TRYPANOSOMA

Three species of Trypanosoma are morphologically the same.

- "African trypanosomes" or "Old World trypanosomes" are protozoan hemoflagellates of the genus *Trypanosoma*, in the subgenus *Trypanozoon*. African trypanosomiasis is a highly lethal meningoencephalitis transmitted to humans by bloodsucking flies of the genus Glossina. Two subspecies that are morphologically indistinguishable cause distinct disease patterns in humans:
    - *T. brucei gambiense*, causing chronic African trypanosomiasis ("West African or Gambian (chronic) sleeping sickness")
    - *T. brucei. rhodesiense*, causing acute African trypanosomiasis ("East African or Rhodesian (acute) sleeping sickness")
- The third subspecies *T. b. brucei* is a parasite primarily of cattle and occasionally other animals, and under normal conditions does not infect humans.

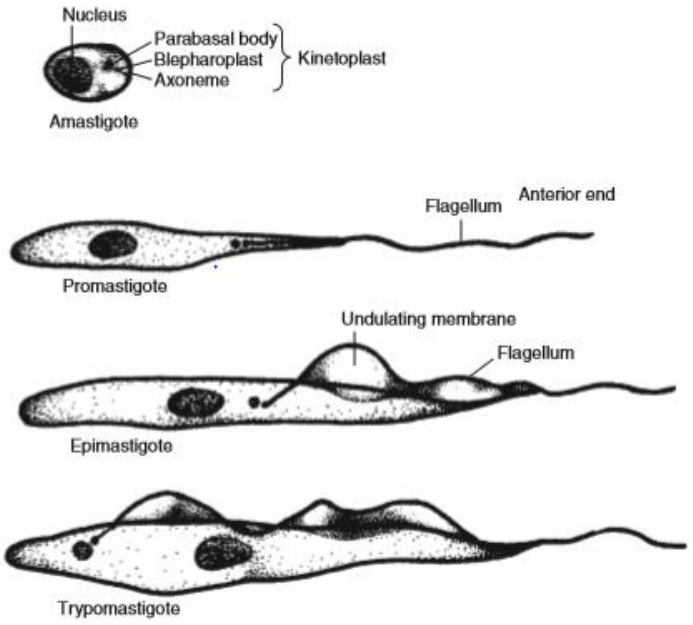


FIGURE 53–4. Stages in the life cycle of the hemoflagellates (Trypanosomidae).

During their passage through insect and vertebrate hosts, flagellates undergo developmental change. Trypanosoma exists in two forms: Epimastigotes and Trypomastigotes.

Within the gut of the insect (and in culture media), the organism assumes the promastigote (Leishmania) or epimastigote (Trypanosoma) form.

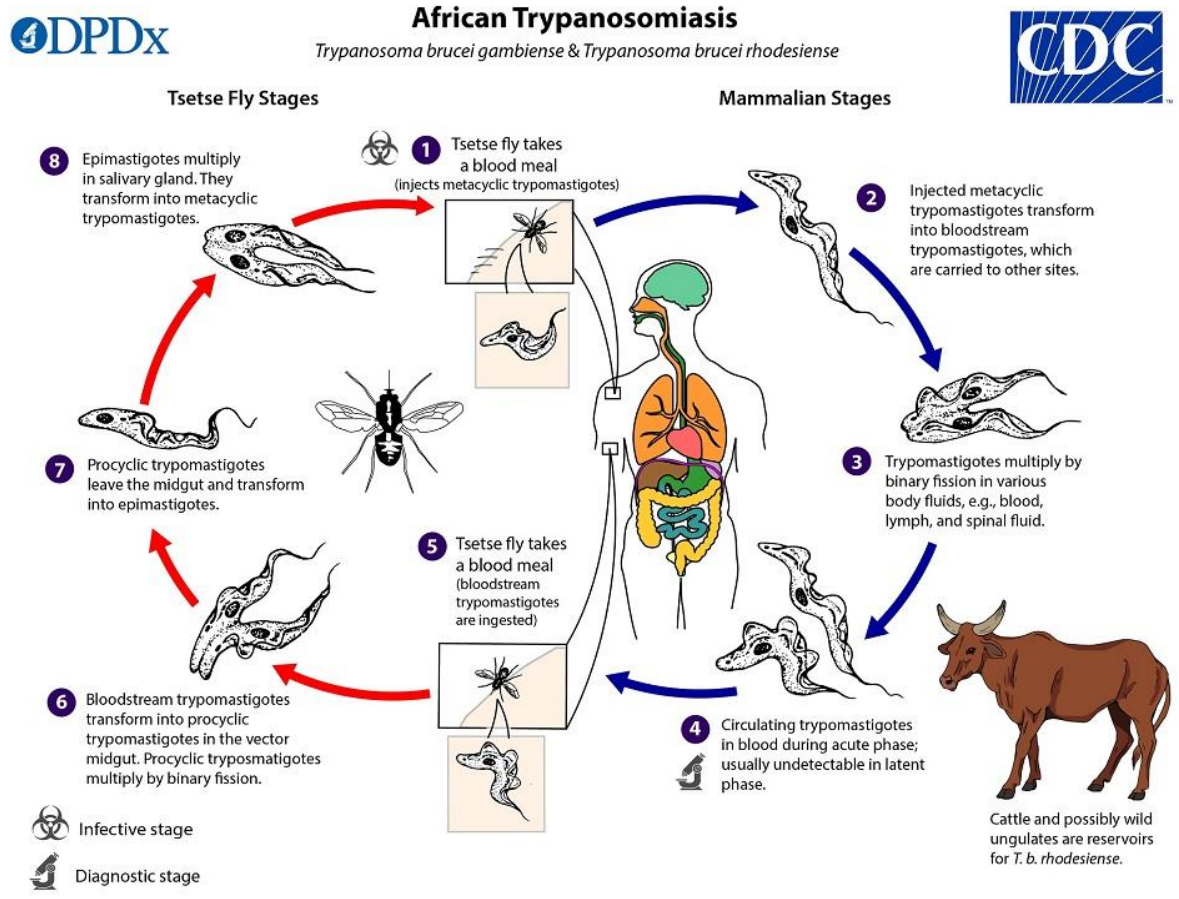
Epimastigote/ Promastigote- These protozoa are motile and fusiform and have a blunt posterior end and a pointed anterior end from which a single flagellum projects. They

measure 15 to 30 μm in length and 1.5 to 4.0 μm in width. The kinetoplast complex of the epimastigote form, in contrast, is located centrally, just in front of the vesicular nucleus. The flagellum runs anteriorly in the free edge of an undulating membrane before passing out of the cell.

In the mammalian host, hemoflagellates appear as **trypomastigotes** (Trypanosoma) or amastigotes (Leishmania, T cruzi). The former circulates in the bloodstream and closely resemble the epimastigote form, except that the kinetoplast complex is in the posterior end of the parasite.

Other forms include: metacyclic trypomastigotes, bloodstream trypomastigotes, procyclic trypomastigotes. (their localization and role are mentioned in the life cycle below).

Life Cycle



During a blood meal on the mammalian host, an infected tsetse fly (genus *Glossina*) injects metacyclic trypomastigotes into skin tissue. The parasites enter the lymphatic system and pass into the bloodstream (1). Inside the host, they transform into bloodstream trypomastigotes (2), are carried to other sites throughout the body, reach other body fluids

(e.g., lymph, spinal fluid), and continue the replication by binary fission 3 . The entire life cycle of African trypanosomes is represented by extracellular stages. The tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host 4 , 5 . In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission 6 , leave the midgut, and transform into epimastigotes 7 . The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission 8 . The cycle in the fly takes approximately 3 weeks. Rarely, *T. b. gambiense* may be acquired congenitally if the mother is infected during pregnancy.

- Newly emerged and young flies are more efficient transmitters of the disease than older flies. A highly variable surface glycoprotein (VSG) coat, which is acquired in the tsetse fly, accounts for this organism's ability to undergo a process of antigenic variation in its mammalian host.
- The parasite enters the bloodstream and trypomastigote stage parasites referred to as slender forms divide by longitudinal fission every 5 to 10 hours. For reasons independent of the host's immune response, multiplication eventually slows and some parasites of a dominant population of organisms assume a short, stumpy appearance. These forms have a more developed kinetoplast–mitochondrial complex and constitute the parasites that are infective to the tsetse fly. Near the end of the episode of parasitemia, both slender and stumpy types may be seen in a single blood specimen.
- Metacyclic trypomastigotes inoculated by a tsetse fly usually contain a population of organisms dominated by a distinctive antigenic type. After a period of time in the vertebrate host, usually a week or so, the antigenic variant type changes. This change is under the control of up to 1000 genes that have been identified in some strains of these organisms that can account for a change in the variant surface glycoprotein antigenic type. Each dominant population usually contains a few organisms that have already undergone antigenic change so that when the host responds immunologically to the dominant population there will be survivors that give rise to the next dominant population.
- Epimastigote and trypomastigote forms develop in tsetse fly. Infectious trypomastigote form injected into the bloodstream of mammalian host from the fly's

saliva. Antigenic variation of glycoprotein coat of trypomastigotes is due to shifting expression of preexisting genes.

AFRICAN TRYPANOSOMIASIS (SLEEPING SICKNESS)

Caused by Tsetse fly confined to Central Africa. Humans major reservoirs of West African sleeping sickness. Savanna antelopes are reservoirs of East African trypanosomiasis.

At present, there is little evidence of coinfections with African trypanosomes and HIV, possibly because the former is primarily rural in distribution and the latter is concentrated in cities and because major immune responses to trypanosomes are largely antibody mediated and bypass T cells.

PATHOGENESIS AND IMMUNE RESPONSIVENESS

- Local chancre at the site of inoculation and lymphadenitis- Multiplication of the trypomastigotes at the inoculation site produces a localized inflammatory lesion. After the development of this 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.
- Intermittent parasitemia with antigenic shifts- Replicating organisms of the dominant antigenic type continuously produce surface glycoproteins. The trypomastigotes disappear from the blood, reappearing 3 to 8 days later as a new dominant antigenic variant arises.
- Parasites localize in blood vessels of heart and CNS with local vasculitis- During parasitemia, trypanosomes localize in the small blood vessels of the heart and central nervous system (CNS). 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. The mechanism by which the trypanosomes elicit vasculitis is uncertain.
- High levels of IgM include specific and nonspecific antibodies- Much of this is shed from the parasite’s surface and serves as a T-cell–independent antigen to directly stimulate B cells to produce antibody. The antibody produced in this fashion is IgM which can bind to the organism, leading to its destruction by lysis and opsonization.
- Immune complexes may cause anemia and vasculitis

The infection stimulates a massive, nonspecific polyclonal activation of B cells, the production of large quantities of IgM (typically 8-16 times the normal limit), and the suppression of other immune responses. Most of this reaction represents specific protective antibodies that are ultimately responsible for the control of the parasitemia. Some, however, consist of nonspecific heterophile antibodies, antibodies to DNA, and rheumatoid factor. Antibodyinduced destruction of trypanosomes releases invariant nuclear and cytoplasmic antigens with the production of circulating immune complexes.

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 usually progresses more slowly. Bouts of fever often persist for years before CNS manifestations gradually appear.

In the terminal stage, the patient develops a lethal intercurrent infection or lapses into a final coma.

DIAGNOSIS

- Microscopic examination of 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.
- Patient may be screened for elevated levels of IgM in the blood and spinal fluid or specific trypanosomal antibodies by a variety of techniques.
- A card agglutination test for trypanosomiasis (CATT), which can be performed on fingerstick blood, can provide serologic confirmation within minutes.
- Subspecies-specific DNA probes may prove useful for the identification of organisms in clinical specimens.

TREATMENT

- If the specimen reveals evidence of CNS involvement, agents that penetrate the blood–brain barrier must be included.
- Most effective agent is a highly toxic arsenical, melarsoprol (Mel B). Although this agent occasionally produces a lethal hemorrhagic encephalopathy, the invariably fatal outcome of untreated CNS disease warrants its use.
- Ornithine decarboxylase inhibitor, eflornithine (DFMO) appears capable, when used alone, or in combination with suramin, of curing CNS disease caused by *T brucei gambiense* without the serious side effects associated with melarsoprol. Unfortunately, it is very expensive.
- If CNS is not involved, less toxic agents, such as suramin, pentamidine, or eflornithine, can be used. In such cases, the cure rate is high and recovery complete.

PREVENTION

Although a variety of tsetse fly control measures, including the use of insecticides, deforestation, and the introduction of sterile males into the fly population, have been attempted, none has proved totally practicable. The tsetse fly is larviparous and carries a larva within its body until mature and ready to pupate. This means flies have a better chance of survival. In addition, adults are strong fliers.

Eradication of disease reservoirs by the early detection and treatment of human cases and the destruction of wild game has had limited success.

Development of effective vaccines are currently underway but are complicated by the antigenic variability of the trypanosomes.

Personal protection can be achieved with insect repellents and protective clothing. Although prophylactic use of pentamidine was once advocated.