

Trypanosomiasis

Terry L Dwelle MD MPHTM

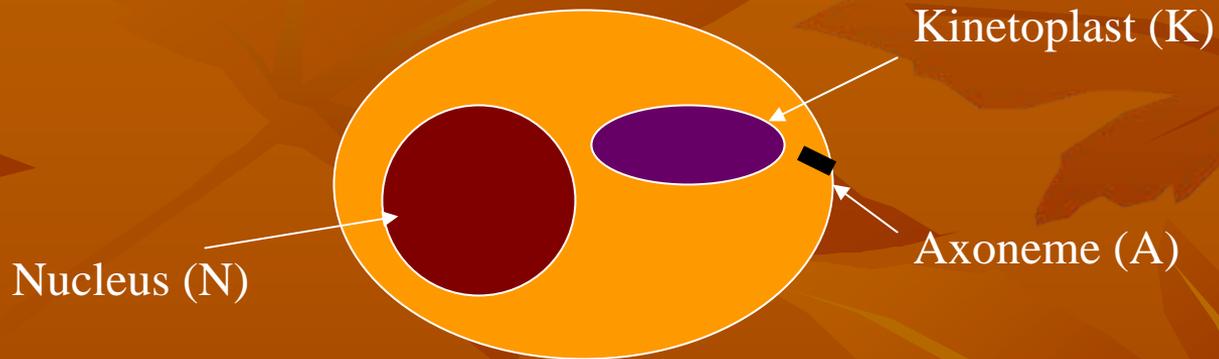
Trypanosomiasis

- African trypanosomiasis
 - *Trypanosoma brucei gambiense*
 - *Trypanosoma brucei rhodesiense*
- American trypanosomiasis
 - *Trypanosoma cruzi*
 - *Trypanosoma rangeli*

Basic Hemoflaggelatology

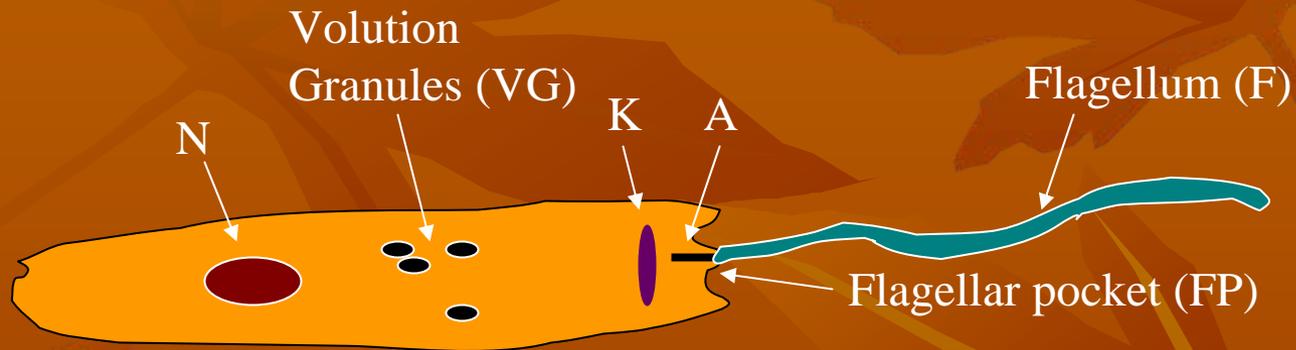
- Found in the blood
- They are also called kinitoplastida (contain kinetoplasts or modified mitochondria)
- Basic forms
 - Amastigotes
 - Promastigotes
 - Epimastigotes
 - Trypomastigotes
 - Metacyclic trypomastigotes

Amastigote (old Leishmania stage)



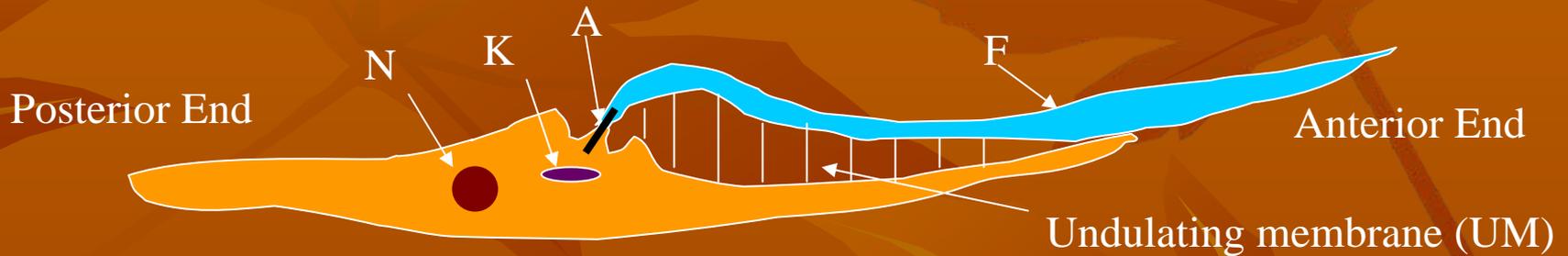
- Slightly oval (2-3 X 3-4 microns)
- Axonemes are like microtubules that are associated with future flagellate motility
- Found inside reticuloendothelial cells
- Multiplies by longitudinal binary fission
- There is generally a small zone between the K and A

Promastigote (old leptomonas stage)



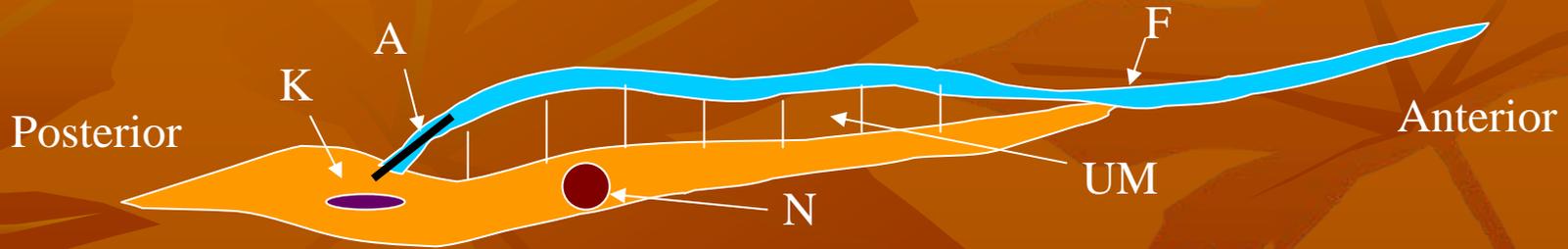
- May have various shapes from short and fat to long and thin
- Occasionally see volutin granules (VG) that represent waste products in the cytoplasm

Epimastigote (old crithidia stage)



- Varies in length (12-75 microns)
- K is always anterior to the nucleus
- F pulls the body through tissues
- Epimastigote has an undulating membrane where the promastigote doesn't
- The undulating membrane causes the body to undulate

Trypomastigote and Metacyclic Trypomastigote



- This is the Trypanosome
- The K is posterior to the N vs the Epimastigote with the N posterior to the K
- Binary fission of the Promastigote, Epimastigote and Trypomastigote are the same (K first followed by the A, F, the N and then the cell)
- Metacyclic Trypomastigote is the same as the trypomastigote but is the infectious stage in the vector

African Trypanosomiasis

- Known as African sleeping sickness
- Endemic in 36 countries and affects from 20,000 to 50,000 annually
- Untreated is universally fatal
- Animal infections may have more impact than human infections by decreasing the food supply (eg cattle, sheep, goats, pigs, chickens)

African Trypanosomiasis

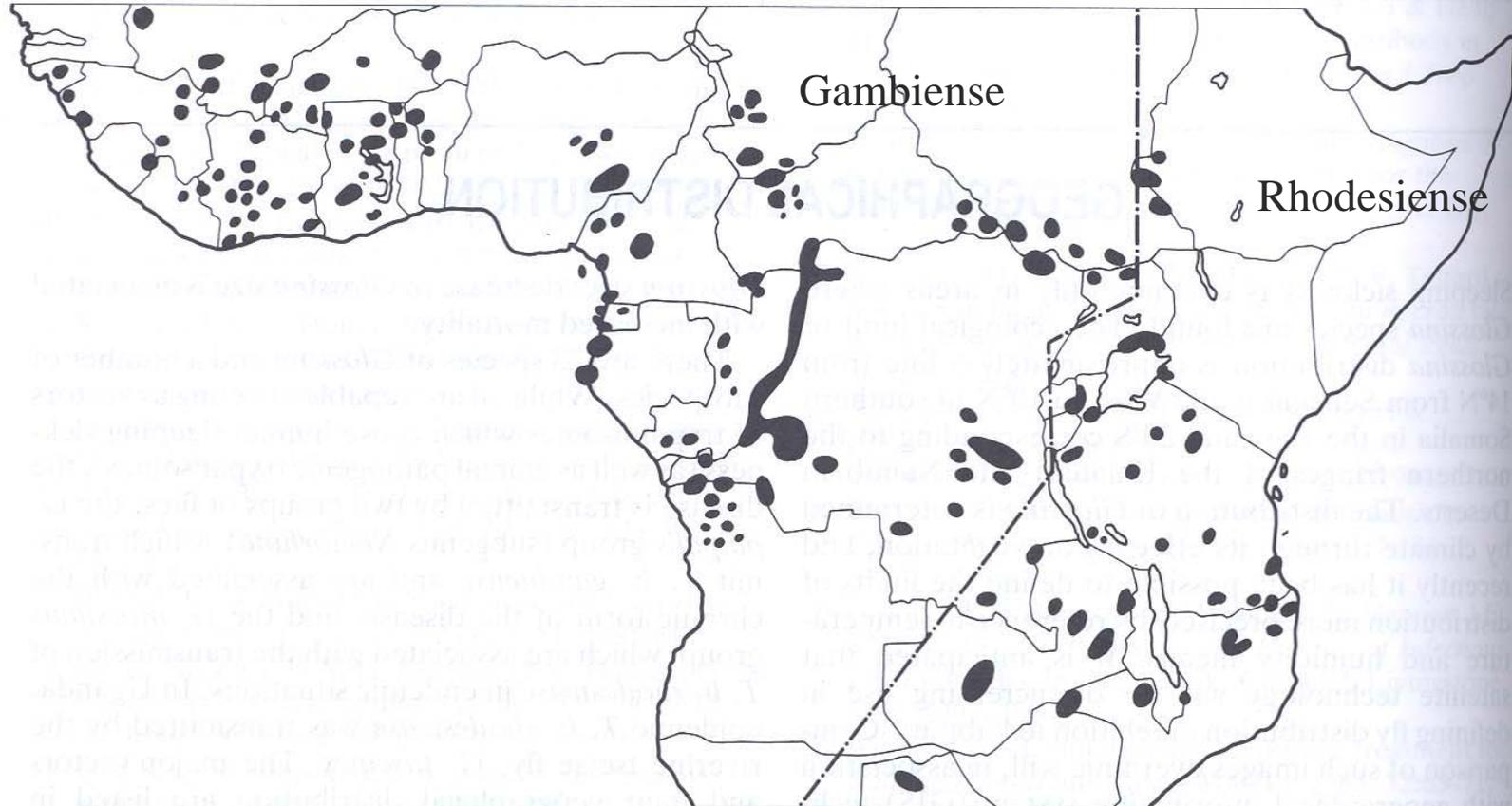
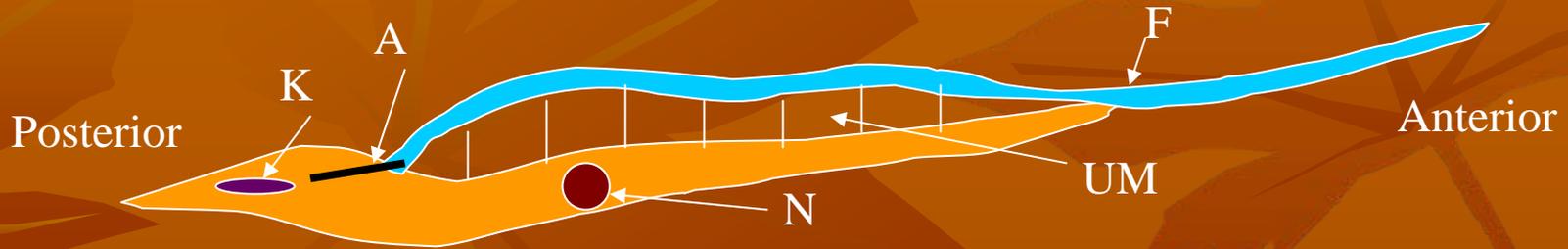


Figure 63.1 Distribution of trypanosomiasis foci in Africa. *T. b. gambiense* areas of distribution to left of dotted line in West and Central Africa; *T. b. rhodesiense* to right of line in East and South Africa.

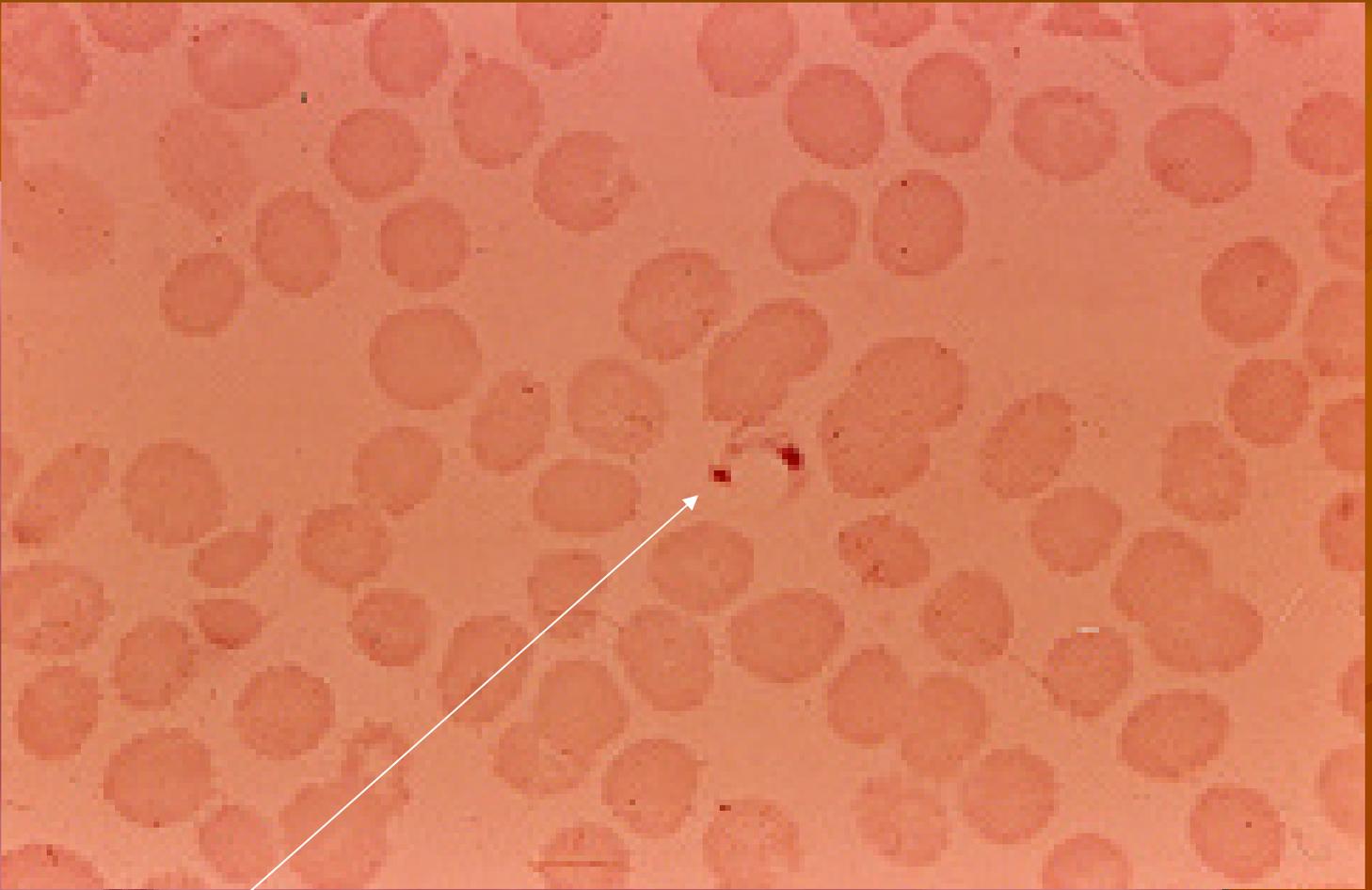
Trypanosoma Rhodesiense

- East African upland savannahs
- Causes sporadic disease

Trypomastigote of *Rhodesiense* and *Gambiense*



- Trypanosome stage can't be distinguished physically from *Gambiense* though biologically and biochemically different
- 14-33 micrometers long
- Smaller kinetoplast than *Trypanosoma cruzi*
- *T. R.* is much less adapted to man therefore causing increased reaction and tissue damage and a much higher mortality than *T. G.*

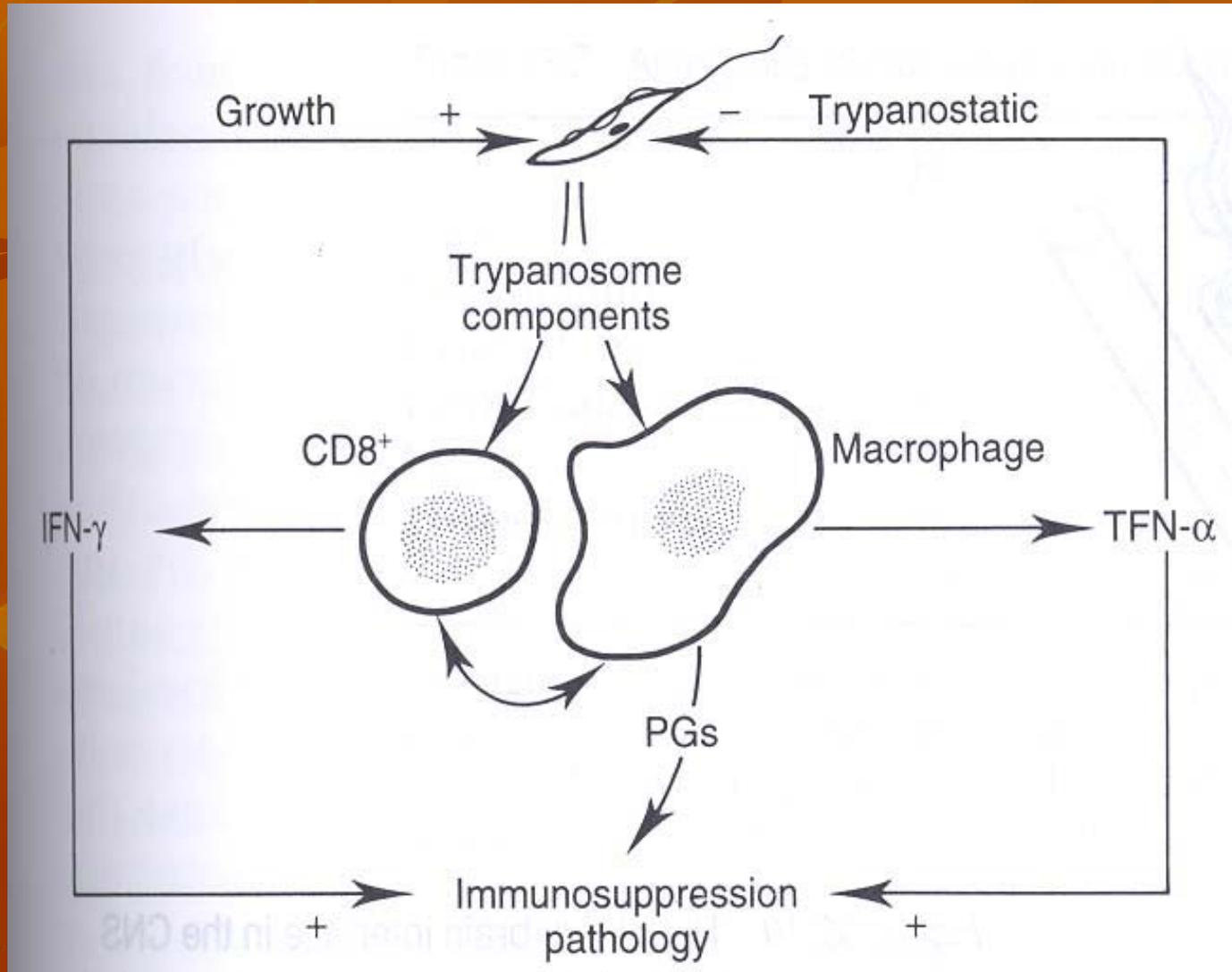


Kinetoplast

Life Cycle

- Host – Animals (eg bushbuck, hartebeeste, lion, hyena, cattle, dogs, reedbuck, waterbuck, sheep, goats, etc.) occasionally man
- Location – Blood, LN's, Spleen, CNS
- Intermediate host – Glossina moristans group (prefers a dry warm climate)
- Infective stage – metacyclic trypomastigote
- The incubation period for T. R. is 3-21 days and is usually 5-14 days. T. G has an incubation period from months to years.
- Commonly seen in hunters, honey and firewood gatherers, fisherman and tourists in game areas

Immunosuppression



From Manson's Tropical Diseases, pp 1187, Saunder's 1996.

Immune Responses

- Trypanosome populations have different antigenic populations

Disease

- I. **Local Tissue – T. chancre – painful boil with interstitial inflammatory reaction**
- II. Lymph-node involvement – hyperplasia of endothelial linings of blood sinuses and perivascular infiltrates of leukocytes. Usually rapid and fulminant course resulting in death within a few months
- III. CNS – “sleeping sickness” with headache, paroxysmal fever, extreme weakness, rapid weight loss, encephalomyelitis, mental deterioration, coma, and death within 1 year

Disease

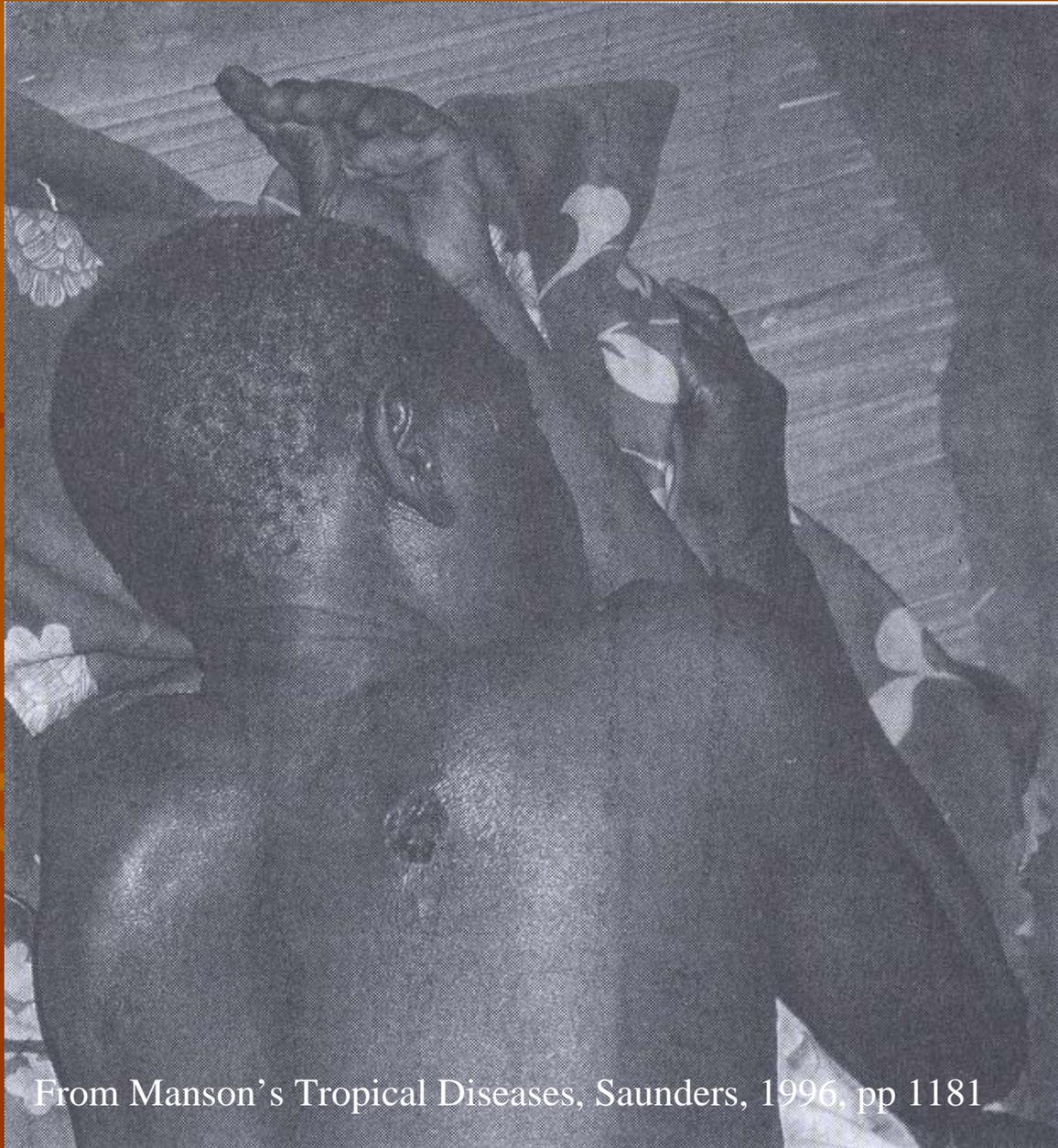
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Parasitemia related signs / symptoms

- Fever
- Headache
- Joint pains and myalgias
- Lymphadenopathy
- Weight loss
- Pruritus
- Rash
- Anemia



From Manson's Tropical Diseases, Saunders, 1996, pp 1181

Other signs and symptoms

- Edema – peripheral, ascites, pulmonary, pericardial effusion
- Cardiac – non-specific ECG changes, CHF
- Endocrine – amenorrhea, impotence, spontaneous abortion
- GI – diarrhea
- CNS – altered reflexes, hyperesthesia, paraesthesia, seizures, aberrant mentation, sleep disturbance, ataxia, slurred speech, paralysis, etc.

Diagnosis – Stage related

I. Tissue phase

- Fluid aspirated from a chancre

II. Hemolymphatic phase

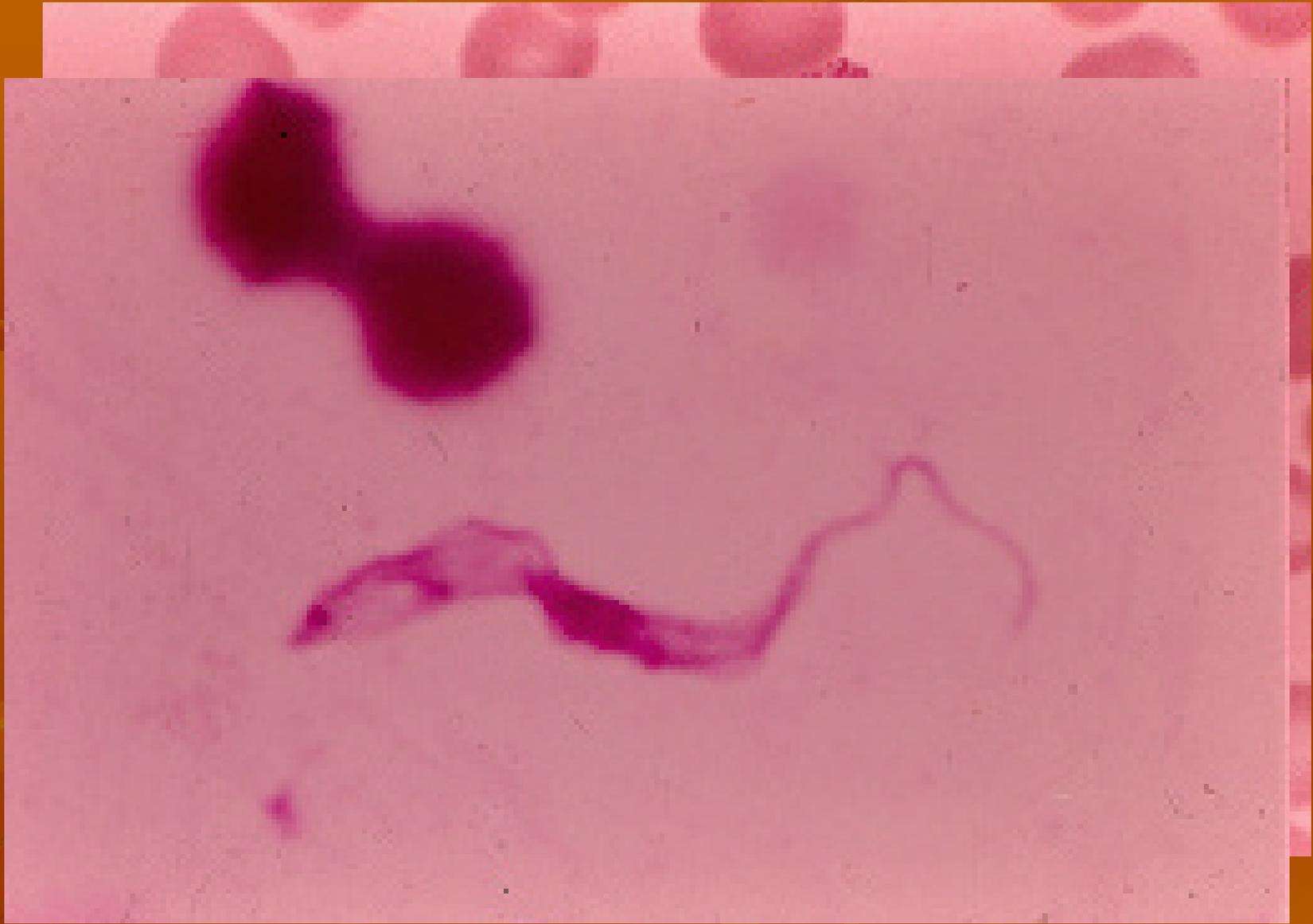
- Lymph-node aspirate
- Concentrated of the blood buffy coat (Giemsa stain)

III. CNS phase

- Double centrifugation technique – Giemsa stain

Diagnosis

- Serum and CSF IgM is often elevated (often 10X over normal)
- CSF protein levels are usually elevated. An increase of protein after treatment may be an indication of relapse.
- Immunofluorescent antibody (IFAT) and ELISA may be useful for screening. IFAT may be useful for assessing cure.
- NNN media can be used for culture but is unreliable due to the few organisms present in most specimens
- Inoculation of mice with heparinized blood



Treatment

	Stage I and II	Stage III
T. Rhodesiense	Suramin	Melarsoprol + Corticosteroids
T. Gambiense	Pentamidine or Suramin	Eflornithine or Melarsoprol + Corticosteroids

Dosages

Pentamidine	4 mg/kg/day X 10 days	4 mg/kg/day X 10 days
Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 7, 14, and 21	20 mg/kg on days 1, 3, 7, 14, and 21
Melarsoprol for T. Gambiense	2.2 mg /kg/day X 10 days	2.2 mg /kg/day X 10 days
Melarsoprol for T. Rhodesiense	2-3.6 mg/kg/day X 3 days; after 7 days 3.6 mg/kg/day X 3 days; repeat again after 7 days	2-3.6 mg/kg/day X 3 days; after 7 days 3.6 mg/kg/day X 3 days; repeat again after 7 days
Eflornithine for T. Gambiense	400 mg/kg/day in 4 doses X 14 days	400 mg/kg/day in 4 doses X 14 days

CDC numbers 404-639-3670, evenings and weekends 404-639-2888

From The Medical Letter, August, 2004, pp 1-12.

Melarsoprol Dosages

- T. Rhodesiense (CDC) doses in mg/kg IV (treatment day) – 0.36 (1), 0.72 (2), 1.1 (3), 1.8 (10,11,12), 2.2 (19), 2.9 (20), 3.6 (max 180 mg) (21,28,29,30)
- T. Gambiense – 3.6 mg/day (max 180 mg) IV on days 1, 2, 3, 11, 12, 13, and 21, 22, 22 (last 3 doses if CSF WBC's > 20)
- Corticosteroids should be given with Melarsoprol to decrease the risk of severe CNS toxicity

Side-Effects

Pentamidine	Vomiting, hypotension, hypoglycemia
Suramin	Fever, joint pains, rash, desquamation
Melarsoprol	Encephalopathy, diarrhea
Eflornithine	Diarrhea, anemia, thrombocytopenia

Prevention

- Avoid biting fly habitats (brushy areas along lakes). Stay in open country.
- Clear brush from around human dwellings
- Destroy breeding grounds
- Traps for flies
- Infected patients should not breast feed or donate blood
- Isolate and treat all cases
- Release sterile male flies
- Insect precautions

Insect bite prevention is effective

- Use insect repellents
- Insecticide sprays containing pyrethrum
- Treated bed-nets and clothing
- “Blousy” long sleeve shirts and pants

Permethrin Application

- Use “4 Week Tick Killer 13.3% solution”
- Pour 2 oz into a large plastic bag with 12 oz water to make a final concentration of 2%
- Place rolled fabric in the bag and gently shake 2 times then let it rest for 2.5 hours.
- Remove the roll
- Hang to dry for at least 3 hours
- Do not let the liquid come in contact with bare skin

Trypanosoma Gambiense

- Western 2/3's of Africa
- Host – Animals (eg dogs, pigs, sheep, cattle, kob, hartebeeste, chicken, etc.) occasionally man
- Intermediate host – Glossina palpalis
- T. G has an incubation period from months to years
- T. G. is associated with a more slowly progressive course
- Congenital infection has occurred with T. G. but not T. R.



Treatment

	Stage I and II	Stage III
T. Rhodesiense	Suramin	Melarsoprol + Corticosteroids
T. Gambiense	Pentamidine or Suramin	Eflornithine or Melarsoprol + Corticosteroids

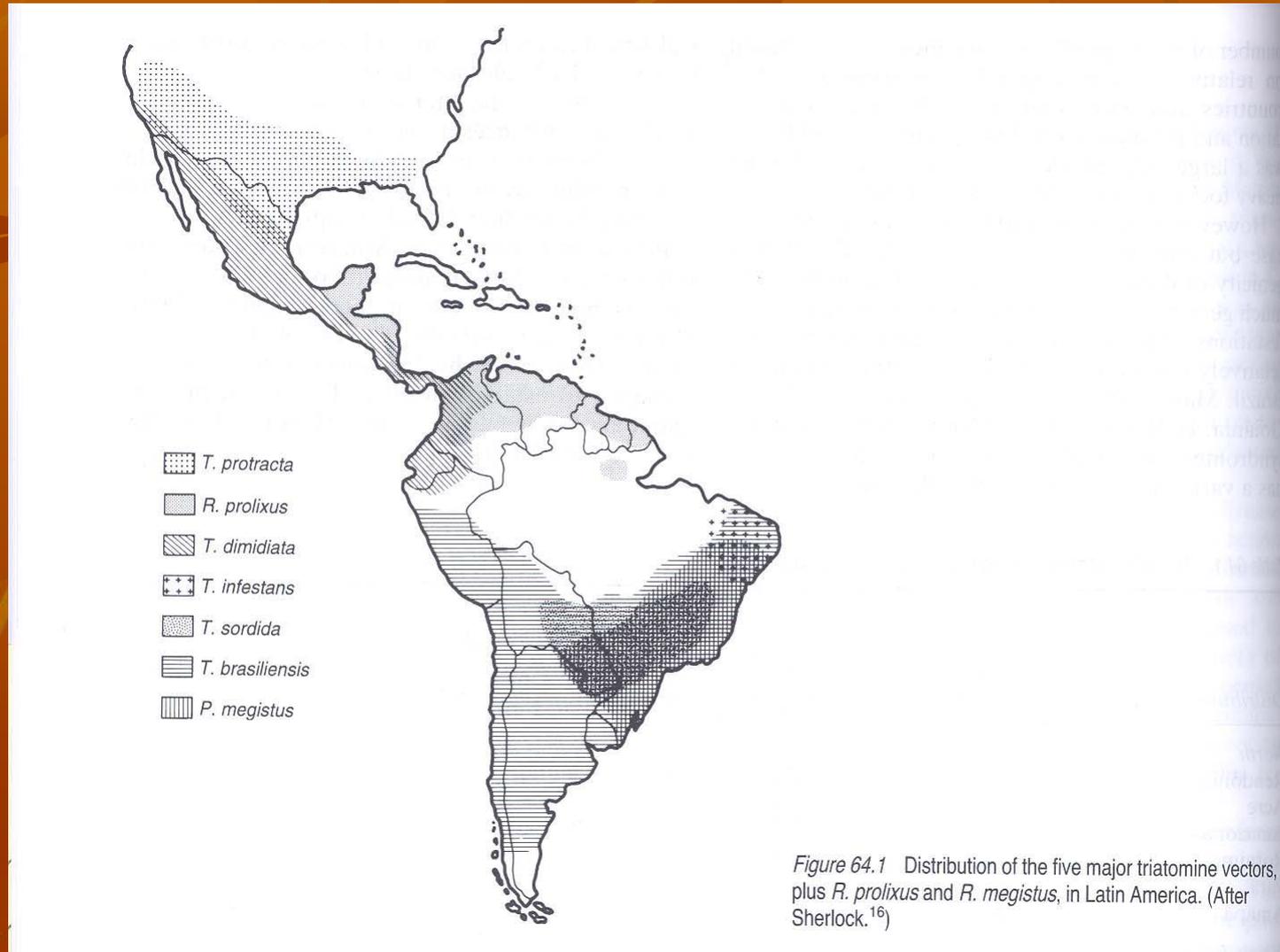
American Trypanosomiasis

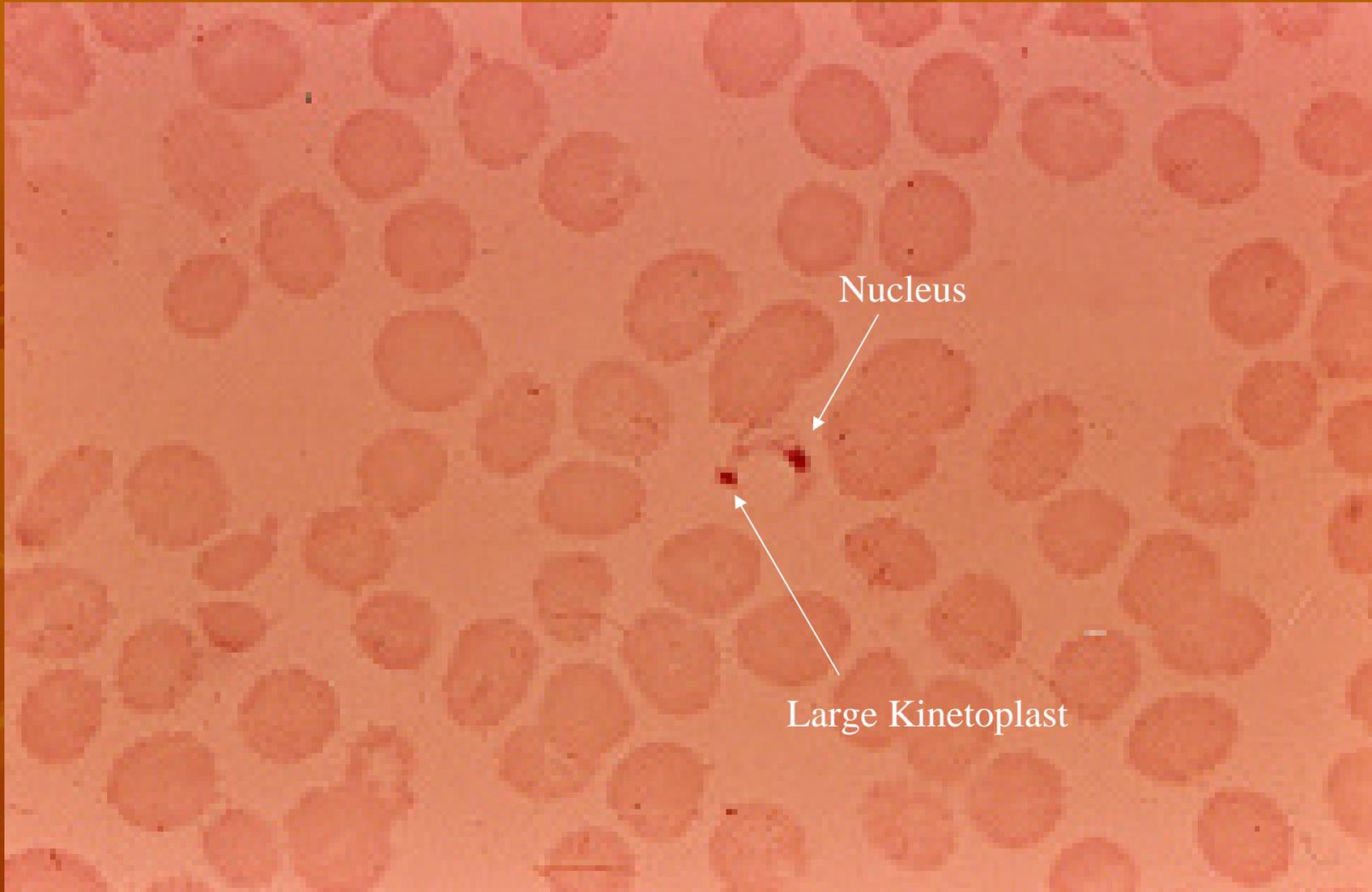
- T. Cruzi, T. Rangeli
- T. Rangeli doesn't cause disease but can be confused with T. Cruzi
- Found in the Americas
- 7-15 million infected in South America
- Important cause of death in South America
- It is relatively common in immigrants from Central and South America

Trypanosoma Cruzi – Chagas disease

- Described by Carlos Chagas in 1909
- Disease range follows the vector – from South West US to Argentina
 - Triatoma infestus and dimidiata
 - Rhodnius prolixus
 - Panstrongylus megistus
- Host – man and at least 100 other species and 8 orders of mammals (eg dogs, cats, opossum, raccoon, armadillo, monkeys, rats, etc.)
- 10-12 million infected with 32 million at risk
- Disease is most commonly seen in Mexico, Central America, and South America
- Zoonotic in US (eg Washington DC, California, Texas) since the bug rarely colonized US homes

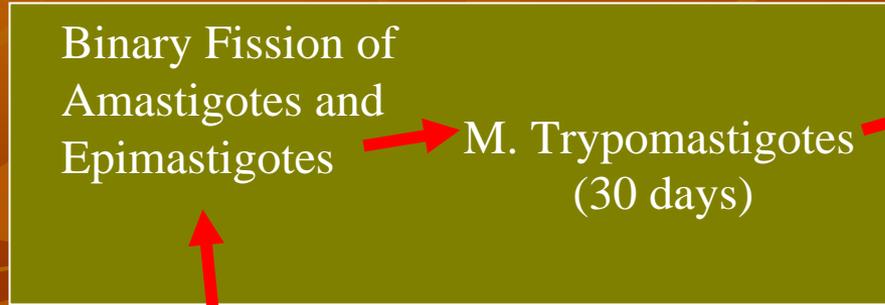
American Trypanosomiasis





Life Cycle

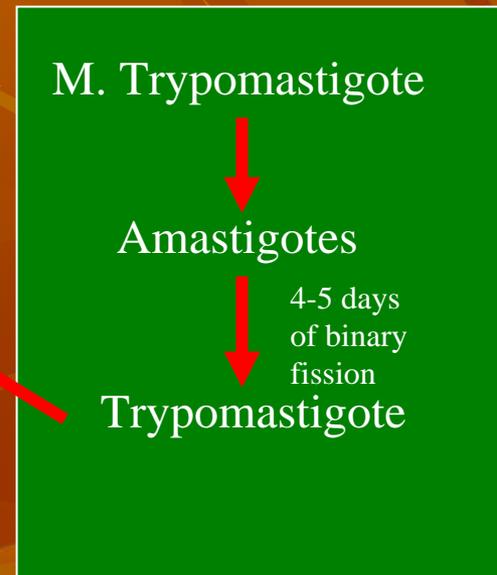
Insect Vector



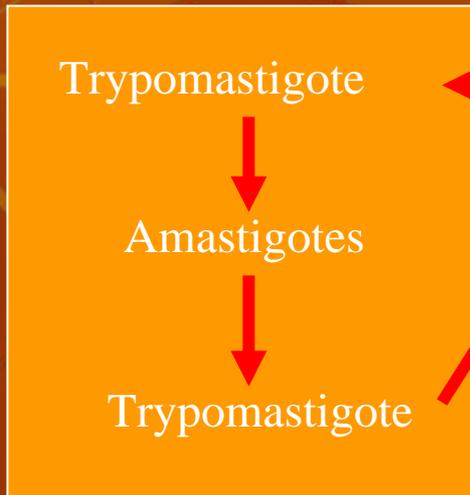
Metacyclic Trypomastigote



Macrophages →



(5-12 days)



Other cells (heart, skeletal muscle, neuroglia, etc)

Acute Symptoms 2-3 weeks



Transmission Factors

- Vector exposure
- Blood transfusions
- Transmammary transmission
- Infected food or meat
- Laboratory accidents
- Land colonization
- Quality of human dwellings

Vector

- Adult insects can fly.
- Feed at night
- Live in holes, like dark, humid sites



Chagas' Disease

Acute

Entry site lesions

Systemic signs and symptoms

Organ involvement

Chronic

Dilation of hollow viscera including the heart

Acute phase

- 95% have no acute phase
- Children have more symptoms
- Acute phase is often followed by a life-long asymptomatic period (70-90% of those infected)
- Some patients experience a subacute progression of illness that can result in a rapid demise.
- 10% fatality rate in the acute phase

Portals of Entry

- Ocular – 48%
- Skin – 24%
- Other / Inapparent – 28%

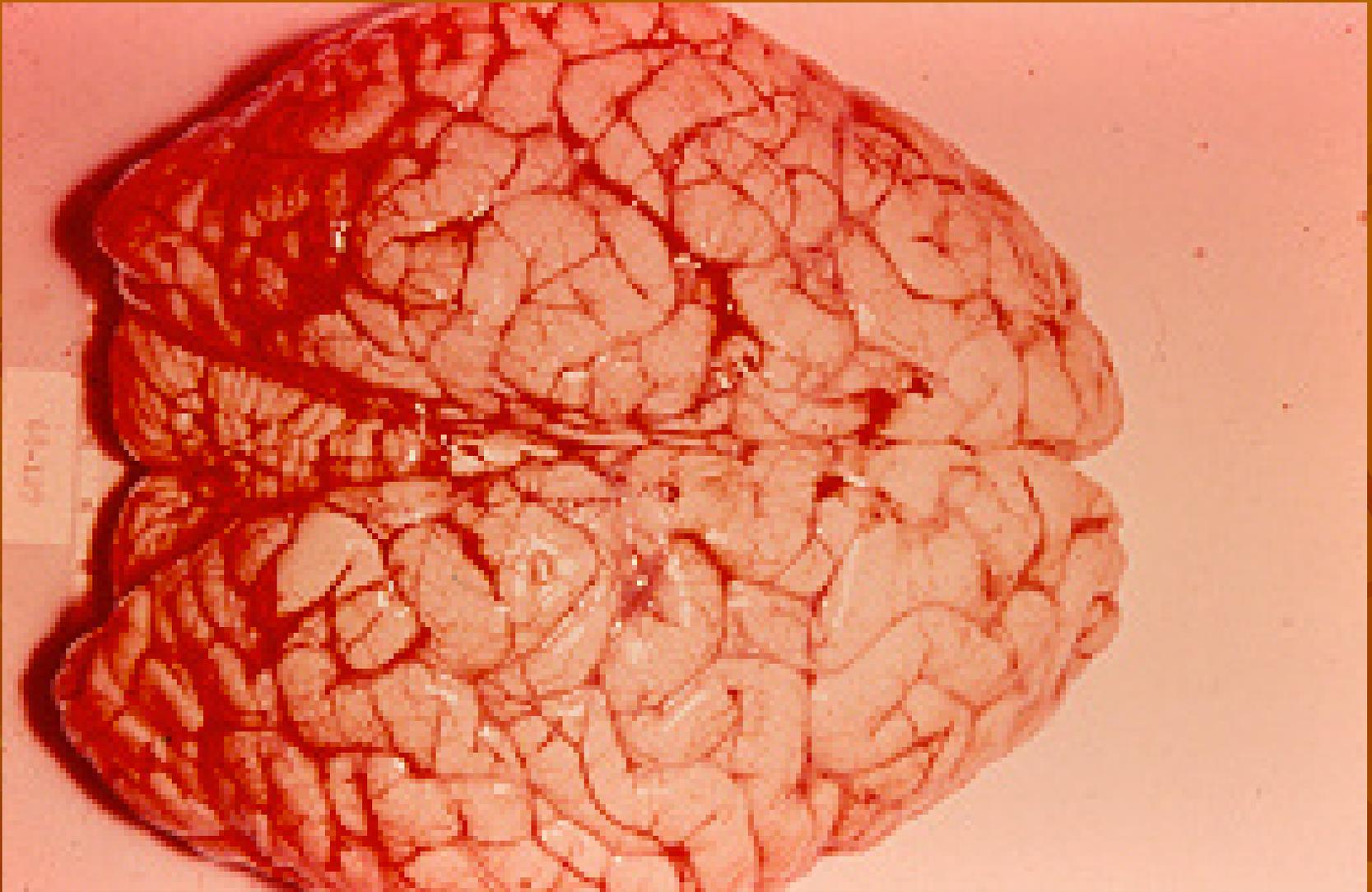
Entry site lesions

- Romana's sign
 - Unilateral, painless, erythematous palpebral edema
 - Occasional swelling of the entire side of the face
 - Preauricular or submaxillary adenopathy
 - Conjunctivitis
 - Dacroadenitis
- Chagoma
 - Erythema, pruritus, painless infiltration of the dermis
 - Central desquamation with rare ulceration
 - Exposed parts of a sleeping person
 - Last for weeks



Organ Involvement

- Hepatosplenomegaly
- Lymphadenopathy
- Muscles
- GI
- Pulmonary
- Heart
- CNS – meningoencephalitis
- Bone marrow
- Skin



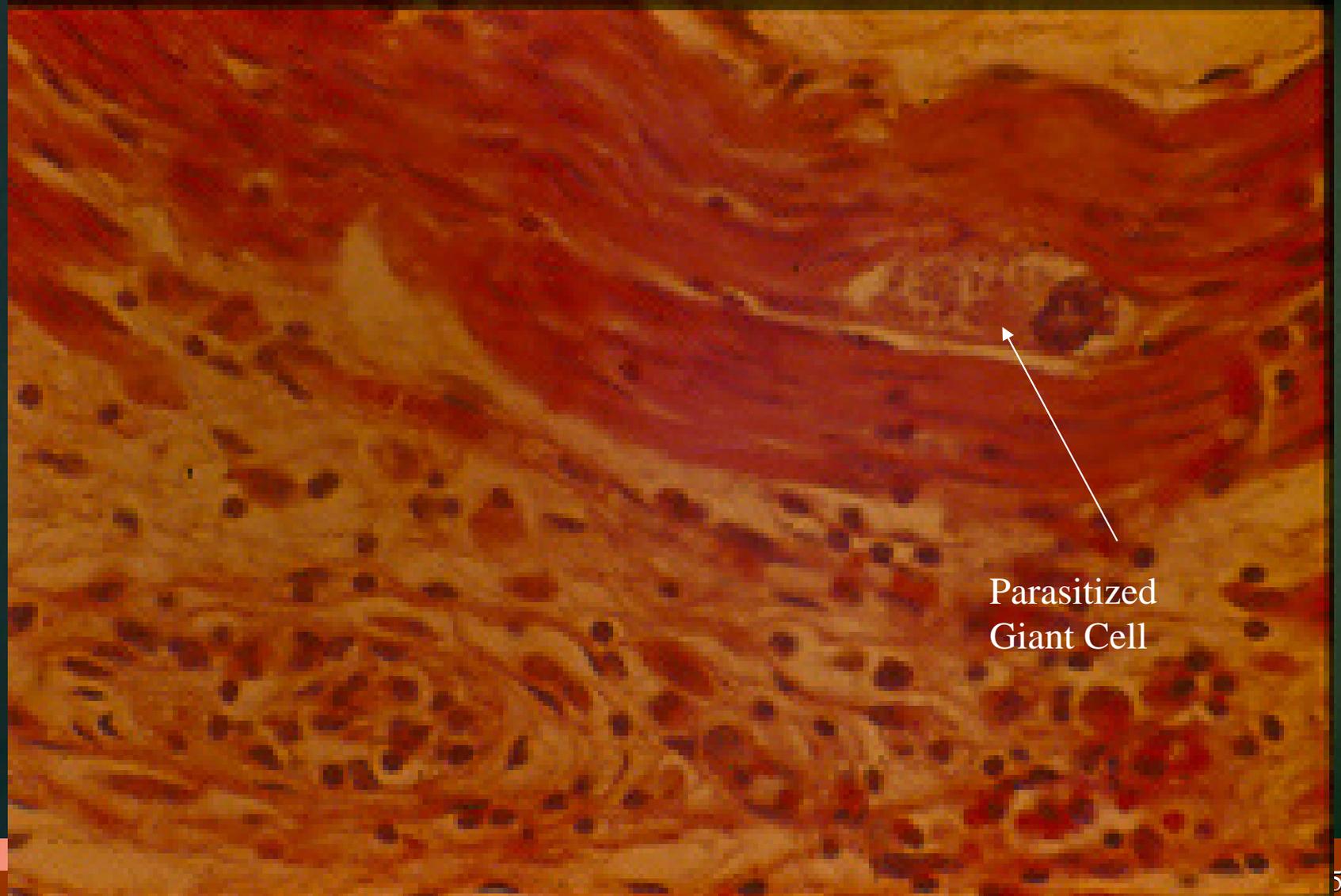
Congenital Chagas' Disease

- Low birth weight
- Hepatomegaly
- Meningoencephalitis with seizures and tremors

Chronic Chagas Disease

- Often seen at 30-40 years old
- Occurs in 10-30% of those infected
- Chronic myocarditis is most common
 - Diffuse multifocal myocarditis with edema and fibrosis
 - Increased thrombosis seen in the heart wall
 - Apical aneurysms occasionally seen
 - EKG is the 1st manifestation (RBBB, PVC's)
 - Sudden death is common
 - May present with CHF, embolism, ruptured aneurysm, vent. fibrillation
- Can see dilation of other hollow viscera
 - Esophagus
 - Colon with megacolon
 - Ureter

5 2 4 6 8 10
1 3 5 7 9 11



Parasitized
Giant Cell

Laboratory Diagnosis

- Acute phase
 - Giemsa stained buffy coat blood smear
 - Biopsy specimen – find Trypomastigotes and Amastigotes
- Chronic phase
 - Culture on NNN media
 - Xenodiagnosis
 - Serology – CF, IHA, IFAT, ELISA, RIPA, Latex Agglutination, Direct Agglutination Tests

Clinical Diagnosis

- No single laboratory test is adequately sensitive and specific to diagnose Chaga's disease
- Generally the diagnosis is made by at least 2 different serologic tests (ELISA, immunofluorescence, indirect hemagglutination) along with clinical and exposure history.



Treatment

Drug	Adult	Child
Benznidazole (not available in the US)	5-7 mg/kg/day in 2 div doses X 30-90 days	≤ 12 yo: 10 mg/kg/day div in 2 doses X 30-90 days
Nifurtimox* (consider with gamma interferon X 20 days)	8-10 mg/kg/day div in 3-4 doses X 90-120 days	1-10 yo: 15-20 mg/kg/day div in 4 doses X 90 days 11-16 yo: 12.5-15 mg/kg/day div in 4 doses X 90 days

*Nifurtimox (Lampit, Bayer, Germany). It is only available under the Investigational New Drug (IND) protocol from CDC Drug Service, CDC, 404-639-3670 (evenings, weekends, or holidays: 404-639-2888).

Control Measures

- Avoid habitation in buildings infested with reduviid bugs (constructed of mud, palm thatch, adobe brick especially those with cracks in walls or roofs)
- Use insecticide impregnated bed nets
- Don't sleep or camp outdoors in highly endemic areas
- Blood and serologic screening of household members of infected patients with common exposure histories
- Serologic screening before and after travel if exposure to the vector is unavoidable
- Eliminate vectors in homes
- Blood and organ donor screening by serology
- Treat donated blood in endemic areas with gentian violet (diluted 1:4000)
- Treat infected (acute and chronic) to prevent progression to cardiac morbidity and congenital infection

Blood Donor Screening for Chagas in the US, 2006-2007

- American Red Cross screened 148,969 blood samples at three collection centers, Los Angeles, Oakland, and Tucson.
- Initial screen with ELISA. If positive it is repeated twice. If the second or third test is positive a RIPA (radioimmunoprecipitation assay) is completed. If the RIPA is positive the specimen is considered positive.
- 63 specimens from 61 donors were ELISA repeat positive. 32 were RIPA positive (51%).
- Prevalence 1/4655.
- On December 13, 2006 the FDA licensed the Ortho T cruzi ELISA test to screen blood donors in the US. It is labeled for testing plasma and serum samples from living cell and tissue donors and from heart beating organ donors but not labeled for general clinical diagnostic use.
- US blood supply began screening all donations for T cruzi on January 29, 2007 and providing testing services for smaller blood collection centers and hospitals that request testing.

American Association of Blood Banks

- All components from blood donations that are repeat reactive by ELISA should be quarantined and removed from distribution
- Donor should be deferred from making donations indefinitely
- Recipient tracing should be done on those specimens repeat positive by ELISA and confirmed with RIPA
- Test at risk family members of confirmed positives with a similar history of exposure to Chaga vectors in an endemic area
- Deferred donors, at risk family members, and potentially infected recipients should be referred to health care providers

Trypanosome Rangeli

- Historically known as T. Ariari
- Seen in Uruguay, Chile, Honduras, Guatemala, Southern Mexico to Brazil where Rhodnius is present
- Larger and more slender than T. Cruzi (26-34 micrometers)
- Has a subterminal kinetoplast
- Host – animals and occasionally man
- Does not cause disease
- Life cycle – similar to T. Cruzi except for method of transmission to humans
- Transmitted by bug bite (anterior inoculative transmission) not from bug feces
- Diagnosis – Blood smear, Culture of blood
- Problem – may be confused with T. Cruzi



Subterminal Kinetoplast