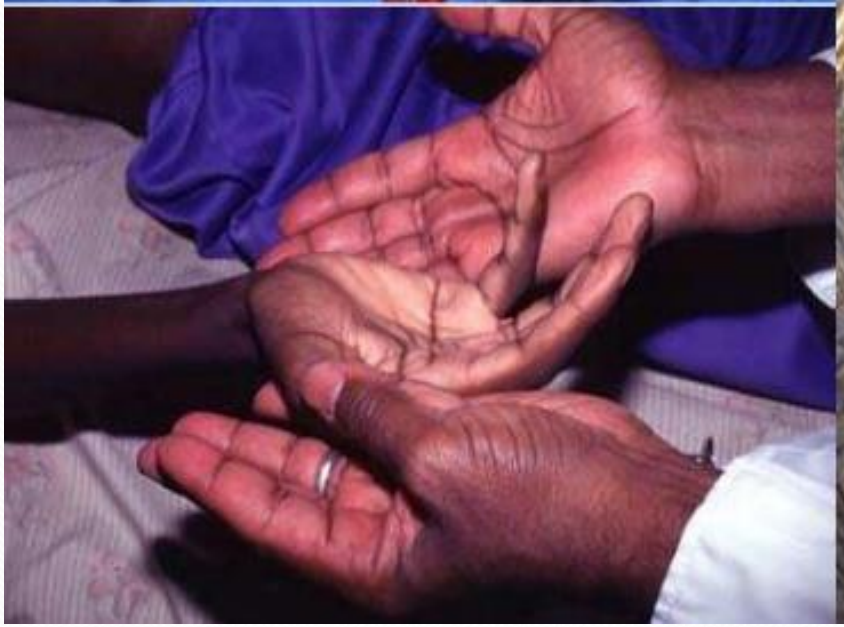
Manifestations

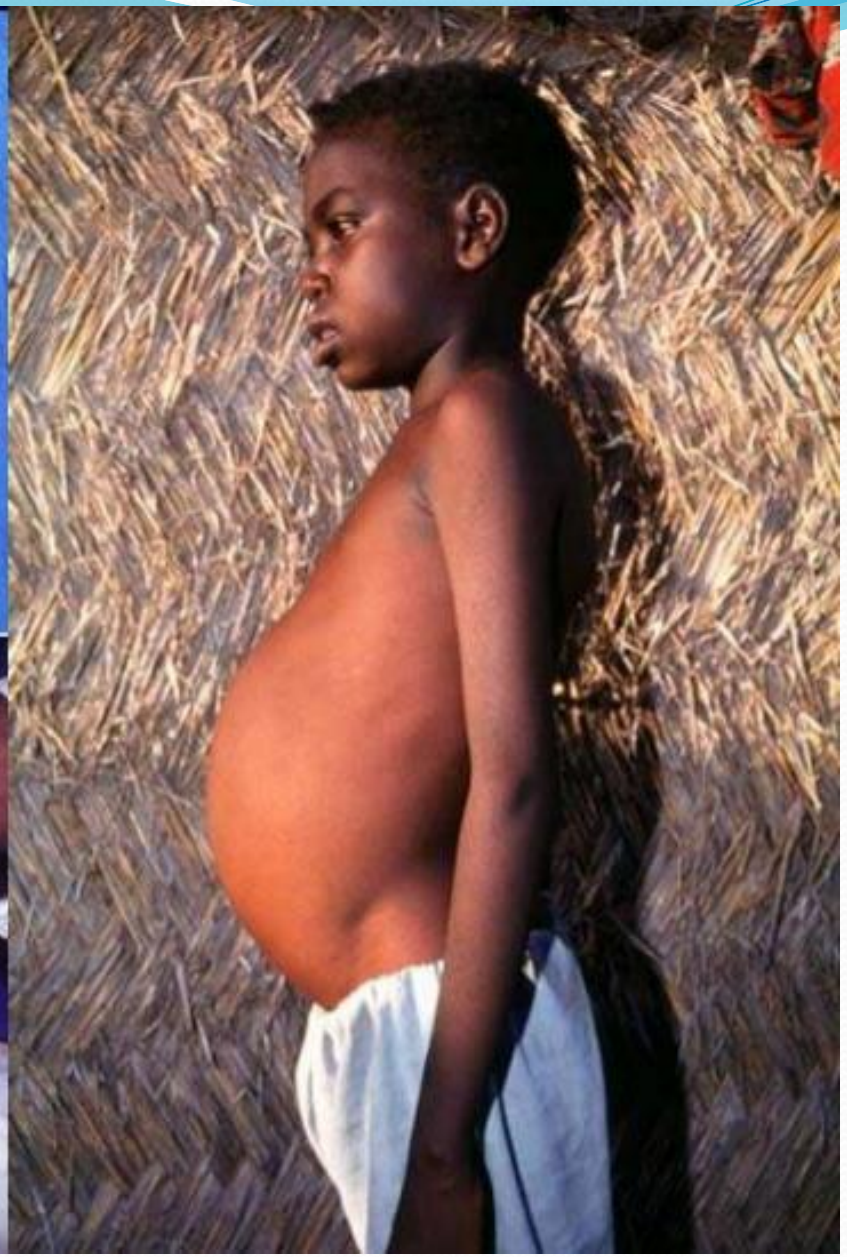
- The majority of infections are asymptomatic
- Symptomatic disease most commonly manifests itself 3 to 12 months after acquisition of the parasite. It is often mild and self-limited
- A minority of infected individuals develop the classic manifestations of kala azar

1. Fever, which is usually present, may be abrupt or gradual in onset. It persists for 2 to 8 weeks and then disappears, only to reappear at irregular intervals during the course of the disease. A double-quotidian pattern (two fever spikes in a single day) is a characteristic but uncommon finding

2. Diarrhea and malabsorption are frequent in Indian cases, resulting in progressive weight loss and weakness
3. Physical findings include enlarged lymph nodes and liver, massively enlarged spleen, and edema.
4. In light-skinned individuals, a grayish pigmentation of the face and hands is commonly seen, which gives the disease its name (kala azar, black disease)
5. Anemia are typical in advanced cases. Thrombocytopenia induces petechial formation and mucosal bleeding. The peripheral leukocyte count is usually low; agranulocytosis with secondary bacterial infections contributes to lethality.
6. Serum immunoglobulin G levels are enormously elevated but play no protective role. Circulating antigen-antibody complexes are present and are probably responsible for the glomerulonephritis seen so often in this disease





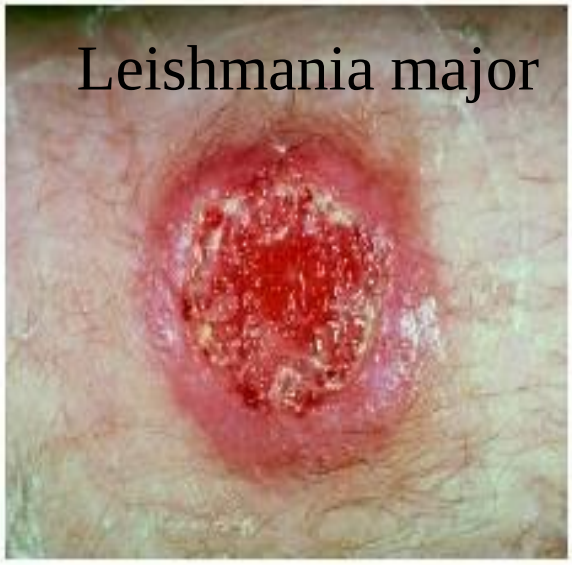


Cutaneous Leishmaniasis

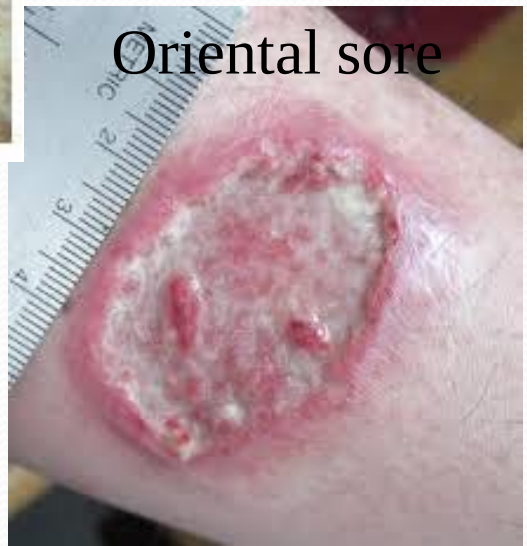
- Leishmania tropica: Anthroponotic cutaneous leishmaniasis: Dry lesions with minimal ulceration
- Leishmania major: Zoonotic cutaneous leishmaniasis: wet lesions with severe reaction
- Oriental sore (most common) classical self-limited ulcer

Leishmania tropica

Leishmania major



Oriental sore



Diagnosis

- The diagnosis is made by demonstrating the presence of the organism in aspirates taken from the bone marrow, liver, spleen, or lymph nodes
- The specimens may be smeared, stained, and examined for the typical Leishman-Donovan bodies (amastigotes in mononuclear phagocytes) or cultured in artificial media and/ or experimental animals
- A rapid, direct, species-specific diagnosis by PCR and probes to kinetoplast DNA is used
- Results of the leishmanin skin test are negative during active disease but become positive after successful therapy

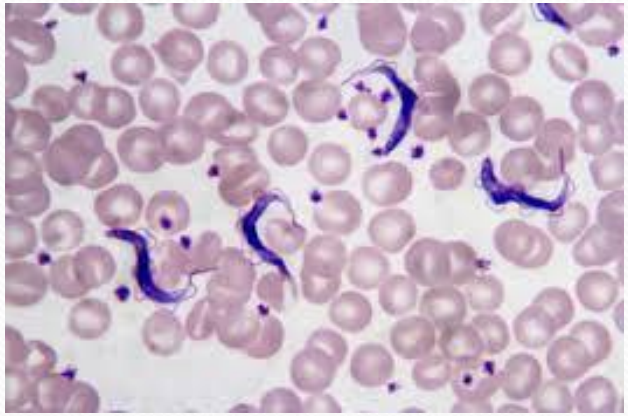
Treatment and Prevention

- The mortality in untreated cases of kala azar is 75 to 90%
- Treatment with pentavalent antimonial drugs lower this rate dramatically. Initial therapy, however, fails in up to 30% of African cases, and 15% of those that do respond eventually relapse
- Control measures are directed at the Phlebotomus vector, with the use of residual insecticides, and at the elimination of mammalian reservoirs by treating human cases and destroying infective dogs

African Trypanosoma (Sleeping sickness)

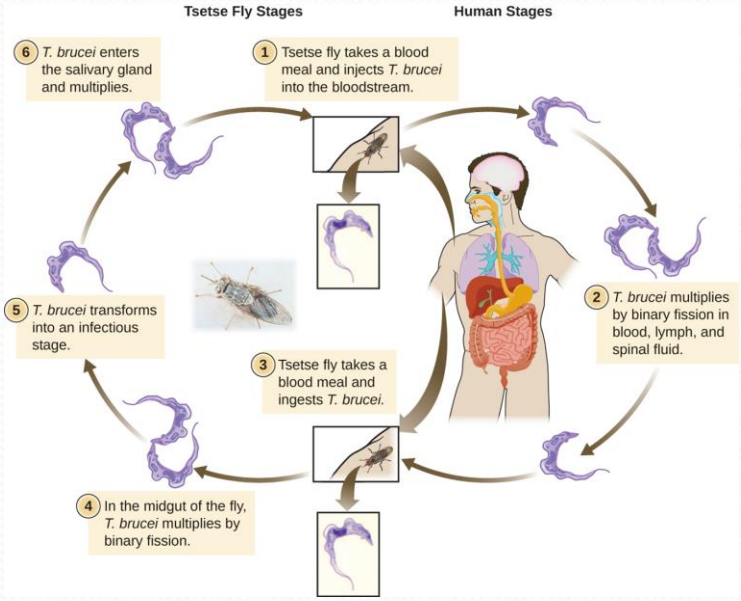
Parasitology

- The trypanosomes that produce these diseases are morphologically and serologically identical. Accordingly, they are considered varieties of a single species, *Trypanosoma brucei*
- The three subspecies, are *T. brucei gambiense, T. brucei rhodesiense,* and *T. brucei brucei*



Life Cycle

- On ingestion by the tsetse fly, and after a period of multiplication in the midgut, they migrate to the insect's salivary glands and assume the epimastigote form
- After a period of weeks they are transformed into trypomastigotes, rendering them infectious to mammals
- When the fly again takes a meal, the parasites are inoculated with the fly's saliva

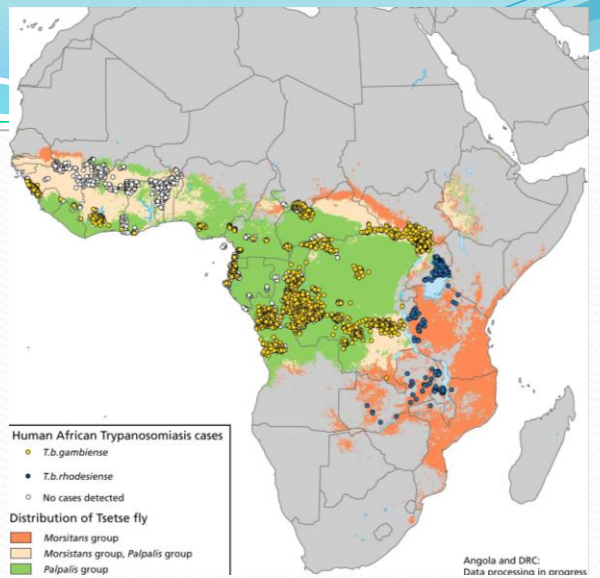


African trypanosomiasis (sleeping sickness)

- African trypanosomiasis is a highly lethal meningoencephalitis
- It occurs in two distinct clinical and epidemiologic forms:

1. West African or Gambian sleeping sickness 98%, found in 24 countries in west and central Africa
2. East African or Rhodesian sleeping sickness 2%, found in 13 countries eastern and southern Africa

Epidemiology

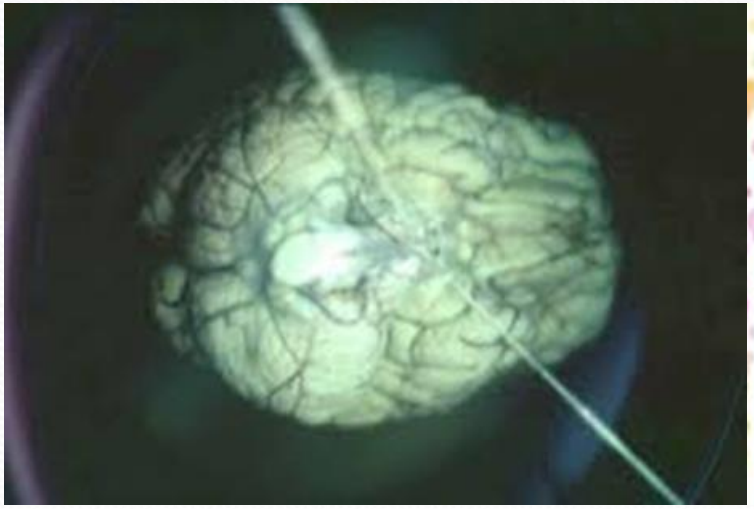


- Sleeping sickness is confined to the central area of Africa by that continent's two great deserts, the Sahara in the north and the Kalahari in the south.
- Sleeping sickness threatens millions of people in 36 countries in sub-Saharan Africa.
- In 1998, almost 40 000 cases were reported, but estimates were that 300 000 cases were undiagnosed
- The infection rate is affected by proximity to water but seldom exceeds 2 to 3% in nonepidemic situations.

Pathogenesis

- Multiplication of the trypomastigotes at the inoculation site produces a localized inflammatory lesion (chancre).
- Organisms spread through lymphatic channels to the bloodstream, inducing a proliferative enlargement of the lymph nodes.
- The subsequent parasitemia is typically low grade and recurrent.
- As host antibodies (predominantly IgM) are produced to the surface antigen they bind to the organism, leading to its destruction by lysis and opsonization.

- During the course of the parasitemia, trypanosomes localize in the small blood vessels of the heart and central nervous system
- This localization results in endothelial proliferation and a perivascular infiltration of plasma cells and lymphocytes. In the brain, hemorrhage and a demyelinating panencephalitis may follow



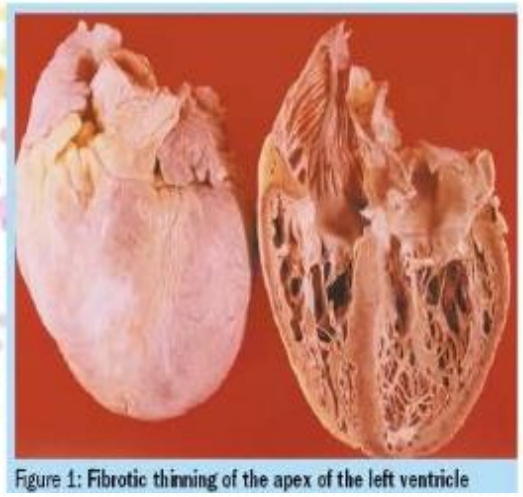
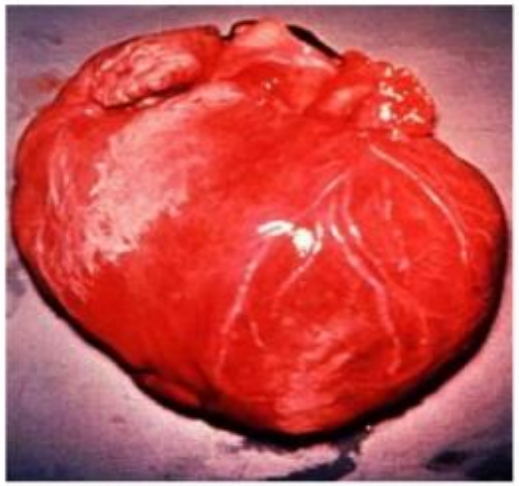


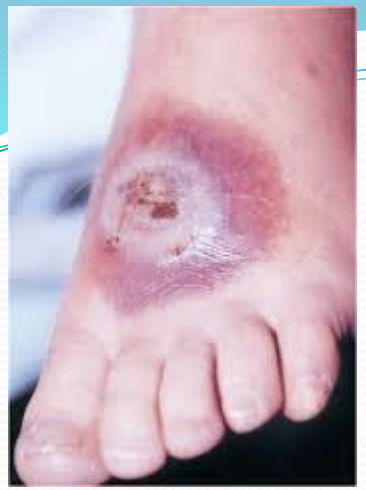
Figure 1: Fibrotic thinning of the apex of the left ventricle

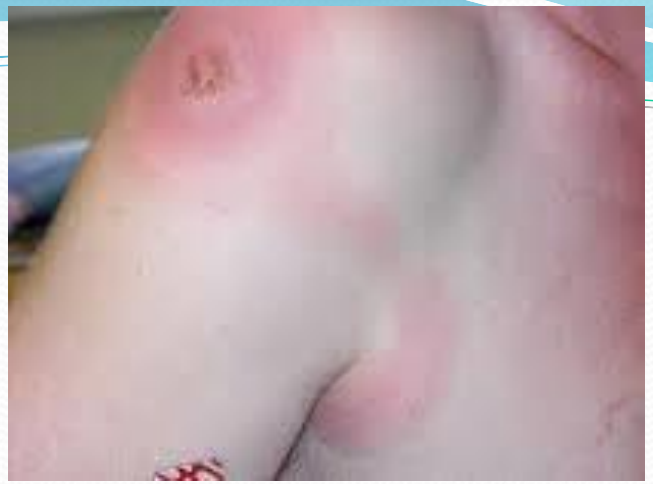


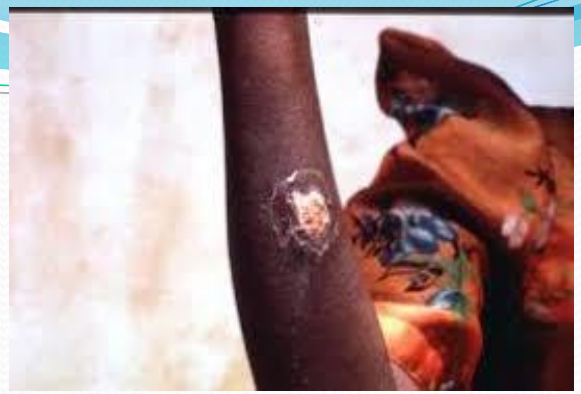
Manifestations

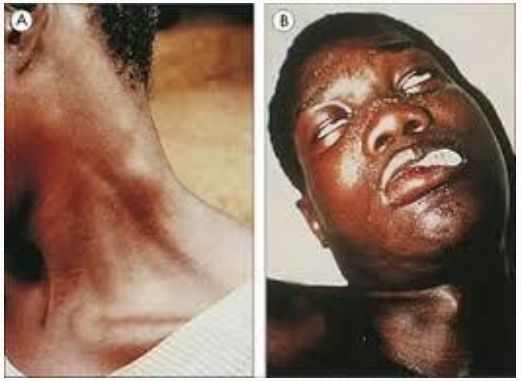
- The trypanosomal chancre appears 2 to 3 days after the bite of the tsetse fly as a raised, reddened nodule on one of the exposed surfaces of the body
- With the onset of parasitemia 2 to 3 weeks later, the patient develops recurrent bouts of fever, tender lymphadenopathy, skin rash, headache, and impaired mentation
- In the Rhodesian form of disease, myocarditis and CNS involvement begin within 3 to 6 weeks. Heart failure, convulsions, coma, and death follow in 6 to 9 months

- Gambian sleeping sickness progresses more slowly. Bouts of fever often persist for years before CNS manifestations gradually appear
- Spontaneous activity progressively diminishes, attention wavers, and the patient must be prodded to eat or talk
- Speech grows indistinct, tremors develop, sphincter control is lost, and seizures with transient bouts of paralysis occur.
- In the terminal stage, the patient develops a lethal intercurrent infection or lapses into a final coma








A
B

Diagnosis

- A definitive diagnosis is made by microscopically examining lymph node aspirates, blood, or cerebrospinal fluid for the presence of trypomastigotes
- Early in the disease, actively motile organisms can often be seen in a simple wet mount preparation smear
- If these tests prove negative, the blood can be centrifuged and the stained buffy coat examined
- Inoculation of rats or mice can also prove helpful in diagnosing the Rhodesian disease
- The patient may also be screened for elevated levels of IgM in the blood and spinal fluid or specific trypanosomal antibodies

Treatment and Prevention

- Lumbar puncture must always be performed before initiation of therapy. If the specimen reveals evidence of CNS involvement, agents that penetrate the blood-brain barrier must be included. Unfortunately, the most effective agent of this type is a highly toxic arsenical, melarsoprol (Mel B)
- If the CNS is not yet involved, less toxic agents, such as suramin, pentamidine, or eflornithine, can be used. In such cases, the cure rate is high and recovery complete
- Tsetse fly control measures, eradication of disease reservoirs, and attempts to develop effective vaccines have been tried with poor effect
- A degree of personal protection can be achieved with insect repellents and protective clothing