

BLOOD AND TISSUES FLAGELLATES (Haemoflagellates)

- The major clinical significance include members of 2 genera
- 1- Genus: *Leishmania* (*L. donovani*, *L. tropica* and *L. major*).
- 2- Genus: *Trypanosoma* (*T. brucei* and *T. cruzi*)

- Several species of *Leishmania* are pathogenic for man:
 - *L. donovani* causes visceral leishmaniasis (Kala-azar, black disease, dum dum fever, black fever)
 - *L. tropica* (*L. t. major*, *L. t. minor* cause cutaneous leishmaniasis (oriental sore, Delhi ulcer, Aleppo boile, Delhi or Baghdad boil).
- Epidemiology: Leishmaniasis is prevalent worldwide, ranging from south east Asia, Mediterranean, north and central Africa, and south and central America.

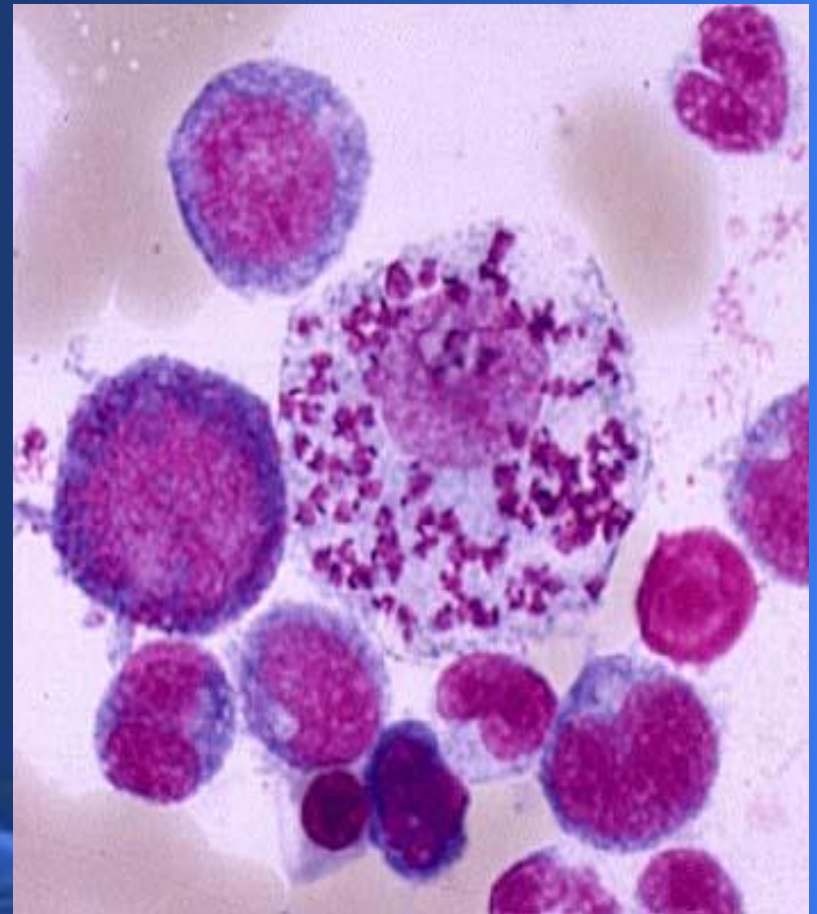
- Most *Leishmania* vector are females sandflies of the genus *Phlebotomus*
- Their primary hosts are vertebrates and Human.
- All species habitat is **obligatory intracellular** (Mostly macrophages).
- **Reservoir hosts:** fox, jackal, rodents and wolves.
- All human *Leishmania* are **zoonotic** pathogenic protozoa.
- All human species have **indirect life cycle**.
- **Mode of infection:** by vector sand fly **bit of skin**.
- **Route of infection:** exposed skin places.
- All human *Leishmania* species are seriously and medically **pathogenic**.

1-Amastigote:

is a stage that does not have a visible external flagella. The term. It is the form the parasite lives in the human macrophages .



Amastigote



2-Promastigote.

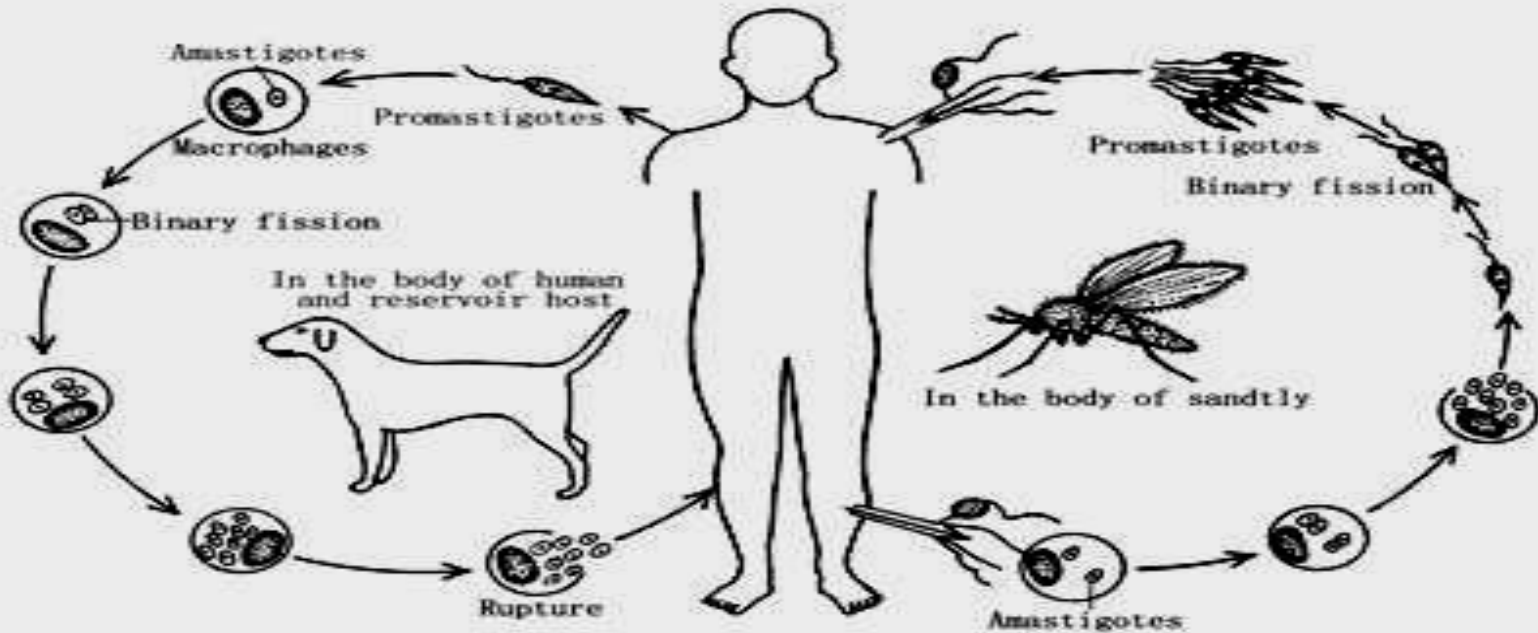
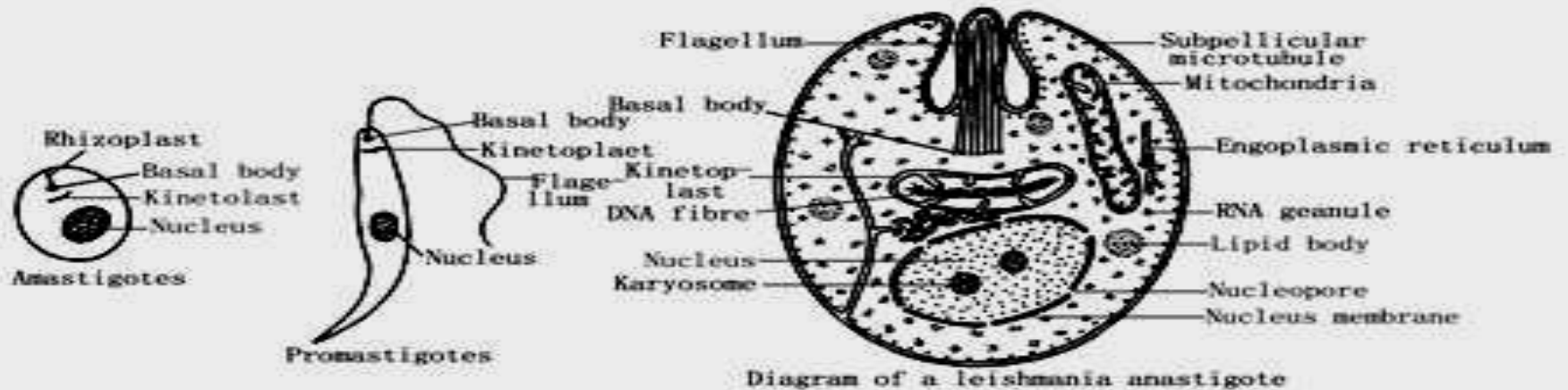
is a stage that does have a visible external flagella. it is the form the parasite lives in the vector sand fly gut.



Promastigote



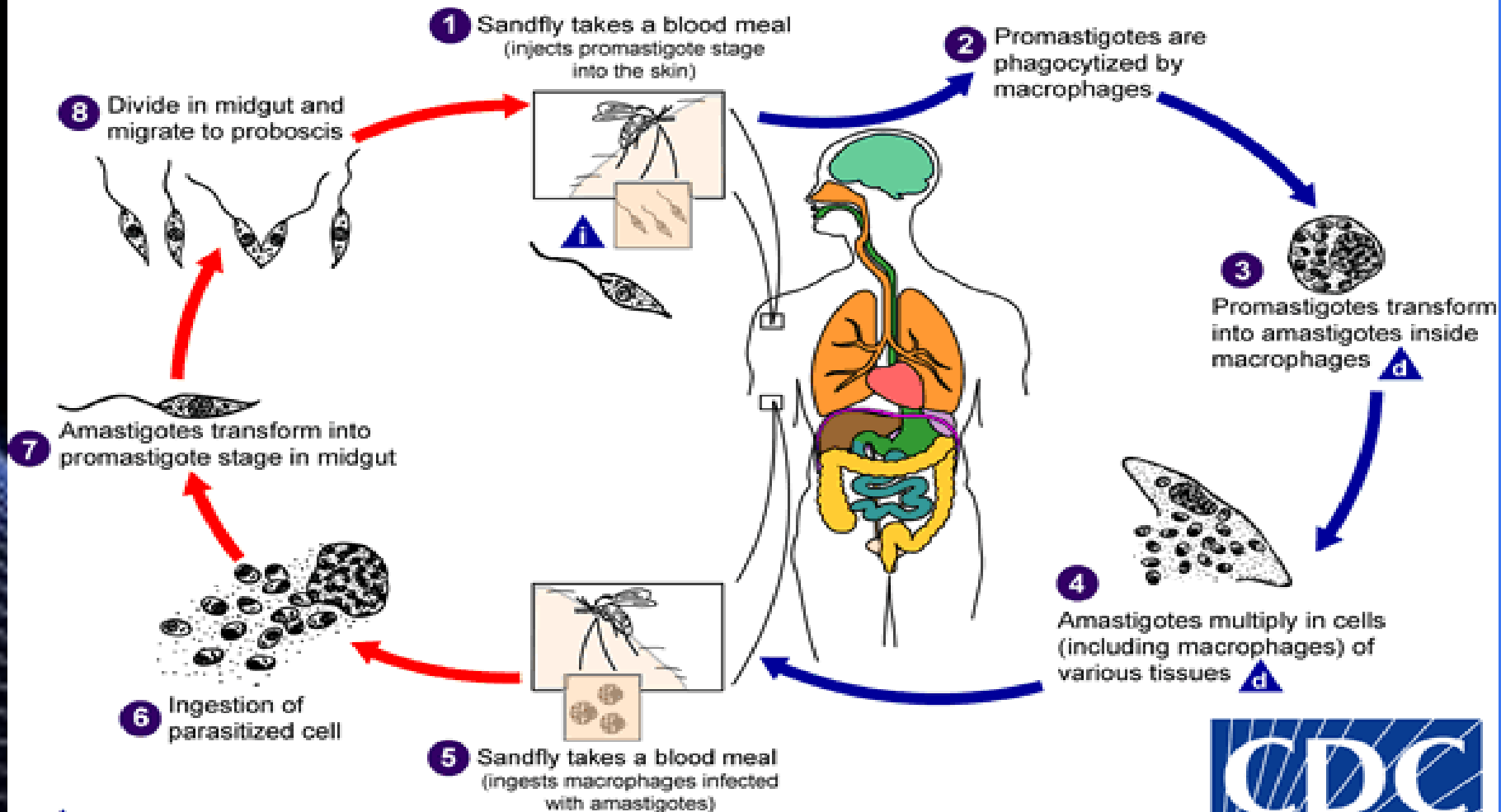
Morphology



Life cycle

Sandfly Stages

Human Stages



Symptoms

- Visceral leishmaniasis caused by *leishmania donovani* (**kala-azar, dum dum fever**):
- They are localized and multiply in the mononuclear phagocytic cells of spleen, liver, lymph nodes, bone marrow, intestinal mucosa and other organs.
- Cutaneous leishmaniasis (*L. tropica*) cause Oriental sore, Delhi ulcer, Baghdad boil
- They multiply locally, producing a papule, **1-2 weeks** (or as long as **1-2 months**) after the bite, which gradually grows to form a relatively painless ulcer.
- The center of the ulcer **encrusts** while satellite papules develop at the periphery.
- The ulcer **heals in 2-10 months** even if untreated but leaves a disfiguring scar.
- The disease may **disseminate** in the case of a **depressed immune function**.

Pathology & Diagnosis

- **Pathology:** Pathogenesis of leishmaniasis is due to immune reaction to the organism, **particularly the cell mediated immunity.**
- Laboratory examination reveals a marked leukopenia with relative monocytosis and lymphocytosis, anemia and thrombocytopenia.
- **IgM and IgG** levels are extremely elevated due to both specific antibodies and polyclonal activation.



Diagnosis:

- ❖ Diagnosis is based on the **history of exposure to sand fly**, symptoms and **isolation of the organisms from the lesion aspirate or biopsy**, by direct **examination or culture**.
- ❖ Skin test (**delayed hypersensitivity: Montenegro test**), **detection of anti-leishmanial antibodies** by immunofluorescence are indicative of exposure
- ❖ In **visceral leishmaniasis** a physical exam may show signs of an enlarged spleen, liver (**hepatosplenomegaly**), and **lymph nodes**.
- ❖ The patient may have been **bitten by sand flies**, or was in an area known for **leishmaniasis**

Treatment and Control:

- Sodium stibogluconate (**Pentostam**) is the drug of choice.
- **Pentamidine isethionate** is used as an alternative.
- Control measure involves the **vector control** and avoidance. **Immunization** has not been effective.

Types of macrophages in different tissues.

<u>Name of cell</u>	<u>Location</u>
▪ <u>Dust cells/</u>	<u>Alveolar macrophages lungs</u>
▪ <u>Adipose tissue macrophages</u>	<u>Adipose tissue</u>
▪ <u>Histiocytes</u>	<u>Connective tissue</u>
▪ <u>Kupffer cells</u>	<u>Liver</u>
▪ <u>Microglia</u>	<u>Neural tissue</u>
▪ <u>Epithelioid cells</u>	<u>Granulomas</u>
▪ <u>Osteoclasts</u>	<u>Bone</u>
▪ <u>Hofbauer cell</u>	<u>Placenta</u>
▪ <u>Sinusoidal lining cells</u>	<u>Spleen</u>
▪ <u>Giant cells</u>	<u>Connective tissue</u>
▪ <u>Peritoneal macrophages</u>	<u>Peritoneal cavity</u>

**ALL THESE CELLS ARE CALLED MACROPHAGES WHICH
ORIGINATED FROM MONOCYTE AND THEIR
FUNCTIONS ARE**

1- DEFENCE MECHANISIM.

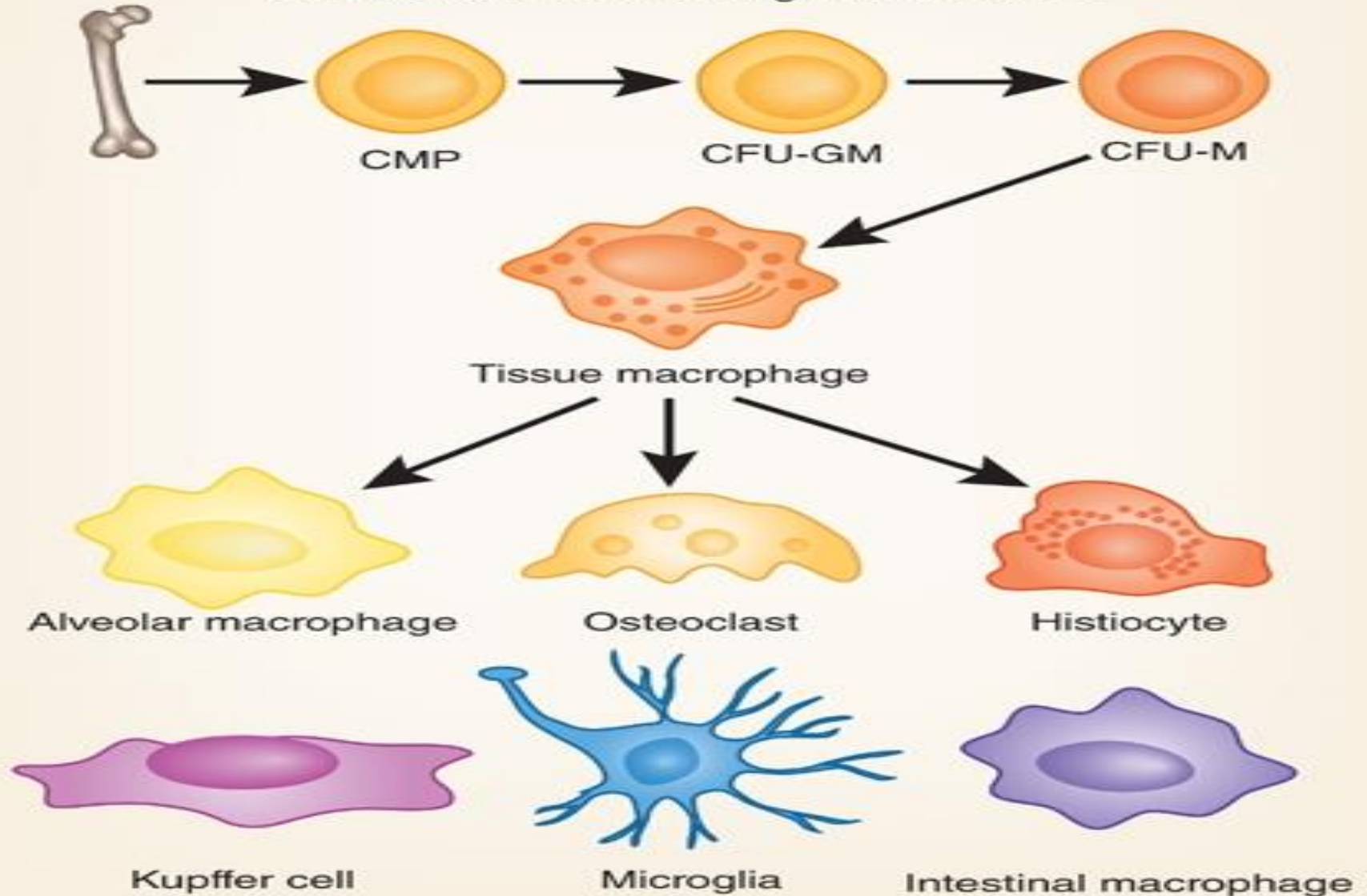
2- PHAGOCYTES OR ENGULF AND DIGEST

**3- ELIMINATE FOREIGN BODIES AND PATHOGENS AND CELLULAR
DEBRIS.**

Macrophage populations

Less-flexible programming—determined during ontogeny

Specific transcription factors and epigenetic modifications direct lineage commitment



TRYPANOSOMIASIS

African trypanosomiasis (Sleeping sickness)

- **Etiology:** There are two clinical forms:
 - 1) **A slow developing disease** caused by *Trypanosoma brucei gambiense*.
 - 2) **A rapidly progressing disease** caused by *T. b. rhodesiense*.
- **Epidemiology:** *T. b. gambiense* is predominant in the western and central regions of Africa, whereas *T. b. rhodesiense* is restricted to the eastern third of the continent.
- **6,000 to 10,000** human cases are documented annually.
- **35 million people** and **25 million cattle** are at risk.
- **Vector:** tsetse fly

- **Habitat:** blood, lymph nodes, brain and CSF.
- **Mode of infection:** insect bite, Blood transfusion.
- **Infective stage:** Metacyclic Trypomastigote.
- **Pathogenic stage:**
- **most prominent symptoms is profound coma.**

American trypanosomiasis (Chagas disease)

- **Chagas' disease** is caused by the protozoan hemoflagellate, *Trypanosoma cruzi*.
- **Epidemiology:** American trypanosomiasis, also known as Chagas' disease
- **Chagas' disease** is scattered irregularly in Central and South America, stretching from parts of Mexico to Argentina.
- **Insect vector:** reduvid bug
- **Route of infection:** skin or placenta or transplantation.
- **Infective stage:** metacyclic trypomastigote

- **Habitat:** nervous system, heart, blood, brain.
- **Pathogenic stage:**
- **Mode of infection**
 - 1-contamination of **wound** with insect faeces.
 - 2-Other modes of transmission include **organ transplantation**
 - 3-through **breast milk**
 - 4- congenitally (from a pregnant woman to her baby) through the placenta.



Trypomastigote



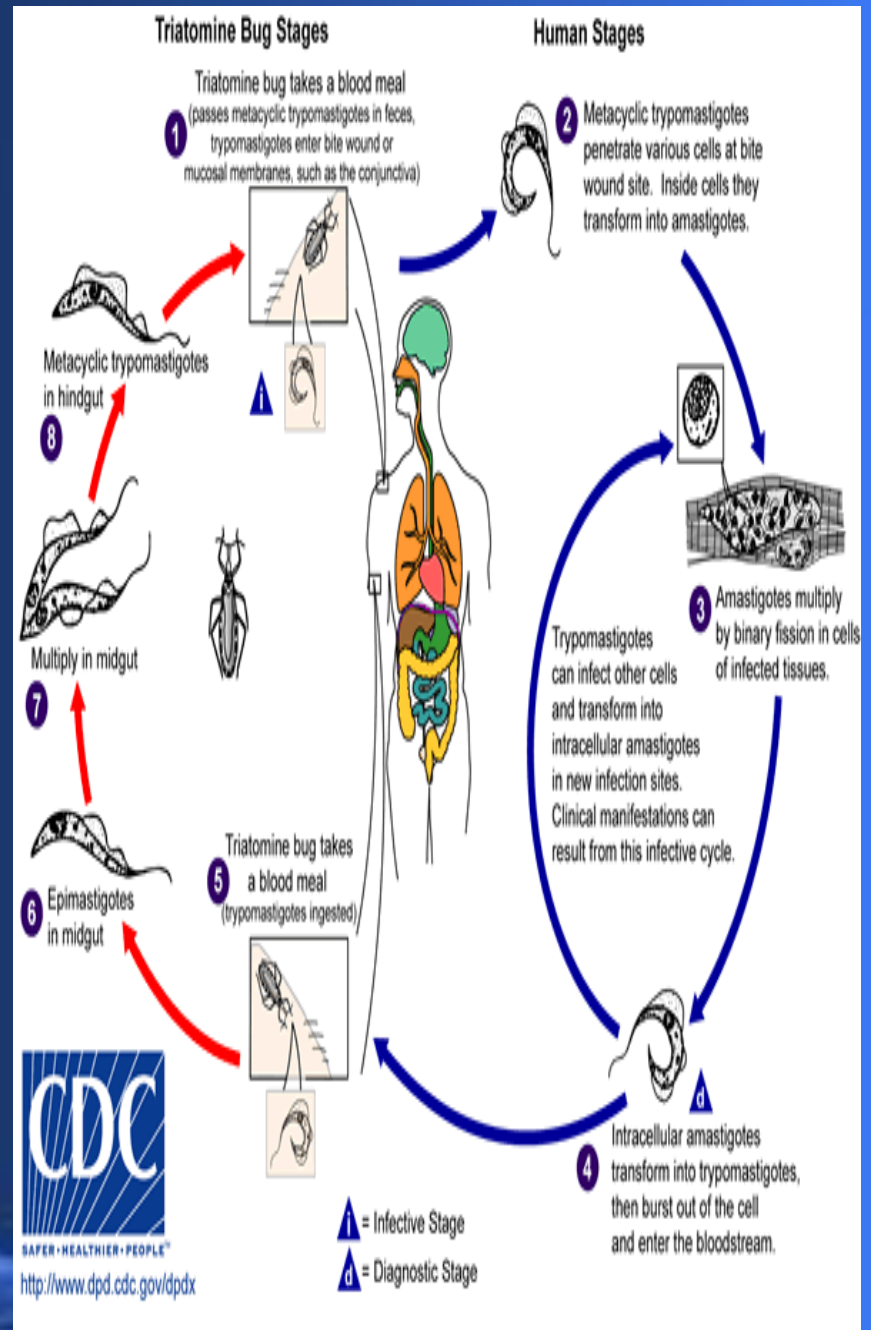
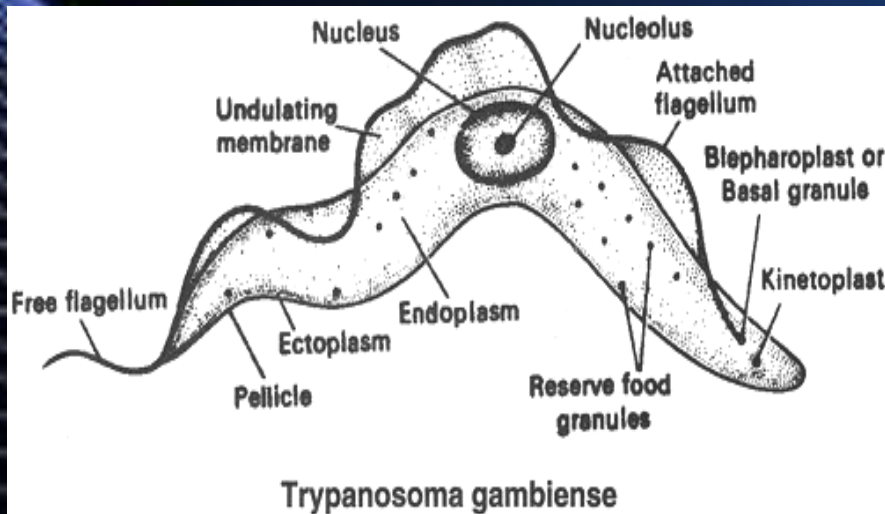
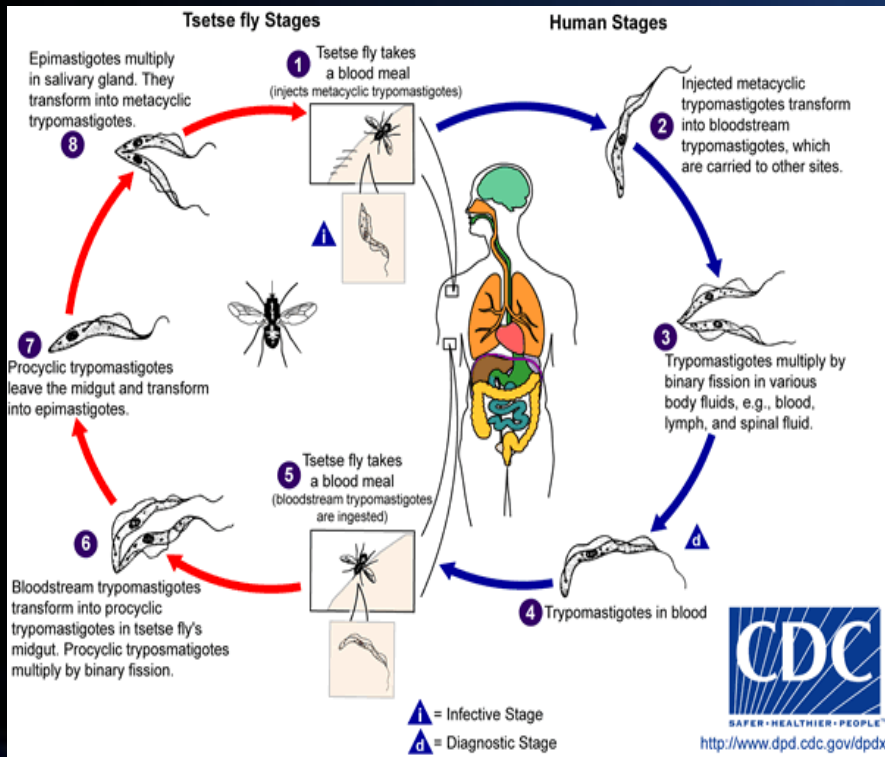
Amastigote



Promastigote



Epimastigote



Phylum: Apicomplexa

(because the apical point of the parasite complex)

(Blood and tissue Sporozoa)

- They are obligatory **intracellular protozoan** protozoa.
- They are unicellular, spor-forming.
- apical complex structure involved in penetrating a host's cells.
- apical complex structures is present at some stage and consist of elements visible with electron microscope.
- Has no organ of locomotion.
- Previously classified as sporozoa or Sporozoans.
- Typically producing **sporozoites during the life cycle**.
- Has asexual life cycle human (As intermediate host)
- Has sexual life cycle in final host (female of anopheles).

They include 2 pathogenic human genera:

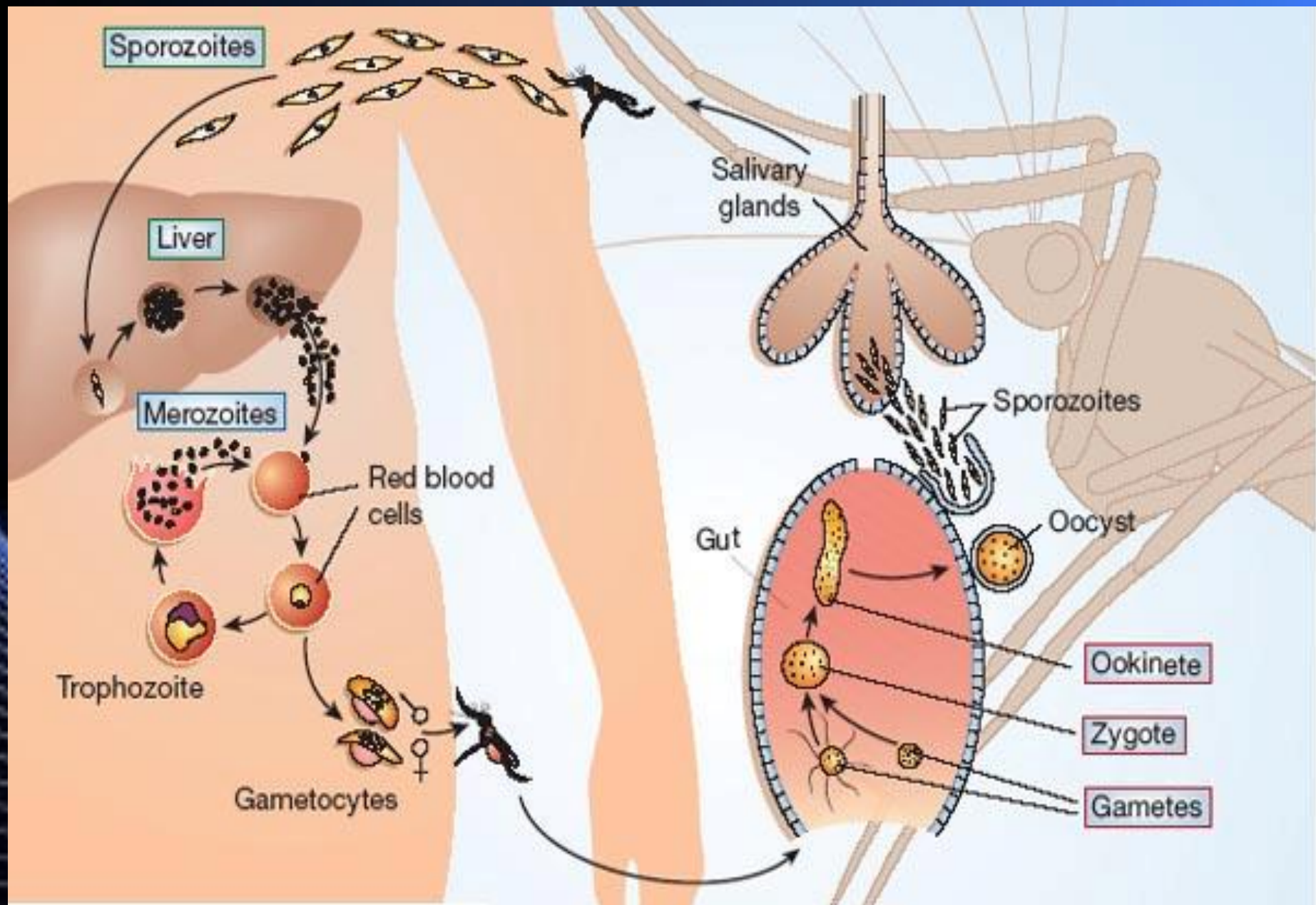
1-Genus: *Plasmodium*

2-Genus: *Toxoplasma*

Apicomplexa Blood and tissue sporozoa

Four *Plasmodium* spp are responsible for human malaria:

- 1- *P. falciparum* → causes (**malignant tertian malaria**) the periodicity of attack becomes tertian (36-48) shortest incubation period 7-10.
- 2- *P. malariae* → causes (**quartan malaria**) are the most common species, the periodicity of attack becomes quartan (every 72 hours) incubation period 18-40.
- 3- *P. vivax* → causes (**benign tertian malaria**) the periodicity of attack becomes tertian (every 48 hours) incubation period 10-17 days
- 4- *P. ovale* → causes (**ovale tertian malaria**) the periodicity of attack becomes tertian (every 48-50 hours) incubation period 16-18 days



Plasmodium (Malaria) in general.

- **Infective stage:** Sporozoite
- **Distribution:** depend on the spp of *Plasmodium*.
- **Life cycle:** Indirect with vector.
- **Vector:** female anopheles mosquito (final host with sexual L.C).
- **Human is the intermediate host** (carries the asexual life cycle) in liver and RBCS.
- **Pathogenic stage:** all liver and RBCS stages.
- **Habitat:** 1-intra-Liver cells 2- Intra-RBCS
- **Diagnostic stage:** All intracellular RBCS STAGES.
- **Prevention:** Measurements to keep vector away from human life and contact.
- **Diagnosis:** Detection of parasite in intracellular of RBC.

Mode of infection

1- insect bite

2-Blood transfusion from infected donors.

3-organ transplantation .

4-congenitally trasplacentally.

5-Needle stick injury: In case of drugs addiction.

Laboratory diagnosis

- Clinically from febrile paroxysm
- Microscopic examination of thick and thin blood films of blood is the method of choice for confirming the clinical diagnosis of malaria and identifying the specific species responsible for disease.
- Serologic procedures are available but they are used primarily for epidemiological study.
- Surveys or for screening blood donors.

Pathogenicity and symptoms

Patients who suffering from malaria infection may developed

- 1- a sudden attack or recurrence of a disease called paroxysm.
Periodicity of attack. These regular paroxysm separated by asymptomatic intervals.**
- 2- relapse: in the life cycle of plasmodium, some sporozoites go under resting phase instead to proceeding further in the cycle, which later forms hypnozoites giving rise to various symptoms. This called relapse.**
- 3- recrudescence: the recurrence of clinical symptoms in a malaria patient because plasmodium is not eliminated either by immune system or treatment failure.**
- 4- clinical incubation period: the time elapsed between exposure to a pathogenic organism and when symptoms and signs are first apparent.**
- 5- biological incubation period: the time elapsed between exposure to a pathogenic organism and when organism are first appear.**

- Man develop infection by female anopheles mosquito by insect bite through skin.

The initial symptoms of malaria are flu-like symptoms and include a high temperature (fever).

After infection liver and RBC, typical picture of malaria is

1- febrile paroxysm. Has three stages

- a) **Cold stage: feel intense cold, vigorous shivering, rigor lasts 15-60 minutes.**
- b) **Hot stage: intense heat (40-40.6 C°) dry burning skin, headache lasts 2-6 hours.**
- c) **Sweating: profuse sweating, declining temperature, exhausted, weak, sleep.**

2-Anemia: due to

- a) suppression of erythropoiesis,
- b) destruction of infected RBC,
- c) Phagocytosis of uninfected RBC.

3-Splenomegally: Massive proliferation of **MΦ** which phagocytized both infected and non-infected RBC.

When the mature schizont ruptures releasing red cells fragments, merozoites, malaria pigments and other parasite debris which phagocytoses by PMNC and macrophages (MØ) and then release pyrogenic factors (IL-1 & TNF) which cause elevation of temperature.

All clinical manifestation in malaria due to products of erythrocytes schizogony and host reaction to them.

Symptoms of malaria briefly



Global Malaria Prevention and Control

- **Most death occur among children living in Africa where a child dies every minute from malaria.**
- **Malaria mortality rates among children in Africa have reduced by an estimated 54% since 2000's.**
- **Diagnosis and prompt treatment to prevent complication.**
- **Avoidance of exposure to mosquitoes at there peak feeding time (usually dusk to dawn.**
- **Insect repellents, insecticide - impregnated bed or other materials.**
- **suitable clothing.**
- **Widespread use of bed nets.**
- **Chemoprophylaxis refer to the administration of a medication for the purpose of preventing disease or infection.**



TREATMENT

1-Bed rest with fluid supply.

2-Drugs

- The drug of choice for treating acute malaria is Chloroquine.
- In 2013 a trial was completed, that studied a single dose alternative drug named Tafenoquine.
- Primaquine used for EEC

2-GENUS *TOXOPLASMA*

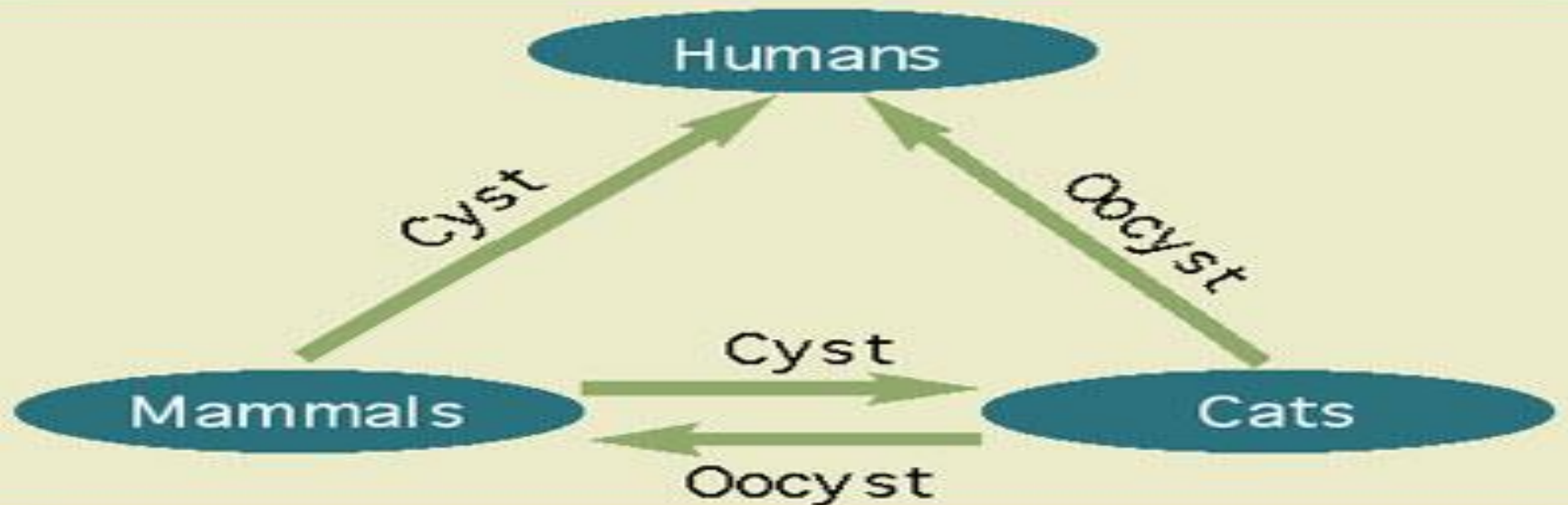
Toxoplasma gondii

- **Disease:** toxoplasmosis.
- It will probably infect almost any mammal.
- Like most of the apicomplexa, toxoplasma is an **obligate intracellular** parasite.
- Life cycle includes two phases called the intestinal (or enteroepithelial) and extraintestinal phases.
- The intestinal phases occurs in cats only (wild as well as domesticated cats) and produces oocyst.
- Extraintestinal phases occurs in all infected animals (including cats) and produced “tachyzoites” and eventually, “bradyzoites”

- **Intermediate host:** human (**Accidental host**), cattle, rodents.
- **Final host:** cats (sexual cycle) gives mature oocyst in faeces.
- **Infective stage:** fecal oocyst from cats, or tissue cyst from cattle or Tachyzoite → from pregnant women by bloodstream.

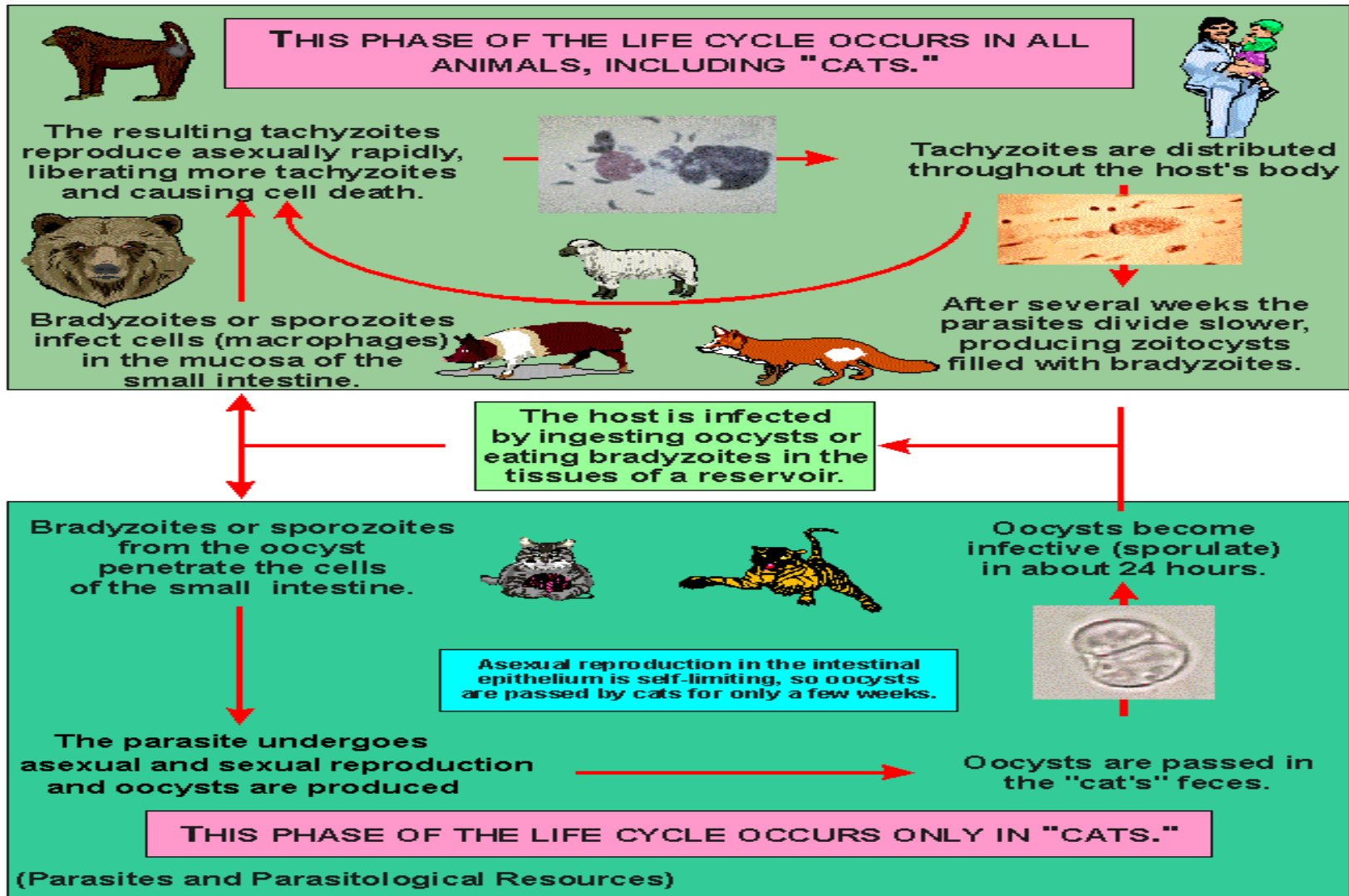
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THE LIFE CYCLE OF *TOXOPLASMA GONDII* (TOXOPLASMOSIS)



Mode of infection mostly:

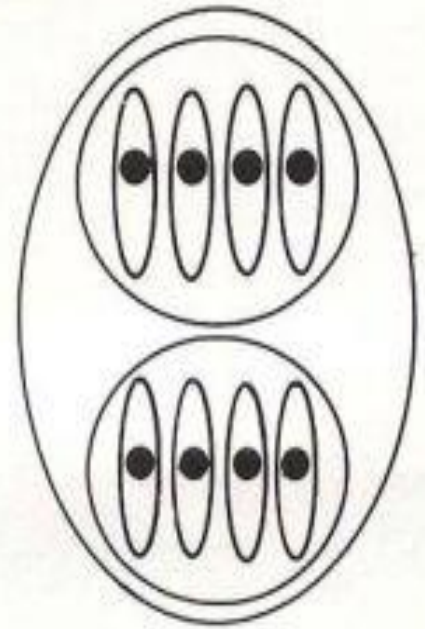
A-Congenitally, transplacentally (from pregnant woman to the fetus).

B-Acquired (orally) by fecal contaminated food with undercooked meat (tissue cyst) or blood transfusion or organ Implantation

Toxoplasmosis in general

- **Rout of infection:** **mouth, placenta**
- **Habitat:** **obligatory intracellular** in different **RES** and all nucleated cell in different organ.
- **Oocyst:** excreted in cat feces contains **2 sporocysts**, each one contain **4 Sporozoites**.

Sporocysts: 2
Sporozoites: 8



In human:

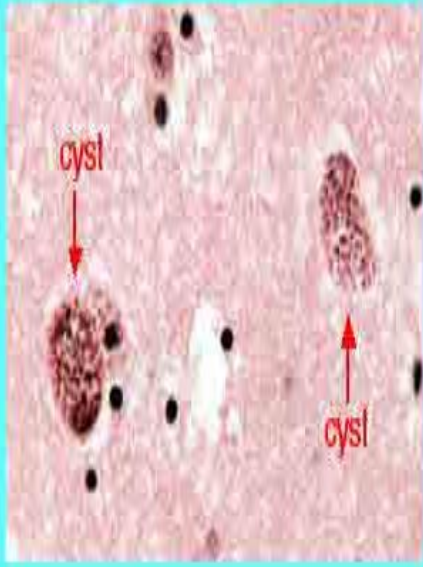
Tachyzoite: trophozoite multiply rapidly.

Bradyzoite: trophozoite multiply slowly.

Toxoplasma gondii morphology

- The name Toxoplasma is derived from the shape of the organism, which is crescent-like (toxos is Greek for “arc”). Plasma mean “form”
- **Has anterior apical end with conoid and posterior rounded end.**
- **The conoid end is believed to be central in breaching the host’s cell membrane.**
- **It has three main secretory organelles used for adhesion and attachment, also facilitated the motility, penetration of the organism.**
- **Central nucleus.**
- **Single mitochondrion, golgi body and rough endoplasmic reticulum (ER)**

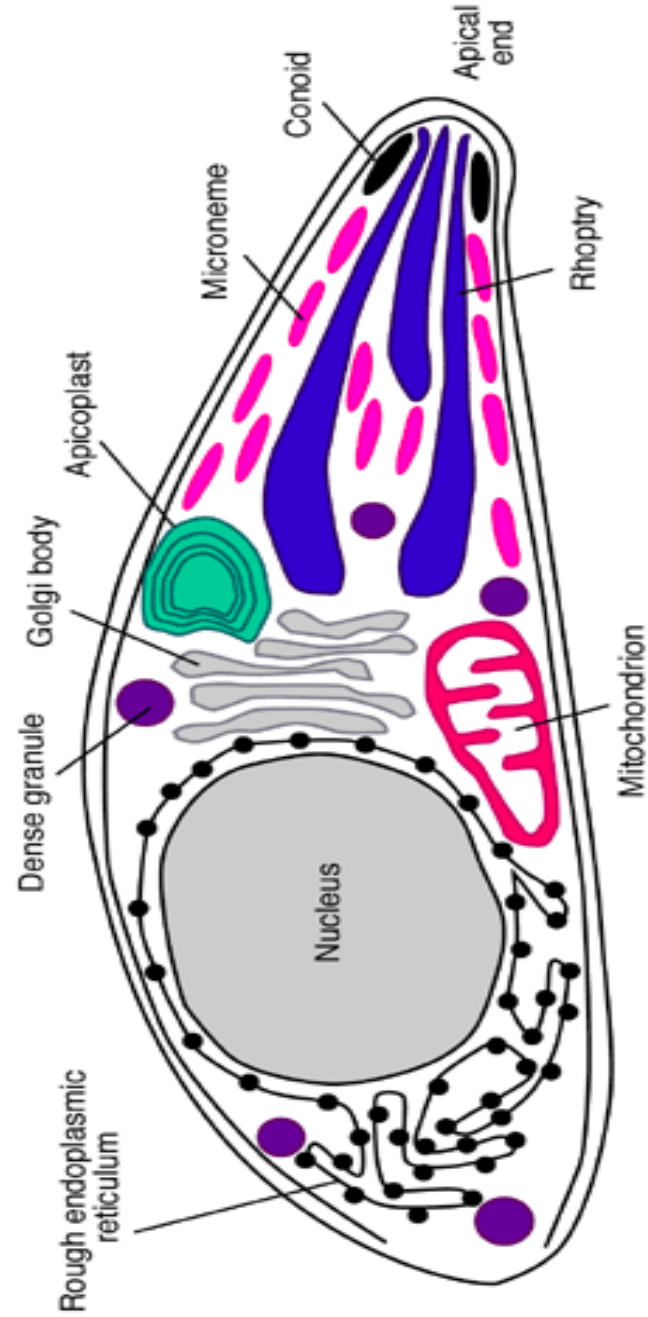
Toxoplasma gondii



T. gondii bradyzoites
in mouse brain
tissue cysts

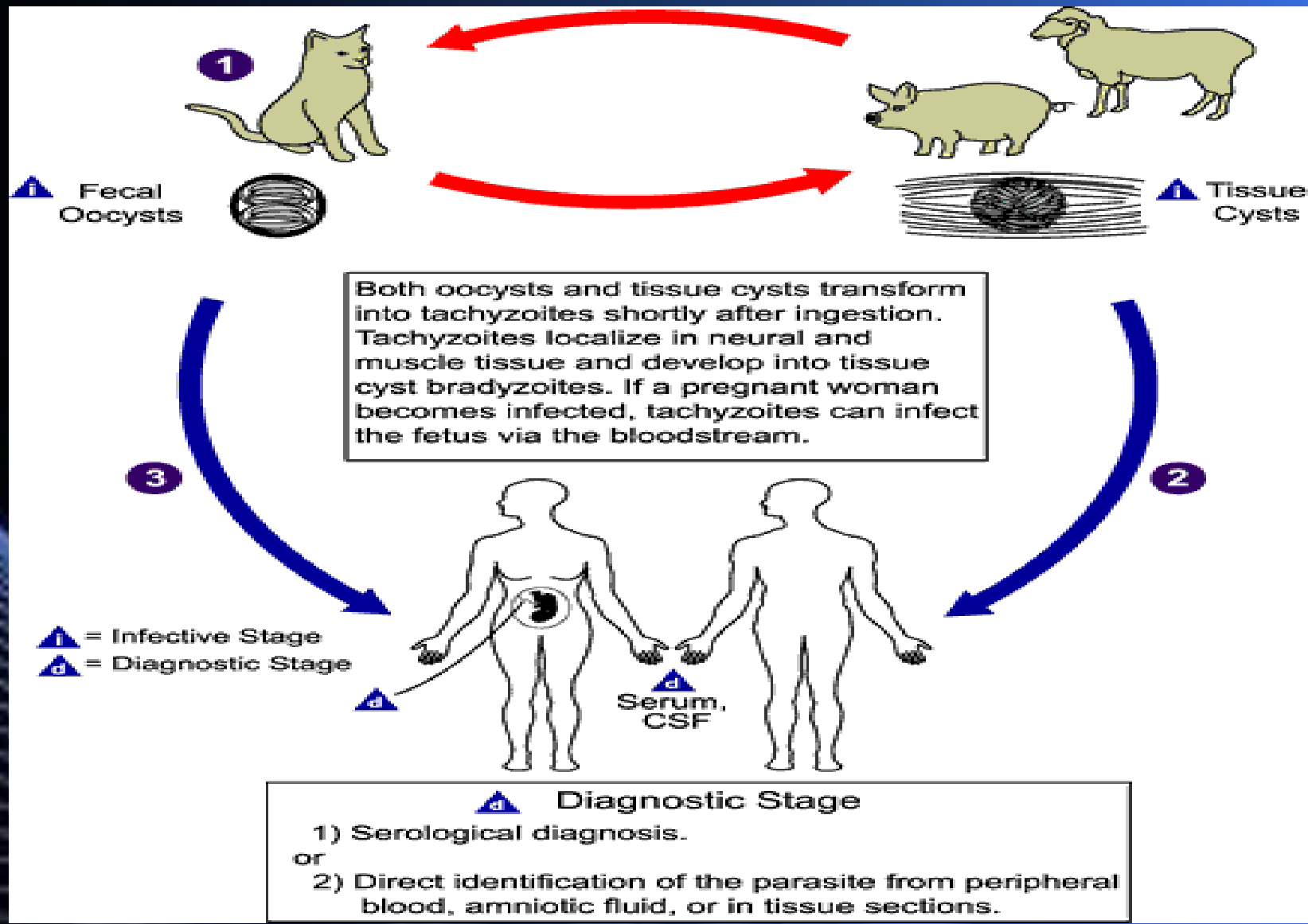


T. gondii tachyzoites
in leukocyte



Ultrastructure of a *Toxoplasma gondii* tachyzoite

life cycle of *Toxoplasma*

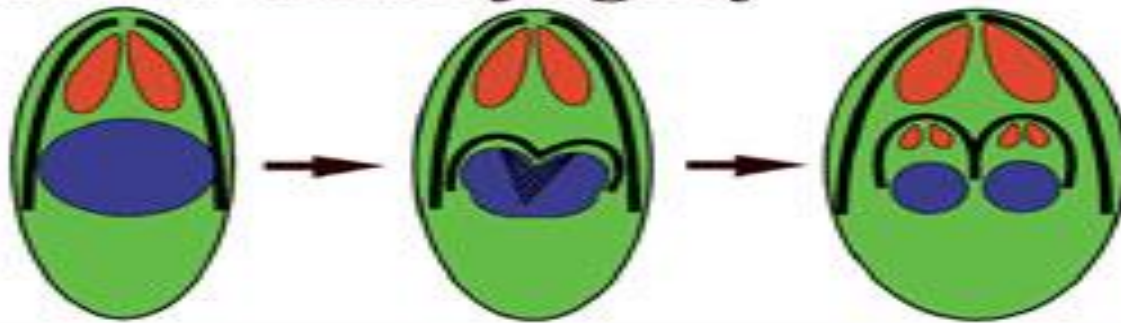


Life cycle of toxoplasma

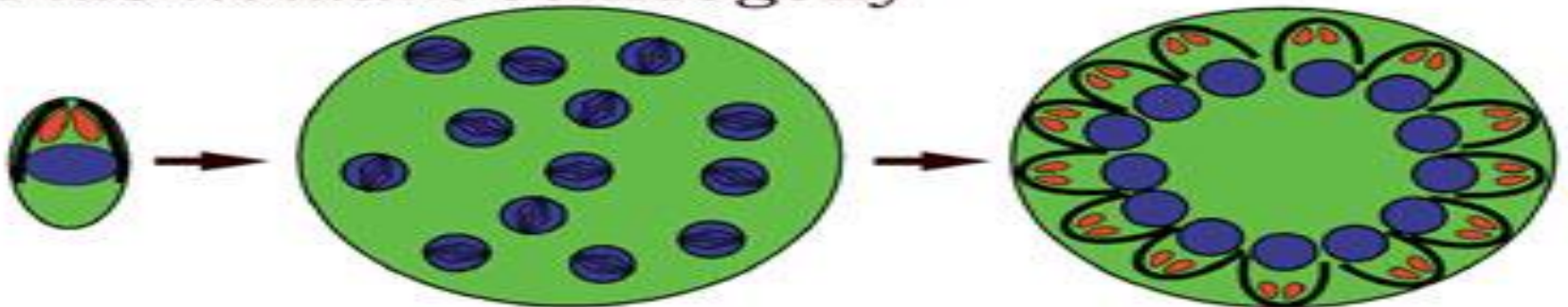
- Toxoplasma is capable of infecting and replicating within any nucleated cells.
- The life cycle divided between sexual and asexual replication.
- The sexual part of the cycle is happen inside cats.
- The asexual component consists of two distinct stages of growth depending on whether the infection is in the acute or chronic phase.
- The tachyzoite stage defines the rapidly growing form of the parasite found during the acute phase of toxoplasmosis, the tachyzoite is the form that can invade cells in the body where it then multiplies rapidly and can destroy cells. They replicate inside cells until they exit the cell to infect neighboring cells.
- In the infected animal, tachyzoite differentiate into bradyzoite and form tissue cyst that first appear in 7 to 10 days postinfection.
- These cyst are found predominantly in the central nervous system and muscle tissue, where they may reside for the life of the host.

- Multiplication is a process called **“endodyogeny”** **which is asexual multiplication in which two daughter cyst are formed with in parent cells**

Toxoplasma endodyogeny



Plasmodium schizogeny



Symptoms

it rarely produces symptoms in normal individuals.

After infection of the intestinal epithelium, the organisms spread to other organisms.

Most primary infection in immunocompetent adults are asymptomatic.

Its serious consequences are limited to:

- 1- Pregnant women.**
- 2- Immune-deficient hosts.**

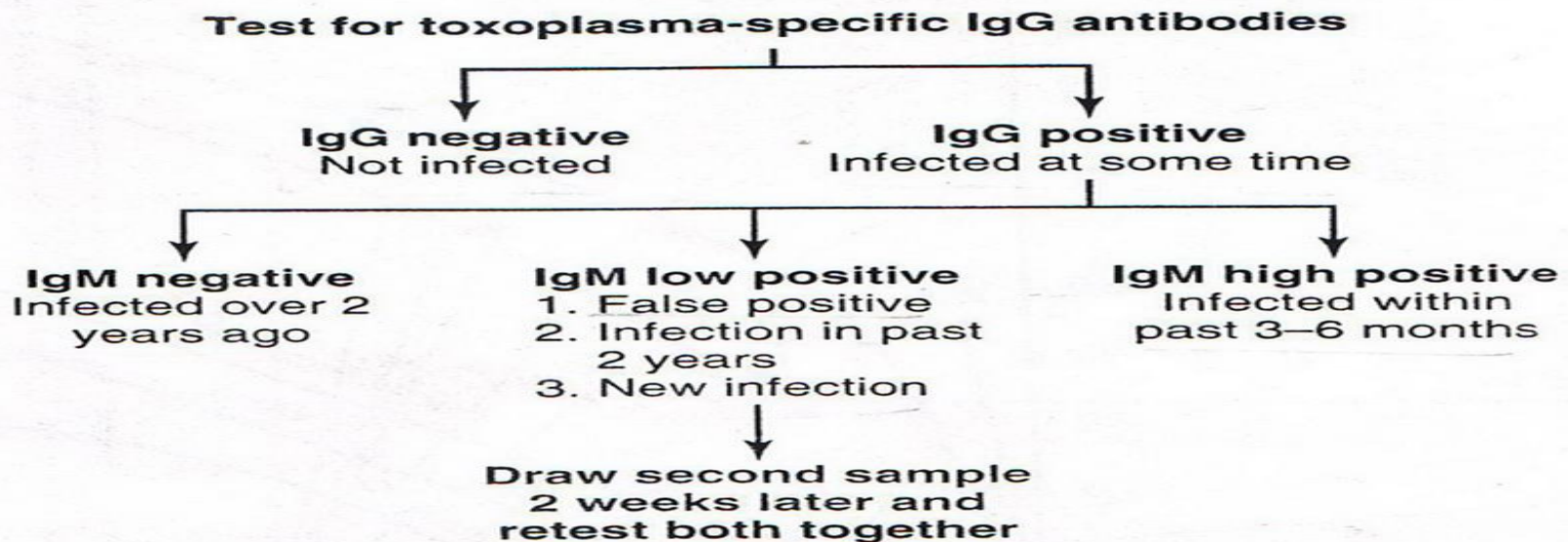
- **an early infection is usually more severe than a later one.**
- **The risk of foetal Infection rises with progress of gestation 25% when the mother acquires primary infection in the 1st trimester, 65% in the 3rd trimester.**
- **conversely, the severity of fetus damage is highest when the infection is transmitted in early infection.**
- **Most babies infected during pregnancy show no sign of toxoplasmosis when they are born.**
- **But many of them develop learning, visual, and hearing disabilities later in life.**

Diagnosis

Detection of the *Toxoplasma gondii* organisms in (blood, body fluid or tissues) or antigen in (blood or body fluid) by enzyme-linked immunosorbent assay (ELISA).

- 1- Serological techniques: By finding specific **IgG** and **IgM**
- 2- Isolation of the parasite and culturing in Animal body.
- 3- by DNA using PCR (polymerase chain reaction) on body fluid, including CSF, amniotic fluid and blood.
- 4- animal inoculation of of suspected tissue in to experimental animals.

ALGORITHM FOR SERODIAGNOSIS OF TOXOPLASMOSIS



Treatment

- **Acute infections:** pyrimethamine or sulphadiazine.
- **For pregnant woman:** spiramycin is a successful alternative drug for toxoplasmosis treatment.

Control

- Pregnant women are advised to avoid cat litter.
- Management to control and handle uncooked and undercooked meat carefully.
- Wearing gloves when handling soil.
- Wash hands with soap and water after outdoor activities.
- when preparing raw meat, wash any cutting boards, sinks, knives that touched the raw meat thoroughly with soap and hot water to avoid contaminating other foods.