Blood and tissue protozoan flagellates of major clinical significance include members of genera *Trypanosoma and Leishmania*

LEISHMANIASIS

Etiology
Several species of *Leishmania* are pathogenic for man:
Old World VL: *L. donovani* causes visceral leishmaniasis (Kala-azar, black - disease, dumdum fever); *L. infantum* (infants, children, sometimes young adults)

- **Old World CL***. tropica, L.major, L. aethiopica* cause cutaneous leishmaniasis (oriental sore, Delhi ulcer, Aleppo, Delhi or Baghdad boil).
-*L. aethiopica:* Old World mucocutaneous leishmaniasis

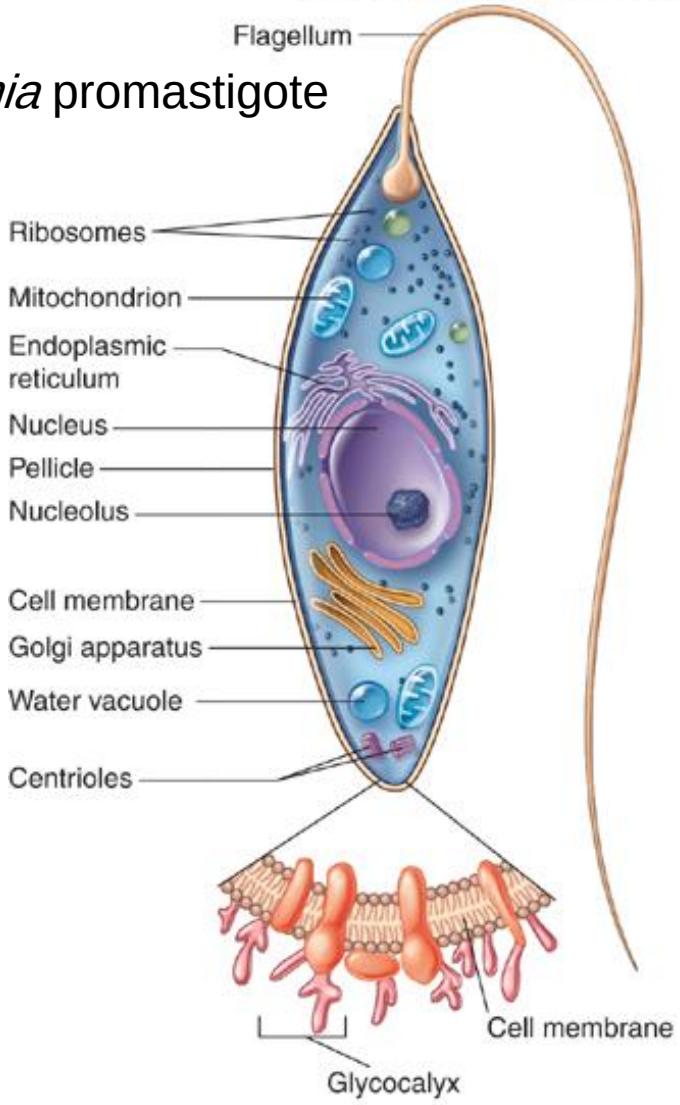
-New World VL:*L. chagasi*
-**New World CL**: *L. mexicana and L. peruviana* are etiologic agents of cutaneous (chiclero ulcer)
L. braziliensis : mucocutaneous leishmaniasis (espundia).

Epidemiology
Leishmaniasis is prevalent world wide: ranging from south east Asia, Indo-Pakistan, Mediterranean, north and central Africa, and south and central America.

Morphology
Amastigote :is oval and measures 2-5 microns
Promastigote (Fig) measures 14 - 20 microns

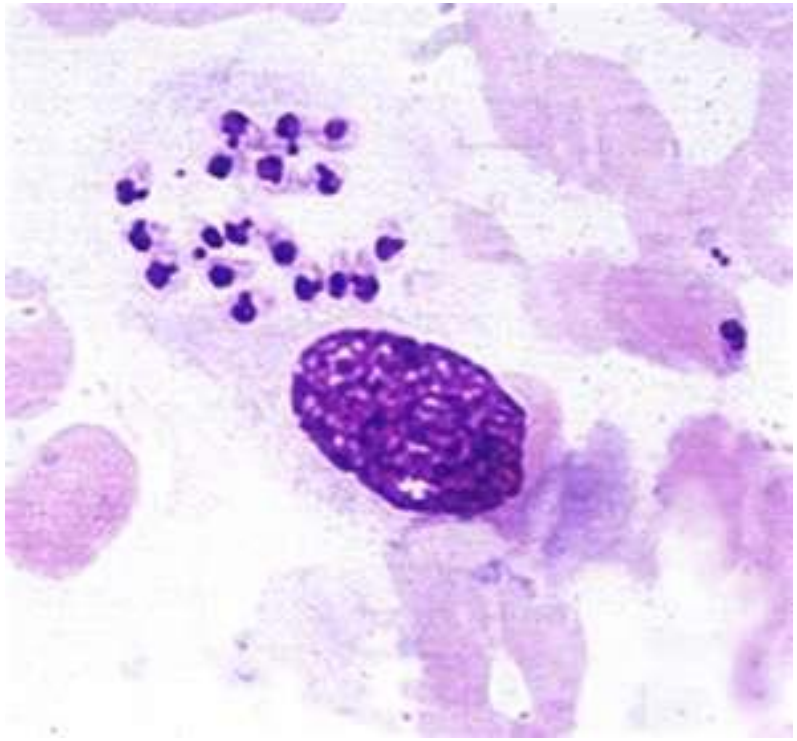
Leishmania promastigote

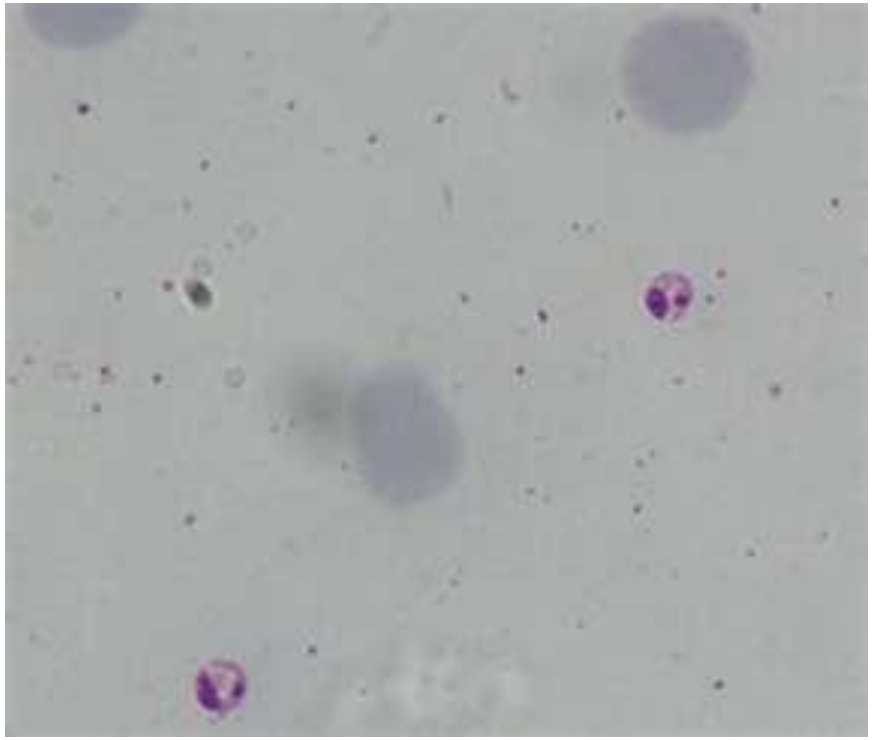
Trypanosoma

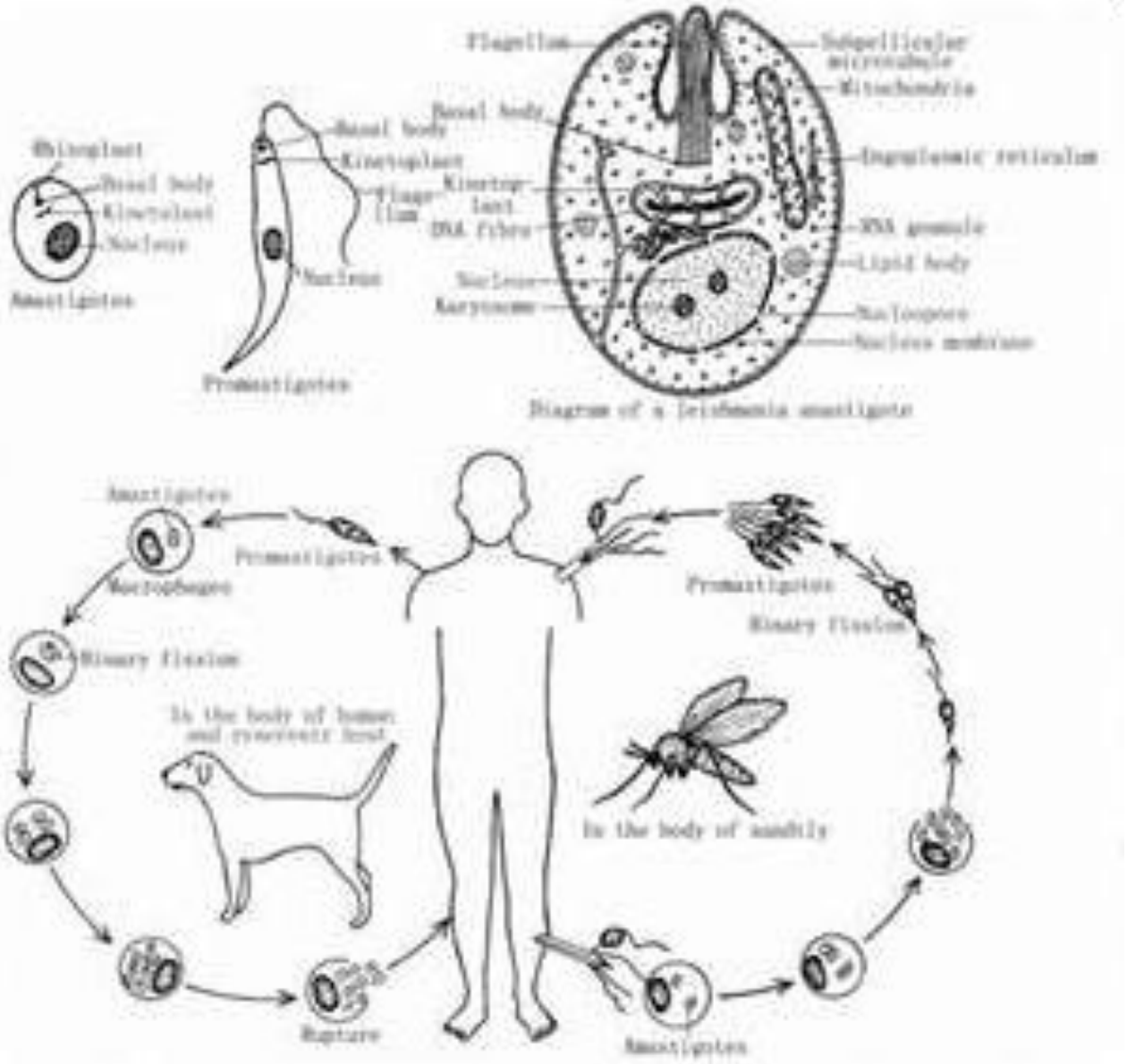


(a) **Protozoan Cell**

(b)






Rhizoplast
Basal body
Kinetolast
Nucleus
Amastigotes
Basal body
Kinetoplast
Flagellum
Nucleus
Promastigotes
Flagellum
Subpellicular microtubule
Mitochondria
Basal body
Endoplasmic reticulum
Kinetoplast
DNA fibre
RNA granule
Lipid body
Nucleus
Karyosome
Nucleopore
Nucleus membrane
Diagram of a leishmania amastigote
Amastigotes
Promastigotes
Macrophages
Promastigotes
Binary fission
Binary fission
In the body of human and reservoir host
In the body of sandfly
Rupture
Amastigotes

Life cycle

The organism is transmitted by the bite of several species of blood-feeding sand flies (e.g. *Phlebotomus*) which carry the promastigote in the anterior gut and pharynx.
The parasites gain access to mononuclear phagocytes where they transform into amastigotes and divide until the infected cell ruptures.

The released organisms infect other cells.

The sandfly acquires the organisms during the blood meal; the amastigotes transform into flagellate promastigotes and multiply in the gut until the anterior gut and pharynx are packed. Dogs and rodents are common reservoirs.

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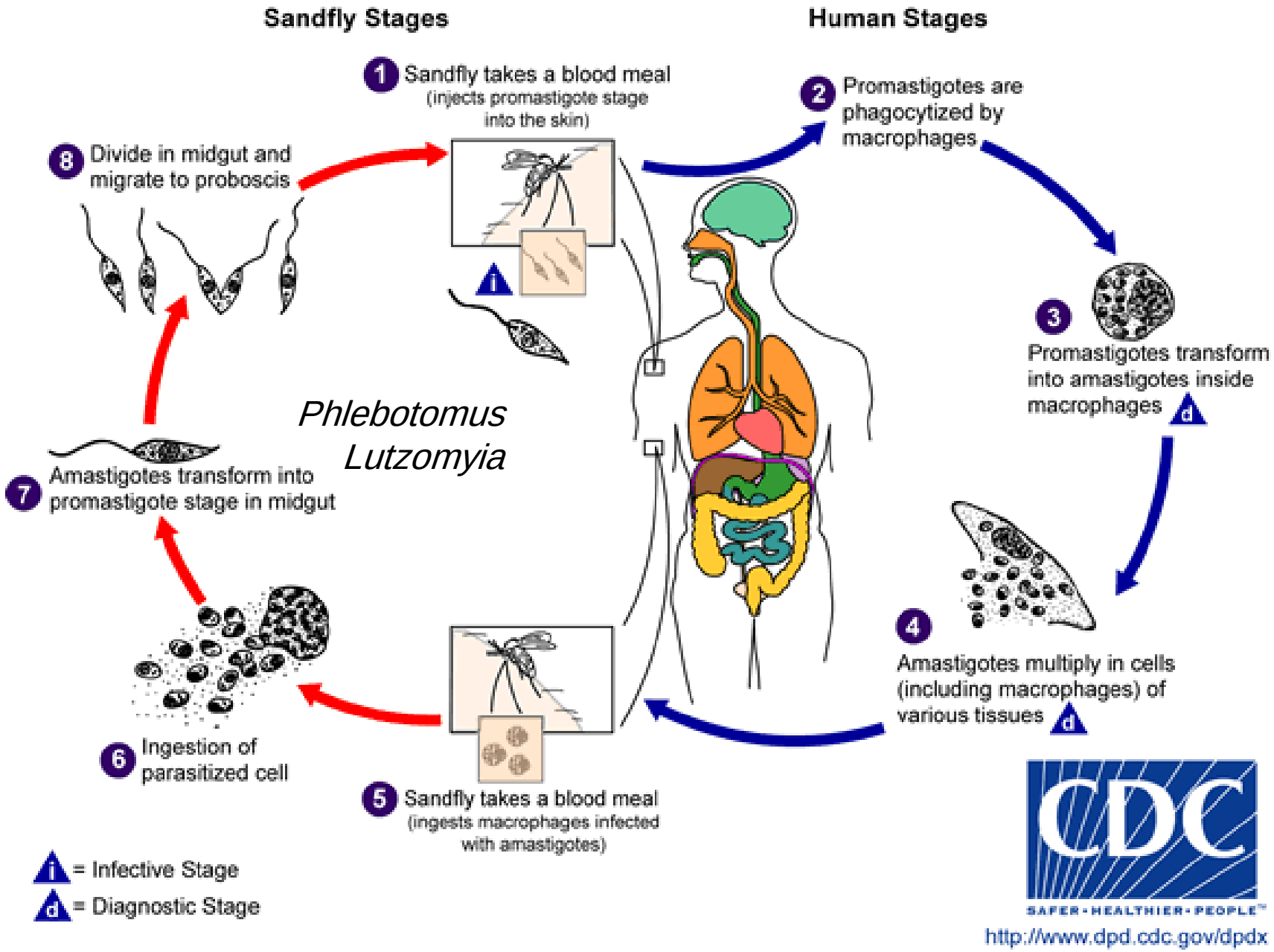
Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage
into the skin)
2 Promastigotes are
phagocytized by
macrophages
3 Promastigotes transform
into amastigotes inside
macrophages
d
4 Amastigotes multiply in cells
(including macrophages) of
various tissues
d
5 Sandfly takes a blood meal
(ingests macrophages infected
with amastigotes)
6 Ingestion of
parasitized cell
7 Amastigotes transform into
promastigote stage in midgut
8 Divide in midgut and
migrate to proboscis
i
Phlebotomus
Lutzomyia
i = Infective Stage
d = Diagnostic Stage
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Symptoms

Visceral leishmaniasis (kala-azar, dumdum fever): *L. donovani* organisms in visceral leishmaniasis are rapidly eliminated from the site of infection

They multiply in the mononuclear phagocytic cells of spleen, liver, lymph nodes, bone marrow, intestinal mucosa.

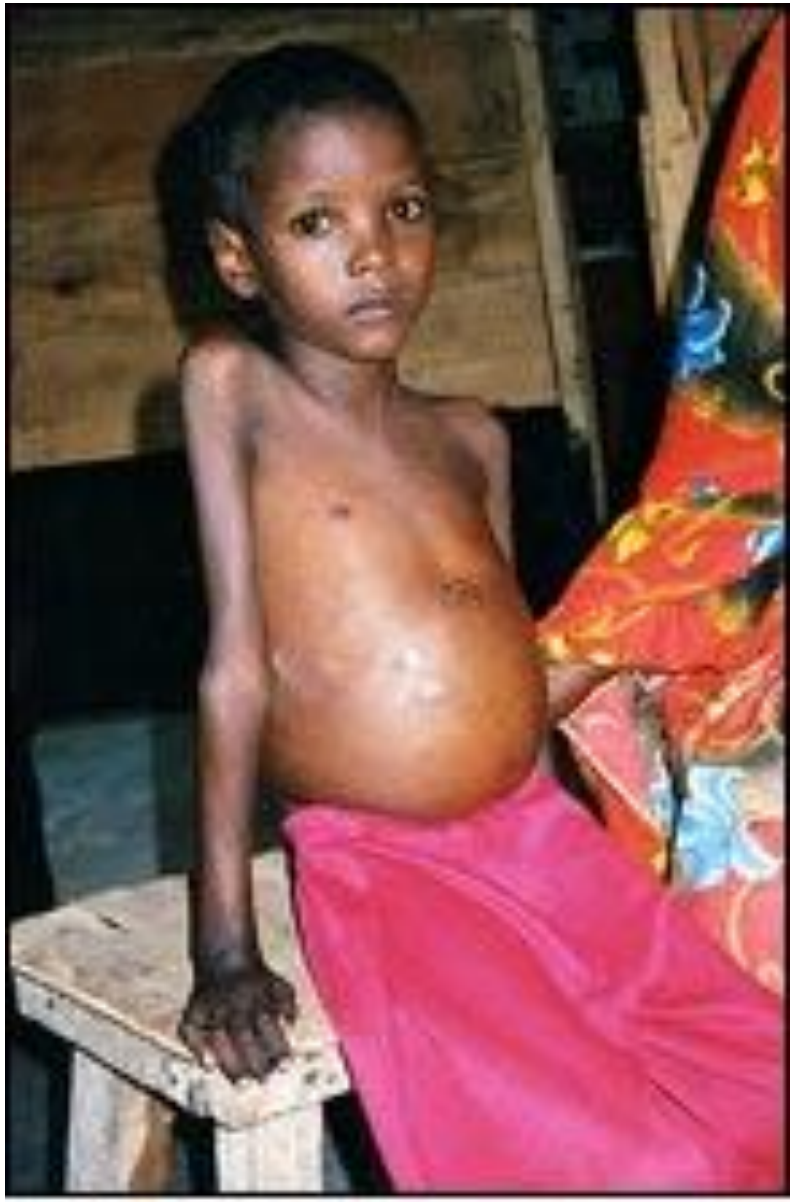
One to four months after infection, there is occurrence of fever accompanied by chills and sweating.

The spleen and liver progressively become enlarged.

With progression of the diseases, skin develops hyperpigmented granulomatous areas (kala-azar means black disease)

Assignment

Untreated disease results in death



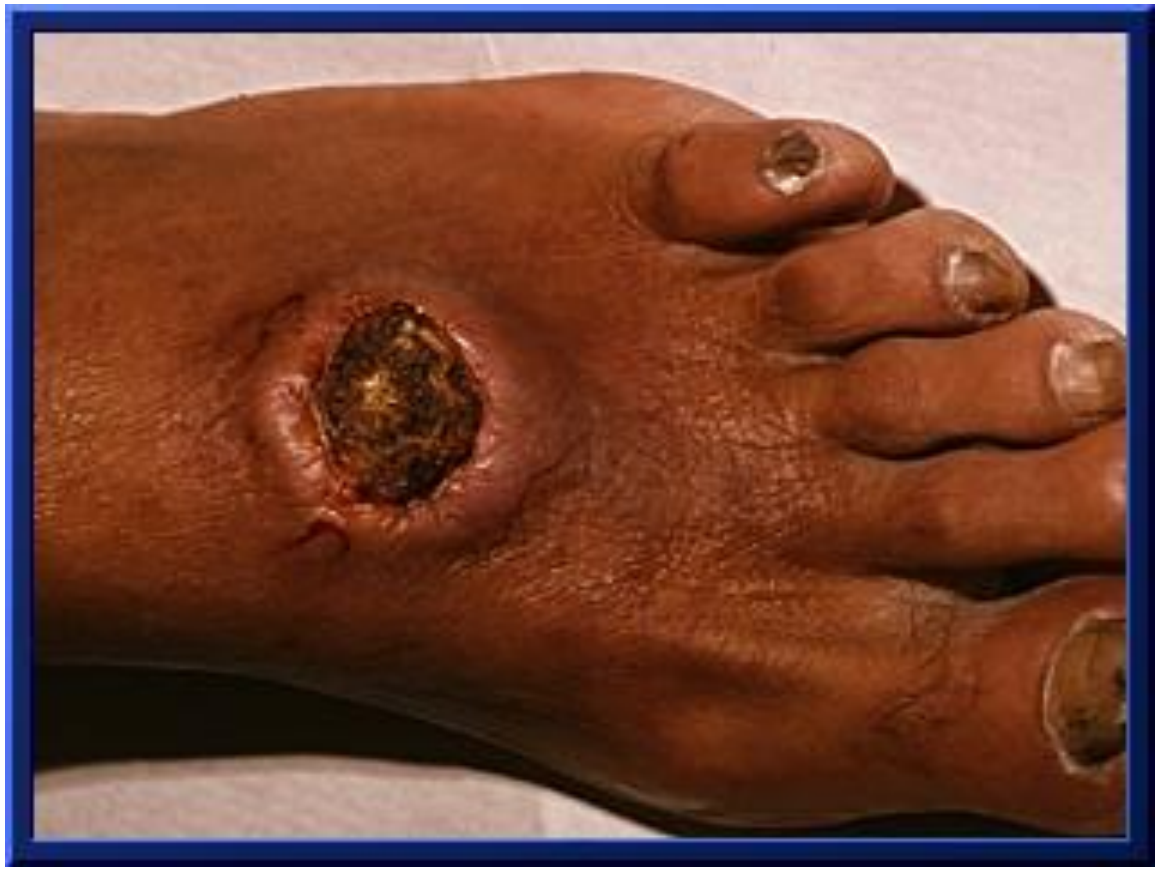
Cutaneous leishmaniasis (Oriental sore, Delhi ulcer, Baghdad boil): the organism multiplies locally, producing a papule, 1-2 weeks (or as long as 1-2 months) after the bite.

The papule gradually grows to form a relatively painless ulcer.

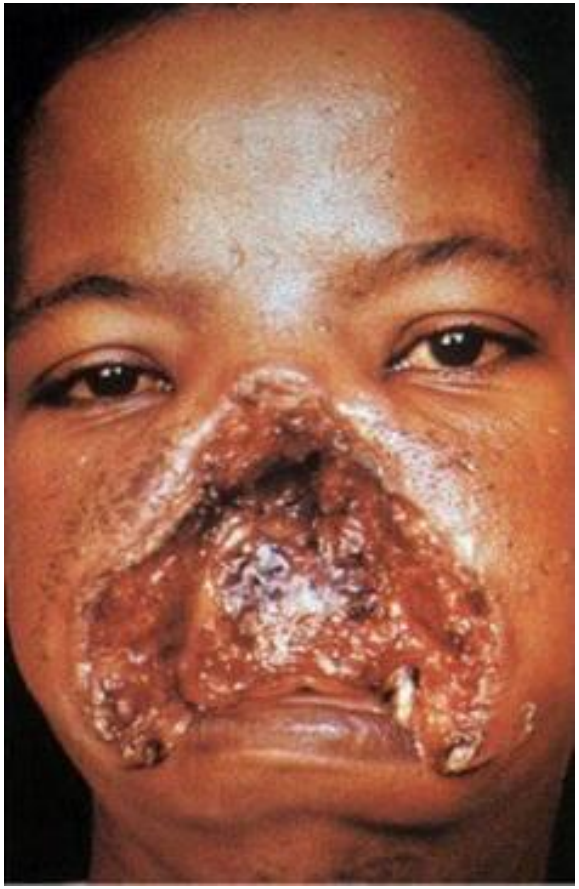
The center of the ulcer encrusts .

The ulcer heals in 2-10 months, even if untreated but leaves a disfiguring scar.

The disease may disseminate in the case of depressed immune function.



Mucocutaneous leishmaniasis (espundia): The initial symptoms of mucocutaneous leishmaniasis are the same as those of cutaneous leishmaniasis, except that in this disease the organism can metastasize and the lesions spread to mucoid (oral, pharyngeal and nasal) tissues and lead to their destruction and hence sever deformity.



Diagnosis
Visceral: Diagnosis is based on a history of exposure to sandfies, symptoms and
isolation of the organisms from bone marrow or spleen (aspirate or biopsy)

Cutaneous: scraping of lesion

Both:
-direct examination or culture (Schneider's medium).
-PCR

Visceral
-detection of anti-leishmanial antibodies by immuno-fluorescence (

Treatment and Control
Sodium stibogluconate (Pentostam) is the drug of choice. Pentamidine isothionate is used as an alternative. Control measures involve vector control and avoidance (bed nets, repellents, window screen). Immunization has not been effective.

Leishmaniasis in Jordan

Cutaneous leishmaniasis (CL): endemic in some regions (ex. Jordan Valley, Wadi Araba, Hallabat)

-Two types:

- The zoonotic (wet) type:
  - caused by *L.major*
  - exist in rural areas
  - The fat jird (*Psammomys*) is the reservoir
- -The anthroponotic (dry) type:
  - caused by *L. tropica*
  - exists in urban areas

TRYPANOSOMIASIS

African trypanosomiasis (Sleeping sickness)

Etiology
There are two clinical forms of African trypanosomiasis: 1) a slowly developing disease caused by *Trypanosoma gambiense* and 2) a rapidly progressing disease caused by *T. rhodesiense*.

Epidemiology

T. gambiense is predominant in the western and central regions of Africa, whereas *T. rhodesiense* is restricted to the eastern third of the continent. 6,000 to 10,000 human cases are documented annually.

Morphology

T. gambiense and T. rhodesiense are similar in appearance: The organism measures 10 - 30 micrometers in length.

Life cycle

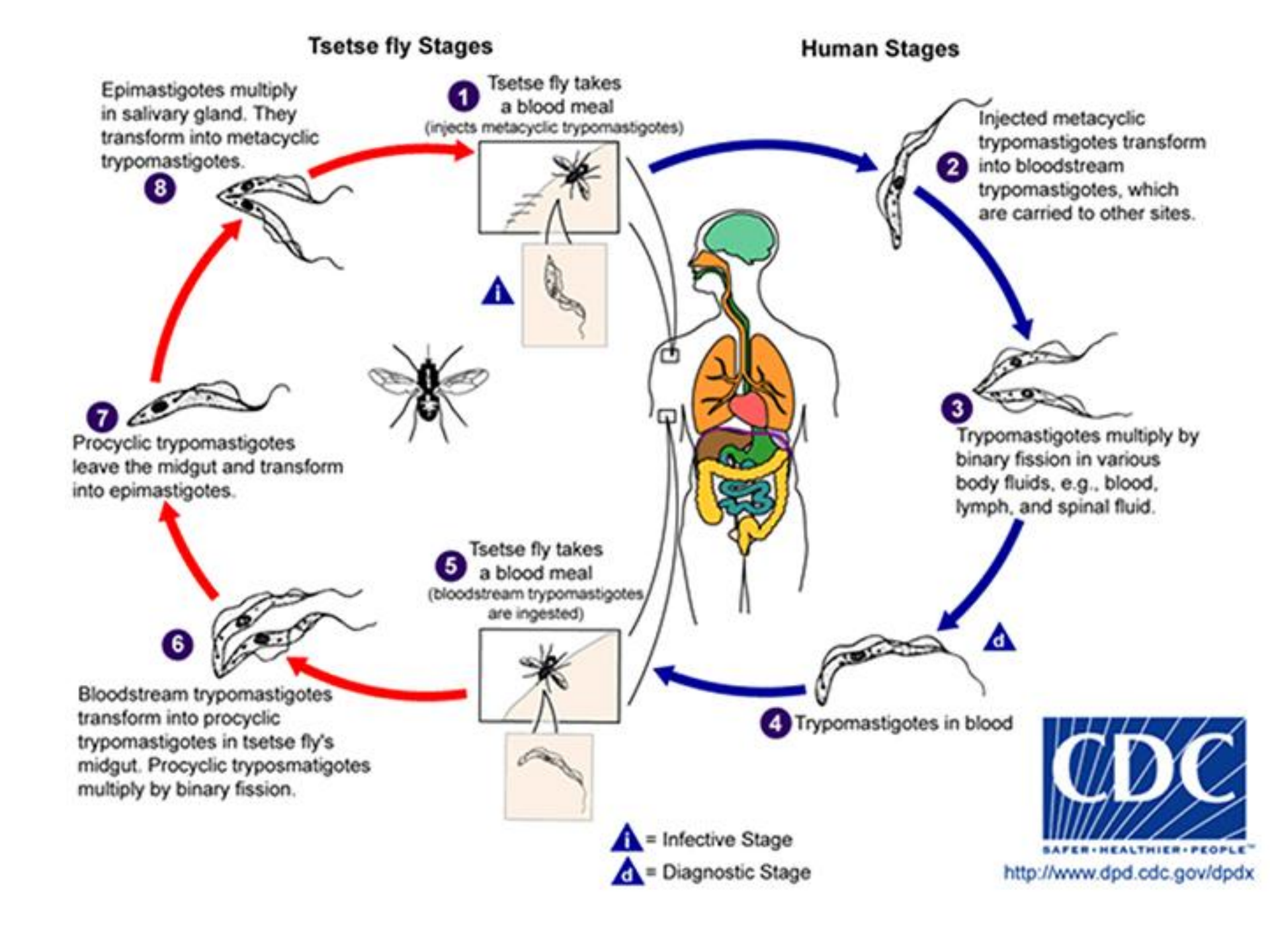
The infective, metacyclic form of the trypanosome is injected into the primary host during a bite by the vector, the tsetse fly.

The organism transforms into a dividing trypanosomal (trypomastigote) blood form as it enters the draining lymphatic and blood stream.

The trypanosomal form enters the vector during the blood meal and travels through the alimentary canal to the salivary gland where it proliferates as the epimastigote form and matures to infectious metacyclic forms.

Trypomastigotes can traverse the walls of blood and lymph capillaries into the connective tissues and, at a later stage, cross the choroid plexus into the brain and cerebrospinal fluid.

The organism can be transmitted through blood transfusion.


Tsetse fly Stages
Human Stages
Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
8
1 Tsetse fly takes a blood meal
(injects metacyclic trypomastigotes)
i
2 Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3 Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
d
4 Trypomastigotes in blood
5 Tsetse fly takes a blood meal
(bloodstream trypomastigotes are ingested)
6 Bloodstream trypomastigotes transform into procyclic trypomastigotes in tsetse fly's midgut. Procyclic tryposmatigotes multiply by binary fission.
7 Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
i = Infective Stage
d = Diagnostic Stage
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Symptoms

The clinical features of Gambian and Rhodesian disease are the same, however they vary in severity and duration.

Rhodesian disease progresses more rapidly and the symptoms are often more pronounced.

Classically, the progression of African trypanosomiasis can be divided into three stages: the bite reaction (chancre), parasitemia (blood and lymphoid tissues), and CNS stage.

Bite reaction: A painful, itchy chancre forms 1-3 weeks after the bite and lasts 1-2 weeks. It leaves no scar.

Parasitemia: marked by attacks of fever which starts 2-3 weeks after the bite and is accompanied by lymphadenopathy

Febrile episodes may last few months as in Rhodesian disease or several years as in Gambian disease.

CNS Stage: The late or CNS stage is marked by changes in character and personality. They include lack of interest and disinclination to work, mental retardation and lethargy, tremors of tongue and limbs, altered reflexes, etc. Males become impotent.

The later stages are characterized by uncontrollable urge to sleep. The terminal stage is marked by wasting and emaciation.

Death results from coma, infection or cardiac failure.

The clinical features of Rhodesian disease are similar but briefer and more acute. The acuteness and severity of disease do not allow typical sleeping sickness. Death is due to cardiac failure within 6-9 months.

Pathology and Immunology

An exact pathogenesis of sleeping sickness is not known, although immune complexes and inflammation have been suspected to be the mechanism of damage to tissues.

Diagnosis
Detection of parasite in the bloodstream, lymph secretions and enlarged lymph node aspirate provides a definitive diagnosis in early (acute) stages.

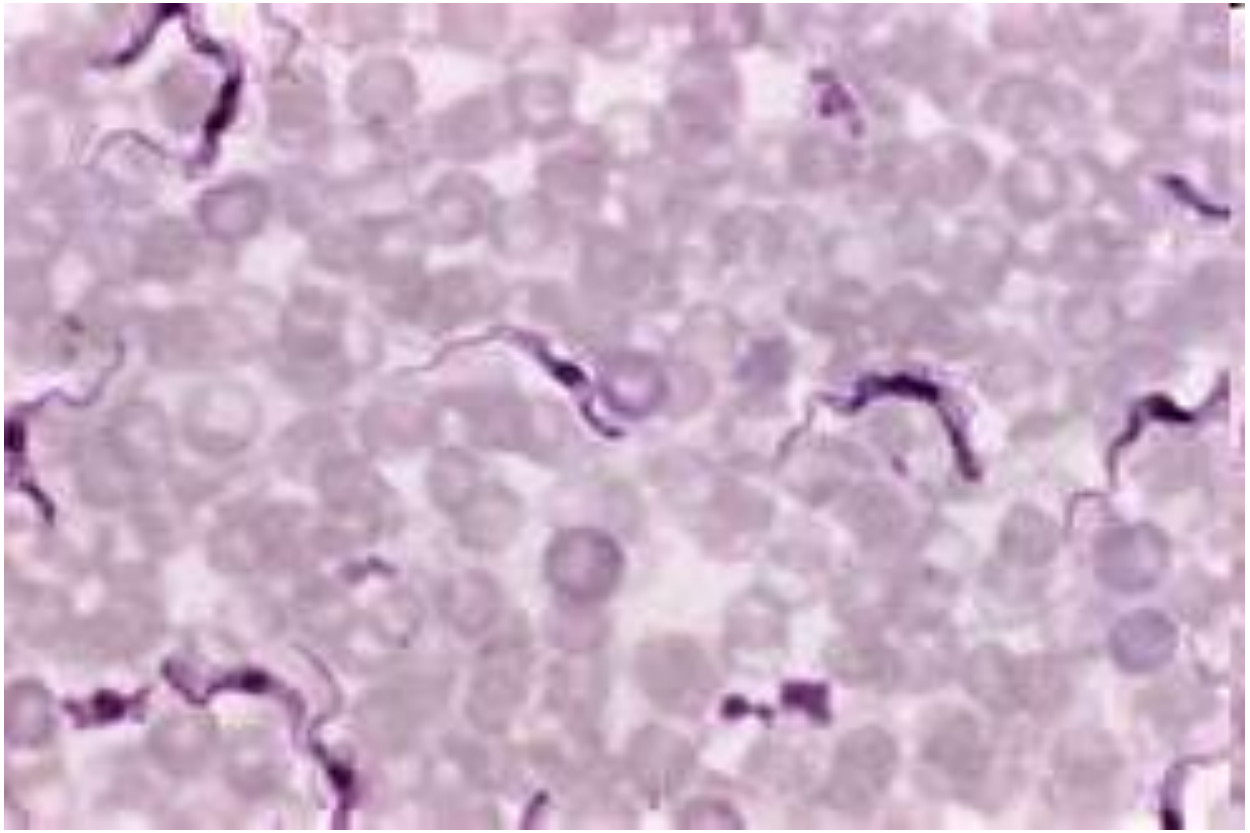
Cerebrospinal fluid must always be examined for organisms.

Serology (enzyme-linked immune assay, immunofluorescence) may be indicative but does not provide definite diagnosis.

Treatment and Control
The blood stage of African trypanosomiasis can be treated with reasonable success with Pentamidine isothionate or Suramin.

Cases with CNS involvement should be treated with Melarsoprol, an organic arsenic compound.

The most effective means of prevention is to avoid contact with tsetse flies. Vector eradication is impractical due to the vast area involved. Immunization has not been effective due to antigenic variation.

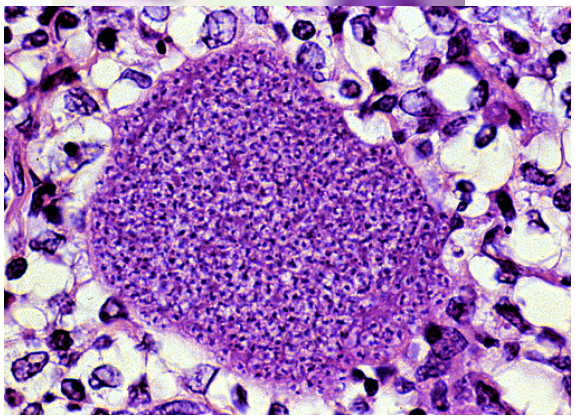


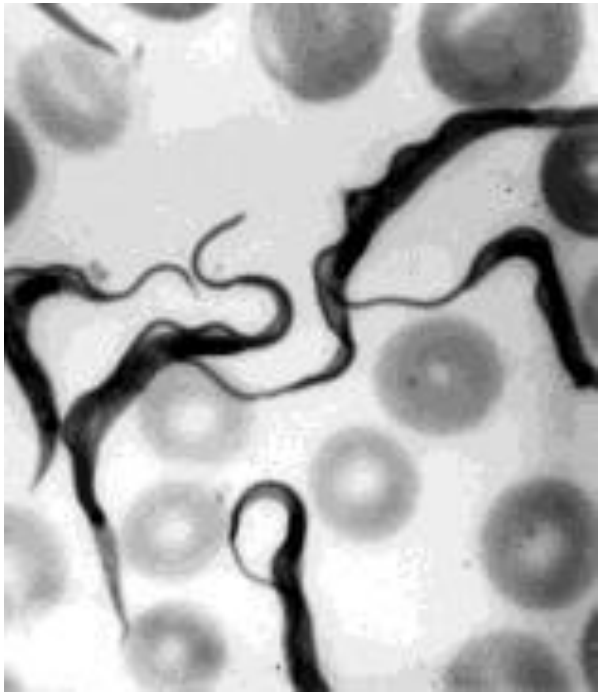
American trypanosomiasis (Chagas' disease)

Etiology
Chagas' disease is caused by the protozoan hemoflagellate, *Trypanosoma cruzi.*

Epidemiology
American trypanosomiasis, also known as Chagas' disease. It is estimated that 16-18 million people are infected by the parasite . About 50,000 people die each year from the disease.

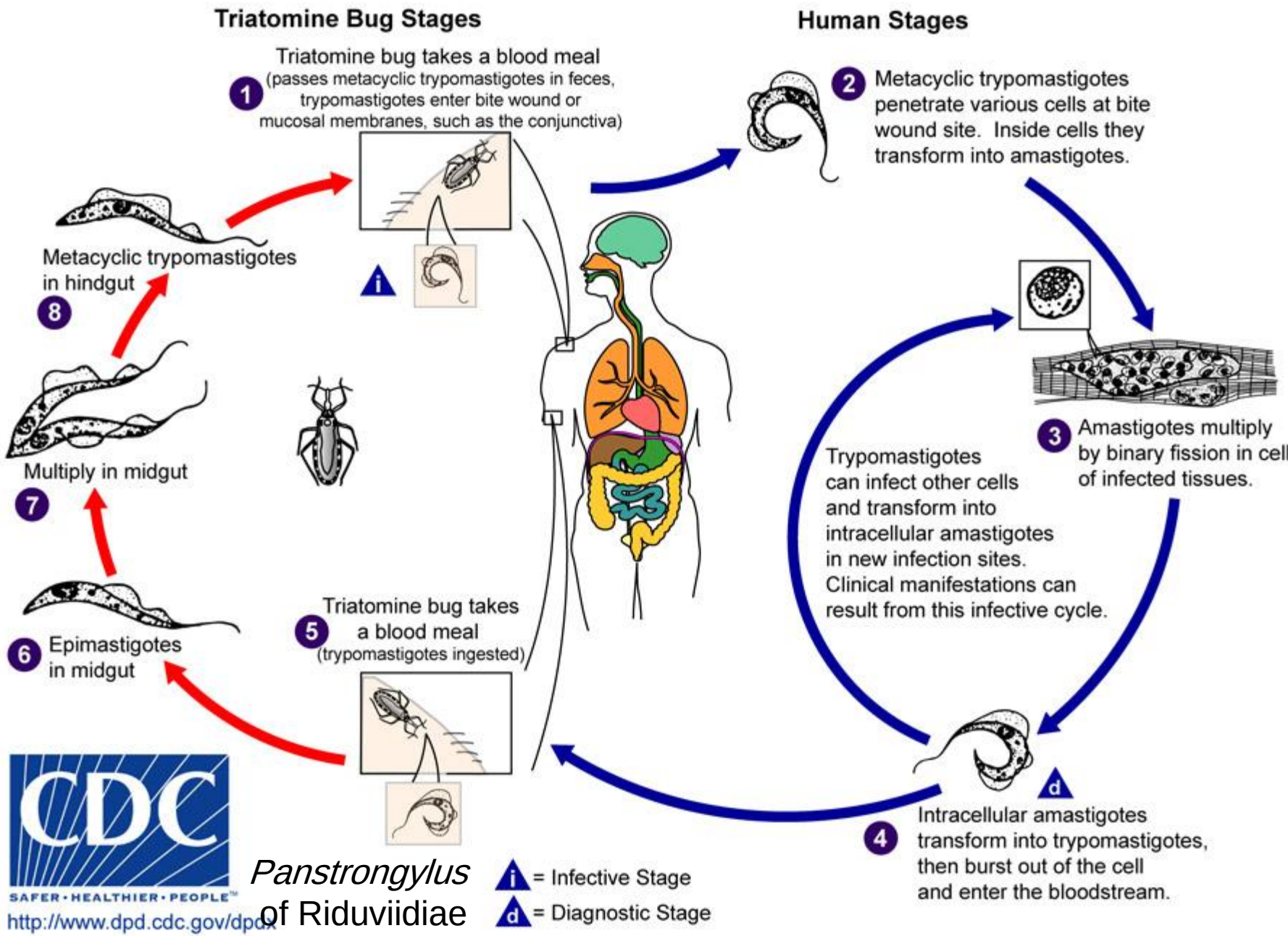
Morphology
2 forms in human :
The trypanosomal (trypomastigote)
The leishmanial (amastigote)





Life cycle

The organism is transmitted to mammalian host by many species of kissing (riduvid) bug (figure 8), most prominently by Triatoma infestans, T. sordida, Panstrongylus megistus and Rhodnius prolixus. Transmission takes place during the feeding of the bug which normally bites in the facial area (hence the name, kissing bug) and has the habit of defecating during feeding. The metacyclic trypamastigotes, contained in the fecal material, gain access to the mammalian tissue through the wound which is often rubbed by the individual that is bitten. Subsequently, they enter various cells, including macrophages, where they differentiate into amastigotes and multiply by binary fission. The amastigotes differentiate into non-replicating trypomastigotes and the cells rupture to release them into the bloodstream. Additional host cells, of a variety of types, can become infected and the trypomastigotes once again form amastigotes inside these cells. Uninfected insect vectors acquire the organism when they feed on infected animals or people containing trypomastigotes circulating in their blood. Inside the alimentary tract of the insect vector, the trypomastigotes differentiate to form epimastigotes and divide longitudinally in the mid and hindgut of the insect where they develop into infective metacyclic trypomastigotes (figure 9C). Transmission may also occur from man to man by blood transfusion and by the transplacental route.



Panstrongylus of Riduviidiae

Symptoms

Chagas' disease can be divided into three stages: the primary lesion, the acute stage, and the chronic stage.

Acute Stage: chills, fever and bone and muscle pains. Adenitis, hepatomegaly, acute myocarditis. In children, Chagas' disease may cause meningo-encephalitis and coma. Death occurs in 5-10 percent of infants.

Chronic Stage: They alternate between asymptomatic remission periods and relapses characterized by symptoms seen in the acute phase. cardiomegaly.

Pathology and Immunology
Autoimmunity: immunity against nerves

Self reading

T. cruzi stimulates both humoral and cell mediated immune responses. Antibody has been shown to lyse the organism, but rarely causes eradication of the organism, perhaps due to its intracellular localization. Cell mediated immunity may be of significant value. While normal macrophages are targeted by the organism for growth, activated macrophages can kill the organism. Unlike T. brucei, T. cruzi does not alter its antigenic coat. Antibodies directed against heart and muscle cells have also been detected in infected patients leading to the supposition that there is an element of autoimmune reaction in the pathogenesis of Chagas' disease. The infection causes severe depression of both cell mediated and humoral immune responses. Immunosuppression may be due to induction of suppressor T-cells and/or overstimulation of macrophages.

Diagnosis
Cardiac dilation, megacolon and megaesophagus in individuals from endemic areas indicate present or former infection.

Definitive diagnosis requires the demonstration of trypanosomes by microscopy or biological tests / xenodiagnosis-(in the insect).
Antibodies are often detectable by complement fixation or immunofluorescence and provide presumptive diagnosis.

Treatment and Control
Nifurtimox , however its side effects limit their prolonged use in chronic cases.

Control measures are limited to those that reduce contact between the vectors and man.
Vaccine is not very successful.