TRYPANOSOMIASES

Trypanosomiases are transmissive endemic diseases, caused by protozoa of the genus *Trypanosoma*. There are two types: *African and American trypanosomiasis.*

AFRICAN TRYPANOSOMIASIS

African trypanosomiasis, also called sleeping sickness, is a transmissive protozoan disease, whose course is associated with fever, lymphadenopathy, skin rash and meningoencepahlitis. There are two clinico-epidemiological forms: ***Gambian*** and ***Rhodesian.***

ETIOLOGY

The causative agents of African trypanosomiasis are flagellate unicellular parasites of the genus *Trypanosoma*:

Trypanosoma brucei rhodesiense – *causes Rhodesian trypanosomiasis*

Trypanosoma brucei gambiense – *causes Gambian trypanosomiasis*

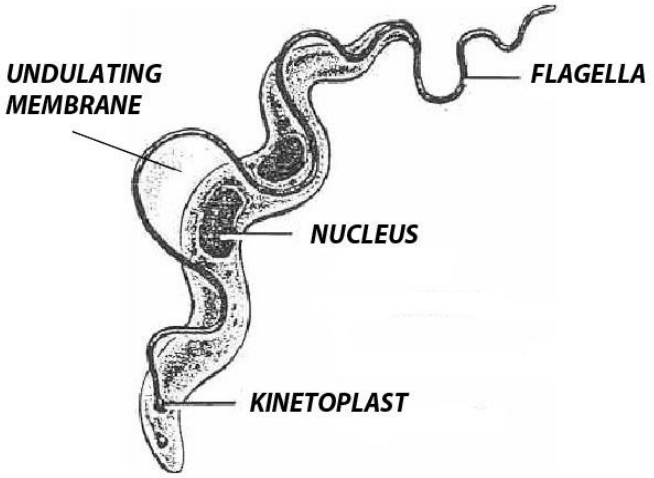
The two do not differ morphologically, neither are they different from the trypanosomes that cause disease in animals.

The parasite has two biological stages:
-***trypomastigote*** in the organisms of infected humans and vertebrate animals;
- ***epimastigote*** in the vectors that transmit the disease – the tsetse flies of the genus ***Glossina***.

ETIOLOGY AND LIFE CYCLE

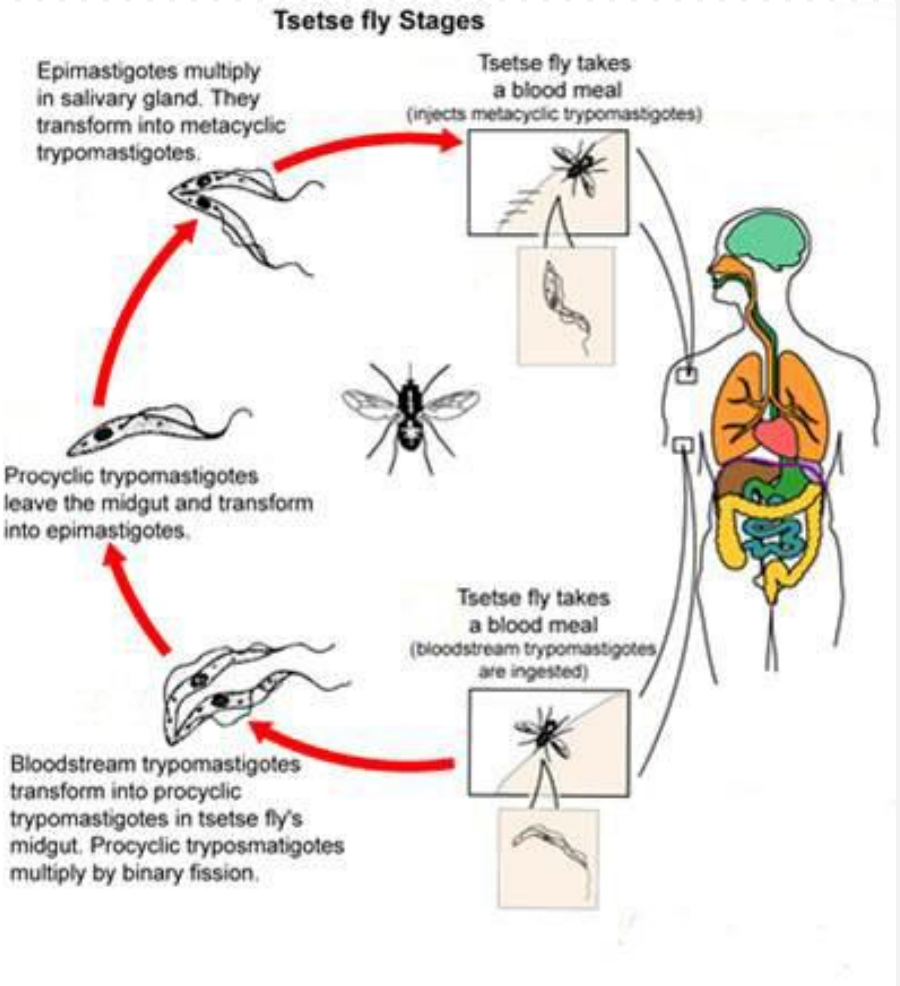
Trypomastigotes, detected in human blood (15-40 μm x 1.5 – 2 μm), possess a centrally located nucleus, a rod-like kinetoplast with a curved flagellum and an undulating membrane.

The shape of parasites are changeable (polymorphic) depending on the level of parasitemia.



ETIOLOGY AND LIFE CYCLE

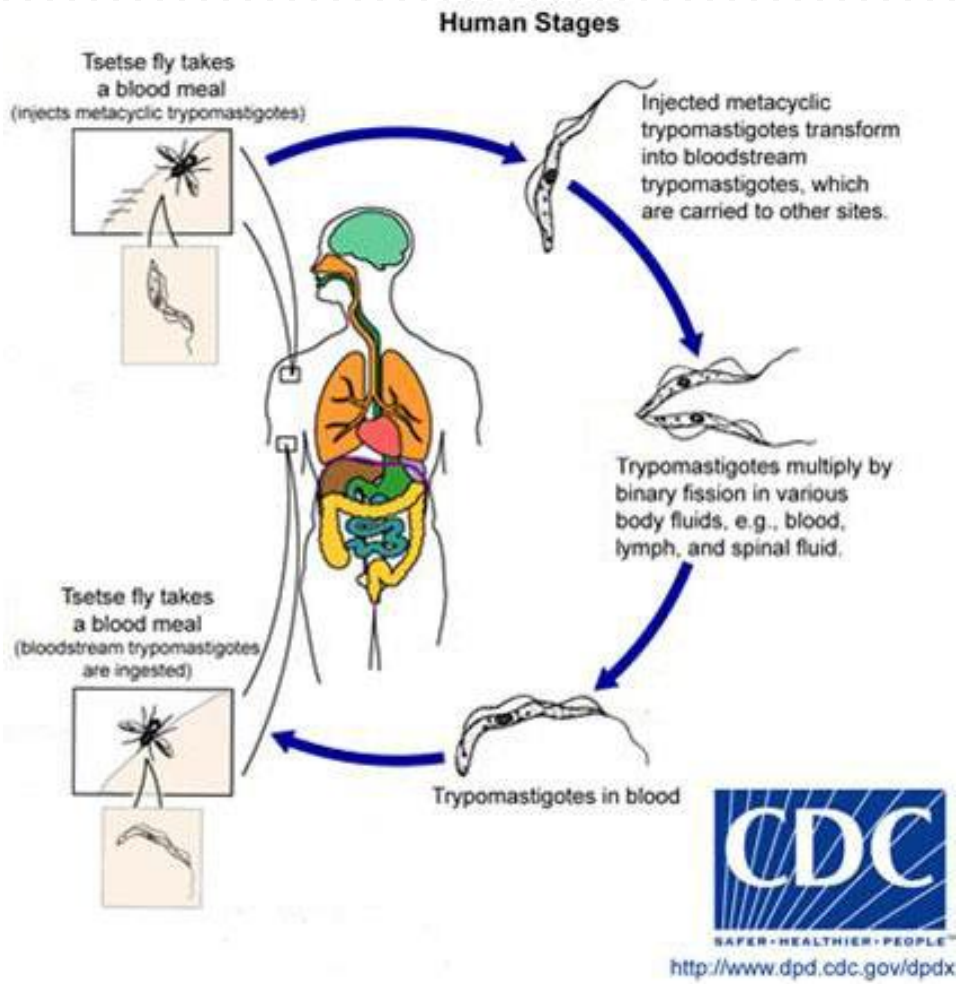
While in the body of a tsetse fly, the parasites develop from epimastigotes to become metacyclic, and this process takes 18 to 35 days. In the vector, metacyclic forms are located in the salivary glands.



ETIOLOGY AND LIFE CYCLE

Metacyclic forms are infective on a subsequent blood sucking from a human.

In the vertebrate host, trypanosomes are located in the blood, the lymph nodes, the brain and the liquor.



PATHOGENESIS AND PATHOLOGY

The **first sign** is a skin lesion (***trypanosomal chancre***), which appears on the site of the tsetse fly bite.

After that, the parasites are disseminated by way of lymph and blood to all organs and tissues of the host.

During the **first stage** of the disease, the trypanosomes migrate to the organs of the retuculoendothelial system (RES) – lymph nodes, spleen and liver. Regional or general lymphadenomegaly with histiocytic proliferation develops, followed by fibrosis.

Due to blood accumulation and hyperplasia of reticuloendothelial cells the spleen and the liver also enlarge

Perivascular infiltrates with parasites are also found in the kidneys, the suprarenal glands and the lung.

PATHOGENESIS AND PATHOLOGY

Functional and morphological data are found indicating damage to the heart muscle, especially in cases of *Rhodesian trypanosomiasis*.

Pancarditis may develop, involving all structures of the heart, including that of the valvular endocardium.

The conduction system of the heart is affected, as well as autonomic cardiac innervation.

As the invasion progresses, chronic myocardiopathy may develop.

At this stage of the disease, normocytic anemia with marked reticulocytosis, thrombocytopenia and increased erythrocyte sedimentation rate (ESR) are found.

The number of platelets is lower, especially in cases of Rhodesian trypanosomiasis, and the development of disseminated intravascular coagulopathy is likely.

PATHOGENESIS AND PATHOLOGY

The **second stage** of *African trypanosomiasis* is associated with involvement of the CNS.

The parasites pass through the blood-liquor barrier and cause inflammatory changes in the brain, the spinal cord and the meninges.

Trypanosomes are mainly found in the frontal lobe, the pons and the medulla oblongata, but they can be found in other brain structures as well.

Brain edema, haemorrhages, and increased intraventricular pressure may occur.

The damages inflicted are similar to those in meningoencephalitis and meningomyelitis.

CLINICAL PRESENTATION

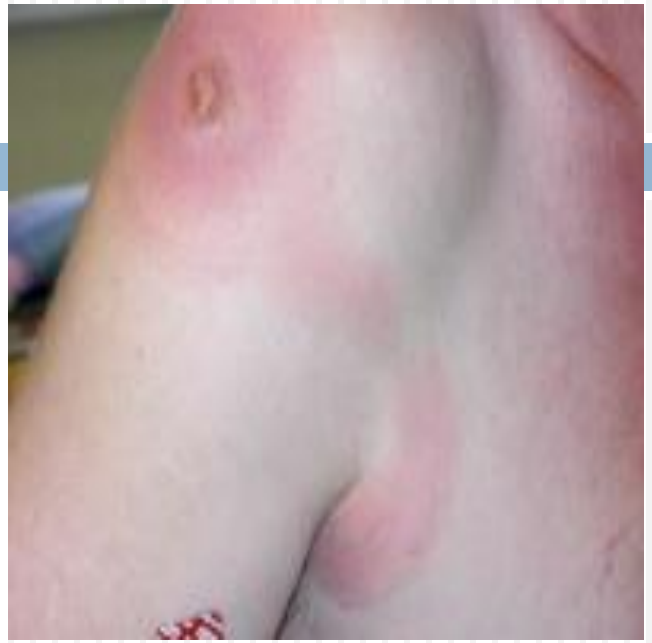
Etiologically, two forms of African trypanoisomiasis are seen: **Gambian**, caused by *Trypanosoma brucei gambiense* and **Rhodesian**, caused by *Trypanosoma brucei rhodesiense*.

The two forms are clinically similar but they differ in dynamics and prognosis of the invasion, geographical distribution, epidemiology and other.

The incubation period is 2 to 3 weeks.

The disease has three stages – initial, haemolymphatic and cerebral.

INITIAL STAGE



The first stage is characterized by skin changes at the site of the infective bite and multiplication of the trypanosomes (initial effect).

A thick hyperemic node forms, several centimeters in diameter, which is slightly painful and surrounded by a pale, wax-like strip – a trypanosomal chancre.

It is usually resorbed in about two weeks, and a pigmented edge remains.

HAEMOLYMPHATIC STAGE

Its onset is associated with the processes of dissemination of the trypanosomes by way of lymph and blood flow and starts with a fever.

The temperature pattern of the body temperature is irregular.

The fluctuations are characterized by periods of apyrexia and septic temperature, as high as 41^0C.

The temperature persists for several weeks to several months, without exhibiting a characteristic curve.

Muscle weakness, anorexia, sleeplessness, transient swellings around the eyes, hands and feet occur.

Marked hyperaesthesia – strong pain at slight pinching (Kerendel's sign) is seen.

Erythematous rash with irregular or round spots (trypanides) appears on the skin of the face, back, chest and limbs.

HAEMOLYMPHATIC STAGE

Examination reveals regional or generalized lymphadenomegaly, and splenomegaly.

Lymphadenitis is more often seen with the Gambian form of the disease.

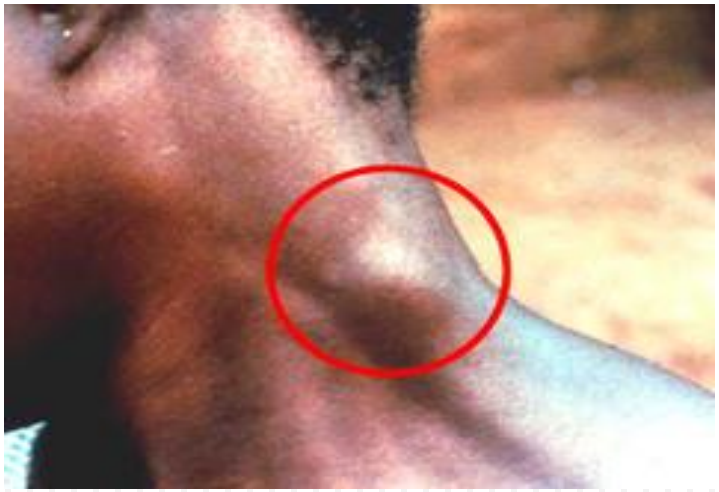
At first, the lymph nodes are movable, painless and soft, but as the disease progresses and fibrosis develops, they become thicker.

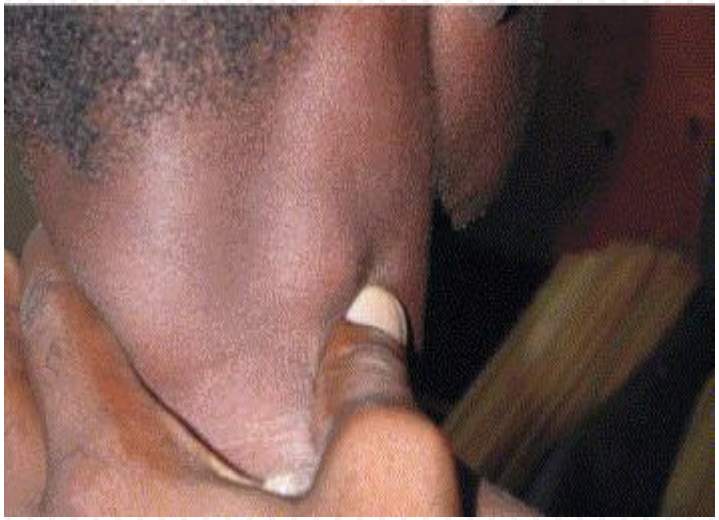
Enlargement of lymph nodes in the posterior cervical triangle (Winterbottom's sign) is a specific symptom of Gambian trypanosomiasis.

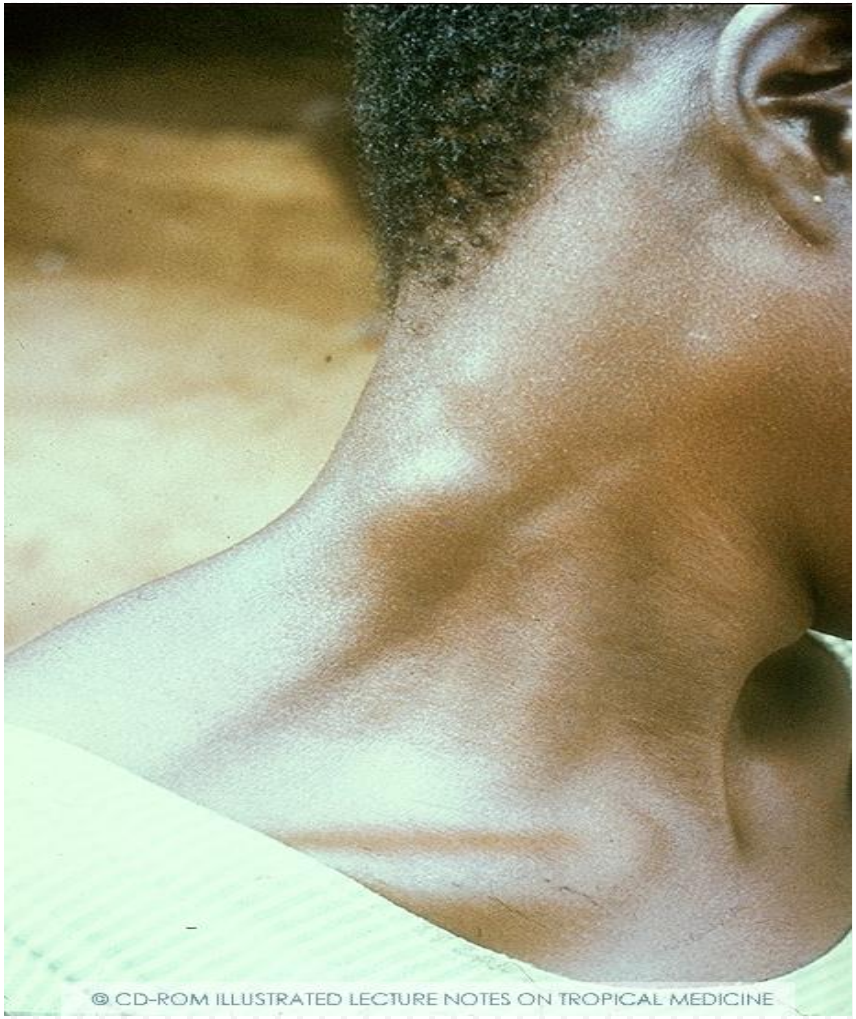
Progressive weight loss is seen in patients.

Paraclinical findings include anemia, moderate leukocytosis and thrombocytopenia.

WINTERBOTTOM`S SIGN







Enlargement of lymph nodes in the posterior cervical triangle

HAEMOLYMPHATIC STAGE

The clinical course of the haemolymphatic stage has a rather irregular pattern.

In some patients the disease takes a subclinical course and they heal spontaneously in several months.

In others the disease evolves and reaches a terminal cerebral stage.

In cases of Gambian trypanosomiasis, this stage is protracted and takes months or years. Lymph node involvement is a very common symptom.

Rhodesian trypanosomiasis takes a galloping course with a lethal outcome in less than a year.

CEREBRAL STAGE

This stage is also called terminal stage, or true sleeping sickness.

It is due to the invasion of parasites into the CNS and the development of meningoencepahalitis.

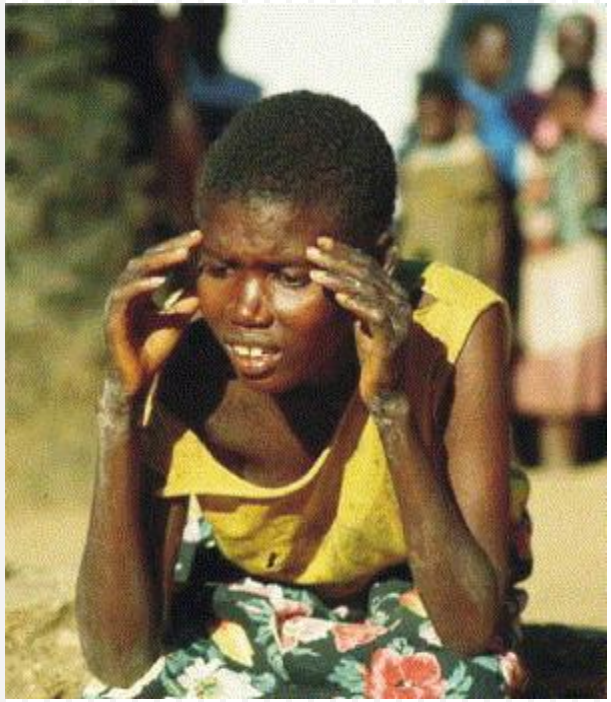
The main symptom is increasing asthenia with worsened day-time somnolence. Sleeping habits reverse, and during the night patients are restless, sleepless, while in daytime they are apathetic, drowsy, with impaired coordination, slow gait, speech disturbances and mask-like face.

Because of lack of appetite, alimentary dystrophy develops, resulting in weight loss, edemata and cachexia.

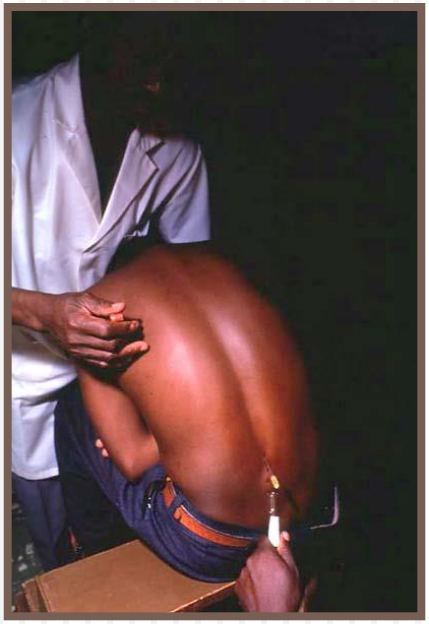
As the disease progresses, blephoraptosis (drooping eyelid), hand tremor, fibrillary muscular trembling, paresis and paralyses occur.

Sometimes meningoradicular syndrome with stiff neck and pathological reflexes of Kernig and Brudzinski are seen.

CEREBRAL STAGE



CEREBRAL STAGE



On lumbar puncture, the cerebrospinal fluid clear, and mononuclear pleocytosis, high protein content and parasites are detected in it.

The cerebral period lasts up to one year.

Patients die because of increasing muscle weakness and cachexia, brain haemorrhages, additional superinfection, or following a comatose state.

Lethality rates in untreated patients may reach 50%.

DIAGNOSIS

The diagnosis is complex and is based on clinical and epidemiological data, objective finding, paraclinical tests, and results from parasitological investigation.

MATERIALS FOR INVESTIGATION:

In the early stage of the disease materials for investigation collected from:
- trypanosomal chancre;
- lymph node;
- blood and serum samples;
- tissue for pathoanatomical analysis;

In the cerebral stage of the disease materials collected from:
- bone marrow samples;
- cerebrospinal fluid.

METHODS OF INVESTIGATION

Microscopic diagnosis is carried out on:

- native preparations from blood or puncture samples, in which trypomastigotes are sought;
- Romanovski-Giemsa-stained preparations - after Romanovski-Giemsa staining, the nucleus of the parasite turns red, while the cytoplasm, the flagellum and the undulating membrane turn blue.

Culture methods - trypanosomes are cultured in NNN, GLSH, Weinmann medium, etc.

Serologycal methods - ELISA, Western blotting, RIF, etc. - have limited applications.

Biomolecular methods - PCR has a good future in diagnosing trypanosomes.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis implies ruling out:

- Tropical malaria;
- Visceral leishmaniasis;
- Lymphadenopathy of a different etiology;
- Sepsis;
- Tuberculosis;
- Primary and secondary meningitides and meningoencephalitides.

TREATMENT

Etiological treatment of Gambian and Rhodesian trypanosomiasis, taking into consideration the disease stage, the mechanism of action, contraindications and possible side effects of the drugs, resistance of the causative agent and the presence of accompanying diseases in each patient.

Before initiating treatment, lumbar puncture is performed to determine the disease stage.

TREATMENT OF THE HAEMOLYMPHATIC STAGE

Suramin and ***Pentamidine*** are prescribed for treatment of the early haemolymphatic stage of African trypanosomiasis.

- ***Suramin sodium*** (*Antrypol, Naphuride, Moranil*), vial of 1.0 g

Therapy begins with 100 – 200 mg, i.v., applied as a test for hypersensitivity.

24 hours after the initial application as follows:
day 1 – 5 mg/kg b.w., i.v.;
day 3 - 10 mg/kg b.w., i.v.;
days 5, 11, 17, 23 and 30 - 20 mg/kg b.w., i.v.

If necessary, this treatment regimen may be repeated after 30 days. *Suramin* may be applied during pregnancy.

- ***Pentamidine isethionate*** (*Lomidin, NebuPent, Diamidine, Pentam*) – vial of 300 mg - 4 mg/kg b.w. i.m. for 10 days.

TREATMENT OF THE CEREBRAL STAGE

In the cerebral stage, ***Melarsoprol*** and ***Eflornithine*** are most commonly used.

- ***Melarsoprol*** – amp. 36 mg/ml;

By slow i.v. infusion at a daily dose of 2.2 – 3.6 mg/kg b.w. for 10 days.

If necessary, this treatment course may be applied three times every other 10 days.

It is used as the drug of choice to treat the Gambian form of the sleeping sickness only in its cerebral stage.

- ***Eflornithine hydrochloride*** *(Ornidyl)* – vial. of 100 ml, 200 mg/ml;

400 mg/kg b.w., i.v., for two weeks.

EPIDEMIOLOGY

SOURCES OF INFECTION

Gambian trypanosomiasis is anthroponosis and infected humans and carriers of trypanosomiasis serve as a source of infection.

Rhodesian trypanosomiasis is a zoonotic infection. The natural reservoir are antelopes. Infected humans are also sources of infection.

MECHANISM, FACTORS AND ROUTES OF TRANSMISSION

Both types of trypanosomiasis are transmissible.

Gambian trypanosomiasis is transmitted by the tsetse fly *Glossina palpalis* and, more rarely, by *Glossina tachinoides*.

Rhodesian trypanosomiasis is transmitted by *G. morsitans*, *G.pallipides* and *G.swynnertoni*.

The infection may be also transmitted in cases of hemotransfusion or transplantation.

SUSCEPTIBILITY AND IMMUNITY

Humans are highly susceptible to *African trypanosomiasis*.

After recovery from the disease, **there is a short-term immunity that is not protective.**

AFRICAN TRYPANOSOMIASIS - DISTRIBUTION

African trypanosomiasis is seen in 36 countries in Sub-Saharan Africa (15° north and south of the equator), where the tsetse biotopes are.

Trypanosoma brucei gambiense is found in foci situated in large territories in West and Central Africa.

The distribution of *Trypanosoma brucei rhodesiense* is quite limited, and its forms are seen in East and South-East Africa.

At present, this form of the parasite is detected in 95% of reported cases of sleeping sickness.

PROPHYLAXIS AND PREVENTION

The measures taken are directed to break the chain infected person (antelope) –vector (tse-tse fly) – susceptible population.

- As far as the patients are concerned, measures taken include early detection, reporting and treatment of the infected.

- Measures regarding the vector include elimination using a variety of methods – genetic, disinsection, and activities to destroy the vector's biotopes.

- Measures oriented to protect the population consist of improving living conditions, health education, control on the migration of the population, individual protection with repellents, protective nets, etc.

AMERICAN TRYPANOSOMIASIS

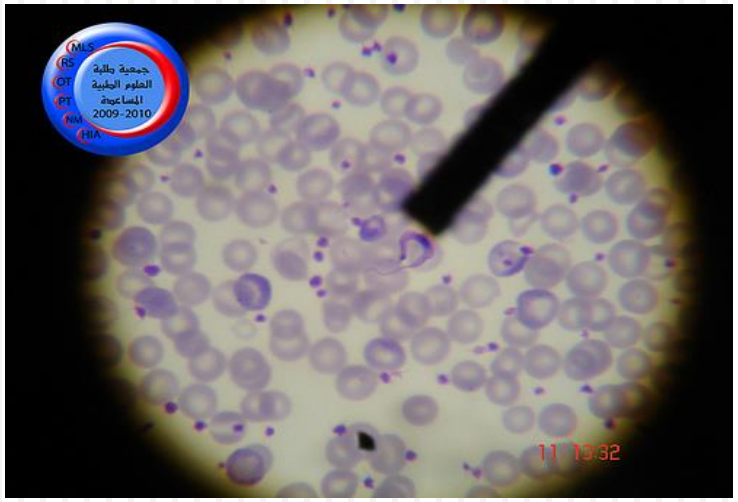
American trypanosomiasis (Chaga's disease) is a transmissive protozoonosis, which takes an acute course with a primary damage, fever and involvement of lymph nodes, the spleen, the liver and the central nervous system (CNS). During the chronic stage of the invasion the heart and the digestive tract are affected in a specific way.

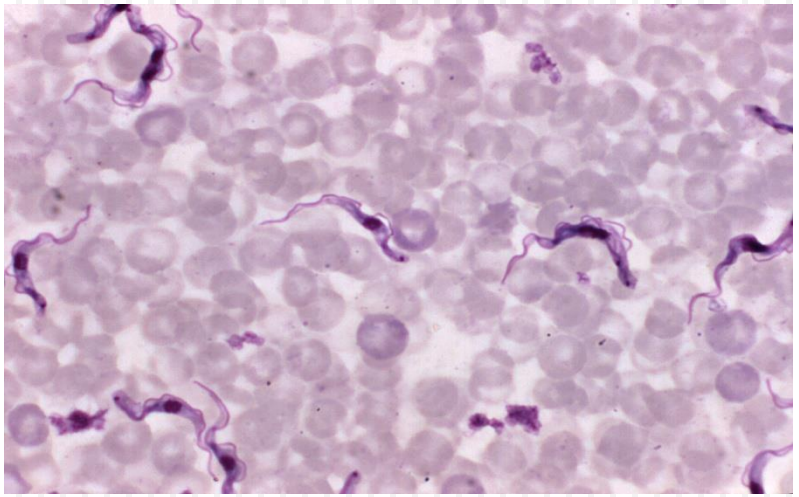
ETIOLOGY AND LIFE CYCLE

The causative agent of **American trypanosomiasis** is a flagellate unicellular parasite - ***Trypanosoma cruzi***.

It has a complex biological cycle and well-expressed morphological variations, as regards the stage of development and multiplication.

In the blood of an infected individual, *trypanomastigote forms* are found, with an elongated body (15-20 μm), with a frontward oriented and markedly polymorphic flagellum. The trypomastigotes do not divide.

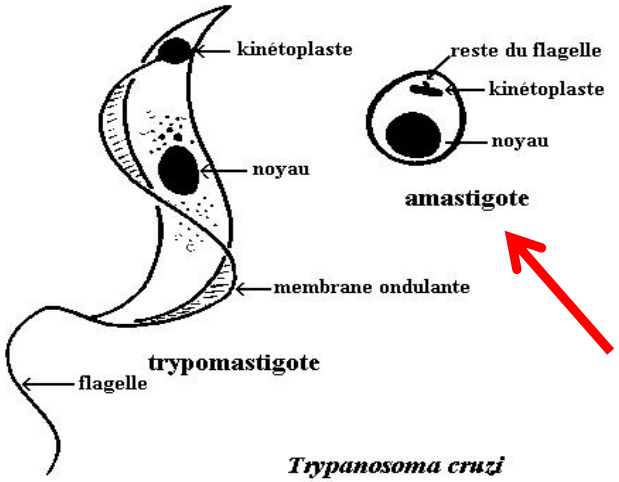




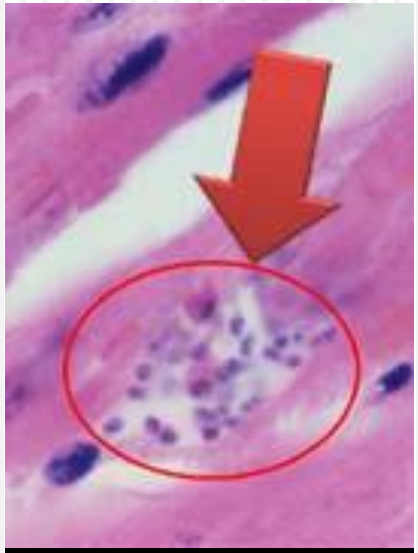
ETIOLOGY AND LIFE CYCLE

The trypomastigotes penetrate the cells of retuculoendothelial system (RES), the skeletal and the cardiac musculature, and the CNS.

Here the trypomastigotes transform into non-flagellate *amastigote forms*, which multiply within the cells through binary division.



Amastigotes of *Trypanosoma cruzi*

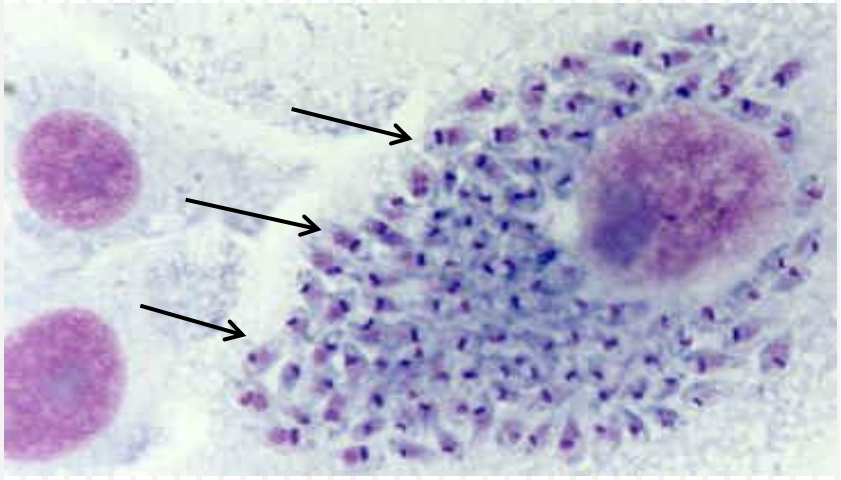


Amastigotes of *Trypanosoma cruzi* in cells of cardiac masculature

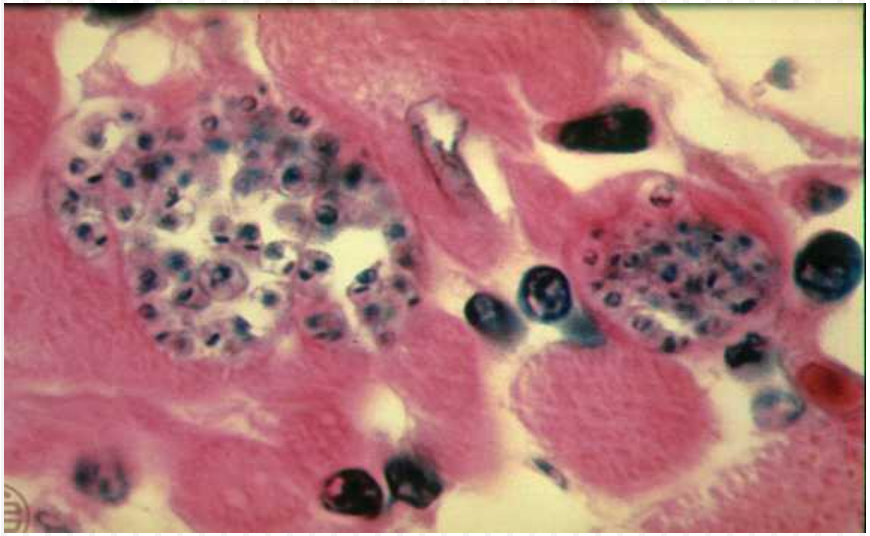
ETIOLOGY AND LIFE CYCLE

The affected cells, in which the amastigotes accumulate, are called pseudocysts. When the pseudocysts rupture, the amasatigotes released invade other cells and the cycle of multiplication is repeated.

Some of the amastigote forms become trypomastigotes and enter the blood circulation of the host, thus making the host a source of infection.



Multiplication of *Trypanosoma cruzi in man* only occurs in the amastigote phase, which grows in a variety of tissue cells especially muscle. In vitro infected fibroblast showing a large number of intracellular amastigotes. (Giemsa stain)



Trypanosoma cruzi. Amastigotes in cardiac muscle (hematoxylin and eosin stain, oil immersion).

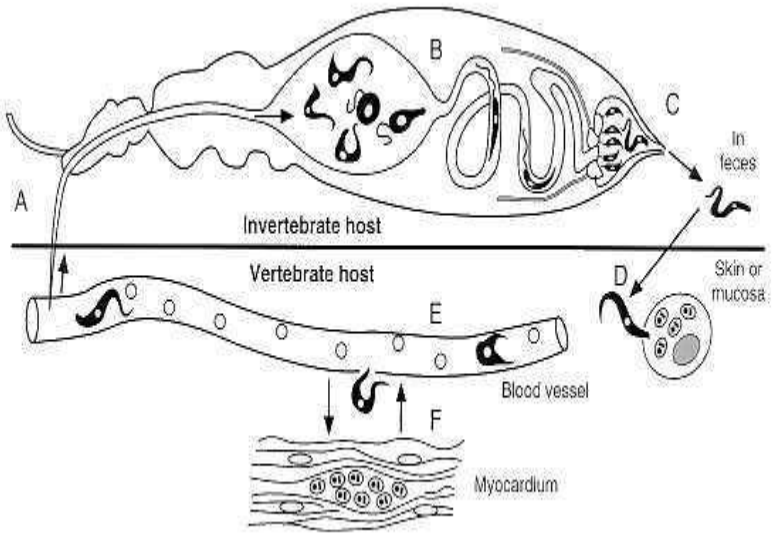
ETIOLOGY AND LIFE CYCLE

The transmissive carriers of Trypanozoma cruzi are blood-sucking insects of the Triatoma genus – Triatoma infestans and Rhodnius prolixus.

Triatoma infestans

Rhodnius prolixus

ETIOLOGY AND LIFE CYCLE



They get infected with trypomastigote forms after sucking blood from humans and animals.

Invasive metacyclic forms develop in the digestive tract of the insects for 10 - 25 days. They are located in the rectum of the insect.

During the next blood-sucking, the trypomastigote forms are excreted with the feces of the vector and infect the host through the bite, injured skin or the conjunctiva.

PATHOGENESIS AND PATHOLOGY

Initially, the trypanosomes multiply in the skin and the regional lymph nodes. At the site of invasion, acute local inflammatory reaction occurs ***(chagoma)***.

Multipilcation of the parasite in the regional lymph nodes leads to lymphadenitis.

After local division, the parasites enter the blood stream and reach all organs and tissues of the host - reticuloendothelial system, the heart, the skeletal and smooth muscles, and the neuroglia.

The multiplication of the amastigotes in the heart muscle leads to destruction of the myocardium, inflammatory exudation and overgrowth of connective tissue.

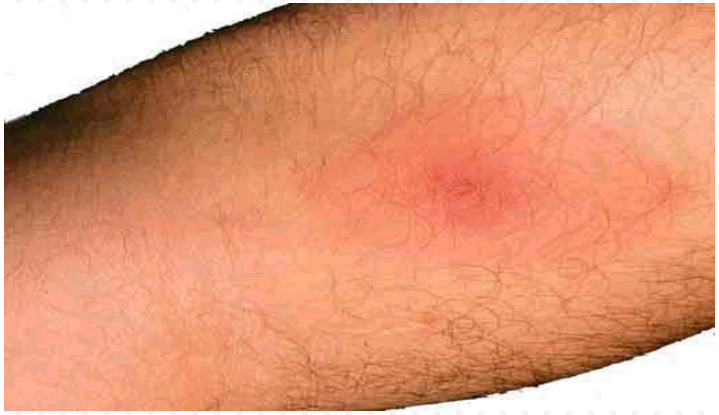
The invasion of the parasites into the CNS is accompanied by inflammatory changes of the cortex and brain structures (meningoencephalitis)

CLINICAL PRESENTATION

The disease course is acute and chronic. However, asymptomatic forms with prolonged carriership have also been reported.

The incubation period is 7 – 14 days.

At the bite site, a skin lesion – chagoma appears - an inflammatory infiltrate, about 5-6 cм in diameter, accompanied by lymphangitis and regional lymphadenitis.



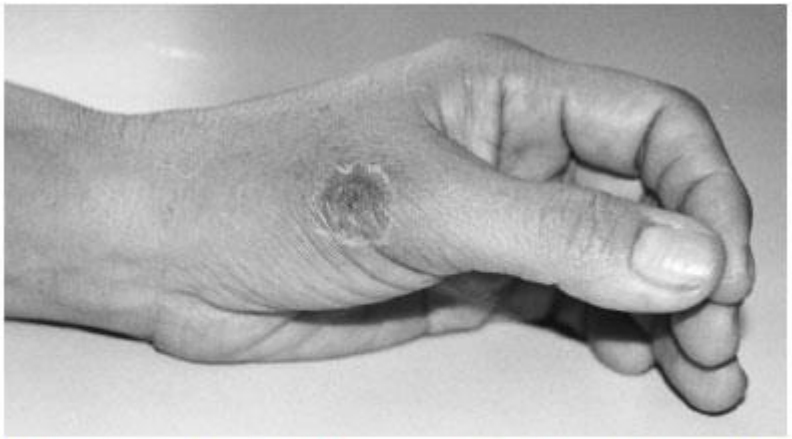
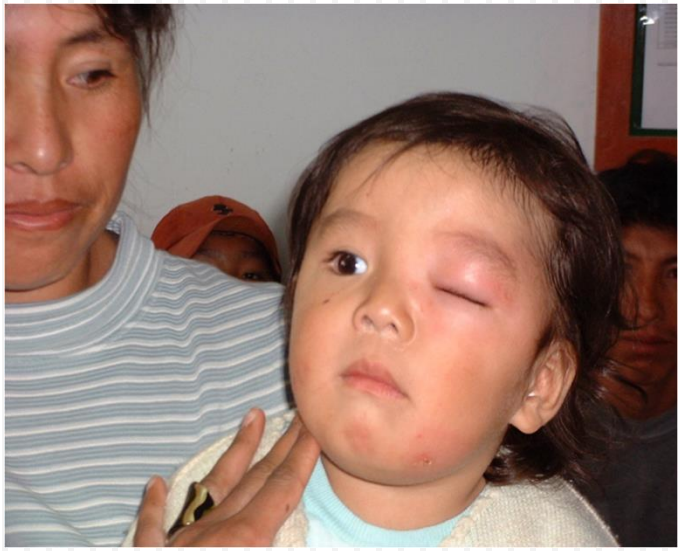
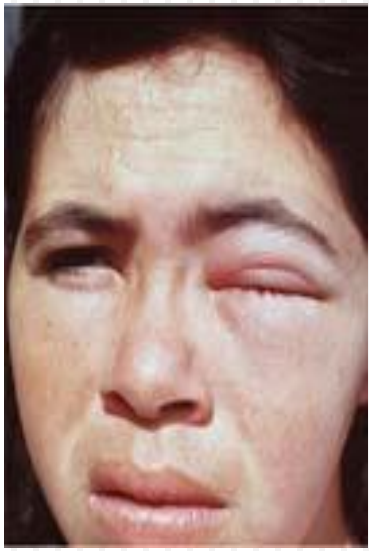


Fig. 1 - Inoculation chagoma on the dorsal surface of the left hand at the base of the thumb, 21 days after accidental inoculation with blood trypomastigote forms of *Trypanosoma cruzi* in a 42-year-old female patient.

CLINICAL PRESENTATION

If the invasion is through the conjunctiva, an unilateral swelling of both upper and lower eyelid develop, as well as conjunctivitis (**Romana's sign**).





The enlargement of the submandibular lymph nodes ipsilateral to the facial edema is known as the **eye-gland complex**.

CLINICAL PRESENTATION

The **acute stage** is associated with the hematogenous dissemination of the parasites and presents like a systemic disease with toxic-infectious syndrome, lymphadenopathy, hepatomegaly and splenomegaly.

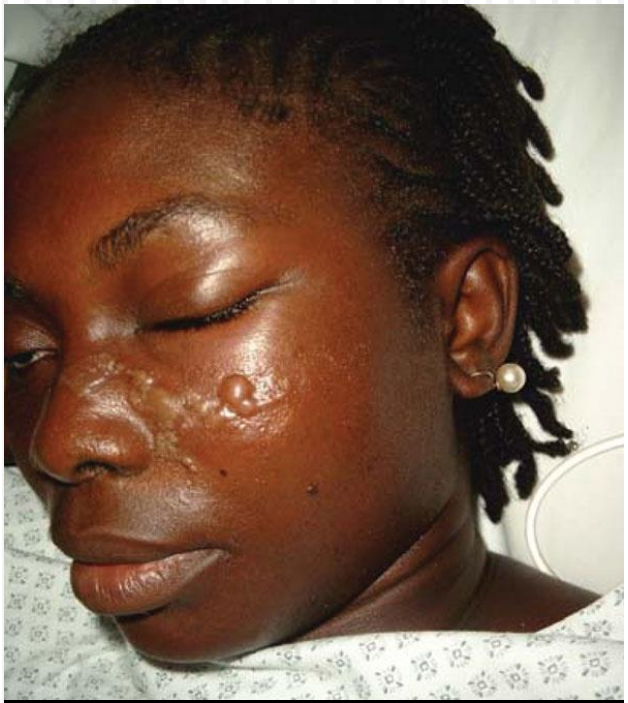
The temperature may be 39-40^0 C and persist for several weeks. The temperature curve is irregular.

Patients present with headache, muscle and joint pains, muscle weakness and anorexia.

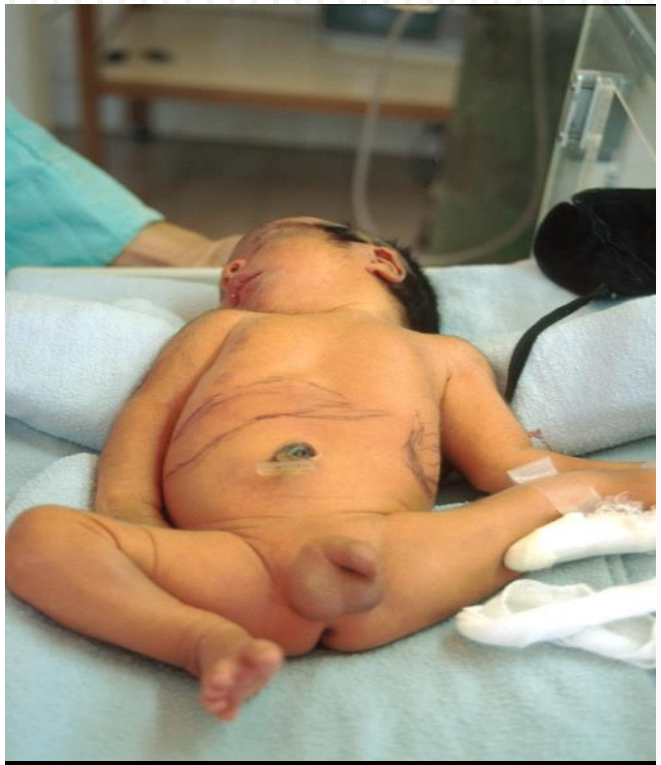
Some present with a transient rash and macules, as well as with local swelling in different parts of the body.

CLINICAL PRESENTATION

The lymph nodes are enlarged, and splenomegaly and hepatomegaly are present.



Romana`s sign. Photo of female patient from French Guiana who lives in a metropolitan area of France. She had fever and unilateral periorbital edema.



Child with hepatosplenomegaly due to congenital Chagas' disease.

CLINICAL PRESENTATION

The heart is affected in a way similar to acute myocarditis, and acute heart failure is the main cause for an early lethal outcome.

Signs indicating cardiac involvement include tachycardia, arrhythmia, ventricular extrasystoles, galloping pulse and ECG changes.

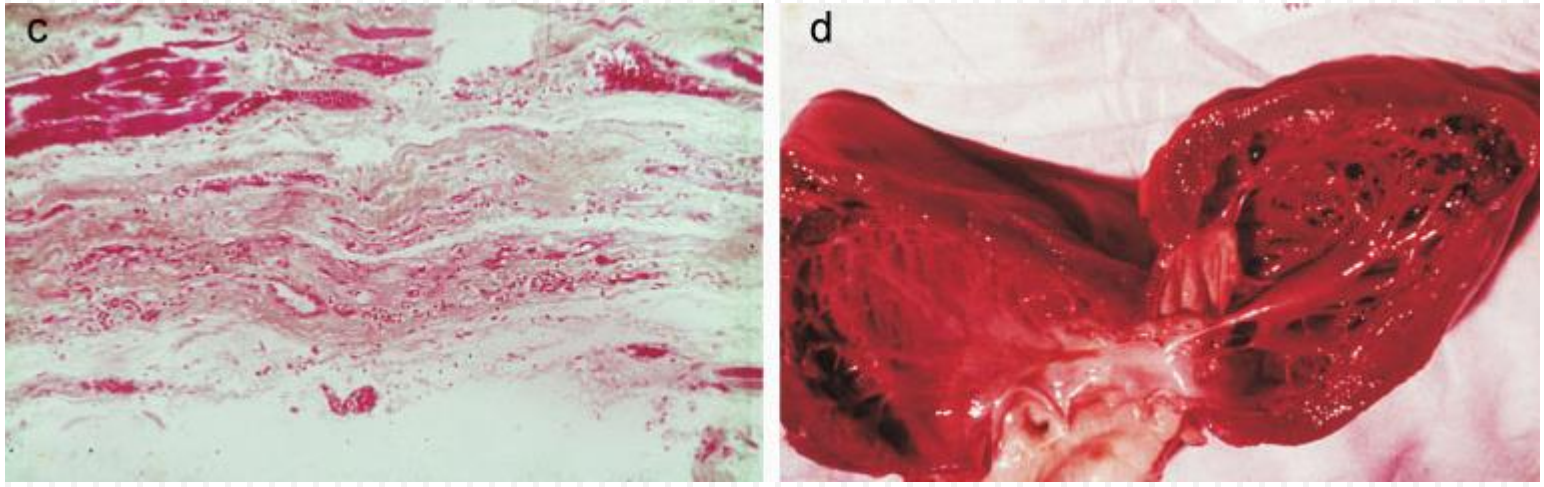
In some cases, the CNS is affected, and meningoencephalitis develops. Such patients are disoriented, with meningoradicular syndrome, aphasia, pareses, paralyses, muscle contractures. When the CSF is examined, trypanosomes are detected.

CLINICAL PRESENTATION

The acute form leads to death after a few months, or else becomes chronic.

It is characterized by chronic cardiomyopathy. Patients complain of tiredness on exertion, quickening heart rate and arrhythmia.

Radiology and percussion reveal broader contours of the heart, and auscultation reveals bradycardia, tachycardia and extrasystoles.



C: Fibrosis of the myocardial conducting system in chronic phase of Chagas disease;
D: Hypertrophy of myocardium and dilatation of the heart cavities with the presence of thrombi in chronic Chagas heart disease

CLINICAL PRESENTATION

ECG changes seen include partial or complete atrioventricular block, ventricular extrasystoles, right femoral block, abnormal QRS complexes and T-waves, atrial fibrillation, etc.

Cardiac abnormalities lead to cardiac insufficiency. Not rarely patients suffer a syncope, or die of sudden cardiac arrest.

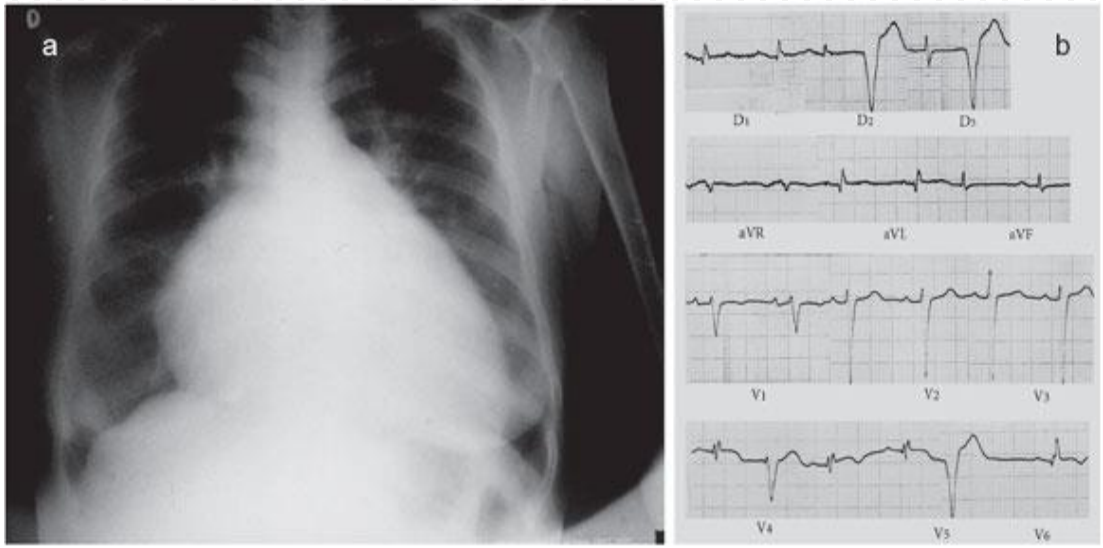
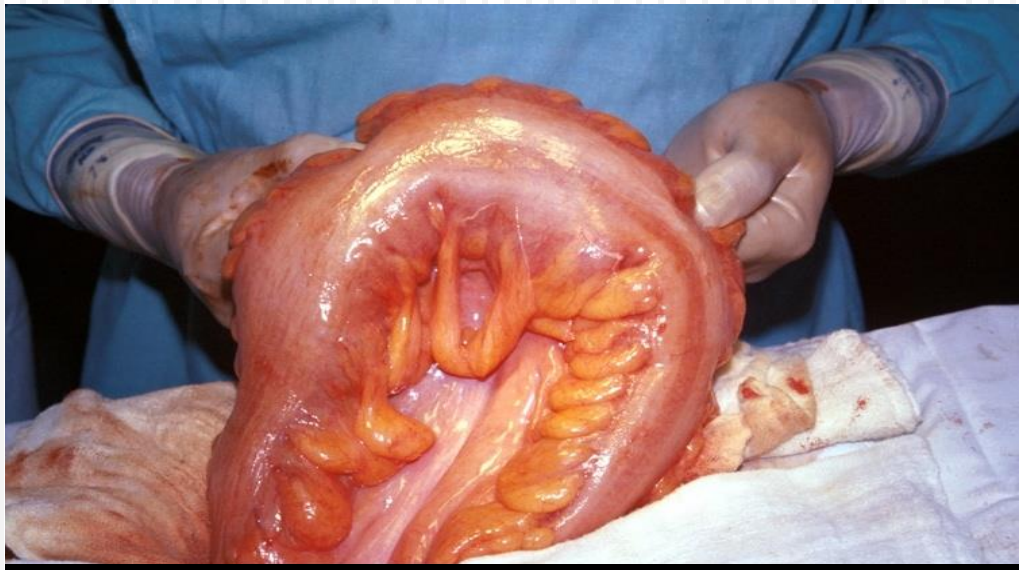


Fig. 6a: r-x showing enlargement of heart in chronic Chagas cardiomiopathy; b: ECG showing ventricle extrasystoles, A-V block, schemia, and myocardial fibrosis in chronic Chagas heart disease (Junqueira et al. 2005).

CLINICAL PRESENTATION

Manifestations due to damaged ganglia of the vegetative nervous system are typical of the chronic stage. Disrupted innervation of the internal organs is associated with widening of the tubular organs – megaoesopagus with dysphagia and regurgitation, megacolon with chronic obstipation, abdominal pain, volvulus and perforation, dilatation of the bronchi, the ureters, the urinary bladder.



Megacolon secondary to chronic infection with *Trypanosoma cruzi*.

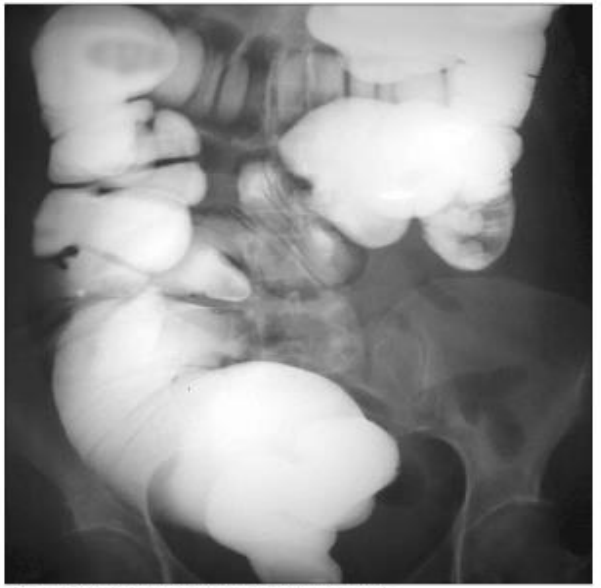
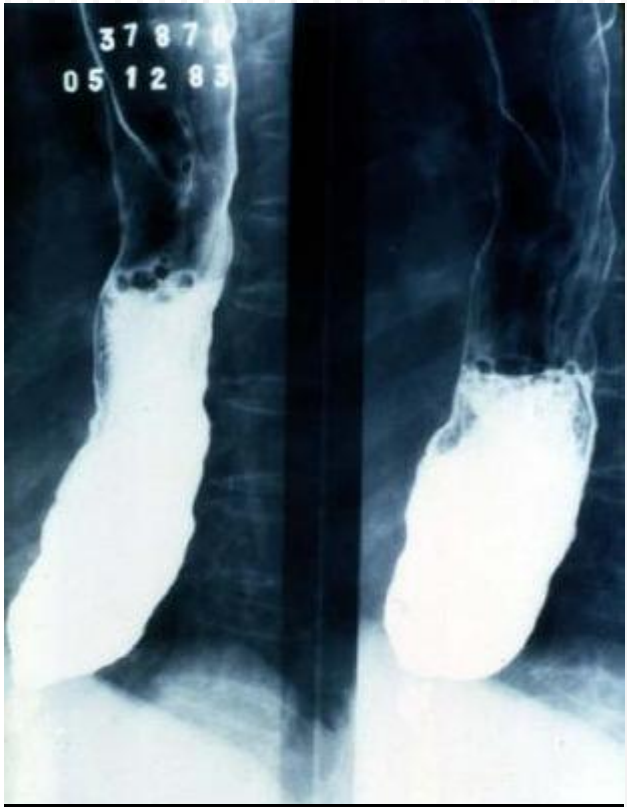
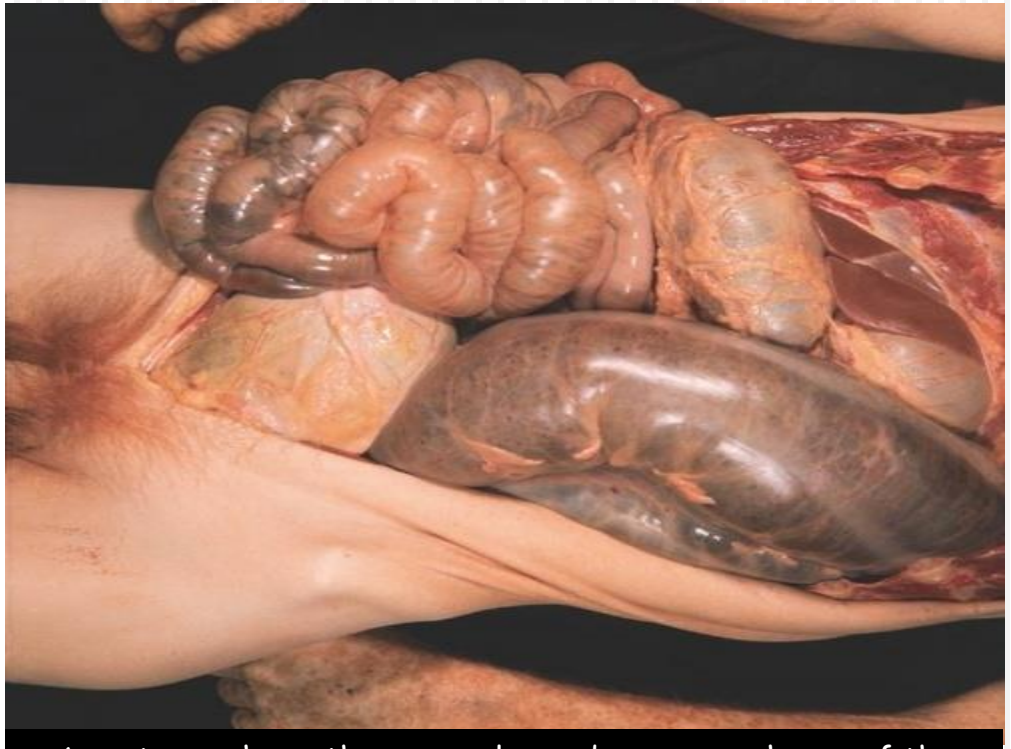


Fig. 1.- Enema opaco que muestra dolicosigma.

CLINICAL PRESENTATION



Chagas megaseophagus



An autopsy shows the megacolon and megaoesophagus of the victim who yielded to American trypanosomiasis, also known as Chaga`s Disease.

The chronic stage of the disease is usually with a lethal outcome, or is severely disabling.

DIAGNOSIS

Materials for investigation

The parasitological diagnosis involves blood investigation. In case of lethal outcome, samples collected postmortem are examined.

Methods of investigation

In the acute stage of the disease, trypanosomes are sought in the blood of the infected person. Native preparations are examined (large blood drop), as well as blood smears stained after Romanowsky-Giemsa.

In the chronic stage of the invasion, the diagnosis is based on proving the presence of specific IgG class antibodies.

Culture methods can also be used to diagnose American trypanosomiasis, such as hemoculture, NNN medium etc.

Biomolecular methods (PCR) possess the highest sensitivity in diagnosing the disease.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes ruling out:

- Tropical malaria;
- Visceral leishmaniasis;
- Cardiopathy of another etiology;
- Sepsis;
- Diseases of the CNS;

ETIOLOGICAL TREATMENT

Patients infected with T. cruzi are treated with ***Nifurtimox*** and ***Benznidazole***. Results, however, are not always satisfactory.

Nifurtimox (Lampit, Bayer 2502) – tabl. 30 mg and 120 mg. Treatment is scheduled for 90 to 120 days. The daily intake for adults is 8-10 mg/kg b.w., divided into three doses.

Benznidazole (Radanil, Rochagan) – tabl. 100 mg.
The daily intake prescribed is 5 mg/kg b.w. for adults, and 10 mg/kg b.w. for children, for 60 days. The daily intake is divided into two doses to be taken every 12 hours.

EPIDEMIOLOGY

SOURCES OF INFECTION

American trypanosomiasis is a disease with a natural and synanthropic distribution of foci.

In natural foci, over 150 mammals are sources of infection. In South America, of great epidemiological importance are rodents, armadillos and opossums.

Dogs, cats and swine are soources of infection in the synanthropic foci. The animals are asymptomatic carriers of the parasite, which is found in their peripheral vessels.

Humans are also sources of infection, even not primary ones.

EPIDEMIOLOGY

MECHANISMS, FACTORS AND ROUTES OF TRANSMISSION

The mechanism of spread is transmissive.

Flying bugs of the subfamily Triatominae serve as vectors.

In the synanthropic foci these are *Triatoma infestans* and *Rhodnius prolixus*, while in the natural foci the vectors include *Triatoma megisti*, *Triatoma spinolai* and *Triatoma brasiliensis*.

Transplacentary mechanism of passing the infection is possible.

Infection can be transmitted in cases of organ transplantation and blood transfusion.

EPIDEMIOLOGY

SUSCEPTIBILITY AND IMMUNITY

Susceptibility to *T. cruzi* is universal, though, according to investigations in endemic regions, part of the local population is resistant to the infection.

This immunity is not sterile and expires after having the disease.

AMERICAN TRYPANOSOMIASIS - DISTRIBUTION

American trypanosomiasis is common in almost all countries in Central and South America to the South of the Tropic of Cancer.

The most affected populations are those of Brazil, the Argentine Republic and Venezuela.

The disease poses social and medical problems for poor inhabitants of rural areas.

PROPHYLAXIS AND PREVENTION

Activities directed to the source of infection include timely detection, treatment and follow up of infected individuals.

Extermination of triatoma bugs with insecticides.

Of great importance for the localizing the foci of American trypanosomiasis are health education, improvement of living conditions, control of emigration of populations, using personal preventive measures, screening of blood donors, etc.

Trypanosomiases, along with malaria, leishmaniases, schistosomiases and filariases are under the control of WHO.