Trypanosomiasis (Sleeping Sickness)

Background

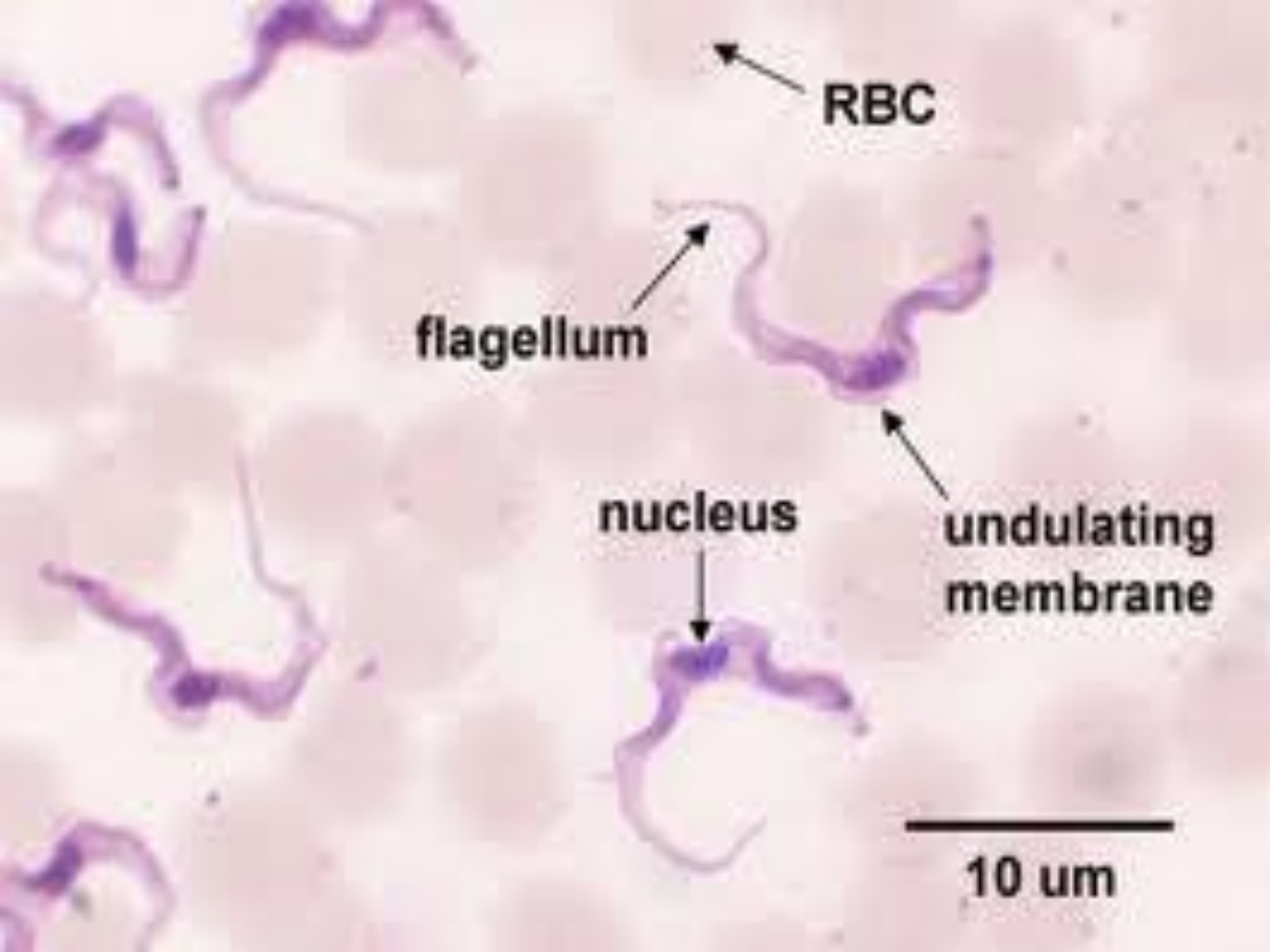
- Human African trypanosomiasis (HAT), also called sleeping sickness
- It is caused by the flagellate protozoan *Trypanosoma brucei*, which exists in 2 morphologically identical subspecies:

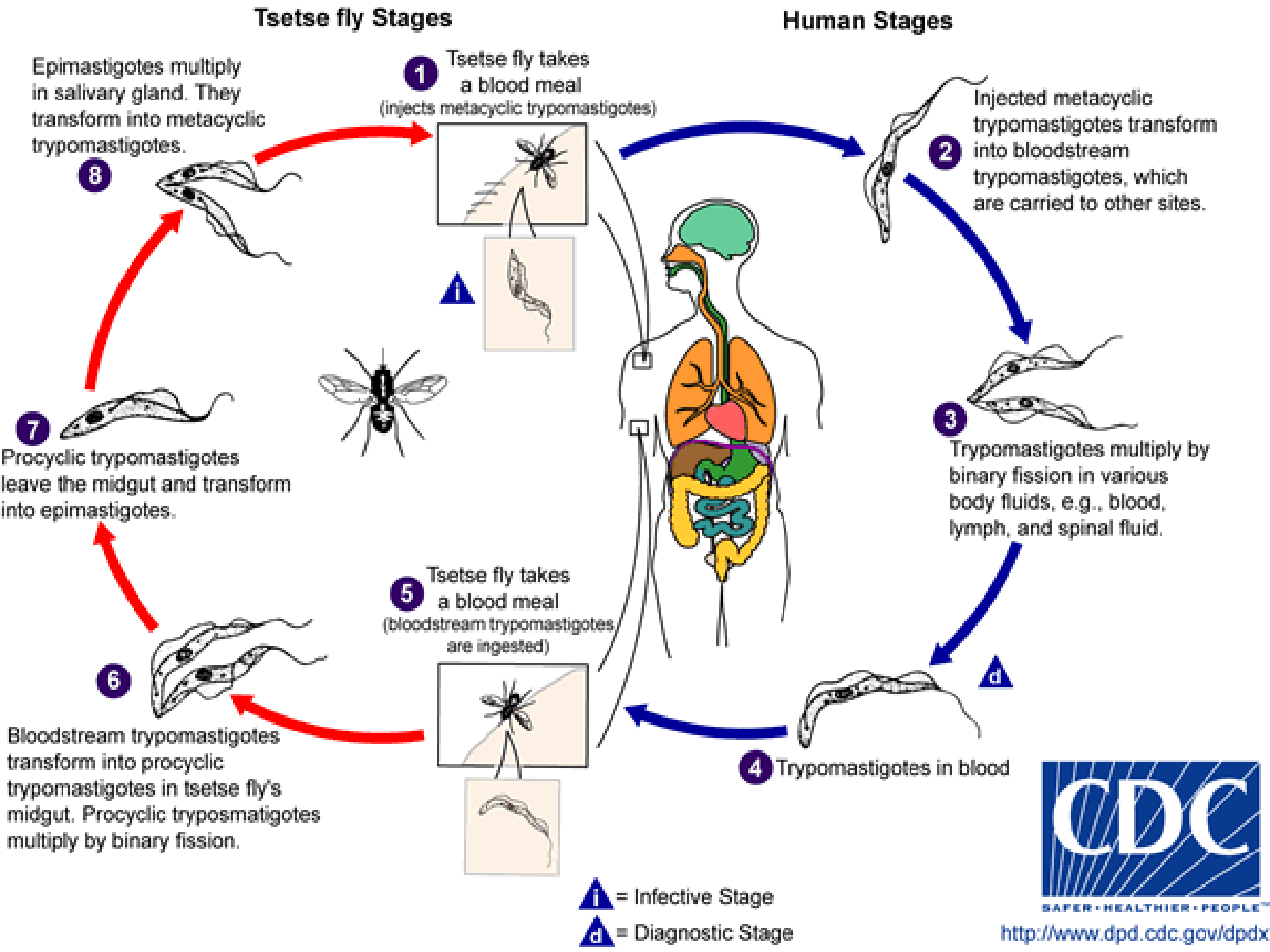
- *Trypanosoma brucei rhodesiense* (East African or Rhodesian African trypanosomiasis)

- and *Trypanosoma brucei gambiense* (West African or Gambian African trypanosomiasis).

Causes

- Both of these parasites are transmitted to human hosts by bites of infected tsetse flies (*Glossina palpalis* transmits *T brucei gambiense* and *Glossina morsitans* transmits *T brucei rhodesiense*), which are found only in Africa.


RBC
flagellum
nucleus
undulating membrane
10 um


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

- The parasites escape the initial host defense mechanisms by extensive antigenic variation of parasite surface glycoproteins known as major variant surface glycoprotein (VSG).
- This evasion of the humoral immune responses contributes to parasite virulence. During the parasitemia, most pathologic changes occur in the hematologic, lymphatic, cardiac, and central nervous systems.

- This may be the result of immune-mediated reactions against antigens on red blood cells, cardiac tissue, and brain tissue, resulting in hemolysis, anemia, pancarditis, and meningoencephalitis

Mortality/Morbidity

- The symptoms of East African trypanosomiasis develop more quickly (starting 1 mo after bite) than the symptoms of West African trypanosomiasis, which can begin months to a year after the first bite

- In West African trypanosomiasis, the asymptomatic phase may precede onset of fevers, rash, and cervical lymphadenopathy.

- If unrecognized, the symptoms then progress to weight loss, asthenia, pruritus, and CNS disease with a more insidious onset. Meningismus is rare. Death at this point is usually due to aspiration or seizures caused by CNS damage.

Clinical Presentation

- **History**

- Stage 1 (early, or hemolymphatic, stage)

- Painless skin chancre that appears about 5-15 days after the bite, resolving spontaneously after several weeks (seen less commonly in *T brucei gambiense* infection)
- Intermittent fever (refractory to antimalarials), general malaise, myalgia, arthralgias, and headache, usually 3 weeks after bite
- Generalized or regional lymphadenopathy (Posterior cervical lymphadenopathy [Winterbottom sign] is characteristic of *T brucei gambiense* African trypanosomiasis [sleeping sickness].)

- Facial edema (minority of patients).
- Transient urticarial, erythematous, or macular rashes 6-8 weeks after onset
- Trypanids (ill-defined, centrally pale, evanescent, annular or blotchy edematous erythematous macules on trunk)

- Stage 2 (late, or CNS, stage) Persistent

- headaches (refractory to analgesics)
- Daytime somnolence followed by nighttime insomnia
- Behavioral changes, mood swings, and, in some patients, depression
- Loss of appetite, wasting syndrome, and weight loss
- Seizures in children (rarely in adults)
- Fevers, tachycardia, irregular rash, edema

- **Physical**
- Stage 1 (early, or hemolymphatic, stage)
- Indurated chancre at bite site
- Skin lesions (trypanids) in light-skinned patients
- Lymphadenopathy: Axillary and inguinal lymphadenopathy are more common in patients with East African trypanosomiasis. Cervical lymphadenopathy is more common in patients with West African trypanosomiasis. The classic Winterbottom sign is clearly visible (ie, enlarged, nontender, mobile posterior cervical lymph node).
- Fevers, tachycardia, irregular rash, edema, and weight loss
- Organomegaly, particularly splenomegaly (*T brucei gambiense* African trypanosomiasis)

Stage 2 (late, or CNS, stage)

- CNS symptoms: The CNS symptoms of West African trypanosomiasis have a slower onset of, ie, months to a year. Symptoms include irritability, tremors, increased muscle rigidity and tonicity, occasional ataxia, and hemiparesis, but rarely overt meningeal signs. East African trypanosomiasis usually has a faster onset, ie, weeks to a month, and does not exhibit a clear distinction between the two stages.
- Kerandel sign, including delayed pain on compression of patient's soft tissue

- Antigen detection tests based on enzyme-linked immunosorbent assay (ELISA) technology have been developed. They have shown inconsistent results and are not yet commercially available.
- Culture of CSF, blood, bone marrow aspirate, or tissue specimens can be performed in liquid media.
- Other tests developed but not frequently used clinically include antibody detection in the CSF and intrathecal space (low sensitivity), polymerase chain reaction (PCR), and serum proteomic tests.
- Research tools such as isoenzyme analysis and restriction fragment length polymorphism (RFLP) are used for definitive subspecies identification.

American Trypanosomiasis (Chagas Disease)

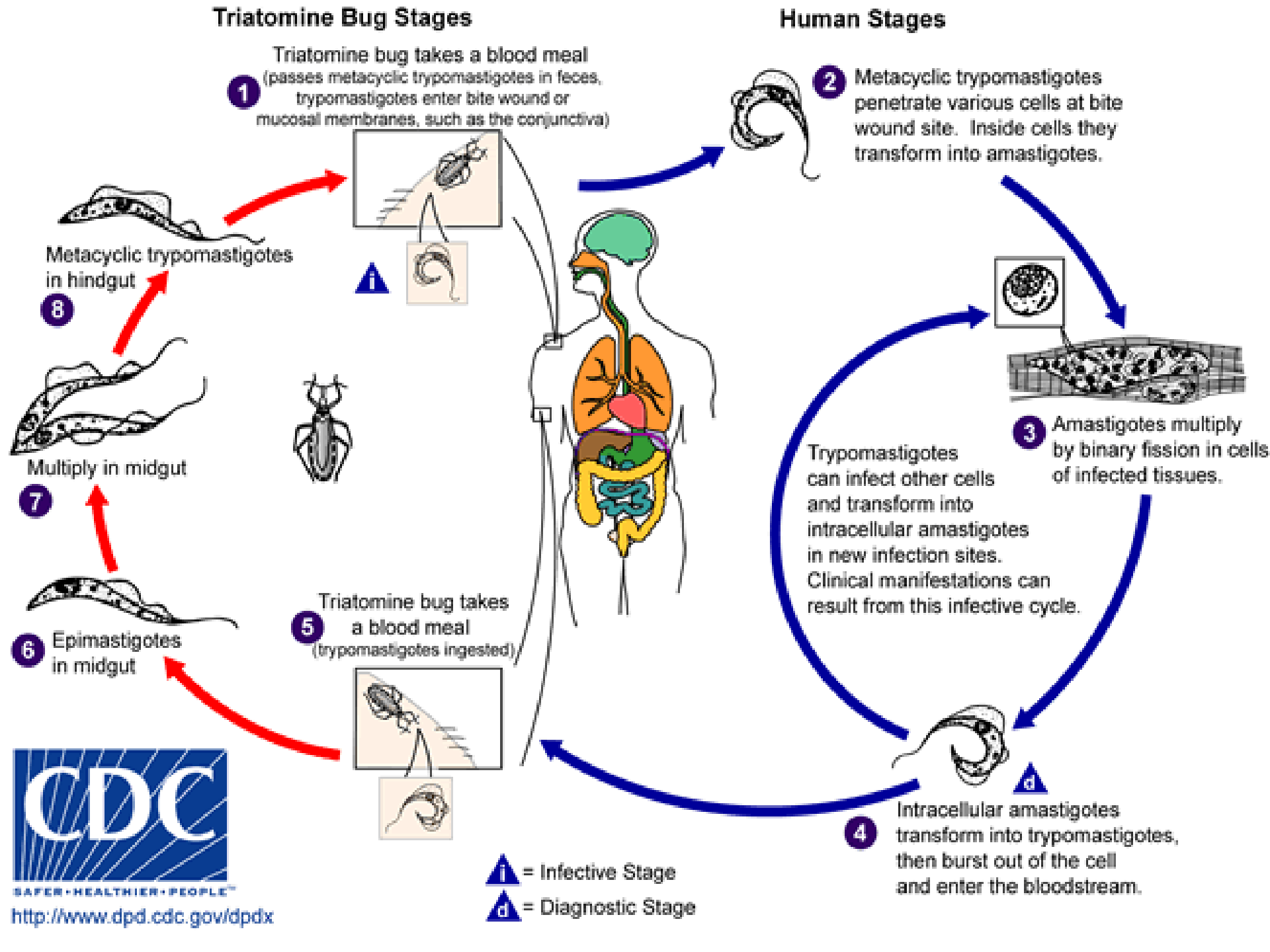
- Chagas disease, or American trypanosomiasis, is caused by the parasite *Trypanosoma cruzi*. Infection is most commonly acquired through contact with the feces of an infected triatomine bug (or "kissing bug"), a blood-sucking insect that feeds on humans and animals.

Infection can also occur from:

- mother-to-baby (congenital),
- contaminated blood products (transfusions),
- an organ transplanted from an infected donor,
- laboratory accident, or
- contaminated food or drink (rare)

Epidemiology

- Chagas disease is endemic throughout much of Mexico, Central America, and South America where an estimated 8 to 11 million people are infected. The triatomine bug thrives under poor housing conditions (for example, mud walls, thatched roofs), so in endemic countries, people living in rural areas are at greatest risk for acquiring infection


Triatomine Bug Stages
Human Stages
Triatomine bug takes a blood meal
(passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)
1
i
Metacyclic trypomastigotes in hindgut
8
Multiply in midgut
7
Epimastigotes in midgut
6
Triatomine bug takes a blood meal
(trypomastigotes ingested)
5
2
Metacyclic trypomastigotes penetrate various cells at bite wound site. Inside cells they transform into amastigotes.
3
Amastigotes multiply by binary fission in cells of infected tissues.
Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle.
d
4
Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.
i = Infective Stage
d = Diagnostic Stage
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Disease

- Chagas disease has an acute and a chronic phase. If untreated, infection is lifelong.
- Acute Chagas disease occurs immediately after infection, may last up to a few weeks or months, and parasites may be found in the circulating blood.
- Infection may be mild or asymptomatic. There may be fever or swelling around the site of inoculation (where the parasite entered into the skin or mucous membrane).
- Rarely, acute infection may result in severe inflammation of the heart muscle or the brain and lining around the brain.

- Following the acute phase, most infected people enter into a prolonged asymptomatic form of disease (called "chronic indeterminate") during which few or no parasites are found in the blood. During this time, most people are unaware of their infection.

- Many people may remain asymptomatic for life and never develop Chagas-related symptoms..

Complications of chronic Chagas disease may include:

- heart rhythm abnormalities that can cause sudden death; a dilated heart that doesn't pump blood well; a dilated esophagus or colon, leading to difficulties with eating or passing stool.

- In people who have suppressed immune systems (for example, due to AIDS or chemotherapy), Chagas disease can reactivate with parasites found in the circulating blood.

Laboratory Diagnosis

Demonstration of the causal agent is the diagnostic procedure in acute Chagas disease. It almost always yields positive results, and can be achieved by:

- Microscopic examination: a) of fresh anticoagulated blood, or its buffy coat, for motile parasites; and b) of thin and thick blood smears stained with Giemsa, for visualization of parasites.
- Isolation of the agent: a) inoculation in culture with specialized media (e.g. NNN, LIT); b) inoculation into mice; and c) xenodiagnosis, where uninfected triatomine bugs are fed on the patient's blood, and their gut contents examined for parasites 4 weeks later.

Antibody Detection

- During the chronic phase of infection, parasitemia is low; immunodiagnosis is a useful technique for determining whether the patient is infected.