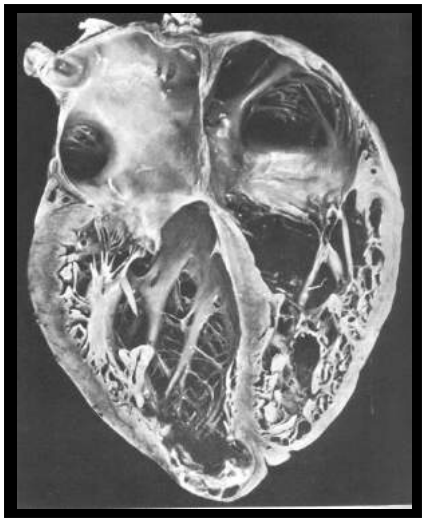
Trypanosomiasis

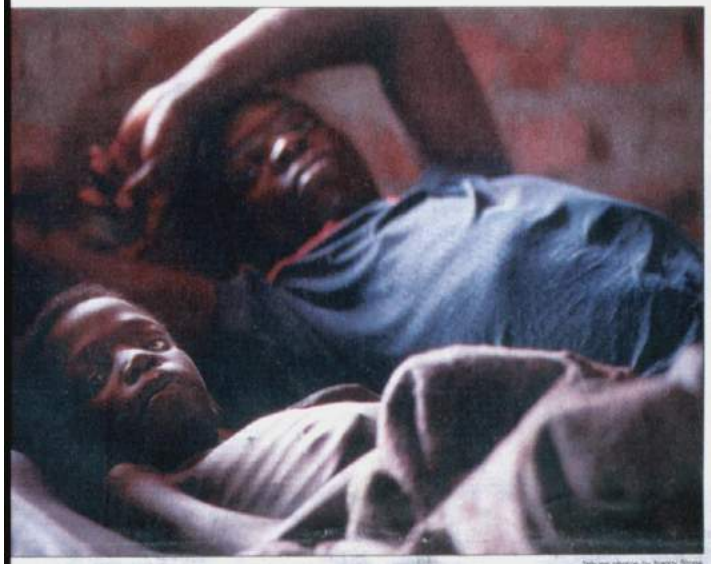
African trypanosomiasis
(Sleeping sleepness)

American trypanosomiasis
(Chagas' disease)



Last decade had many raging epidemics throughout subSahara

Plagues of old reclaim continent



Tribune photos by Nancy Stone

o Dousa, 10, and his father, Paul Khamis, are patients at a hospital in Ikba, Sudan, built for people with sleeping sickness. o was severely malnourished when he first arrived because he wasn't awake long enough to eat properly.

Health care is regressing, life expectancy is going down.
Sleeping sickness, once vanquished, is killing again.
And in a post-Cold War world, few appear to care.

The New York Times

NEW YORK, FRIDAY, JULY 18, 1997

Epidemic Rakes Sudan; Among Century's Worst

CNN interactive

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CNN
S. TIME WELL SPENT

Battling the deadly bite of the tsetse fly

February 28, 1998
Web posted at: 2:08 p.m. EST (1908 GMT)

(CNN) -- On the African continent, in the narrow band between the 15th parallels that bookend the equator, a tiny fly is jeopardizing the lives of 55 million people and could be responsible for one of the largest epidemics of this century.

The narrow arc along the equator ventures through 36 sub-Saharan nations, 22 of which are among the most underdeveloped in the world. In every land, the tsetse fly thrives.

DISCOVER Vol. 19 No. 8 (August 1998)
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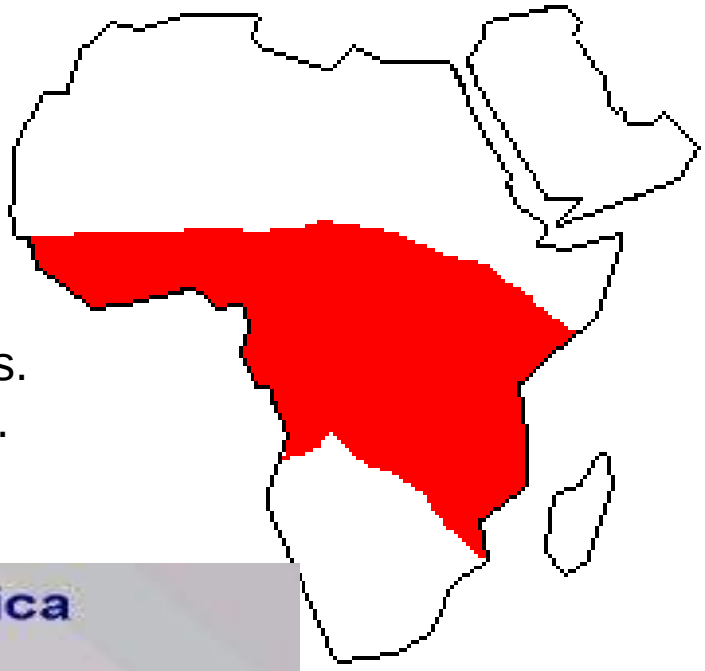
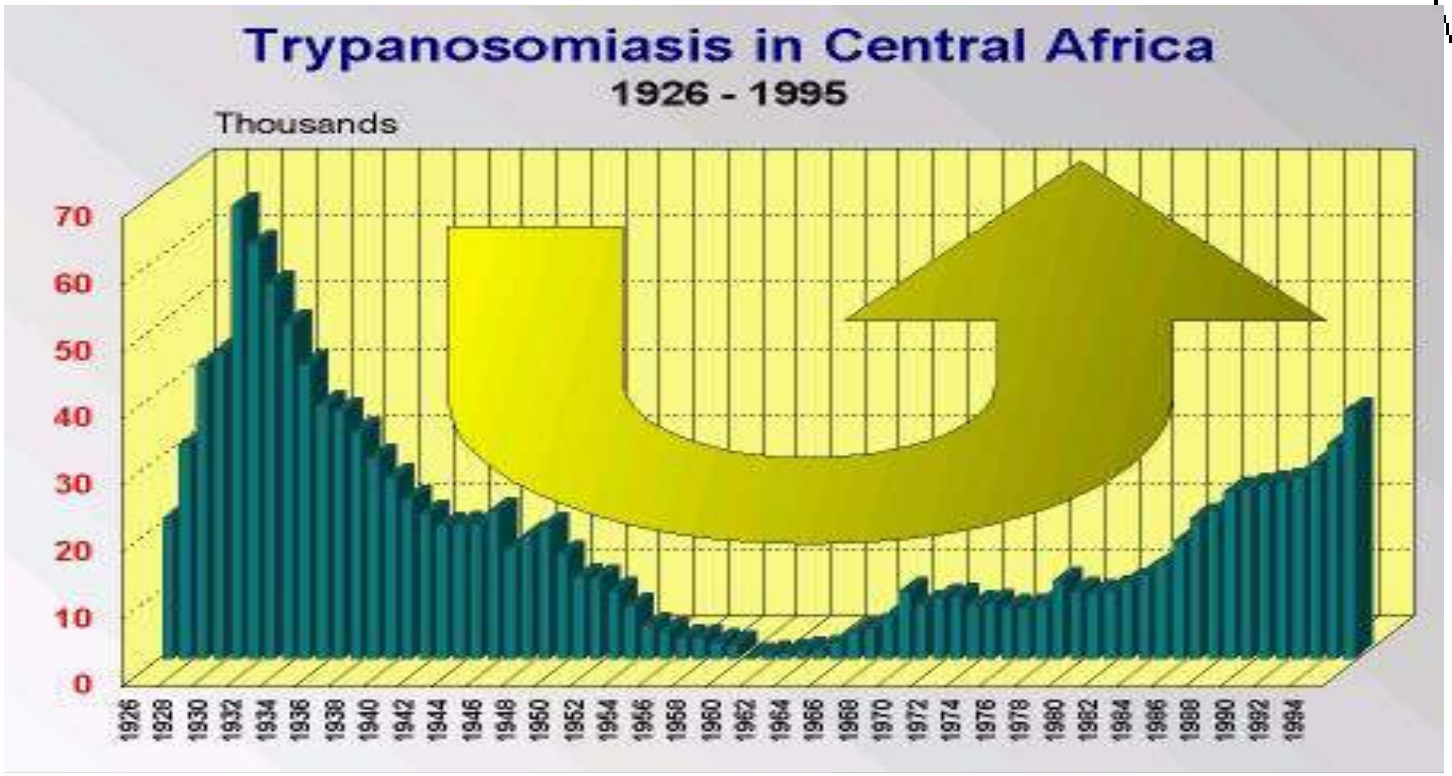
A Sleeping Storm

Sleeping sickness - once thought to be vanquished - is raging back across Africa. At the center of the epidemic, an American doctor is trying to clear a small patch of good health.

By Carl Zimmer

60 million people at risk in 36 countries
300,000-500,000 new cases/year
most will die within two years
66,000 deaths/year
These parasites easily develop resistance to drugs.
The current drug treatments are toxic to humans.



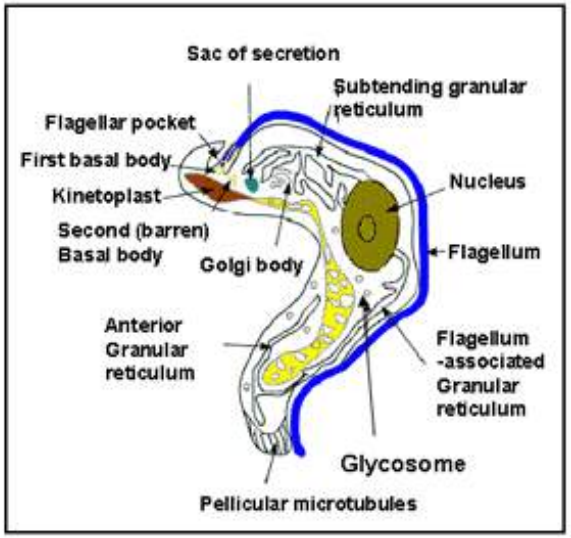


Annual Morbidity & Mortality of Selected Parasitic Diseases

	Number Infected	Number deaths
African Sleeping Sickness	300 thousand	> 30 thousand(10%)
Malaria	500 million	2.7 million (0.5%)
Ascariasis	1.2 billion	60 thousand (0.005%)

WHO (1997)

Kinetoplastida: Trypanosomes



Kinetoplast: single large mitochondrion containing material that stains darkly with histochemical techniques.

Three families:

Bodonidae-free living

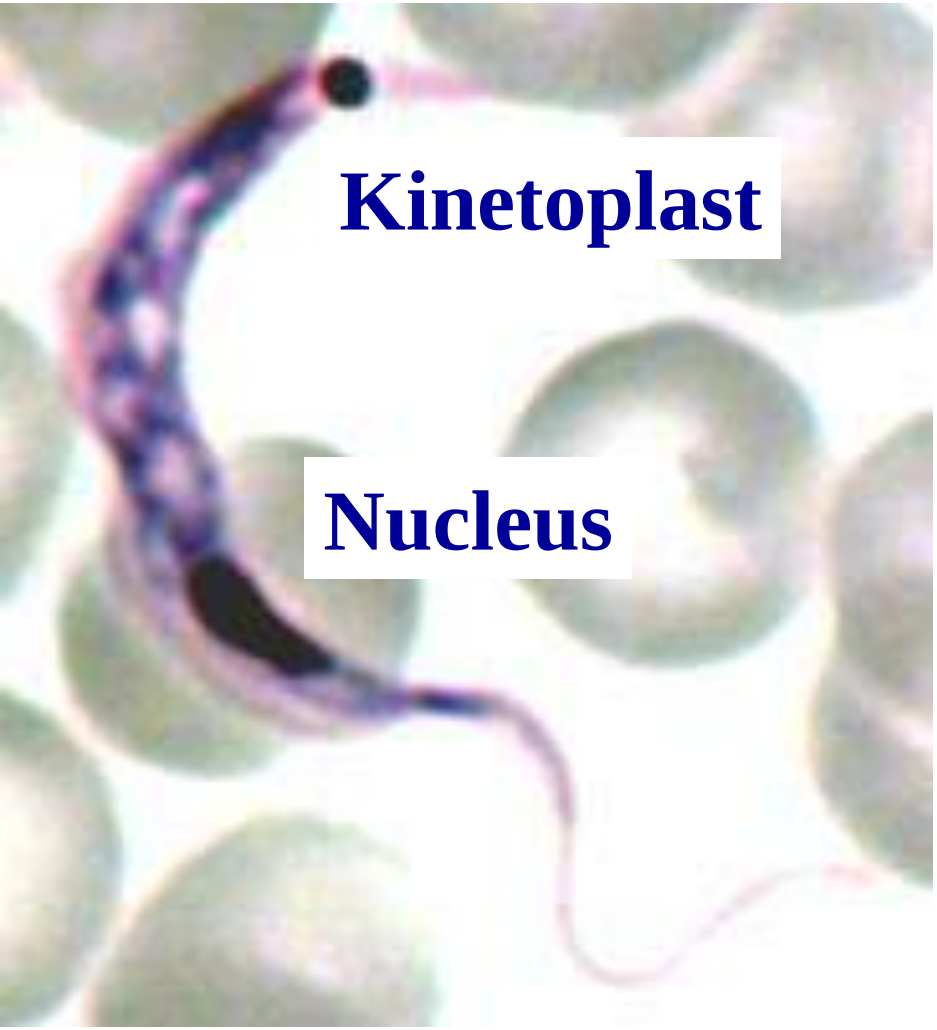
Cryptobiidae-parasites of fish and invertebrates

Trypanosomatidae- some members important to humans and domestic animals

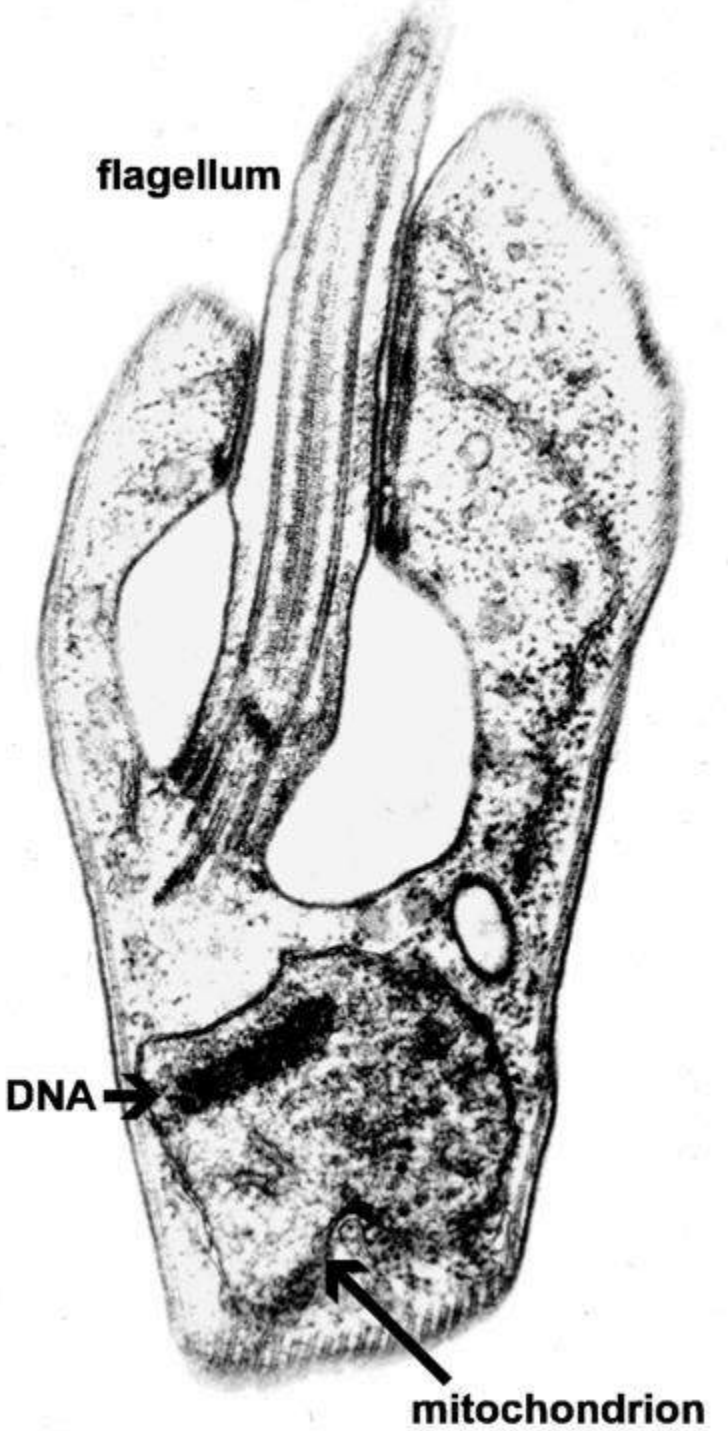
Heteroxenous (most) – require more than one living host to complete life cycle

Hemoflagellates – dependence on blood

KINETOPLASTIDS

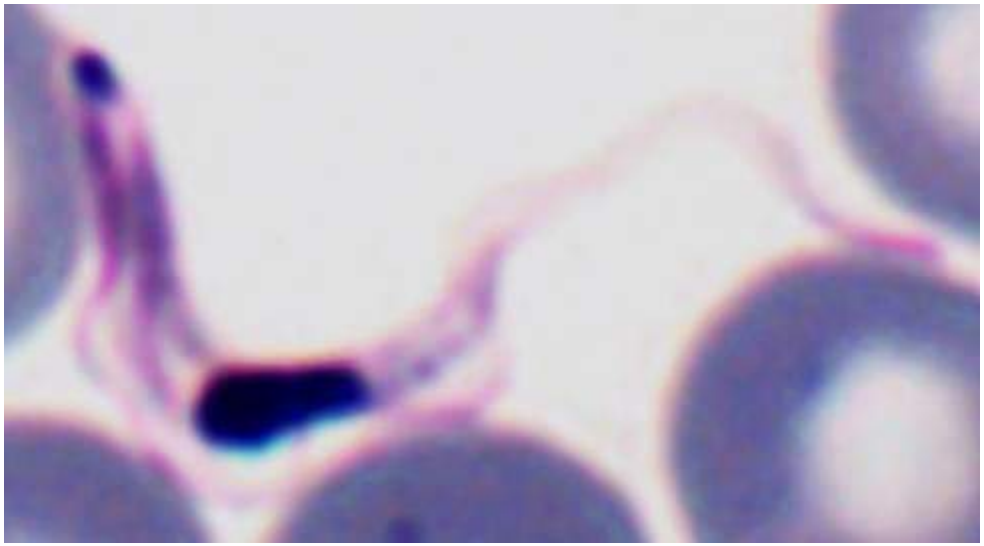


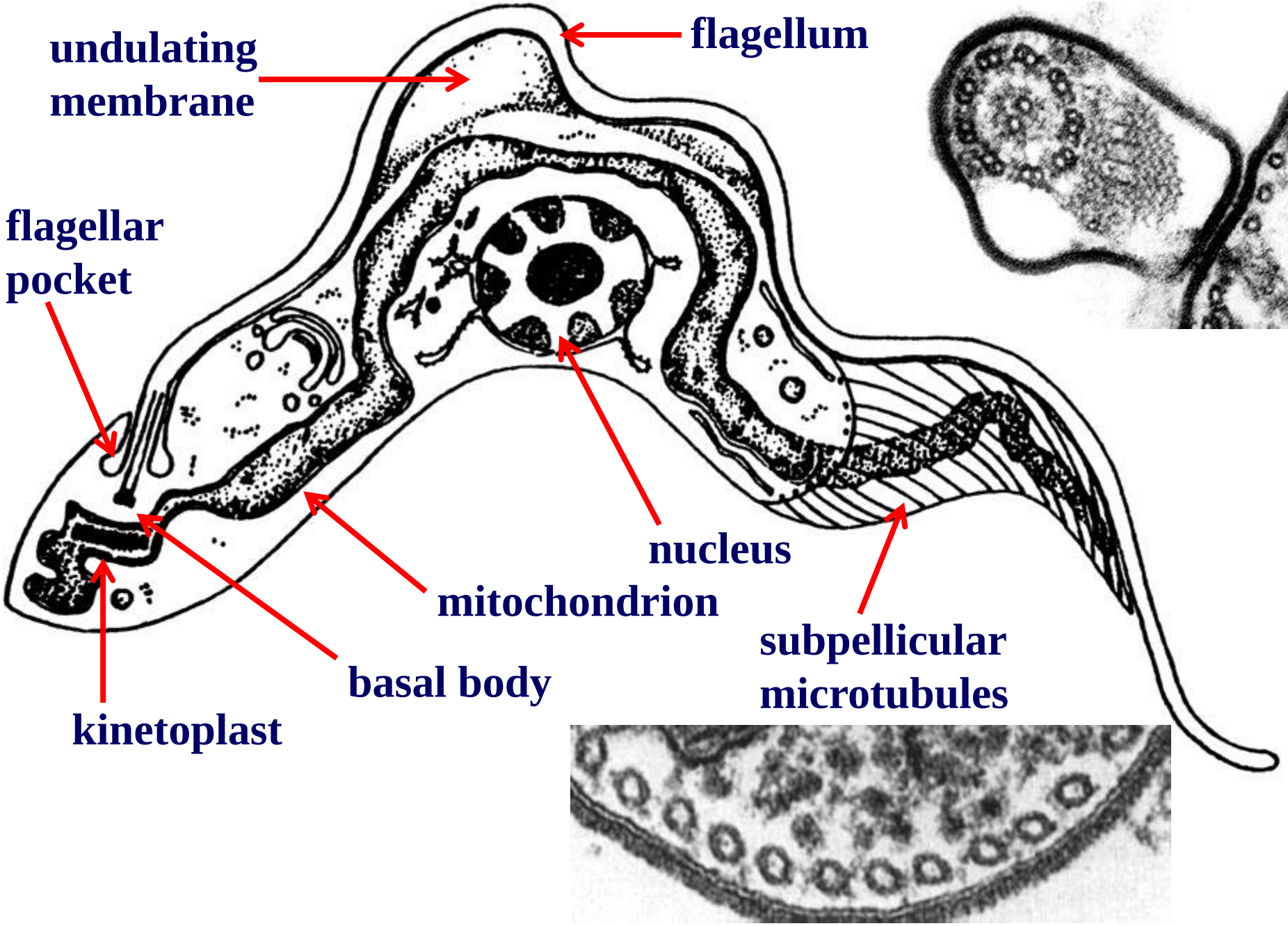
- widespread parasites
  - animals (fish→humans)
  - insects
  - plants
- monophyletic group
  - related to euglenoids
- unifying feature = kinetoplast
  - Giemsa staining structure

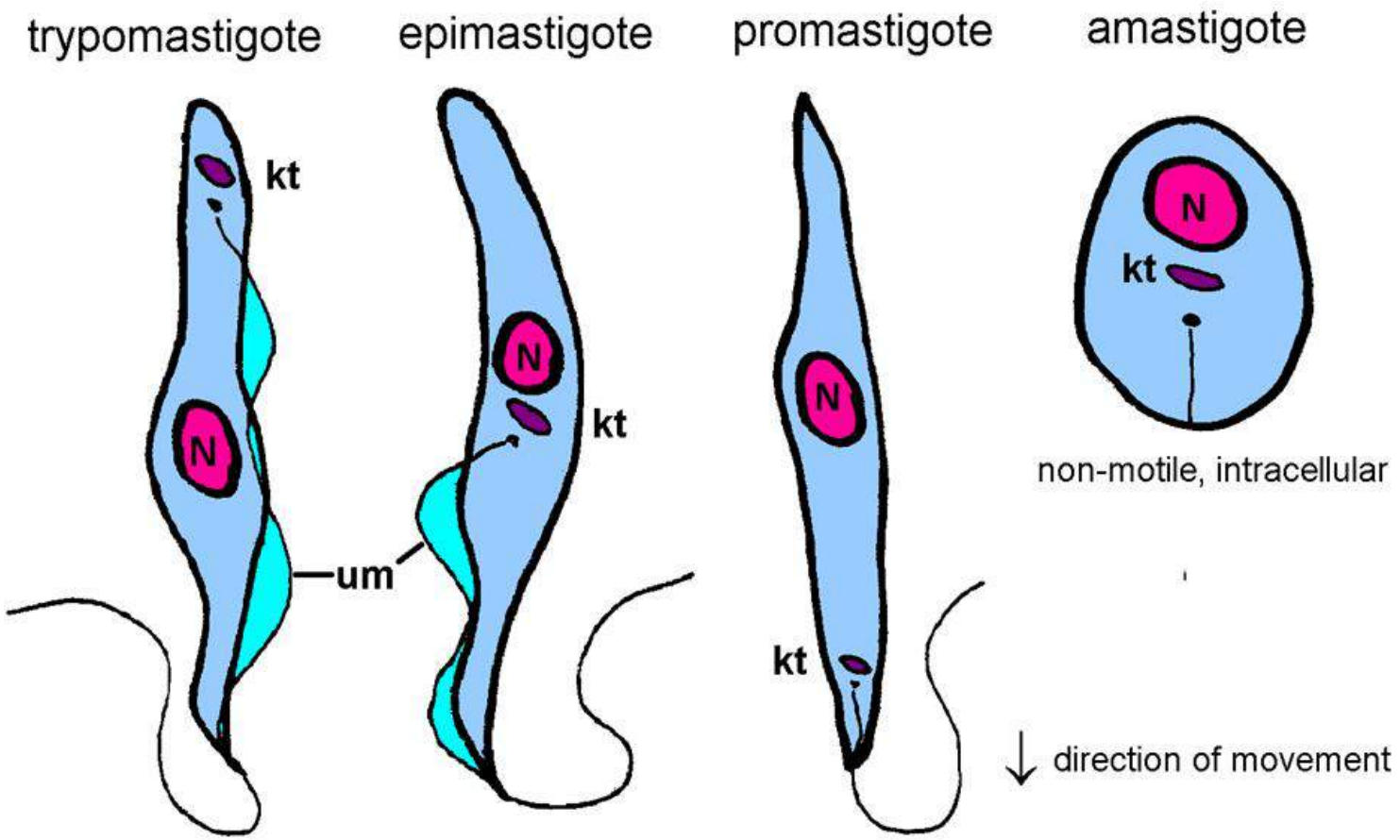


KINETOPLAST

- mitochondrial DNA
- located near base of flagellum
- initially believed to function in movement




undulating membrane
flagellum
flagellar pocket
nucleus
mitochondrion
basal body
kinetoplast
subpellicular microtubules



- Morphological stages - mastigote (from subphylum Mastigophora)– mastix (Gr.) for whip
  - Trypomastigote – in the blood stream; flagellum runs entire length from posterior

African Trypanosomiasis: History

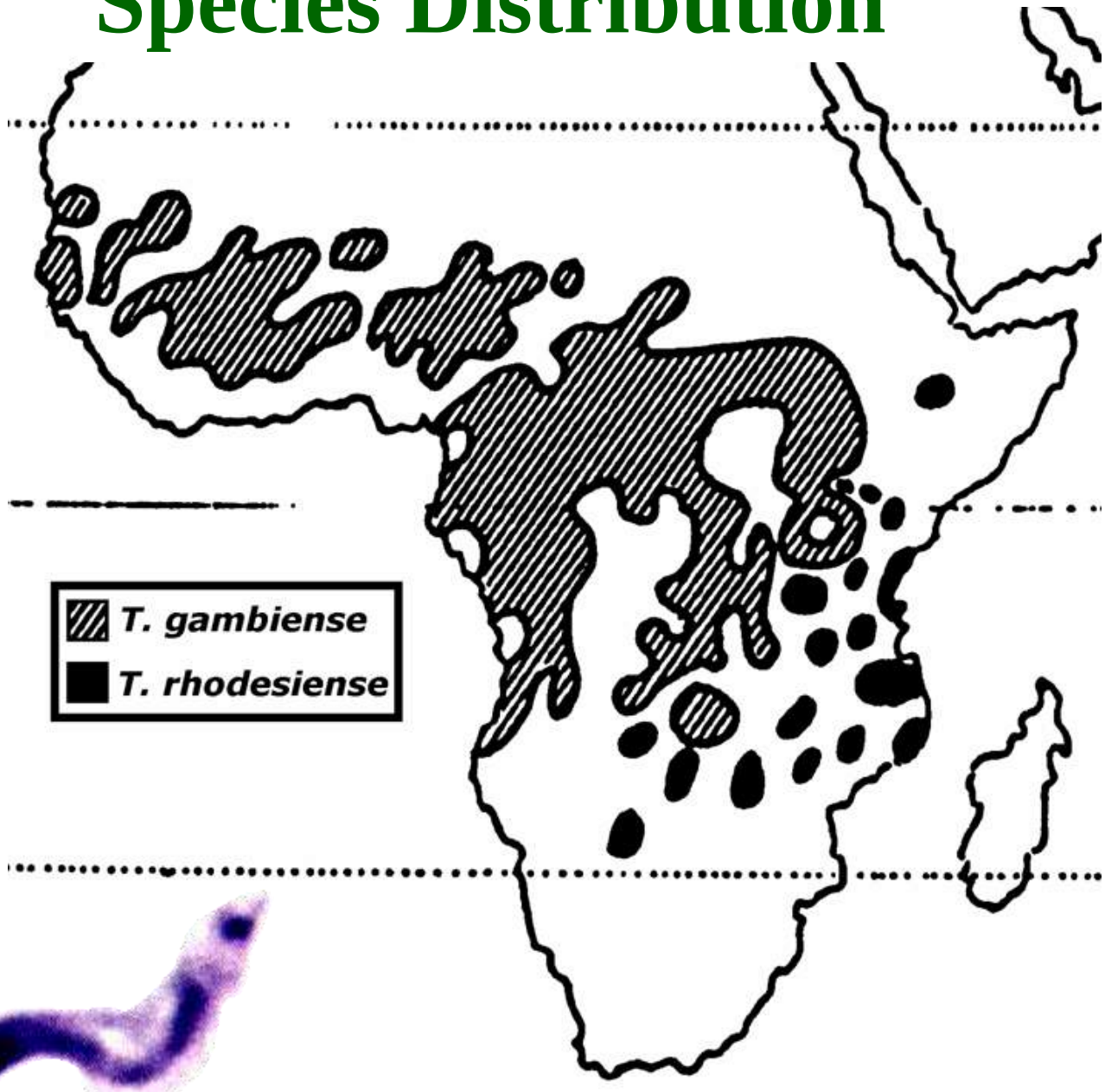
- Recognized as far back as 14th century
- Only in 20th century has magnitude of problem been elucidated
- Progress towards elimination ensued over the first half of the century after recognition of agent, vector, and development of treatment regimes

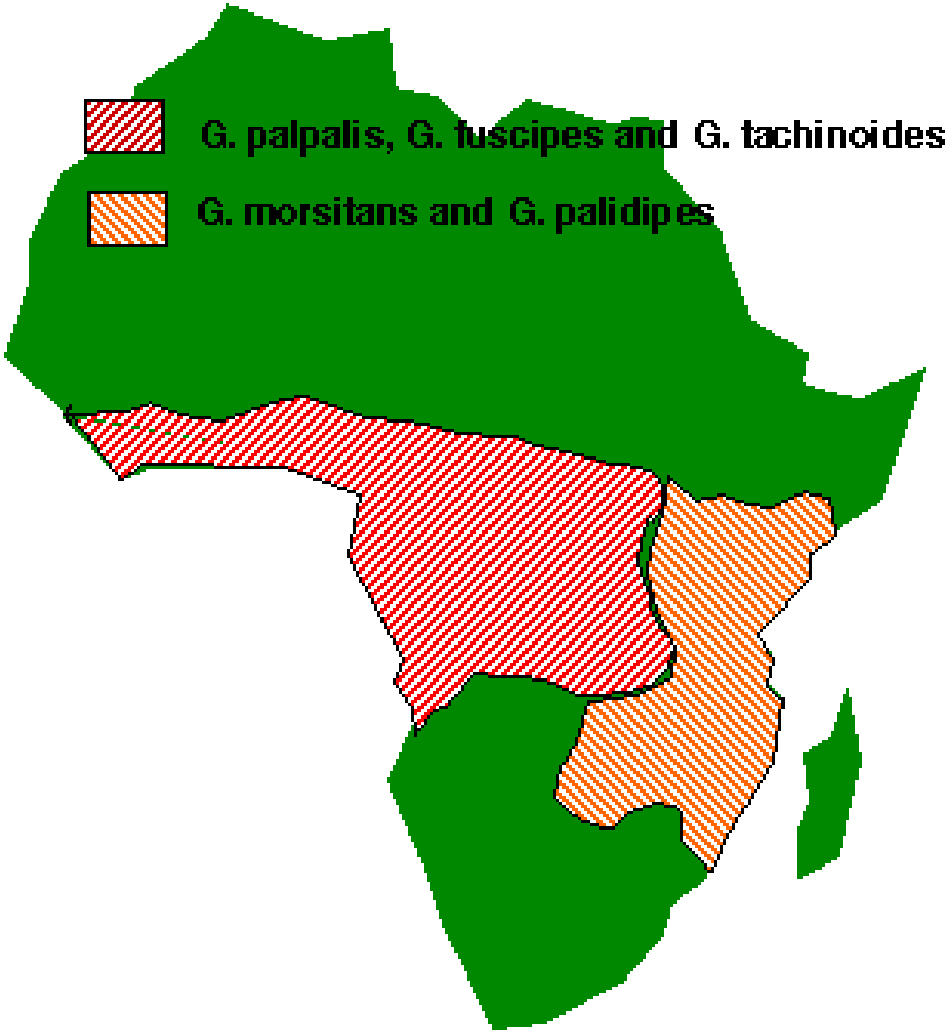
Trypanosoma brucei complex

T. b. brucei	**game animals/livestock (nagana)**
T. b. rhodesiense	**E. African trypanosomiasis**
T. b. gambiense	**W. and Central African sleeping sickness**

•A systemic protozoan disease, organisms grow in blood, lymph, CSF, and intercellular spaces

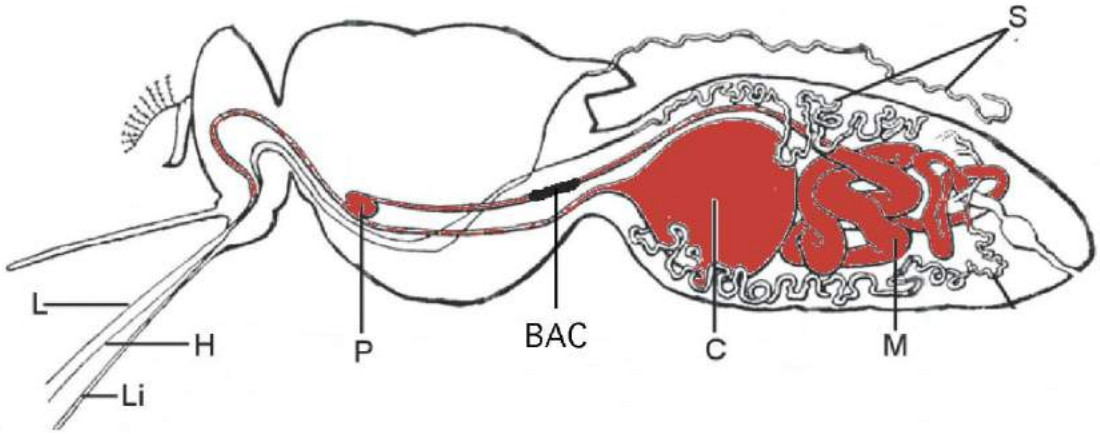
Species Distribution





The savanna vectors *G.morsitans* and *G. palidipes* are responsible for the transmission of *T. rhodesiense* in East Africa, while the principal vectors of west African sleeping sickness are *G. palpalis, G. fuscipes* and *G. tachinoides*.

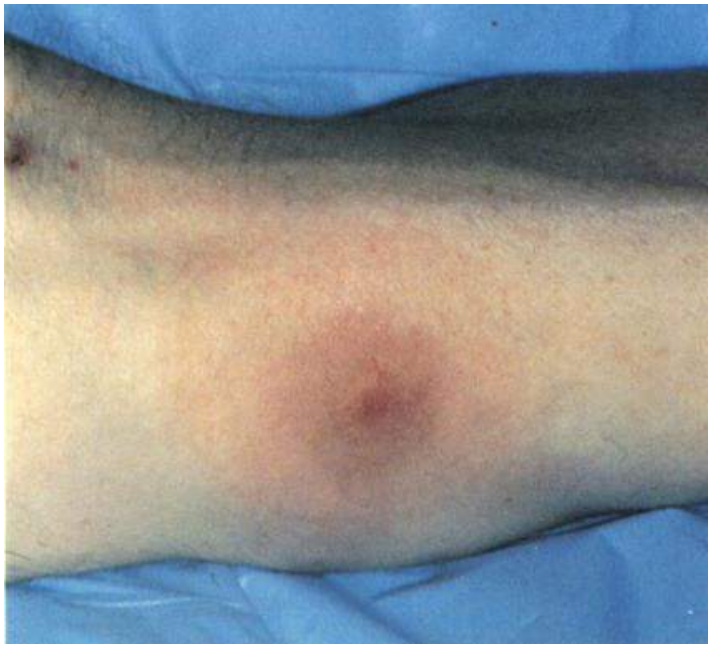
African trypanosomiasis: Epidemiology

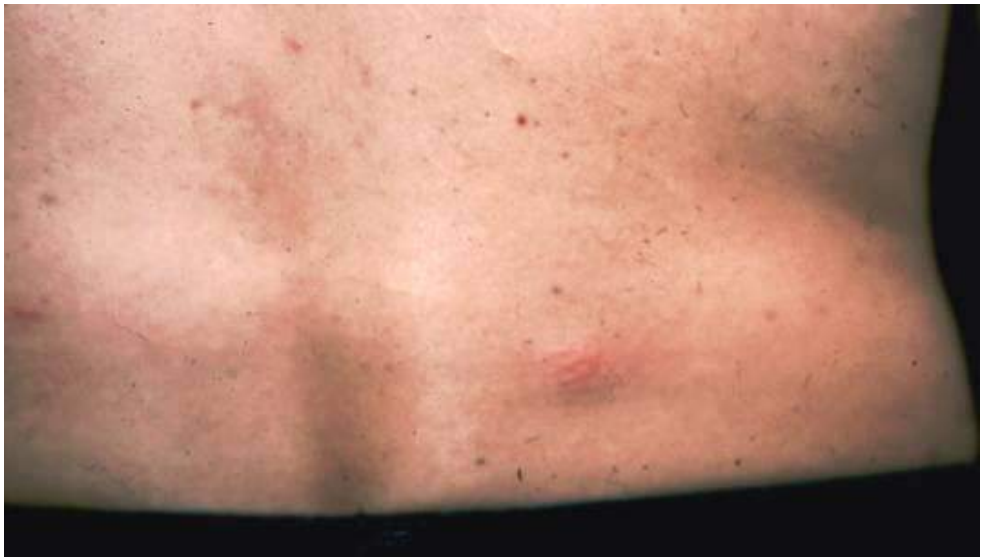


- Vector:
  - *Glossina spp.* - tsetse fly
  - Name stems from sound made in flight; means “fly” in Tswana
  - Order: Diptera (true flies)
  - Hemataphagous - piercing/sucking fly (biting fly is really a misnomer)
  - Holometabola – complete metamorphosis
    - egg – larva (4) - pupa - adult
  - Only found in sub-saharan Africa and isolated area of Arabian peninsula

Infection

- tsetse are pool feeders
- metacyclic trypomastigotes in saliva and enter bite wound

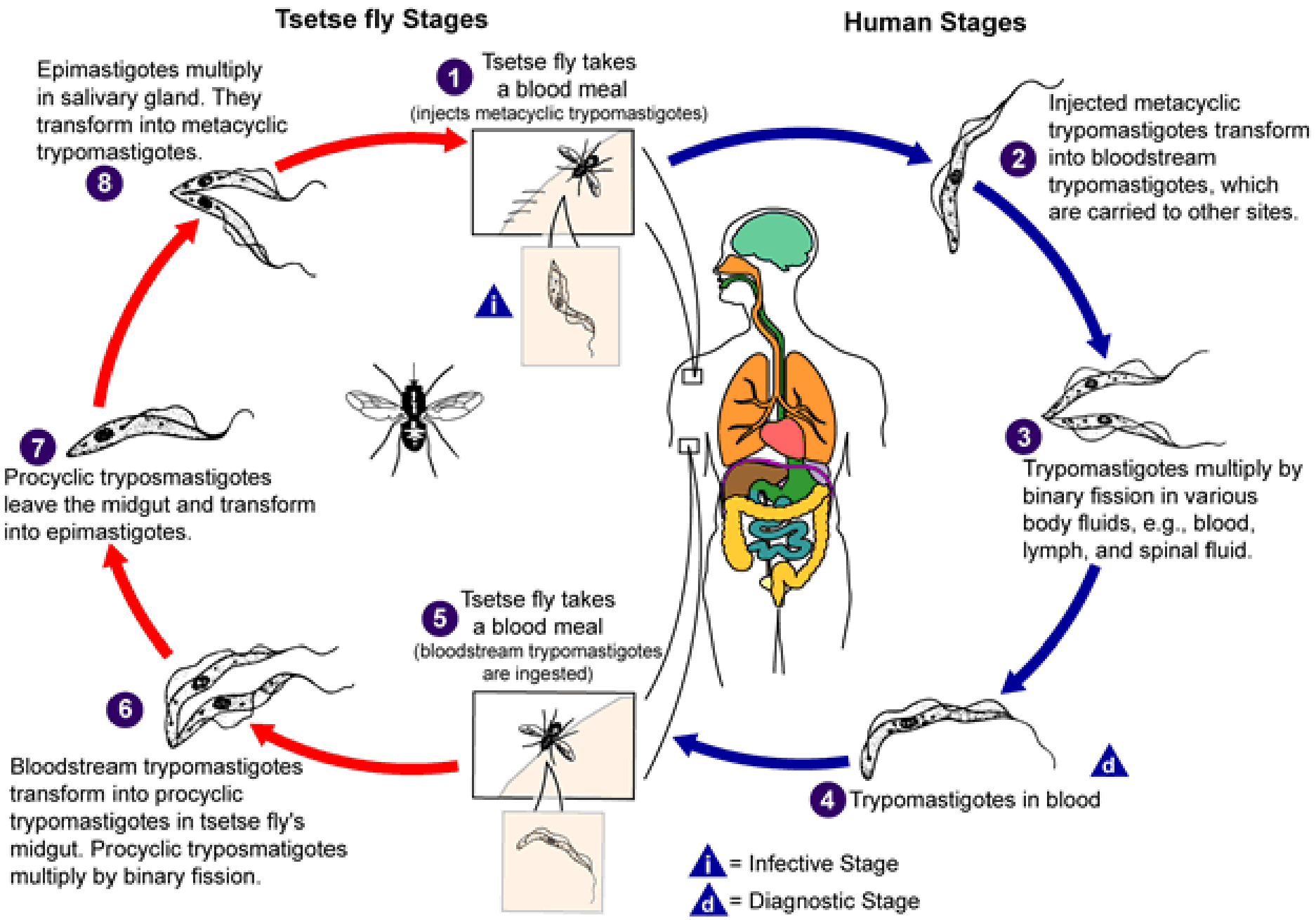




Tsetse Bite

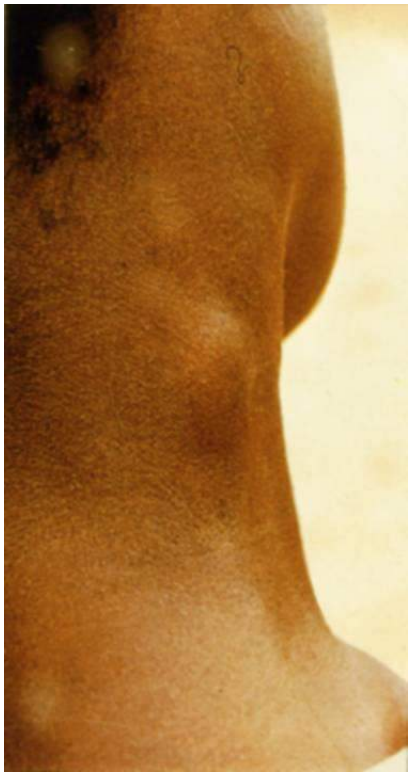
± pain

± hypersensitivity

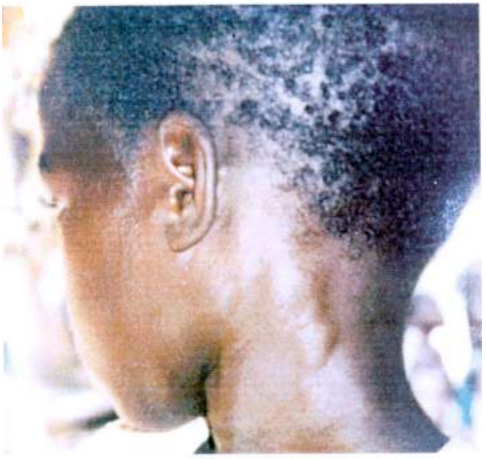

Tsetse fly Stages
Human Stages
Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.
8
1 Tsetse fly takes a blood meal
(injects metacyclic trypomastigotes)
i
2 Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other 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 tryposmastigotes leave the midgut and transform into epimastigotes.
i = Infective Stage
d = Diagnostic Stage

African trypanosomiasis: Clinical features

- Pathogenesis - general
  - Typanosomes live in blood, lymph nodes, spleen – therefore not intracellular
  - Particularly abundant in intercellular spaces in brain
  - Clinical course dependent on host susceptibility
    - *T.b.brucei* - vertebrate hosts (equidae, dogs, some ruminants) exhibit acute disease with death in ~ 2 weeks
    - If survive, blindness common in dogs

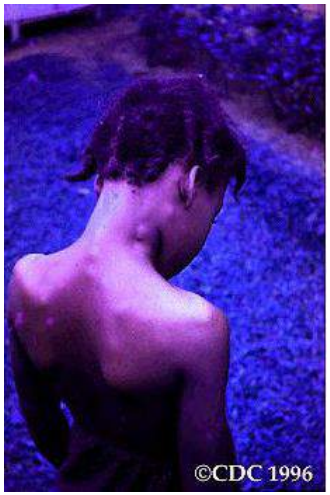


African trypanosomiasis: Clinical features



Pathogenesis

- Humans
  - Local reaction: painful sore at site of bite, disappears after a couple of weeks
  - Trypanosomes reproduce rapidly once enter blood and lymph system – lymphadenopathy, generalized invasion of all organs
  - Winterbottom's sign – swollen nodes at base of skull; sign of certain death according to slave traders



African trypanosomiasis: Clinical features

- Pathogenesis
  - Circadian rhythms - alterations in endogenous rhythms correlate with clinical symptoms
  - Suprachiasmic nucleus (SCN) – “biological clock” – regulates hormonal, sleep, body thermostat activity
  - Spontaneous rhythm of SCN is altered with trypanosome infection

African trypanosomiasis: Clinical features

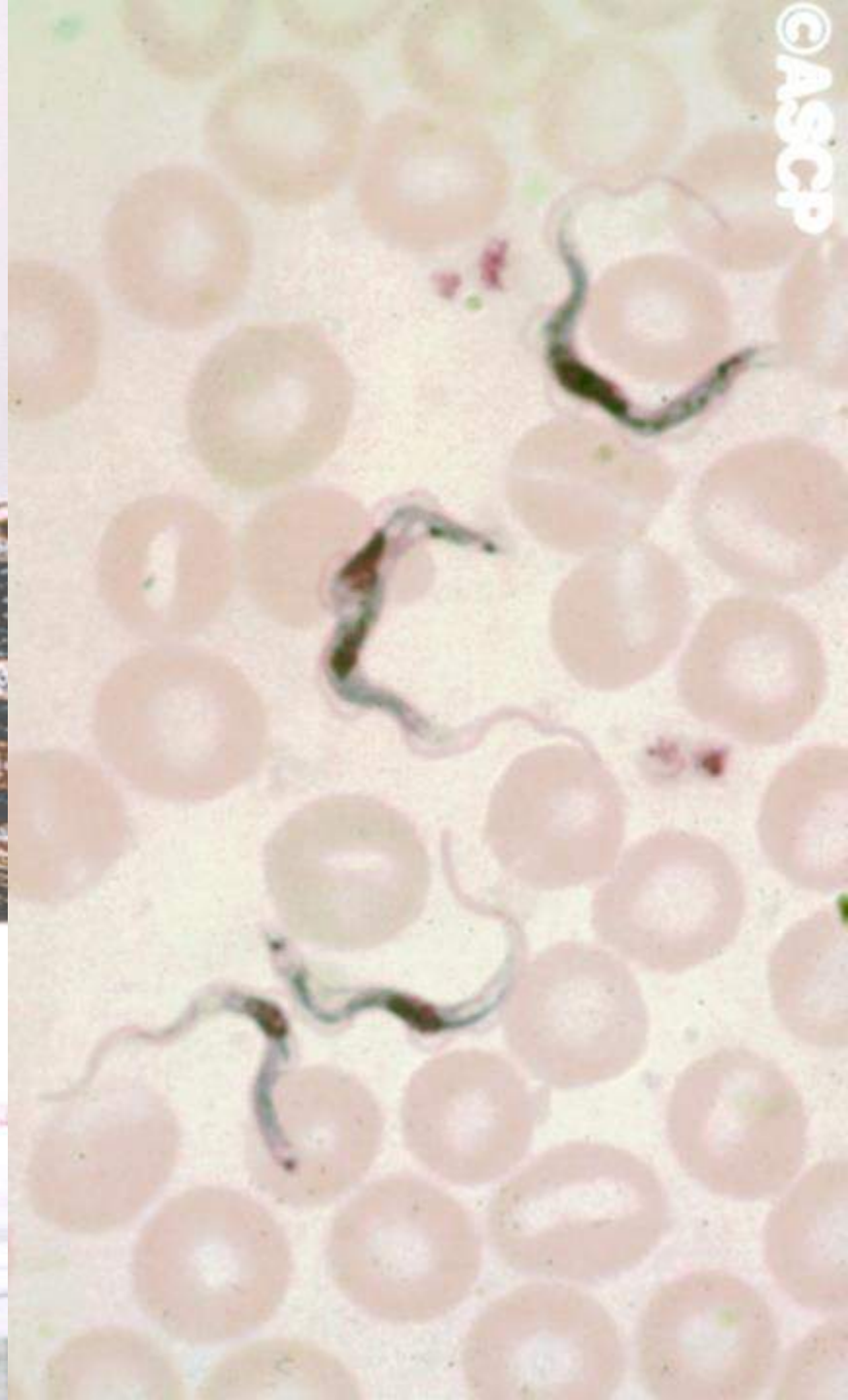
- Incubation period
  - Rhodesiense days to weeks
  - Gambiense much longer - months to years
- Clinical signs - early stages
  - painful chancre at site of bite
  - fever
  - intense headache, insomnia
  - lymphadenopathy, localized edema, rash
  - anemia

African trypanosomiasis: Clinical features

- Clinical signs - late stages
  - severe wasting
  - somnolence
  - CNS signs – increased apathy, dullness, tremors, convulsions, coma, death
- Gambiense more protracted course
- Rhodesiense more rapidly fatal
- both forms are always fatal without treatment

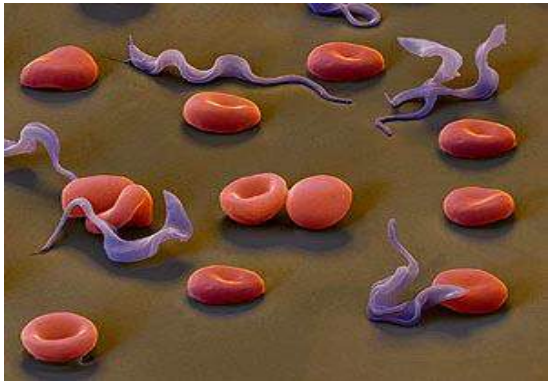
CNS Disease Course and Symptoms

- parasites crossing blood-brain barrier result in CNS involvement and nervous impairment
  - described as meningoencephalitis
  - increased apathy and fatigue
  - confusion and somnolence
  - motor changes including tics, slurred speech, incoordination
  - convulsions, coma
- progression to CNS involvement is rapid (weeks) in *Tr* and slow (6-12 months) in *Tg*
- death results from disease (eg., convulsions, hyperpyrexia) or other infections


©ASCP

BLOOD STAGE

The earliest sign of a generalized infection is fever; there may also be malaise, headache and pains in the joints. Five to12 days after infection trypanosomes are found in the bloodstream. They are scarce in *T. gambiense*, and more abundant i.e.10^5/ml in *T. rhodesiense.* Trypanosomes also enter the lymphatics. The influx of B-cells results in lymph node enlargement and the lysis of trypanosomes release toxic materials that stimulate macrophages to release tumor necrosis factor. The release of trypanosome toxic factors and lymphokines gives rise to a cyclic (or relapsing) fever with an approximate cycle of 7-10 days.



trypomastigotes in the blood

LATE STAGE

In the Rhodesian form there is a rapid illness with invasion of the CNS via lymphatics within a few weeks. Patients may die of myocarditis even before the CNS is invaded. In the Gambian form the disease progresses in a more insidious fashion with personality changes, insomnia or irritability signaling invasion of the CNS. CNS involvement may not occur until one or more years after infection. Inflammatory changes lead to a demyelinating meningoencephalitis; there is cerebral edema, hemorrhages, pericarditis, and anemia. The encephalopathy leads to apathy, somnolence and coma. Death is often caused by infections such as pneumonia.

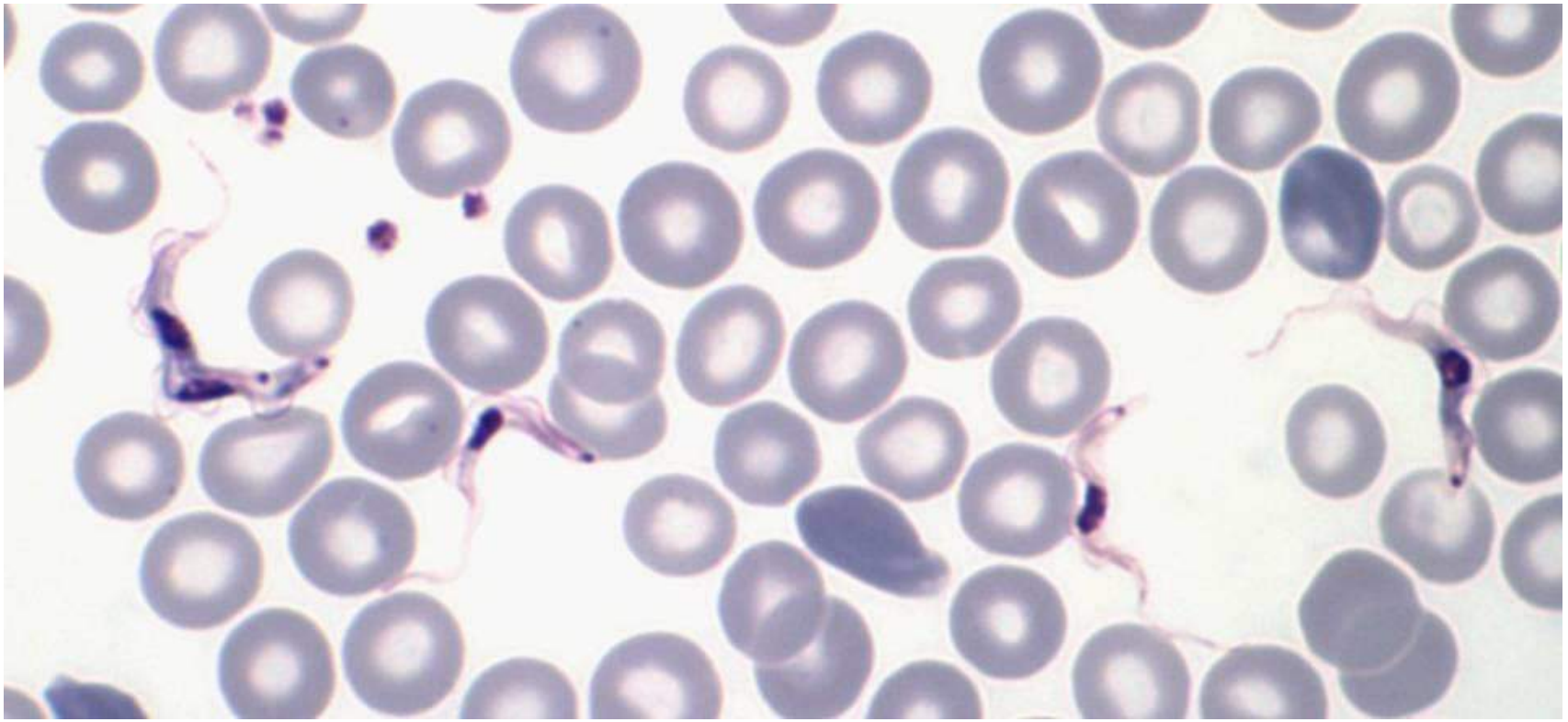
African Sleeping Sickness

African trypanosomiasis: Diagnosis

- direct examination of aspirate or smear - wet mount for motile trypomastigotes
- concentration techniques usually required before microscopic examination
- animal inoculation/isolation - for *T. b. rhodesiense*
- CATT (card agglutination trypanosome test) - useful for gambiense screening and surveillance
- serology
  - antibodies: IFA, ELISA; high levels of IgM common

African trypanosomiasis: Diagnosis

- *T. b. rhodesiense* (geimsa stain of blood smear)



Get the right treatment……..

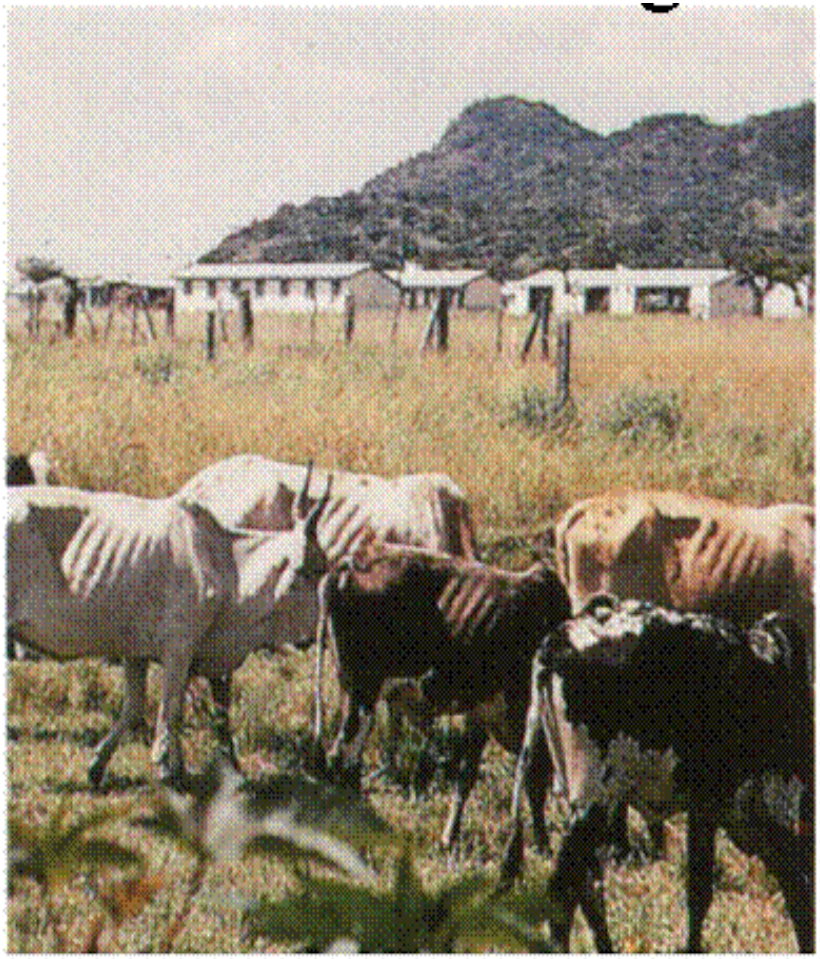
Drugs for Neglected Diseases initiative

Currently available treatments for sleeping sickness melarsoprol, eflornithine, pentamadine, and suramin are few and limited due to age, toxicity, and lost efficacy in several regions. Treatment is stage-specific, with more toxic and more difficult-to-administer treatments (melarsoprol, eflornithine) for stage 2 disease. Few projects for improved treatments are currently in clinical development, and none has the potential to dramatically change either the treatment or control options for this disease.

Most drugs are old, difficult to administer in poor conditions and by no means always successful.

Nagana

In the early 1890s the British colonial farmers of Zululand were faced with the decimation of their European breeds of cattle by a wasting disease called nagana a word meaning in Zulu "in low or depressed spirits." Native cattle were unaffected. Primary agents: *T. congonense, T. vivax; T.b. brucei*



Sensitive:
Zebu

Trypanotolerant:
N'Dama

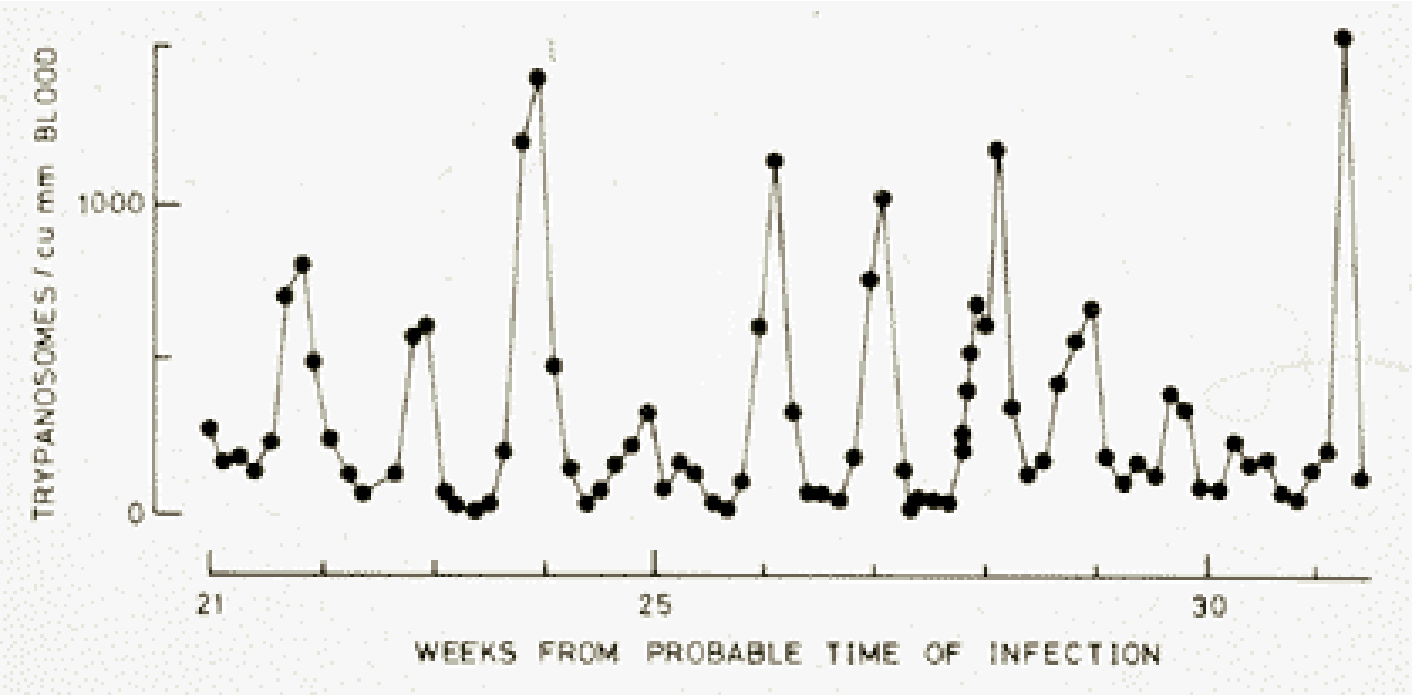
- Economic impact on agriculture
  - Major reduction in food production
    - >3 million deaths per year
    - 50% reduction in herd size
    - 25% reduction in milk production
    - 20% loss in calving

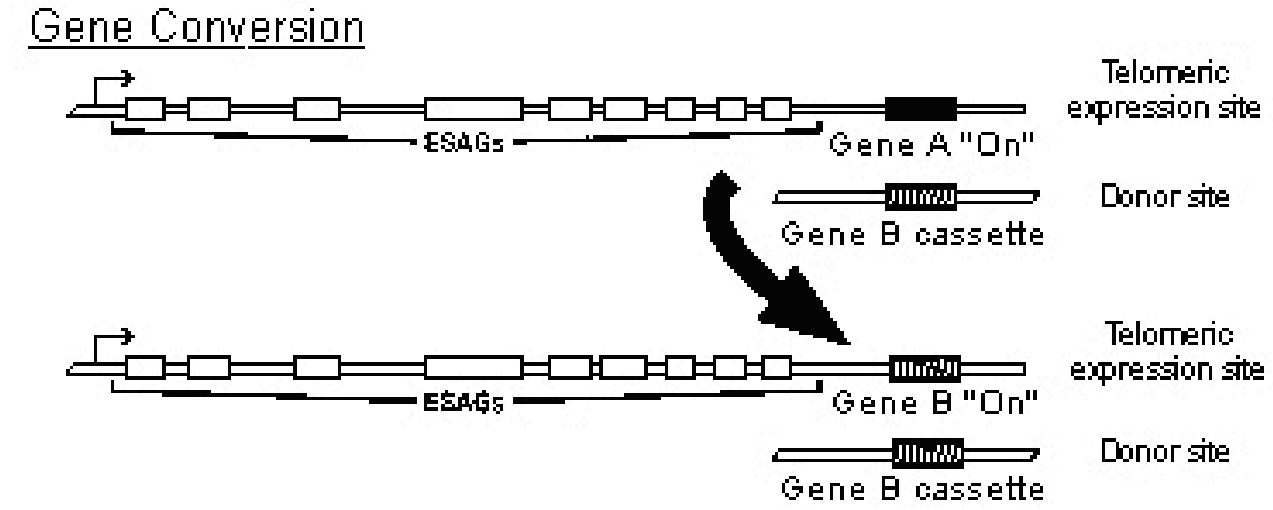
Losses in meat production, milk yield and tractive power are estimated to cost approximately $ 500 million annually and, if lost potential in livestock and crop production are also considered, the disease costs Africa an estimated $ 5 billion per year. Complete control of tstetse would result in an increase in beef production of 1.5 million tons per annum.

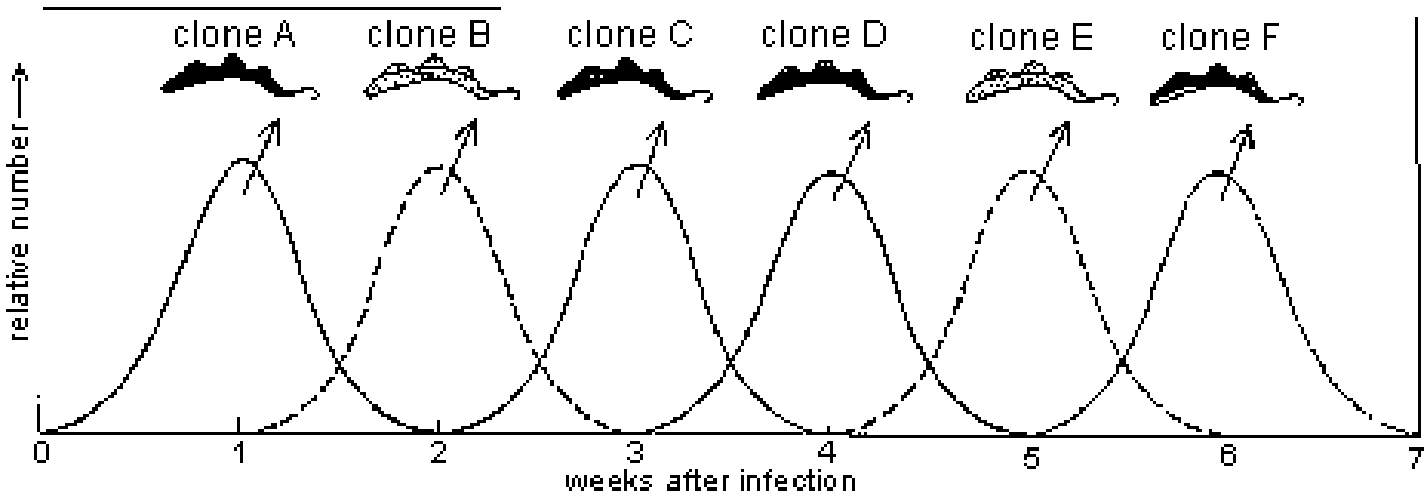
African trypanosomiasis: Epidemiology

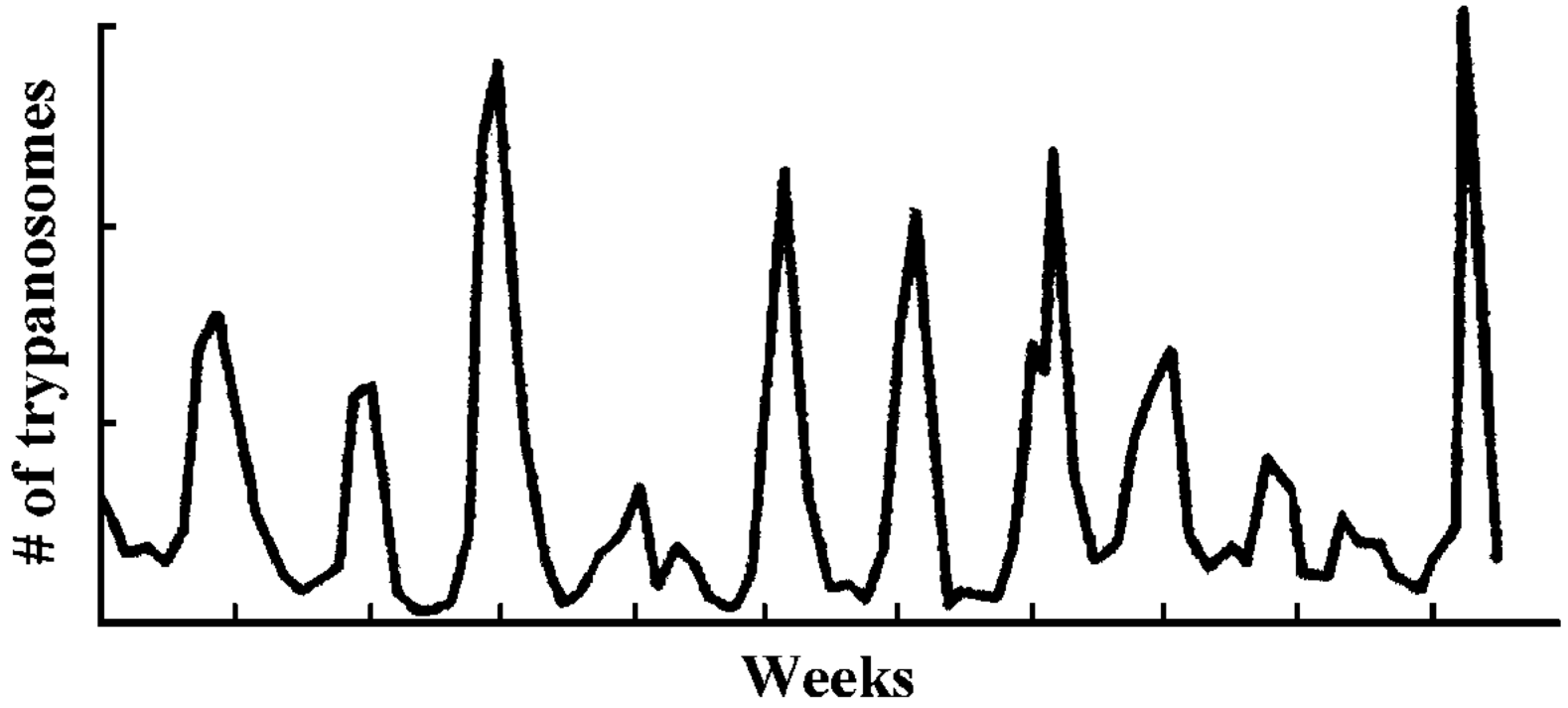
- Reservoir:
  - *T.b.gambiense* - primarily humans; wild and domestic animals not established
  - *T.b.rhodesiense* - wild animals, especially cervidae (bushbuck, antelope); cattle
  - Trypanotolerant species
    - Wild animals more than domestic livestock
    - N'Dama (predominant breed of *Bos taurus* in Africa); certain other breeds

The release of trypanosome toxic factors and lymphokines gives rise to a cyclic (or relapsing) fever with an approximate cycle of 7-10 days.



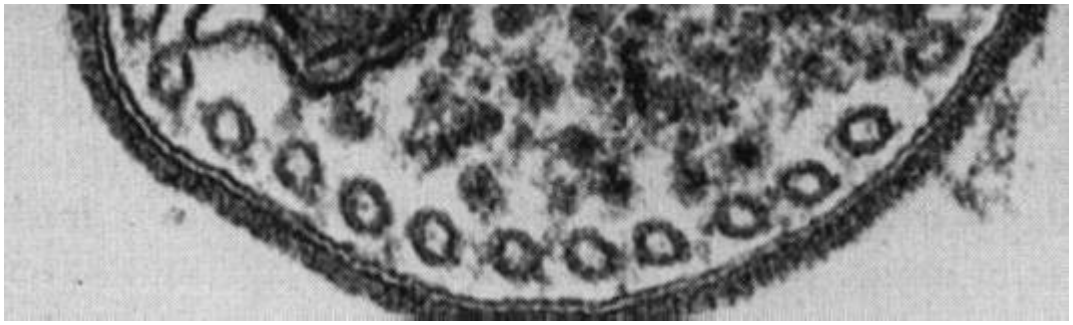

Gene Conversion
Telomeric expression site
ESAGs
Gene A "On"
Donor site
Gene B cassette
Telomeric expression site
ESAGs
Gene B "On"
Donor site
Gene B cassette


clone A
clone B
clone C
clone D
clone E
clone F
relative number
0
1
2
3
4
5
6
7
weeks after infection

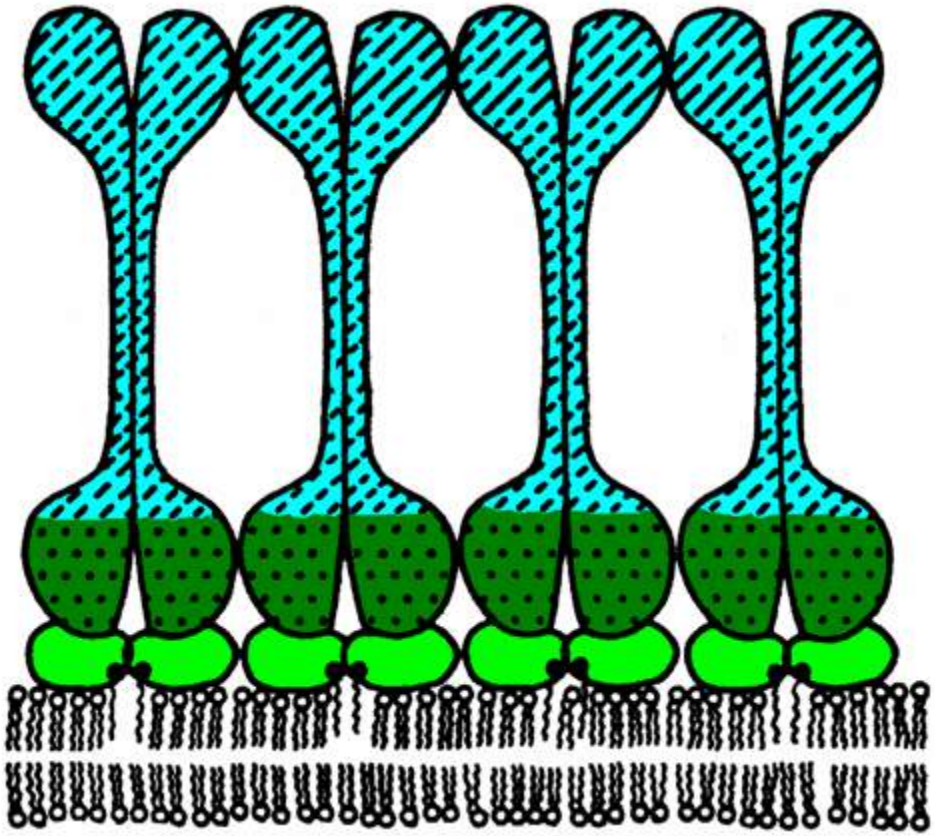


- **VSG is immunogenic and host response clears parasites**
- **some trypanosomes will change VSG coat**
- **this population expands until host develops immunity against new VSG**

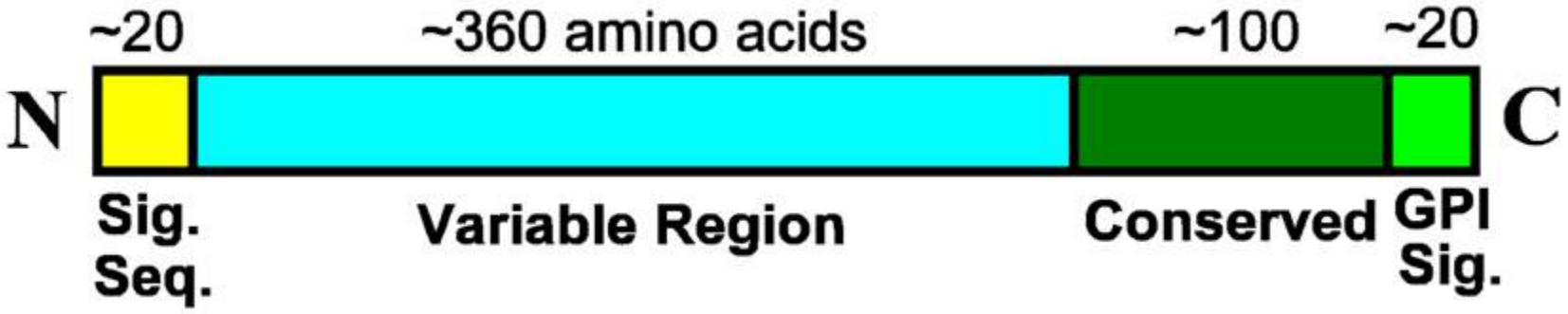
Variable Surface Antigen



These types of antigen variants are called VATs = variable antigenic type. The molecules responsible for the VAT are present on the surface of the trypomastigote as a 12-25 nm thick coat; each has a molecular size of 60kD with ~500 amino acids and 20 monosaccharide units. These molecules are called VSGs = variant surface glycoproteins. It is the VSG that gives rise to the VAT. The switch rate is 1 / 10,000 to 1 / million per division, and there are 10 million glycoprotein copies of VSG per trypanosome. ~ 10% of the trypanosome genome is devoted to VSG.



- **100's of VSG genes**
- **conserved regions not accessible**
- **switch rate = 10^{-3}-10^{-5} per generation**



It is the frequent switching of the VSG forming the Surface Coat that accounts for antigenic variation. Each VSG is encoded by an individual VSG Gene. *Trypanosoma brucei* contains hundreds of VSG Genes, accounting for about 10% of the genome.

If this system could be disrupted, our immune systems might be able to eliminate trypanosome infections. Much research is directed toward understanding how trypanosomes regulate antigenic variation.

Trypanosomes appear to exert tight control over the expression of VSG genes. We don't know why this is so important to them, but it might be an intrinsic side effect of the switching mechanisms that the trypanosome has evolved.

A central question is how do the trypanosome express only one of the hundreds of VSG genes at any time in any individual cell? What regulates the timing of a switch and what regulates the order in which VSG genes are expressed?

Other animal disease-causing trypanosome species

Trypanosoma congolense causes Ngana in cattle and is transmitted by the tsetse fly. Wild animals are a reservoir.

Trypanosoma vivax is an important disease of cattle, sheep, goats and horses (Souma) that can be transmitted either by the tsetse or by the common stable fly. It also infects wild animals but is not pathogenic. It has spread outside the tsetse belt, even to Indonesia and the New World. In the tsetse, the parasites only are in the proboscis.

Trypanosoma evansi causes "Surra" in camels and also horses. This was the first pathogenic trypanosome discovered. Found throughout mid to Northern Africa and the Middle East. Has been introduced by the Spaniards into the New World. Transmitted mechanically by tabanid flies. Some strains lack the kinetoplast DNA.

Trypanosoma equiperdum causes "Dourine" in horses. This is a venereal disease and has no insect vector. Was introduced into Europe, Russia, Siberia, Middle East, Indonesia and even North America. Some strains lack the kinetoplast DNA.

Summary

	T. gambiense	*T. rhodesiense*	*T. brucei*
Distribution	**W. Africa**	**E. Africa**	
Glossina vector	**palpalis group**	**morsitans group**	
Disease	**Chronic (months-years)**	**Acute (weeks-months)**	
Parasitemia	**Low**	**High**	
CNS involvment	**Late**	**Early**	
Host	**Human**	**Human & Game Animals**	**Cattle & Game Animals**

ARE THERE ANY POSITIVE THINGS TO SAY ABOUT THIS PARASITE?

There is a single case report of sexual transmission of West African sleeping sickness. This is not an important route of transmission. A case of sexually transmitted sleeping sickness was the focus of an episode of House.