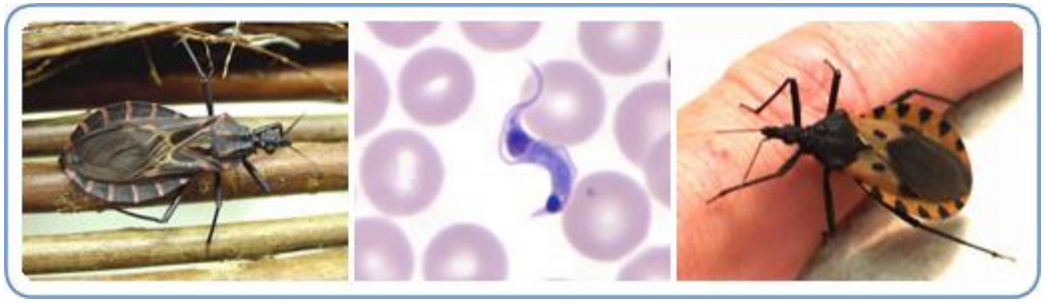
Trypanosoma brucei
(Sleeping sickness)

Trypanosoma cruzi
(Chagas disease)



Blood & Tissue Protozoa I: haemoflagellates

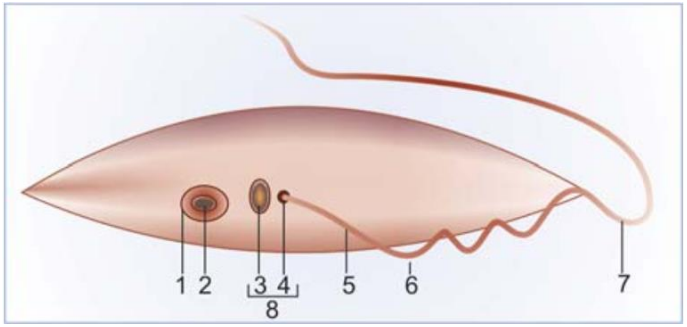
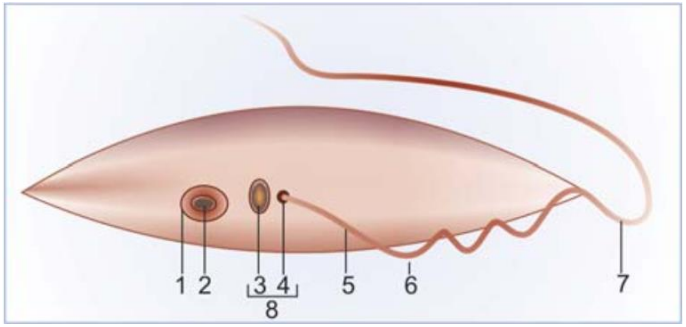


FIGURE 13.1 Basic morphology of haemaglagellates

1. Nucleus
2. Karyosome
3. Parabasal body
4. Blepharoplast
5. Axoneme
6. Undulating membrane
7. Flagellum
8. Parabasal body and blepharoplasty together constitute the kinetoplast



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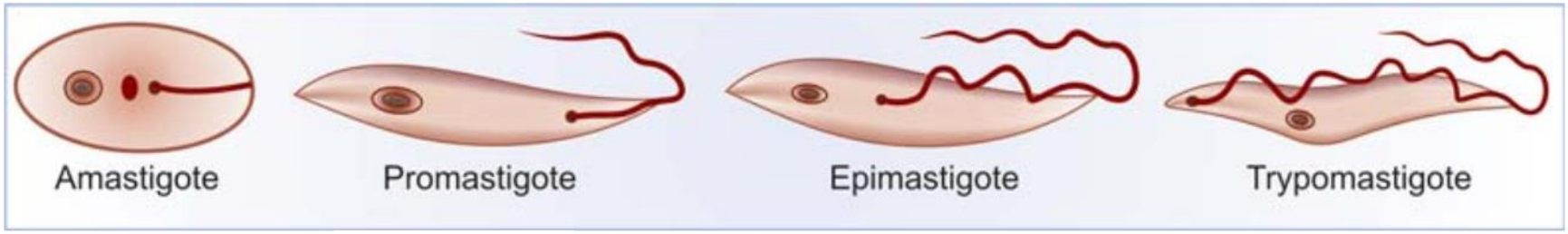
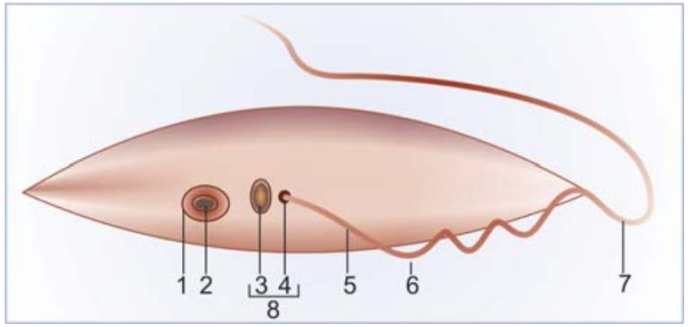


FIGURE 13.2 Morphological stages of haemoflagellates



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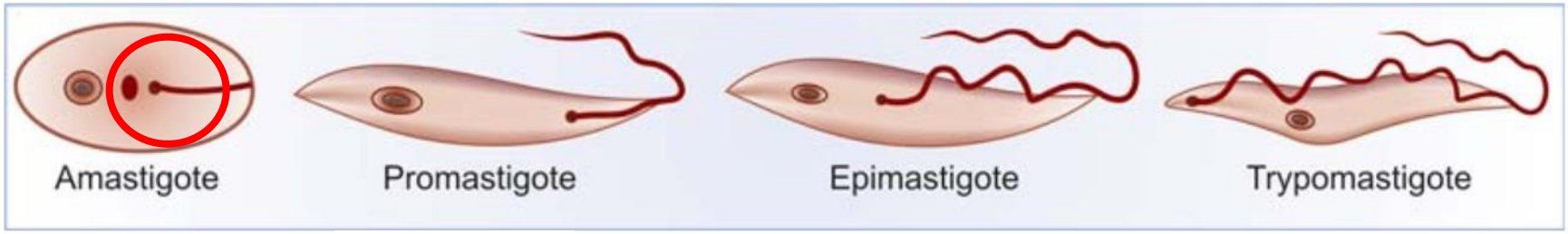
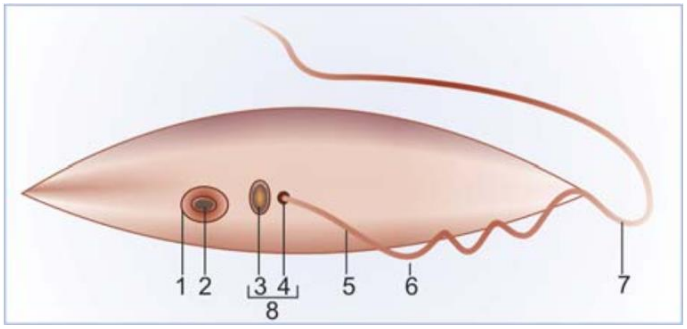


FIGURE 13.2 Morphological stages of haemoflagellates

AMASTIGOTE

Round/oval shape
without single flagellum



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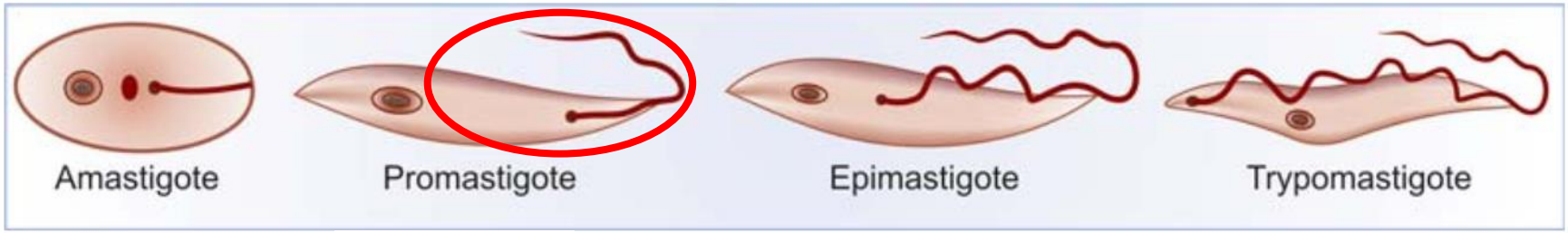


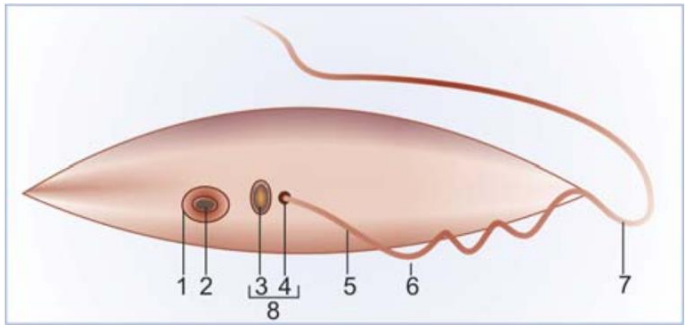
FIGURE 13.2 Morphological stages of haemoflagellates

AMASTIGOTE

Round/oval shape
without single flagellum.

PROMASTIGOTE

Elongated shape
with single flagellum.



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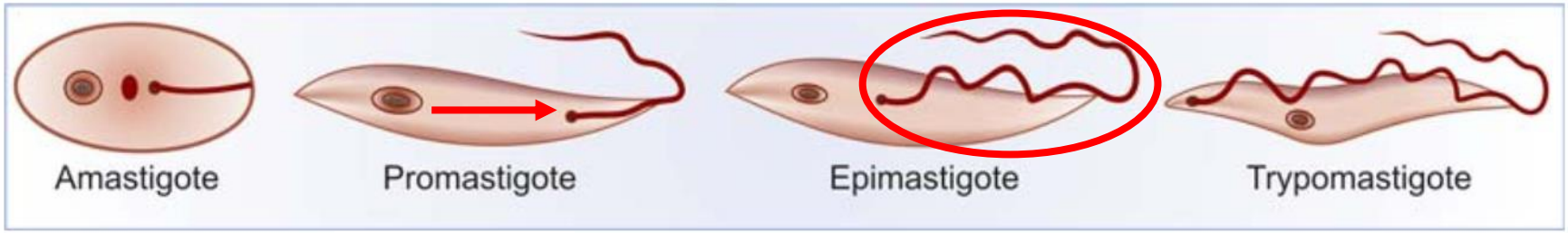


FIGURE 13.2 Morphological stages of haemoflagellates

AMASTIGOTE

Round/oval shape without single flagellum.

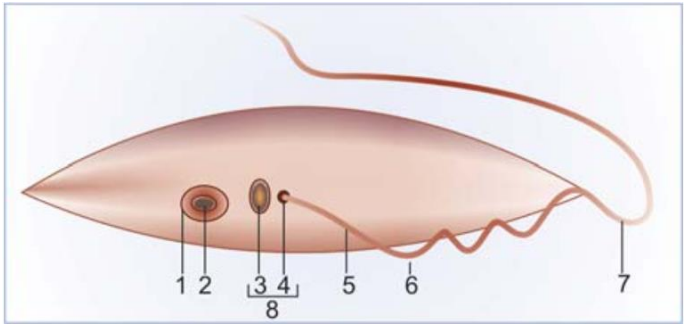
PROMASTIGOTE

Elongated shape with single flagellum.

EPIMASTIGOTE

Elongated shape undulating membrane covers half of the cell

with single flagellum.



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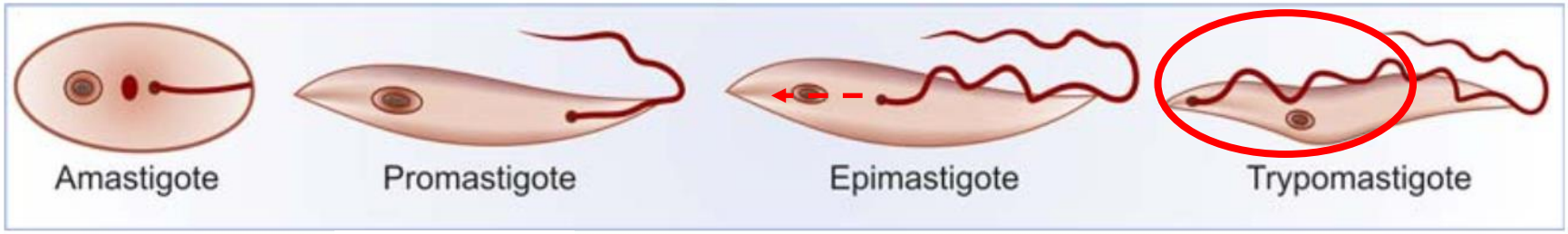

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AMASTIGOTE

Round/oval shape without single flagellum.

PROMASTIGOTE

Elongated shape with single flagellum.

EPIMASTIGOTE

Elongated shape undulating membrane covers half of the cell with single flagellum.

TRYPOMASTIGOTE

Elongated shape undulating membrane covers the length of the cell with single flagellum.

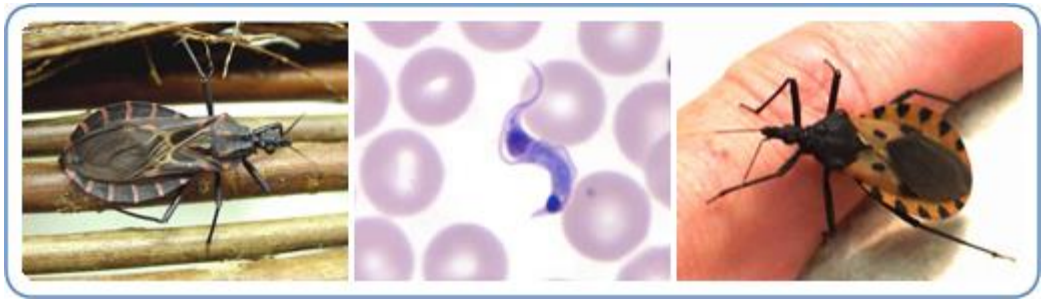
Topic Learning Outcomes

At the end of the lecture, students will be able to:

1. define trypanosomiasis and leishmaniasis
2. describe the general morphology and life cycle
3. describe the epidemiology of these parasites in the world
4. describe the pathogenesis
5. describe the clinical manifestations
6. identify common methods used in the diagnosis
7. list cdc-recommended treatment regimens
8. describe appropriate prevention measures

Trypanosoma brucei
(Sleeping sickness)

Trypanosoma cruzi
(Chagas disease)



Blood & Tissue Protozoa I: Flagellates
Trypanosoma spp.

Definition

Trypanosomiasis
Infection caused by haemoflagellate, *Trypanosoma* spp.

1. African trypanosomiasis	2. South American trypanosomiasis (Chagas' disease)
T. brucei gambiense	*T. cruzi*
T. brucei rhodensiense	*T. rangeli* (non-pathogenic)
T. brucei brucei (not infective)	
Tsetse fly	Reduviid bug

1. African Trypanosomiasis

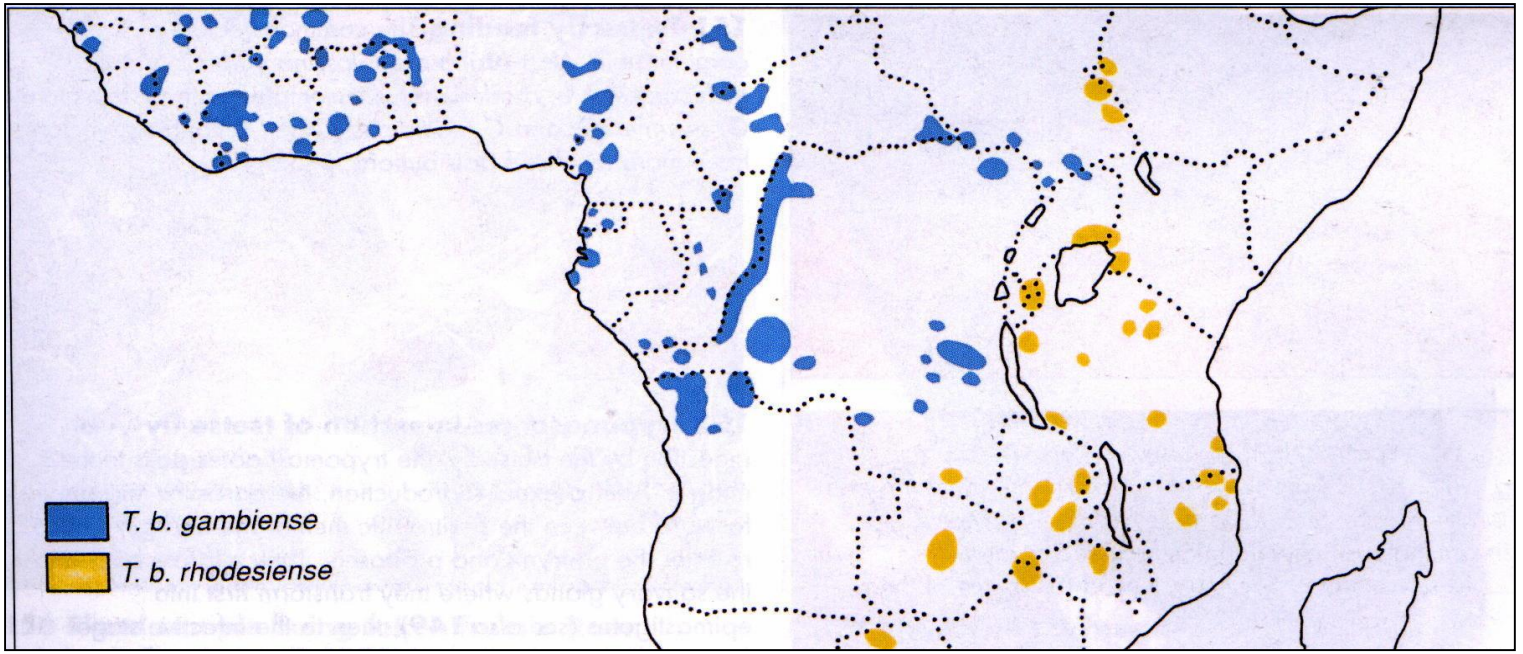
This disease is caused by flagellated protozoan parasites that belong to the *Trypanosoma brucei* complex and are transmitted to human by tsetse flies.

It is a severe disease, which is fatal if left untreated. It is closely related to a widespread infection of cattle known as N'gana, which restricts cattle rearing in many prime areas of Africa.

Sleeping sickness claims comparatively few lives annually, but the risk of major epidemics means that surveillance and ongoing control measures must be maintained.

(World Health Organization Tropical Diseases Research: WHOTDR)

Geographical Distribution



36 countries in sub-Saharan Africa.

7 countries: disease is highly endemic.

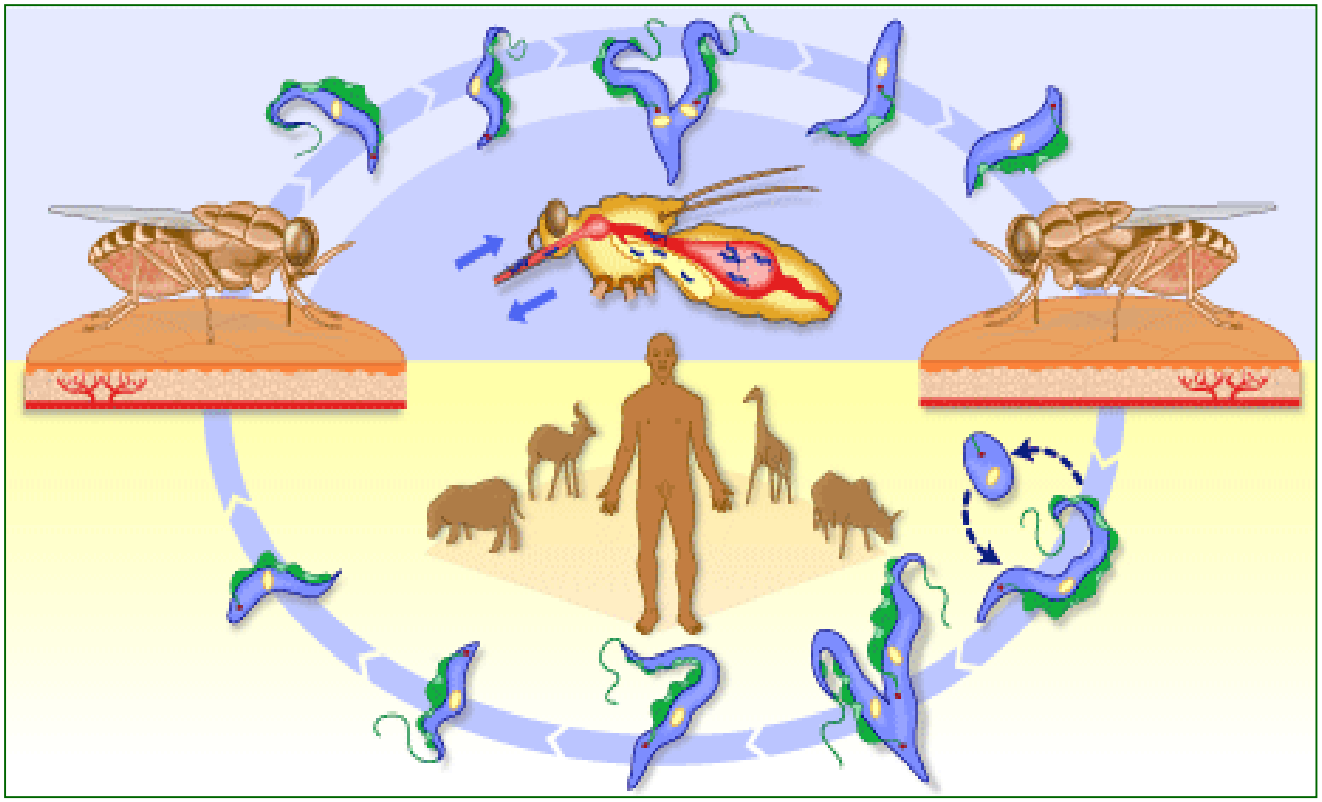
4 countries: disease is endemic.

12 countries: disease has moderate endemicity

13 countries: epidemiological status is poorly understood.

(WHOTDR)

Life Cycle



Mode of transmission

Biting by the infected tsetse flies (*Glossina spp.)*

Blood transfusion

Congenital infection

Laboratory accidents

A self-limited inflammatory lesion
It may appear a week or so after the bite

African Trypanosomiasis

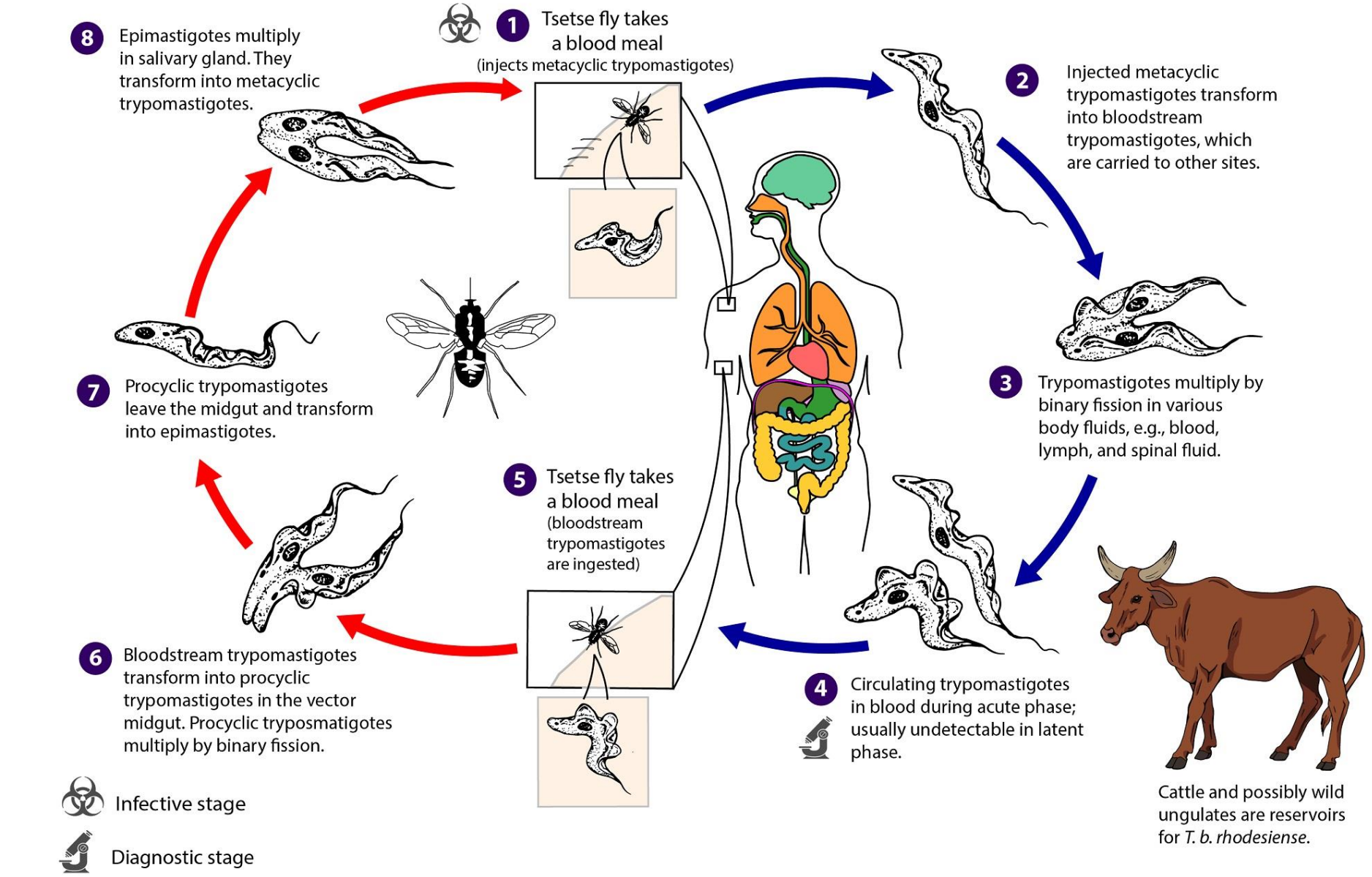
Trypanosoma brucei gambiense & Trypanosoma brucei rhodesiense

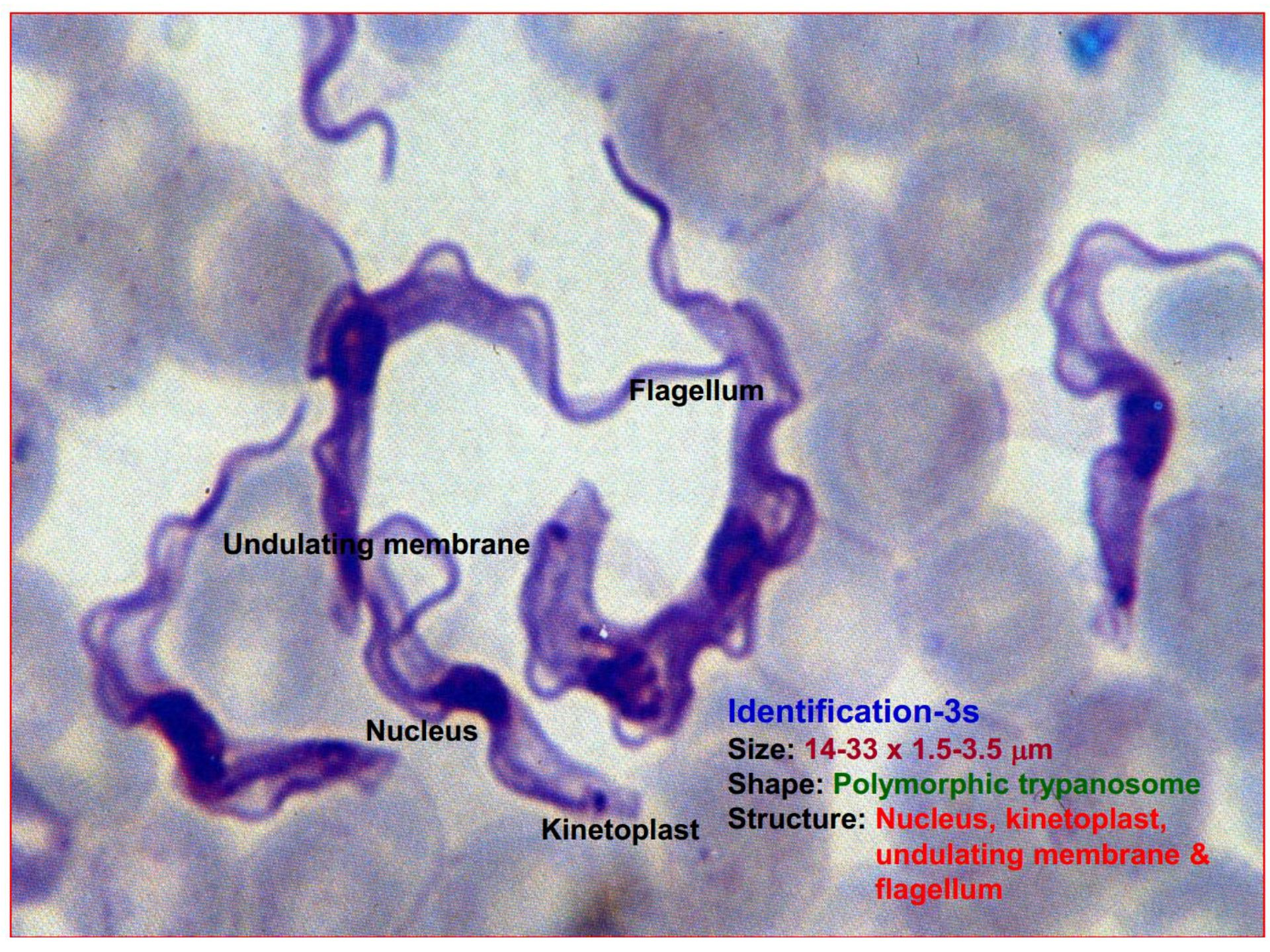
DPDx

CDC

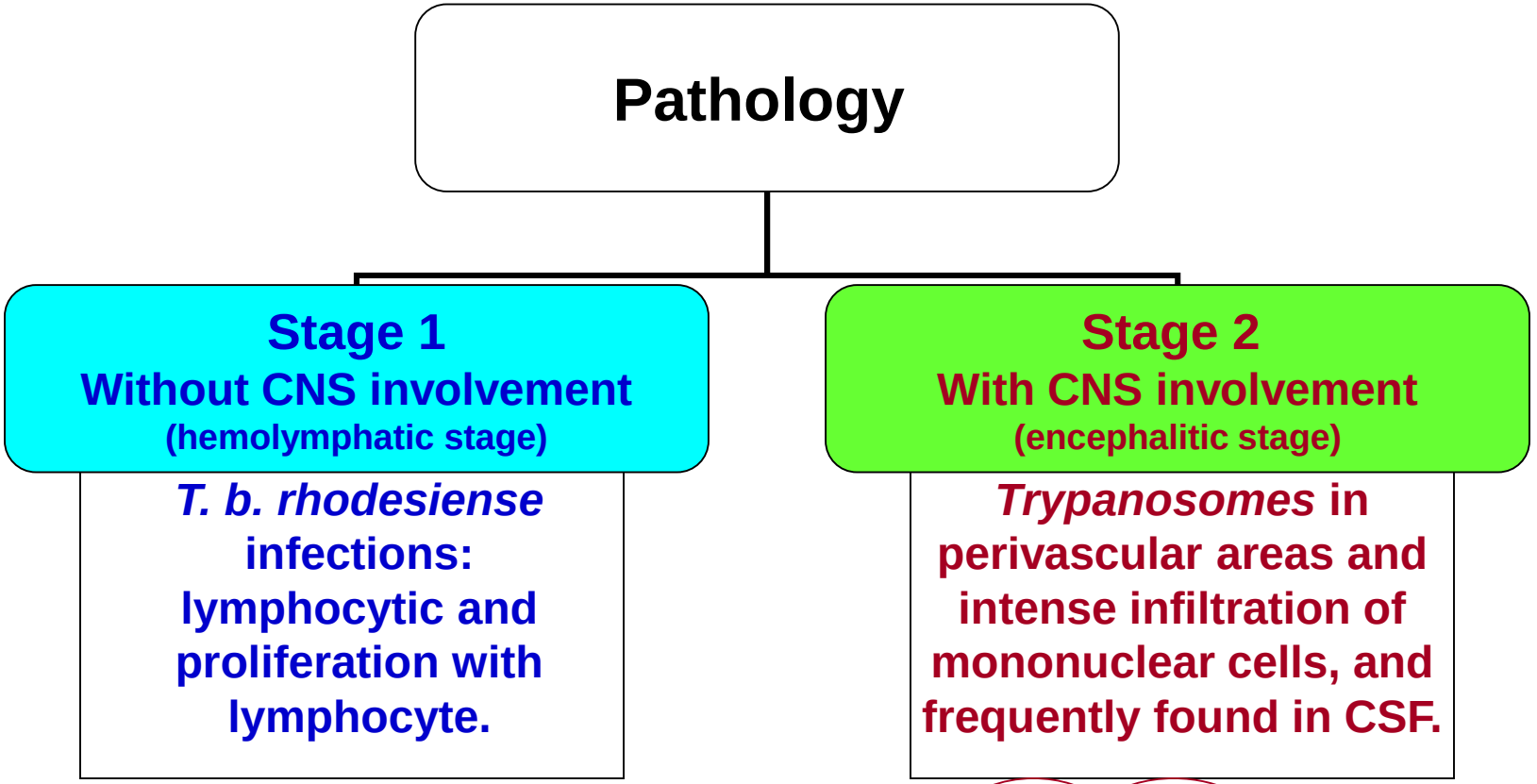
Tsetse Fly Stages

Mammalian Stages




Flagellum
Undulating membrane
Nucleus
Kinetoplast
Identification-3s
Size: 14-33 x 1.5-3.5 μm
Shape: Polymorphic trypanosome
Structure: Nucleus, kinetoplast, undulating membrane & flagellum

Pathology



CSF and plasma analyses: a role for both pro-inflammatory and counter-inflammatory cytokines in determining the severity of the meningoencephalitis of late stage disease. **(Kennedy, 2006)**

Clinical Manifestation

Stage 1
Without CNS involvement
(hemolymphatic stage)

Fever--chancre
Lymphadenopathy
discrete, movable, rubbery and nontender.
Winterbottom's sign
cervical lymphadenopathy.

Stage 2
With CNS involvement
(encephalitic stage)

Wide range of CNS: neuropsychiatric, motor and sensory abnormalities.
Severe post-treatment reactive encephalopathy (PTRE).

Potentially fatal complications of melarsopol treatment of late-stage disease in 10% of which half die.

(Kennedy, 2006)

Diagnosis

Microscopy & Staining

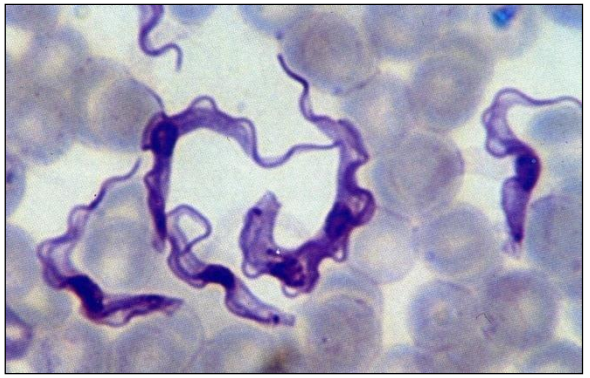
Serodiagnosis

Aspiration (LN, BM, *etc*.)

Lumbar puncture (CSF finding)

Animal inoculation

Serum proteomic signature



There is no universal consensus as to how late-stage disease should be diagnosed using CSF criteria, and this has been very problematic in Human African Trypanosomiasis (HAT).
(Kennedy, 2006)

The signature, improved diagnostic tests, disease staging and identification of potential drug targets in HAT).

(Agranoff *et al*, 2005)

LN: Lymph node
BM: Bone marrow

Treatment

African trypanosomiasis

West African trypanosomiasis

Stage 1.disease

Disease (*T. b. gambiense*)

Suramin
Pentamidine
Eflornithine

Stage 2. disease

Eflornithine

East African trypanosomiasis

Stage 1.disease

(*T. b. rhodesiense*)

Suramin
Pentamidine

Stage 2. disease

Arsenic melarsoprol
Suramin
If melarsoprol toxicity
Arsenic trypasamide + suramin

Treatment has always been difficult, especially when the disease has reached an advanced stage with central nervous system involvement, as few effective drugs are available.
(WHOTDR)
The occurrence of drug resistance and vaccination does not appear to be feasible.
(Luscher *et al*, 2007)

Pentamidine
not effective against late-stage disease and some parasite strains are resistant to it.

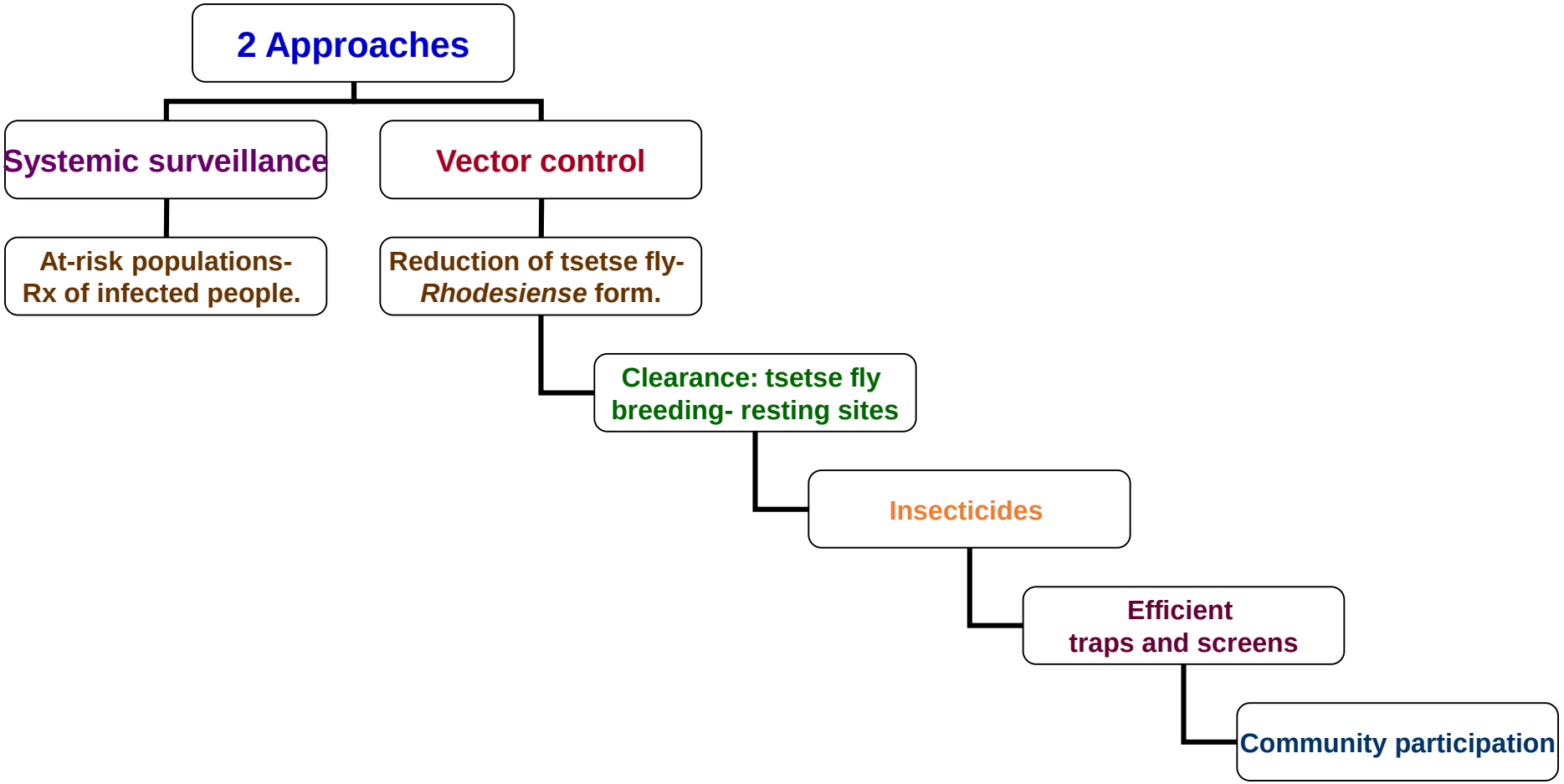
Suramin
has to be administered intravenously and can have adverse side-effects.

Melarsoprol
an arsenical drug developed over 50 years ago, is used against late-stage disease, but often induces serious - sometimes fatal - side-effects.

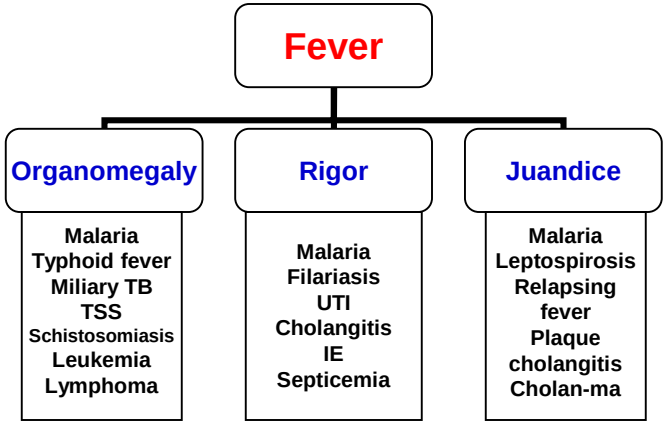
A new drug, eflornithine
an anticancer agent, promising results against the gambiense form and new treatment regimes have been discovered that should halve the cost of treatment.

Ascofuranone
Japanese group has developed for HAT without side effects.
(Ohta, 2006)

Prevention and Control



Differential Diagnosis



Splenomegaly	Massive splenomegaly
Infective:	Malaria, Kala azar
Malaria, Kala azar	CML
Trypanosomiasis	Myelofibrosis
Infective hepatitis	Extrahepatic portal HT
Congestive:	
Schistosomiasis	
Cirrhosis, CHF	
Constrictive pericarditis	
Blood disease:	
Leukaemia	
Lymphoma	
Hemolytic anaemia	
Tumors, Miscellaneous	

Hepatosplenomegaly	Hepato-lymphadenopathy
Infective:	Acute leukaemia
Malaria	Lymphoma
Infective hepatitis	IM
SBE	Disseminated TB
Congestive:	Sarcoidosis
CHF	
Pericarditis	
Blood diseases:	
Leukaemia	
Lymphoma	
Chronic hemolytic anaemia	

Anaemia	Granolumatous inflammation
Bone marrow infiltration	Parasitic infections
Hypersplenism	Schistosomiasis
Autoimmune hemolysis and bleeding	Ascariasis
Malaria	Filariasis etc.
Helminths infections	TB, Leprosy, Syphilis
Tuberculosis	CMV, EBV infections
Malabsorption	Fungal infections
Blood diseases	Tumors
Malignancy	Sarcoidosis
AIDS	Cat-scratch disease

PKDL	CNS involvement /abnormal CSF
Syphilis	Cerebral malaria
Leprosy	Crytococcal meningitis
Yaws	Viral meningoencephalitis
	Meninglcoccal meningitis
	Meningovascular syphilis

2. American Trypanosomiasis

This disease is a zoonosis caused by protozoan parasite *Trypanosoma cruzi.*

By the early 1990s,
Chagas disease was ranked by the World Bank
as the most serious of the parasitic diseases in Latin America
with a socioeconomic impact considerably greater than
that of the combined effects of all other parasitic infections.
(World Bank, 1993)

Chagas disease remains a significant public health issue
and a major cause of morbidity and mortality
in Latin America.
(Marin-Neto *et al*, 2007)

Epidemiology

75% of the acute phase were seen in children less than 10 years of age.

(reviewed in Teixeira 1987)

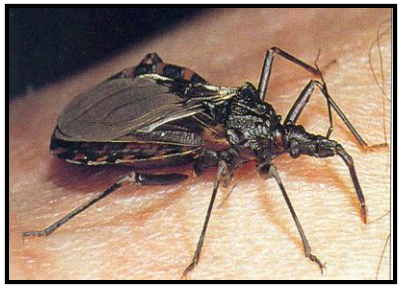
Approximately 12 million people with positive immunologic tests (indeterminate phase) for the parasite.

(Macedo, 1999)

18% of chronic chagas disease prevalence were seen of the street cleaners Brasilia, Brazil.

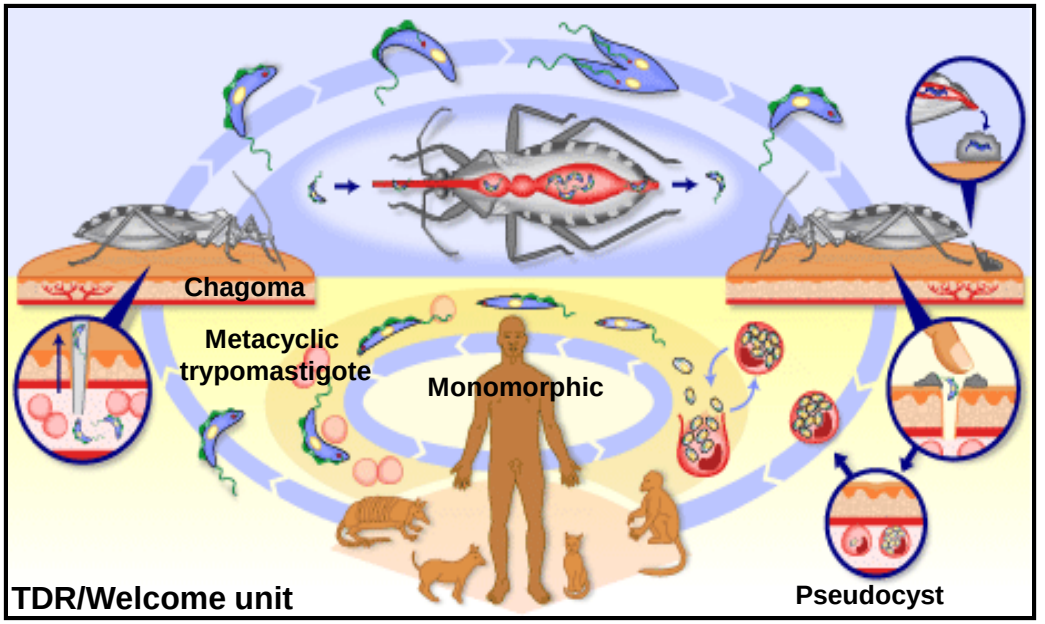
(Lauria-Pires *et al*, 2000)

Life Cycle



Mode of transmission

Biting by infected bugs
Blood transfusion
Congenital infection
Laboratory accidents



18 countries in 2 ecological zones.

Southern Cone, where vector insects live inside human homes.
Northern South America, Central America and Mexico, where the vector lives both inside and outside dwellings.

Histo-pathological changes.

Acute Chagas disease
Intermediate phase
Chronic Chagas disease
Chronic Chagas mega syndromes

Trypanosoma cruzi

DPDx

Triatomine Bug Stages

Mammalian Stages

1. Triatomine bug takes a blood meal
(passes metacyclic trypomastigotes in feces, trypomastigotes enter bite wound or mucosal membranes, such as the conjunctiva)

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.

4. Intracellular amastigotes transform into trypomastigotes, then burst out of the cell and enter the bloodstream.

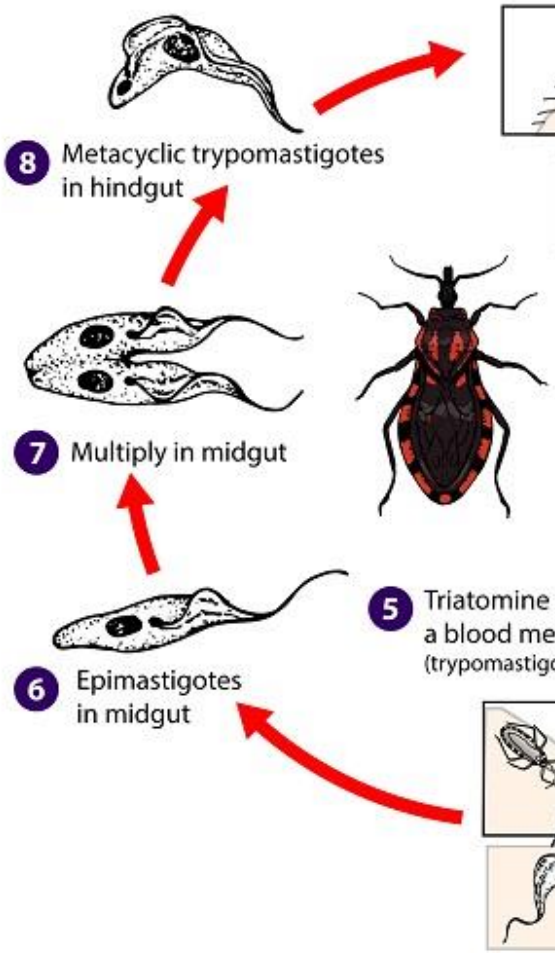
Trypomastigotes can infect other cells and transform into intracellular amastigotes in new infection sites.

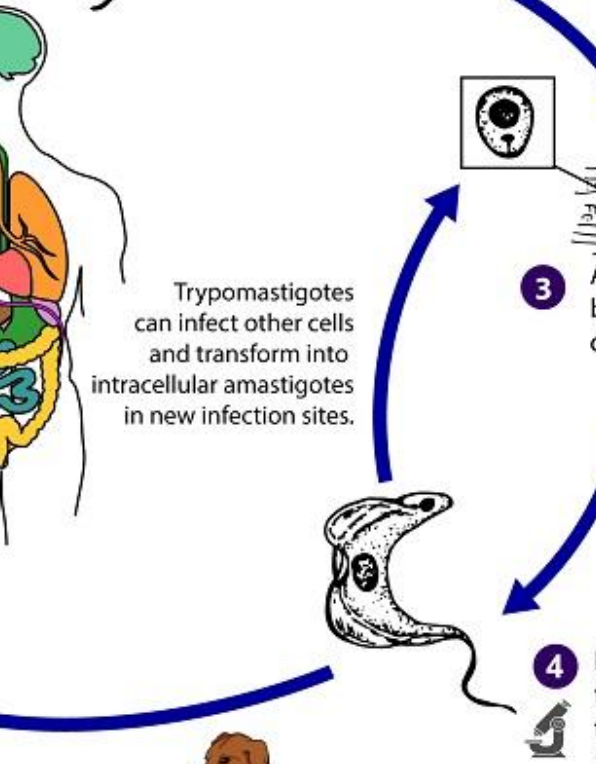
5. Triatomine bug takes a blood meal
(trypomastigotes ingested)

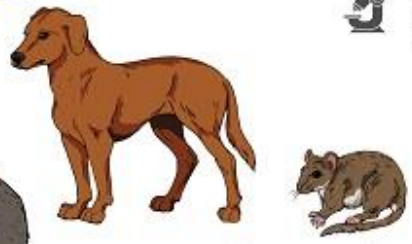
6. Epimastigotes in midgut

7. Multiply in midgut

8. Metacyclic trypomastigotes in hindgut







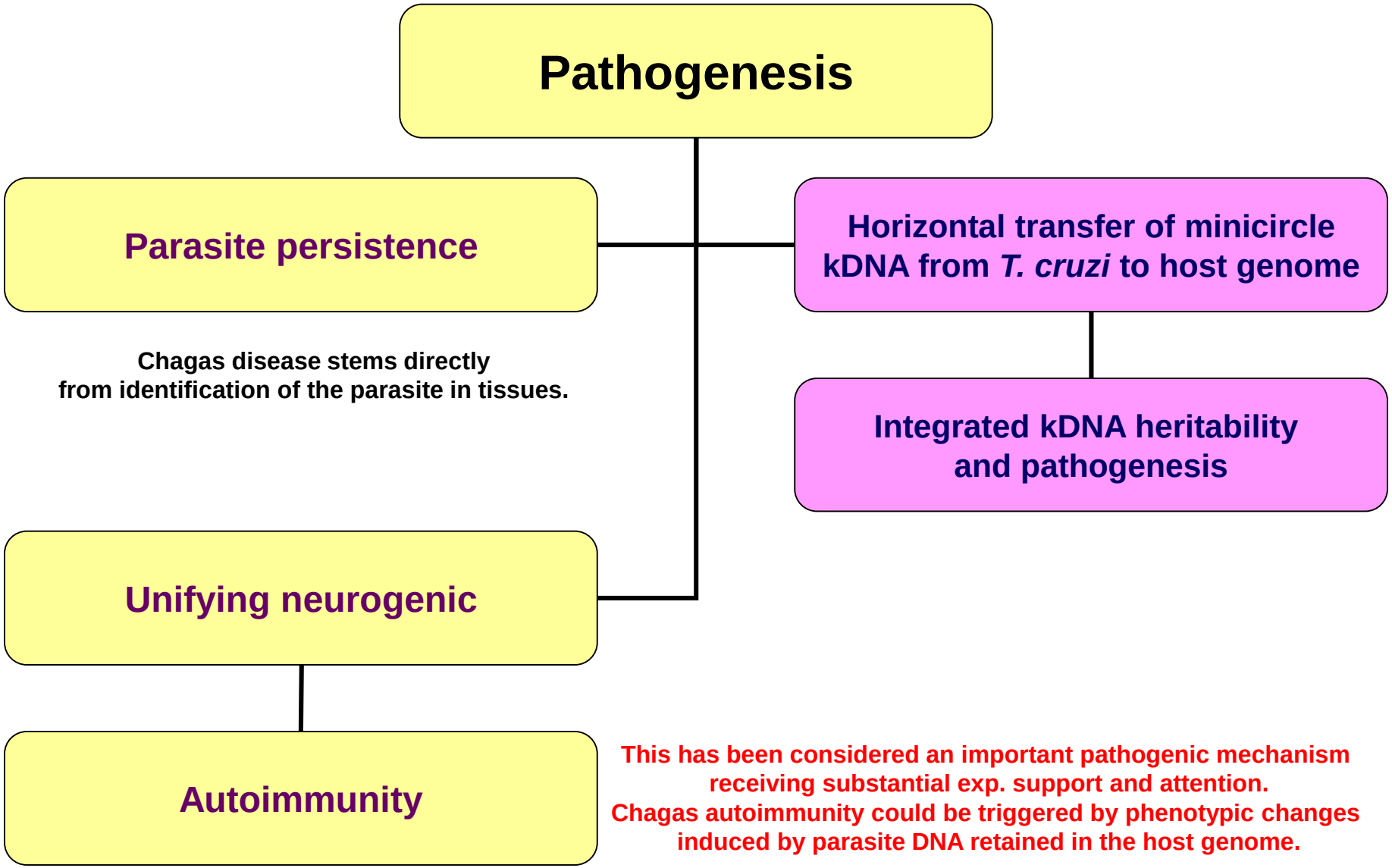
Many mammalian species have been recognized as *T. cruzi* reservoir hosts.

CDC

Infective stage

Diagnostic stage

Pathogenesis



(Teixeira *et al*, 2006)

Pathology

Pathology

Acute phase

Heart:
enlarged, dilated flabby, and congested.

Striated heart & skeletal muscle:
amastigotes (pseudocyst) in the absence of inflammation.

CNS-frequent:
CSF in 72.7% of cases. (Hoff *et al*, 1985)

Meningitis & encephalitis.

Brain:
congestion and edema.

Brain tissue:
inflammation around small blood vessels, vascular hemorrhage, microgial cell nodular proliferation in the white and gray matter.

Intermediate phase

Minimal inflammatory heart lesions.
(Mady *et al*, 1982)

Skeletal muscle:
Spotty inflammation, target cell lyses and degeneration.
(Sicca *et al*, 1995)

Inflammatory lesions:
heart, digestive tract, and skeletal muscle are similar to those seen in chronic patients but much lower degree.

In digestive tract:
Lesions reaching the parasympathetic ganglia and neuronal cell depopulation have been observed.
(Lopes, 1999).

Chronic phase

Effacement of the apex of the left ventricle: aneurismal dilatation.

Thrombus embolic phenomena in the brain and lungs: the ultimate death.

Inflammatory infiltrates present in every case.

The parasite is seen more commonly in areas of the myocardium spared from inflammatory Infiltrates.

Ganglionitis, neuron degeneration, and neuron drop-out are unique.

Chronic mega syndrome

Inflammatory lesions in parasympathetic ganglia lying between the smooth muscle layers (Auerbach's plexus) and in the sub-mucosal (Meissner's plexus) of the hollow viscera.

The most conspicuous lesions parallel those in the heart and associate inflammatory mononuclear cell infiltrates with the minimal rejection unit that appears to be a common pathological denominator.

Clinical Manifestation

Chagas disease (CD)

Acute phase

Lesion: erythema and swelling (chagoma) in immuno-competent but not immuno-compromised.

Romana's sign; unilateral painless edema (palpabrae, periocular tissue).

Fever, malaise, edema of the face. Lymphadenopathy. Hepatosplenomegaly.

Death: 1/1000 acute infected related to heart failure or meningitis and encephalitis.

Indeterminate phase

Remains a life-long source of the parasite. 1/3 will develop chronic disease.

Criteria:
1. Positive IgG and/or the present of parasite.
2. Absence of s/s.
3. Absence of ECG abnormalities.
4. Regular size of heart, esophagus and colon (X-ray).

2/3 remain in this condition.
Life span ≈ n. person.
Disqualified from blood donation.

Chronic phase

Cardiomyopathy has made CD the most lethal endemic ID in the western world.
(Cubilos-Garzon, 2004)

The main Life threatening features: heart failure, arrhythmias and throbmoembolism.

Heart enlargement: ominous sign-poor Prognosis.

Increase in ECG alteration recorded on two occasions 10 years apart.
(Lauria Pires *et al*, 2000)

Digestive form

GI disorders are among the most s/s.

Esophageal alterations occurs earlier.
(Reviewed in Macedo, 1999)

Megaesophagus (ME):
Men (20-40 years).
Dysphagia & regurgitation of food.

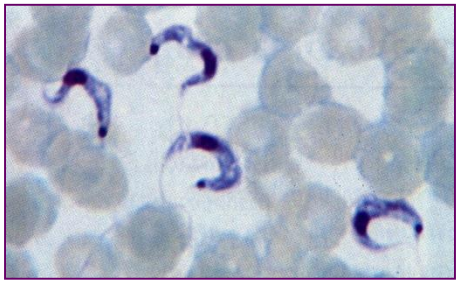
Megacolon (MC):
Later course: constipation
Intestinal obstruction and rupture (complication).
(Reviewed in Prata, 1999)

ME and MC
Endemic
Specific T. cruzi Ab.
Positive nucleic acid test (NAT) assays.

Diagnosis

Evaluation of cure

Parasitological evaluation



Direct examination
of blood in fresh or stained preparation or by concentration methods.

Hemoculture
is the second parasitological method of choice: chronic chagas disease.

Xenodiagnosis

Polymerase Chain Reaction (PCR)
2 to 3 times higher for chronic cases.

Serological evaluation

The most simple, more broad and reliable in chronic cases (almost 100%) (IIF, HGT and ELISA).
The presence of parasite Ag.

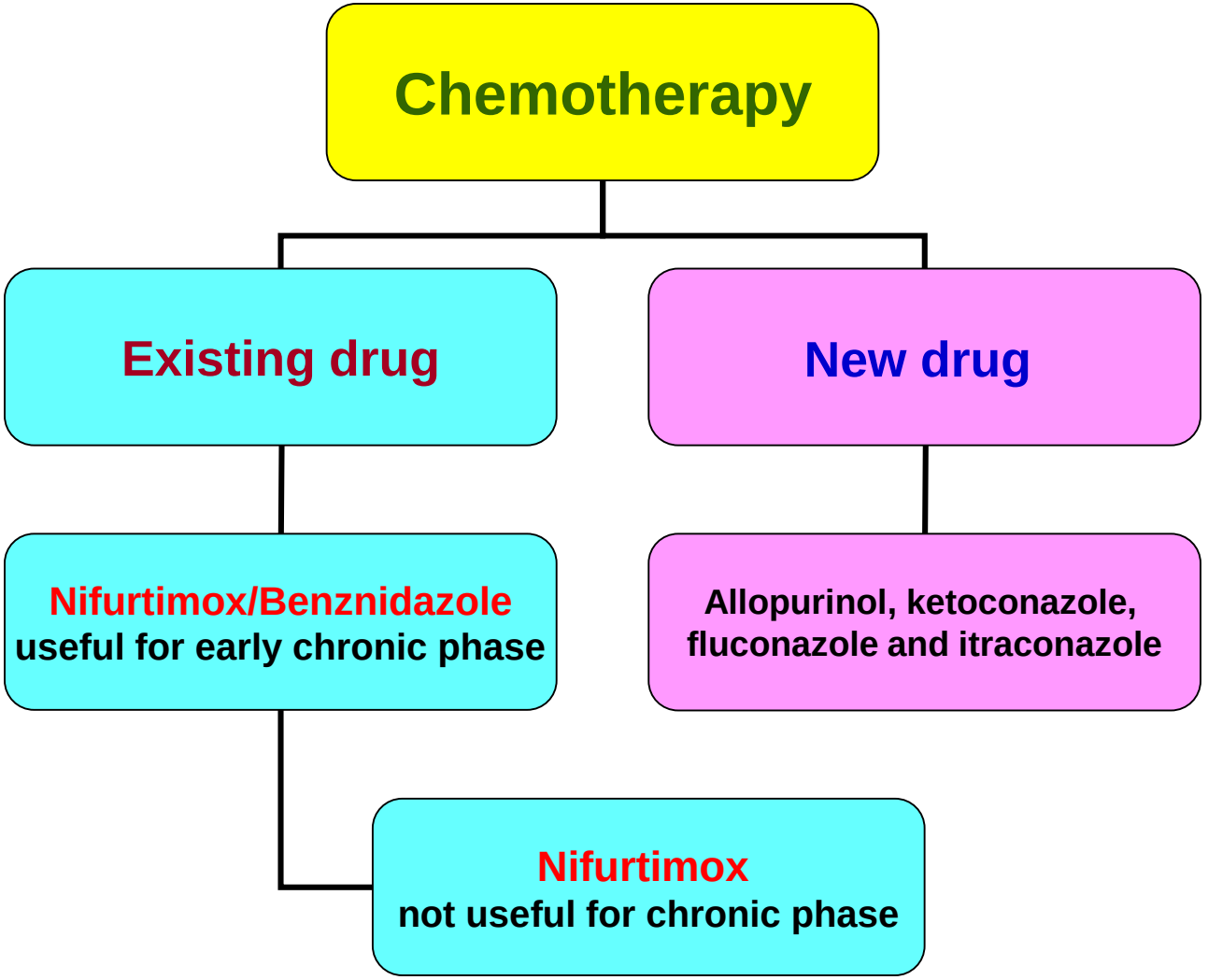
After chemotherapy is perhaps the most difficult and long topic to be addressed.

Clinical evaluation

Anamnesis, clinical examination, and non-invasive tests such as ECG, endoscopy, biopsies for histological, histochemical studies and X-ray.

Treatment

***T. cruzi* antigens can stimulate autoimmunity, so the prospects for an effective vaccine are slim.**



Diagnosis

Acute phase
60% cure rate

Direct examination: wet smear/stained.
Concentration methods
(centrifugation/quantitative buffy coat).
Determination of IgM level.

Congenital infection

In cases of children from infected mothers.
Serologically positive.
Who presented *T. cruzi* in the blood of umbilical cord.
IgM in the serum soon after birth.
IgG after 6 months.

Accidental infection

Serological test and treatment immediately begins during 10-15 days.
Repeating the serology after 15, 30, and 60 days.

Chronic phase

Recent chronic phase:
last 10 years of infection, children up to 12 years or adults- occasionally infected in endemic areas of by BT in a known interval of time.

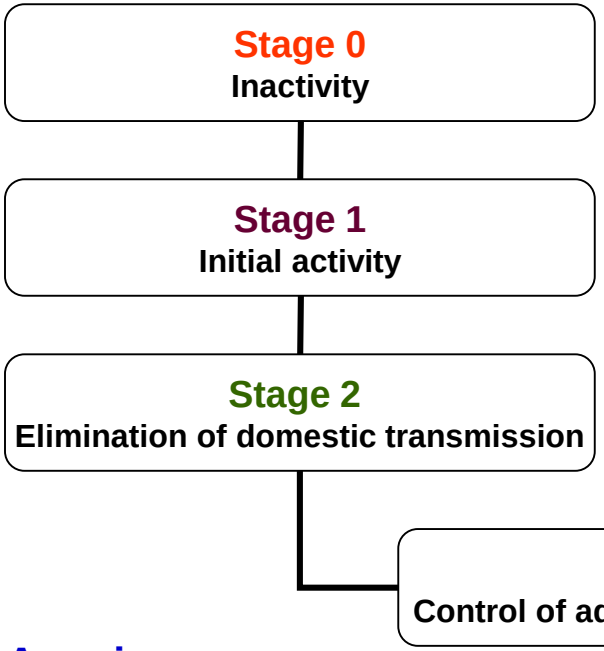
Late chronic phase:
more than 10 years of infection, parasitological cure 10-20%, Rx is selective.

Organ transplant:
serology for both donor and recipient during immunosuppression, Rx both parties.

Reactivation phase
Immunosuppression

Reactivation: meningoencephalitis/ acute myocarditis.

Prevention & Control



Lack of epidemiological data, or a national incapacity to acknowledge or investigate what data may exist (except Guyana).

Recognition that the disease exists, that transmission occurs, and that steps can be taken at a national level to ameliorate the individual and Community impact of the infection.

Eliminated by the professionally applied treatment with modern pyrethroids.

To prevent their establishment of the vectors.

No more domestic vector transmission.

No more chronic infection, rare case of transfusion.

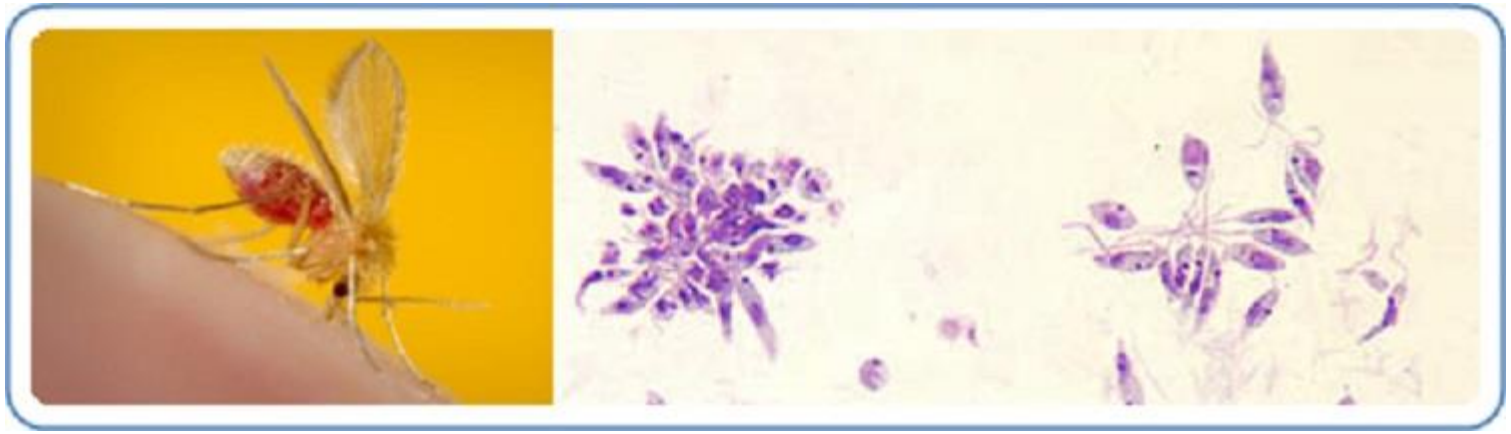
Complete control-Latin America

1. Launching adequate national programmes in those existing disease but not yet properly considered by the national health authorities.
2. Improving and maintaining the existing programmes.

(Brazil: Schofield & Dias, 1999; Dias, 2000: Vinhaes, 2002)

a. to maintain the political priority of the programme until its consolidation.
b. to improve and refine epidemiological surveillance-peripheral level and supported by regional and national technical reference groups
c. to improve and refine methods and strategies fot the control of peridomestic infestation by secondary vector species.
d. to cover 100% of blood transfusion with prior serological selection.
e. to improve medical and social attention to the remaining chagasic individuals.

(Dias *et al*, 2002)



Blood & Tissue Protozoa I: flagellates
Leishmania spp.

Definition

Leishmaniasis

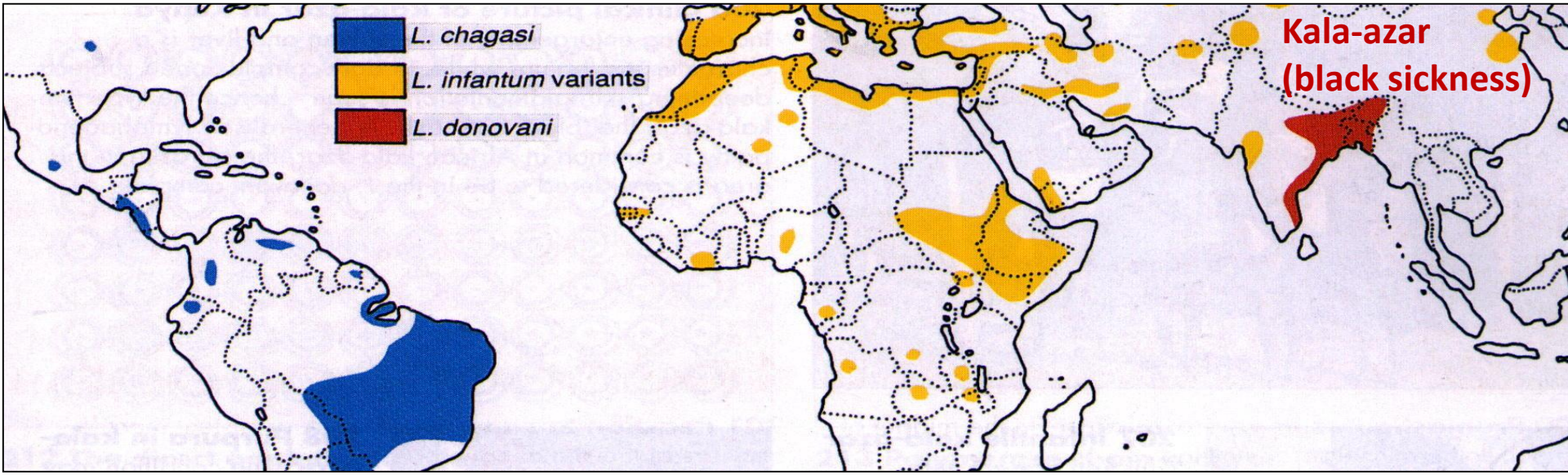
caused by 20 species of *Leishmania and* transmitted by 30 species of sand fly, is characterized by diversity and complexity.

(Desjeux, 1990; Ashford, 1997)

Anthroponotic (human-human transmission) was found in only 2 *Leishmania* species.

L. donovani	**visceral leishmaniasis (VL) in Indian subcontinent and east Africa**
L. tropica	**cutaneous leishmaniasis (CL) in the old world.** **(Magill, 1995)**
L. braziliensis	***m*uco-cutaneous leishmaniasis**
L. Mexicana	***m*uco-cutaneous leishmaniasis**

Epidemiology

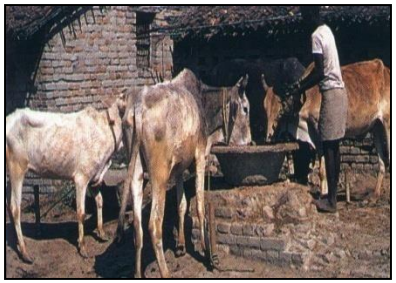


An estimated 350 millions population is at risk and 10 million people are affected from this disease worldwide.

Two million cases occur annually, a gross underreporting of the cases from endemic regions, and a progressive increase in the cases of leishmaniasis being reported from the newer areas.

(Bora, 1999)

Life Cycle

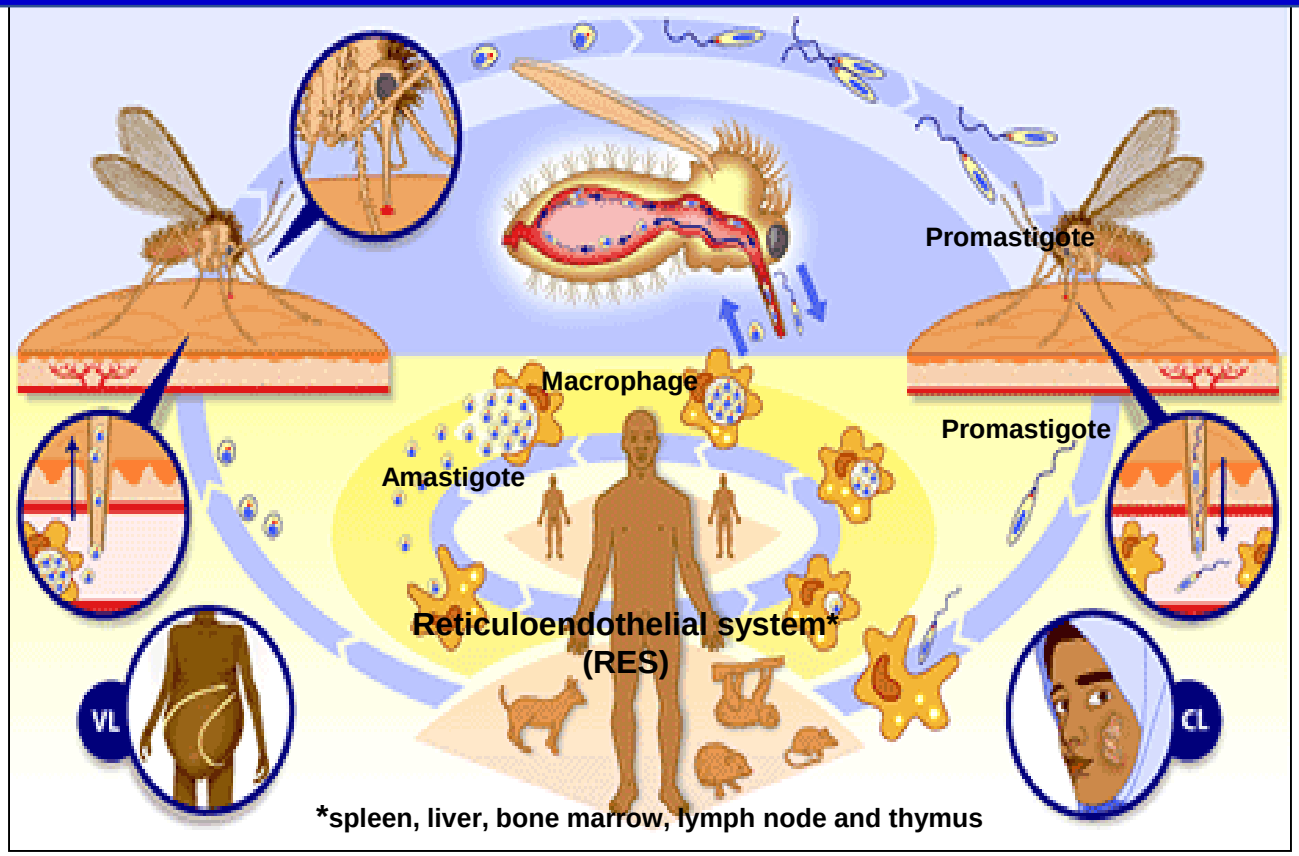


Mode of transmission

Biting by infected sandfly

Blood transfusion

Congenital infection



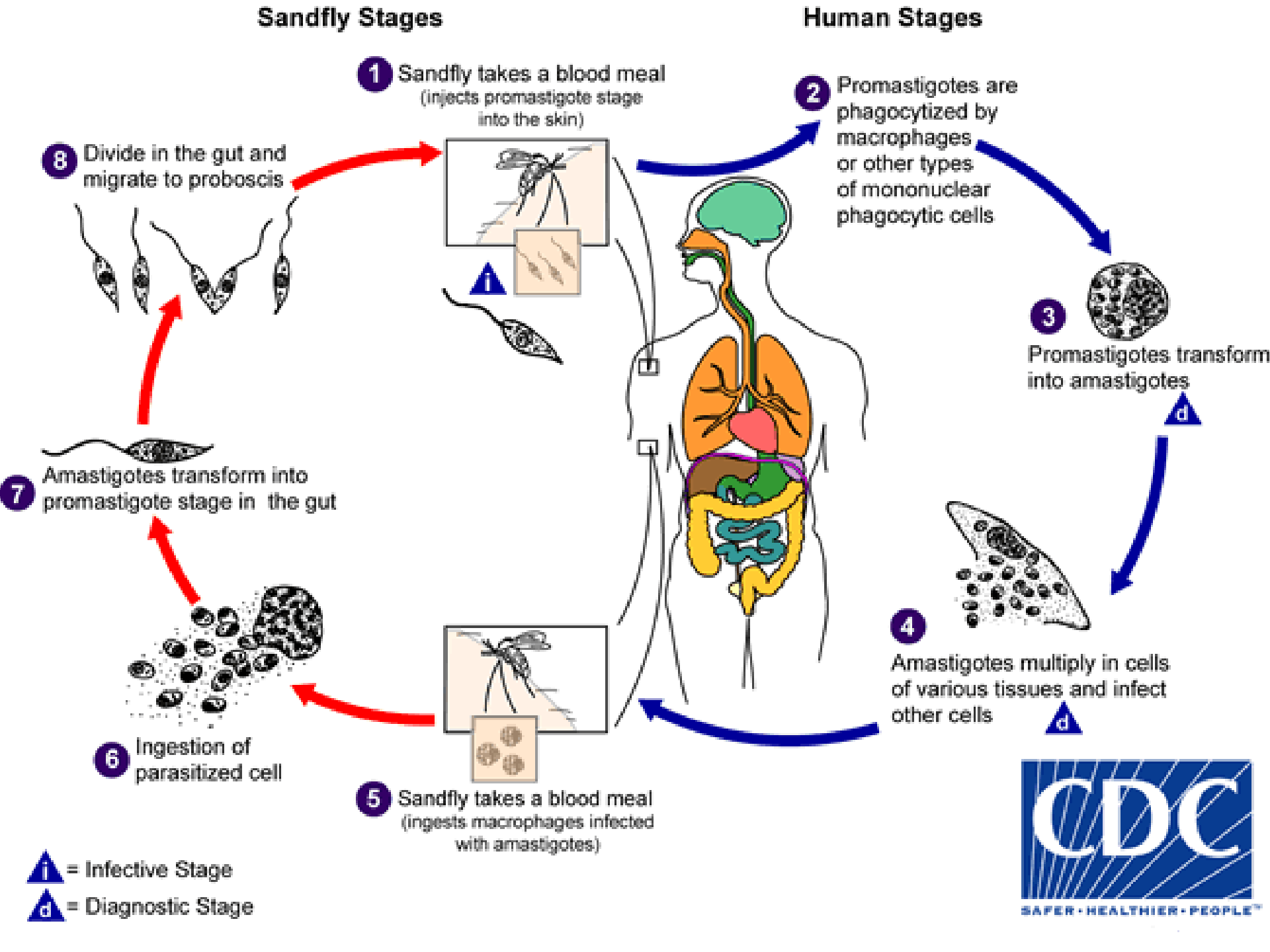
granuloma → histiocyte + amastigote with epithelial and giant cells

↓

local LN

↓ **hematogenously**

macrophages → liver, spleen, BM, etc.


Sandfly Stages
Human Stages
1 Sandfly takes a blood meal
(injects promastigote stage
into the skin)
2 Promastigotes are
phagocytized by
macrophages
or other types
of mononuclear
phagocytic cells
3 Promastigotes transform
into amastigotes
4 Amastigotes multiply in cells
of various tissues and infect
other cells
5 Sandfly takes a blood meal
(ingests macrophages infected
with amastigotes)
6 Ingestion of
parasitized cell
7 Amastigotes transform into
promastigote stage in the gut
8 Divide in the gut and
migrate to proboscis
i = Infective Stage
d = Diagnostic Stage
CDC
SAFER · HEALTHIER · PEOPLE™

Clinical Manifestation

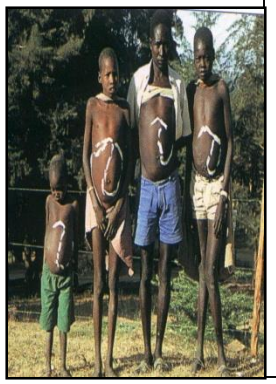
Visceral leishmaniasis (VL)

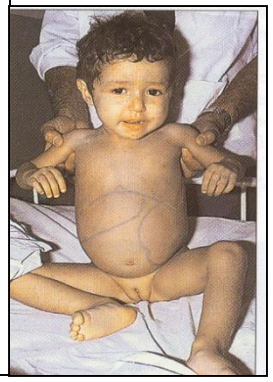
- **Asymtomatic (subclinical)**
- **Acute course**
- **Chronic course**

The incubation period from weeks --> months --> years.

Prolonged and irregular fever often with chill and rigor.
Splenomegaly (nontender, massive)
Lymphadenopathy
Hepatomegaly
Pancytopenia
Progressive anemia
Weight loss
Hypergamma-globulinemia (IgG).
Hypoalbuminemia
(Berman, 1997)
Fatal if left untreated.

Generally; cachetic, febrile with heavily parasitized --> life-threatening disease.



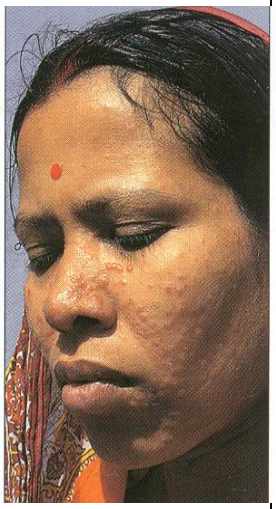


Reactivation

Visceral leishmaniasis
(VL)

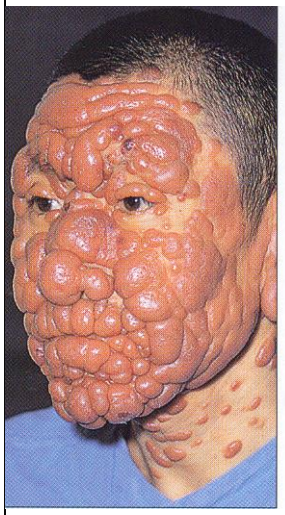
After recovery from | **months or even years**

Post kala-azar dermal leishmaniasis
(PKDL)



Incidence of 50% in Sudan and 1-3% in India.
(Kalter, 1994; Ramesh and Mukherjee, 1995)

Histiocytes in the skin as macules, papules, nodules may grow and coalesce to resemble advanced lepromatous leprosy.



HIV/ AIDS

Visceral leishmaniasis can represent newly acquired as an opportunistic infection in HIV-infected patients or reactivated of a latent focus of infection.

Most coinfected (HIV/VL) patients who have clinically evident leishmaniasis have CD4 count < 200 cells/mm^3.

The risk of VL among AIDS patients increased by 100-1000 times in endemic areas, while VL accelerates the onset of AIDS in HIV infected people.

(Singh *et al*, 2006)

HIV/ AIDS: Challenge

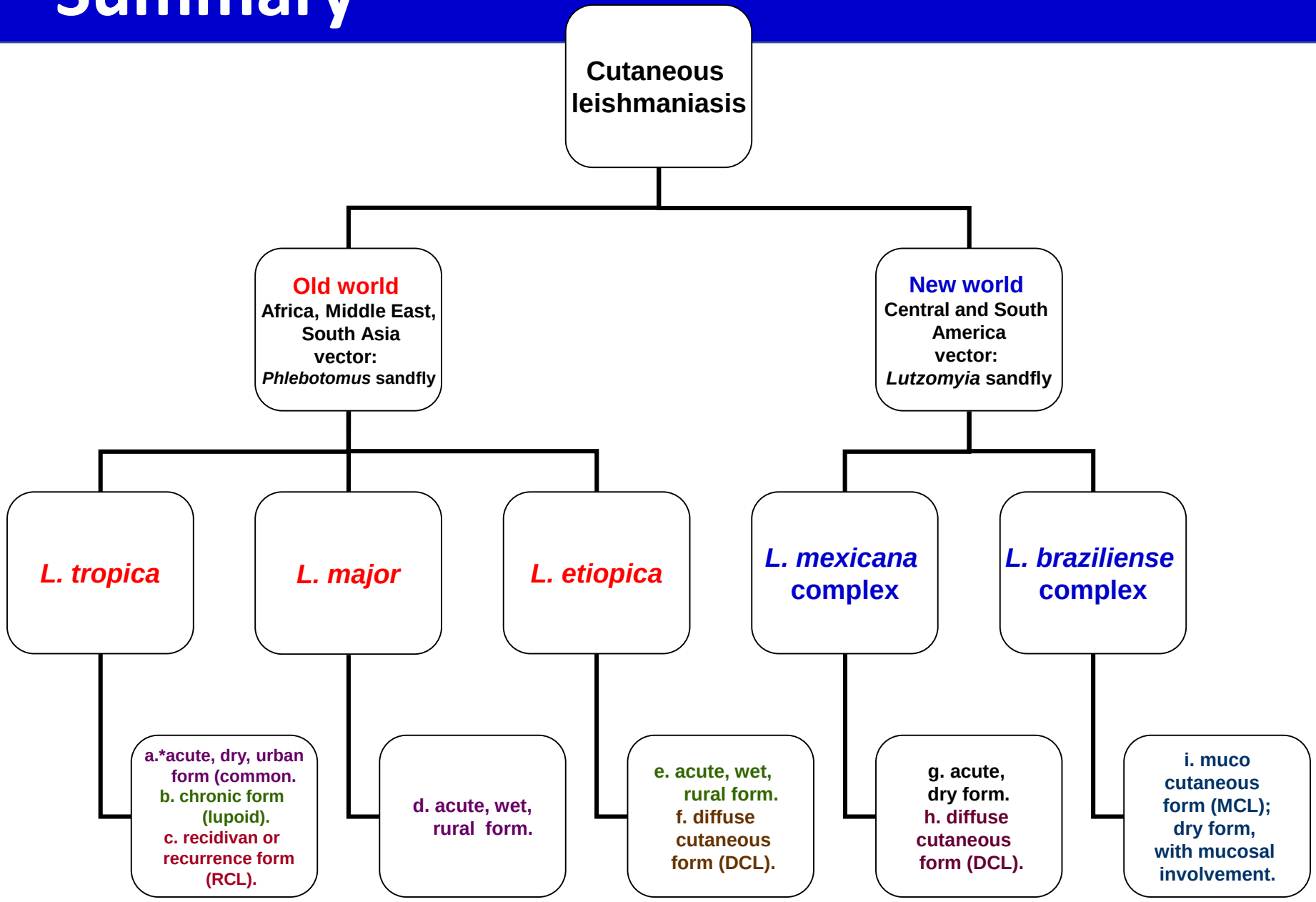
It is becoming an important opportunistic infection among persons infected with HIV-1 in both infections and endemic.

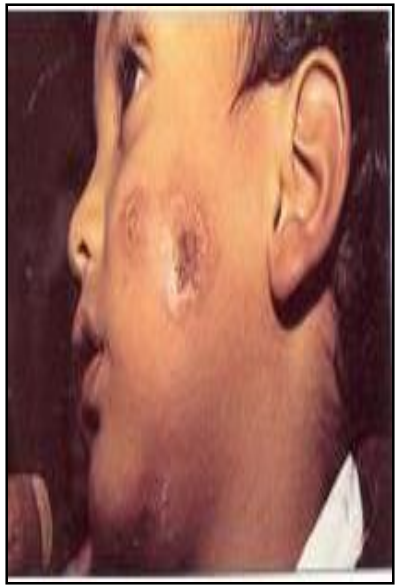
In HIV-infected patients even relatively avirulent *leishmanial* strains can disseminated to the viscera.

H/O HIV-infected patients who have been in leishmaniasis-endemic area.

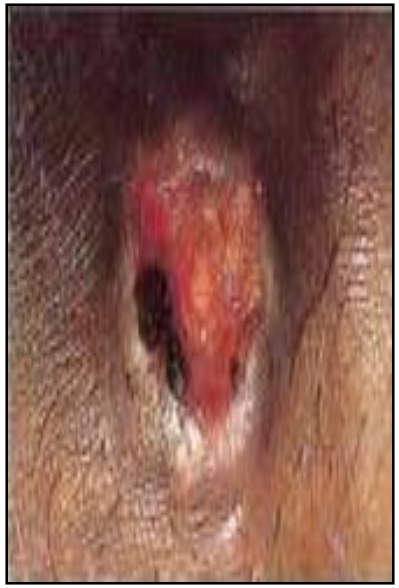
Relapse in HIV/VL co-infected patients poses the current modality in its chemotherapy.

Summary

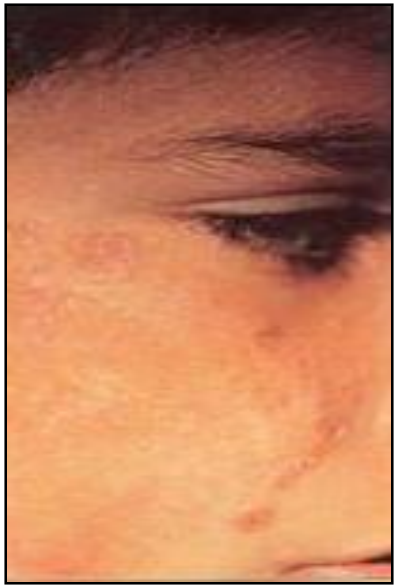

Cutaneous leishmaniasis
Old world
Africa, Middle East, South Asia
vector:
Phlebotomus sandfly
New world
Central and South America
vector:
Lutzomyia sandfly
L. tropica
L. major
L. etiopica
L. mexicana complex
L. braziliense complex
a.*acute, dry, urban form (common.
b. chronic form (lupoid).
c. recidivan or recurrence form (RCL).
d. acute, wet, rural form.
e. acute, wet, rural form.
f. diffuse cutaneous form (DCL).
g. acute, dry form.
h. diffuse cutaneous form (DCL).
i. muco cutaneous form (MCL); dry form, with mucosal involvement.



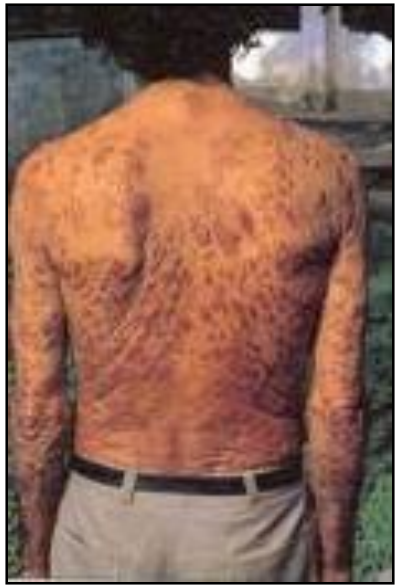
Dry form



Wet form



Recidivans or recurrence form (RCL)



Diffused form (DCL)

Leishmania tropica, L. major and *L. aethiopica*

(Old World cutaneous leishmaniasis, Oriental sore, Delhi boil or Baghdad boil)

Limited to cutaneous tissues, occasionally to mucous membranes
lesion → a reddish and itchy papule that gradually enlarges
exudate discharge precedes ulceration of skin
lesion enlarges with firm surrounding rim.

Leishmania braziliensis and *L. mexicana complexes*

(New World leishmaniasis, American leishmaniasis, uta, chiclero or espundia)

Clinical appearance identical to that of Old World leishmaniasis some forms may produce mucocutaneous involvement.

Diagnosis

Demonstration (Microscopy)

The most commonly used method.
Amastigotes : the tissues or cultured.
Spleen and BM: the most common specimens.
Demonstration of parasite in splenic smear: the only gold standard diagnosis.

Isolation (Culture)

Culture: improve sensitivity of detection but often done when other methods fail.
Promastigote: preparing Ag for immunodiagnosis, exp. animals and *in vitro* screening drugs.
(Singh *et al*, 2006)

Species identification

Helpful in epidemiologically, treatment, prognosis determination of global travelers who are not immune to parasite and develop unusual manifestations.
(Grogl *et al*, 1993; Kreutzer *et al*, 1993)

The complexity.
Share its clinical features with others e.g., malaria, typhoid, TB, or etc.
Co-infection.
Sequestration of the parasite in LN, BM, spleen.

Serodiagnosis

Highly sensitive and non-invasive.
Ab>Ag detection.
DAT-ELISA: the most commonly used methods.
DAT: field use, 91-100% sensitive.
ELISA: potential serodiagnostic tool but cross reaction has also been recorded.

DNA detection (definite breakthrough)

Non invasive, sensitivity and specificity
-diagnosis and prognosis of VL.
Species identification.
Distinguish between relapse and re-infection.
(Osman *et al*, 1998; le Fichoux *et al*, 1999)

Treatment

Chemotherapy

Monotherapy

Parerteral agents
Sodium stibogluconate
Pentamidine isethionate
Amphotericin B and its lipid formulations
Paramomycin

Oral agents
Miltefosine
Azoles (ketoconazole, fluconazole, itraconazole, *etc.*)
Sitamaquine

Immunomodulators
Interferon gamma (IFN-r)

Combined therapy
Sb^v + IFN-r
Sb^v + Miltefosine
Sb^v + Paromomycin
Miltefosine + Paromomycin

Monotherapy
Parenteral form

Antimonial agent

Backbone or solo drug for > 70 yrs.
> 10 mg/kg, od, for 6-10 days.
> 20 mg/kg, od, for 30 days.
> 120 days for PKDL.
Low cost & excellent effectiveness.

↑ resistance or unresponsiveness.
Intensive transmission of anthroponotic *L. donovani*.
Poor supervision or compliance.
Products made from unknown manufacturer (fatal cardiotoxicity).

Pentamidine

Previously used as a second line of drug.

The first line to be used in refractory to Sb^v.

Its efficacy gradually ↓ over the years, 70% cure rate.
(Jha *et al*, 1991)

Serious side effects
Irreversible IDDM
Shock
Hypoglycemia
Death

Unsuitable as a viable alternative to Sbv for VL.

Amphotericin B

The most effective drug- high cure rate.

Widely used for VL during the last 10 years.

0.75-1.0 mg/kg for 15 infusion on alternate days:
97% cure rate.
(Mishra *et al*, 1992; Thakur *et al*, 1999)

Major drawbacks.
Prolong period for hospitalization.
Equipment required for dose monitoring.
High incidence of adverse events (occasionally serious).

Paromomycin

1980s-CL in topical form.

Effective, well tolerated as cheap as Sb^v.

16 mg/kg, im, for 21days:
93% cure rate.
(Jha *et al*, 1998; Thakur *et al*, 2000)

The first line treatment in Bihar, India.

In 2002 Gate foundation-WHOTDR-Institute of One World Health: Efficacy-tolerability.

The cheapest drug: US 10-20/adult course.

Treatment

Chemotherapy

Monotherapy

Parerteral agents
Sodium stibogluconate
Pentamidine isethionate
Amphotericin B and its lipid formulations
Paramomycin

Oral agents
Miltefosine
Azoles (ketoconazole, fluconazole, itraconazole, *etc.*)
Sitamaquine

Immunomodulators
Interferon gamma (IFN-r)

Combined therapy
Sb^v + IFN-r
Sb^v + Miltefosine
Sb^v + Paromomycin
Miltefosine + Paromomycin

Monotherapy

Oral agents

Miltefosine
Several alkylphospholipid derivatives

A landmark event as the 1st line oral.

Phase I/II in adult
100-150 mg for 28 days.
(Sundar *et al*, 1998)
Its efficacy in Sb^v resistant cases.
(Sundar *et al*, 2002)

Teratogenic VS
in pregnancy & women
Of child bearing age
not observing contraception.

Prolonged half-life
Emergence of resistance.

Azoles
Ketoconazole & fluconazole

Active against a wide range of promastigotes and Amastigotes.
(Berman *et al*, 1986; Beach *et al*, 1988; Hart *et al*, 1989)
Undergone evaluation –VL, India
(Wali *et al*, 1990, 1997).
Not enough to induce clinical cure.
(Sundar *et al*, 1990-1998)

Stimaquine
8-aminoquinoline analog

To date, little is known about its efficacy and toxicity.
It has been tested in VL patients in Kenya and Brazil with limited success.
(Sherwood *et al*, 1994; Dietze *et al*, 2001)

Immunomodulators

Interferon-gamma

Clinical trials was reported to be useful in severe or Sb^v refractory VL Brazil.
(Badaro *et al*, 1990)
In India, low cure rate.
(Sundar *et al*, 1994)

Treatment

Chemotherapy

Monotherapy

Parerteral agents
Sodium stibogluconate
Pentamidine isethionate
Amphotericin B and its lipid formulations
Paramomycin

Oral agents
Miltefosine
Azoles (ketoconazole, fluconazole, itraconazole, *etc.*)
Sitamaquine

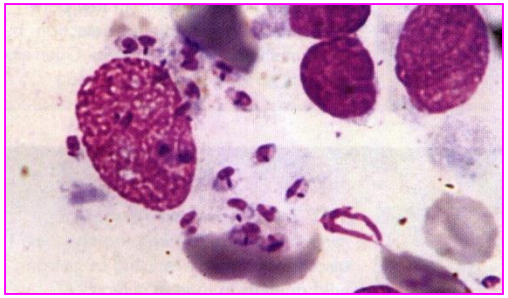
Immunomodulators
Interferon gamma (IFN-r)

Combined therapy
Sb^v + IFN-r
Sb^v + Miltefosine
Sb^v + Paromomycin
Miltefosine + Paromomycin

Combination therapy

Emergence of resistance → **Misuse of the drug Sb^v resistance** → Drug free interval Prevent renal toxicity & tolerance of parasite to Sb^v (Singh *et al*, 2006)

↓ duration of treatment → **Sb^v +Paromomycin** — Reported of its superiority than Sb^v alone. (Thakur *et al*, 1992, 1995; Jha *et al*, 1998)



Sb^v + IFN-r — To be useful in Brazil. (Badaro *et al*, 1990) but not in India. (Sundar *et al*, 1994)

Sb^v + Miltefosine — Less suitable due to toxicity and variation of parasite sensitivity. (Singh *et al*, 2006)

Miltefosine + Paromomycin — Less toxicity. May fulfill the objective for one short h/l and one long h/l. (Singh *et al*, 2006)

Prevention & Control

3 approaches

Vector control

DDT is now stopped.
Other insecticides are expensive.
Pyrethroids impregnated fabrics (bed bets and curtains)
Insecticide paints (emulsified form) to prevent the transmission of disease.

Serodiagnosis

At the infective stage.
Followed by a prompt treatment.
Prevent the evolution to overt disease.
Reduce morbidity and mortality.
Reduce the parasite load and transmission rate (human: reservoir host).

Health education

To the population and physicians serving in endemic area.
To improve the awareness regarding transmission, clinical features, importance of complete treatment, and mode of prevention.

Summary of Haemoflagellates

Species	Amastigote	Promastigote	Epimastigote	Trypomastigote	Transmission	Insect Vectors	Nonhuman Reservoir Hosts
Trypanosoma							
T. brucei gambiense	None	None	1. Salivary gland and gut of tsetse flies 2. Culture	1. Blood, lymph nodes, brain and cerebrospinal fluids of mammals	Anterior station or bite	Tsetse flies *Glossina* spp *G. palpalis* *G. tachinoides* *G. fuscipes*	Pig, ?goats ? cattle
T. b. rhodesiense	None	None				*Glossina* spp *G. pallidipes* *G. morsitans* *G. fuscipes*	Wild and domestic ungulates
T. cruzi	1. Intracellular, especially striated and smooth muscle, also brain. 2. Cell cultures	None	1. Intestine of vector bugs 2. Culture	1. Blood and tissues of mammals 2. Rectum of vector bug 3. Culture and cell cultures	1. Posterior station by contamination with bug feces 2. Blood transfusion	Different genera and spp of triatomide bugs	Opossums, wild rodents, dogs, guinea pigs
Leishmania							
L. donovani *L. infantum* *L. chagasi*	1. Intracellular in R-E system liver, spleen, bone marrow, blood monocytes 2. Macrophage cell cultures	1. Midgut and pharynx of sandfly vector	None	None	Anterior station or bite	Sandflies *Phlebotomus* or *Lutzomyia* Spp	Dog, sloth, jungle or desert rodents
L. mexicana and *L. braziliensis* complexes	1. Macrophages of skin and mucous membranes 2. Macrophage cell cultures	2. Culture	None	None			
L. major *L. tropica* *L. ethiopica*	1. Macrophages of skin 2. Macrophage cell cultures		None	None			