• 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 boil, 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.
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.
Morphology
Symptoms

- Visceral leishmaniasis caused by *leishmania donovani* (kala-azar, dumdum fever):
  - They are localize 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 multiplies locally, producing of 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 encrust 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: 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 immuno-fluorescence 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.
<table>
<thead>
<tr>
<th>Name of cell</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dust cells/</td>
<td>Alveolar macrophages lungs</td>
</tr>
<tr>
<td>Adipose tissue macrophages</td>
<td>Adipose tissue</td>
</tr>
<tr>
<td>Histiocytes</td>
<td>Connective tissue</td>
</tr>
<tr>
<td>Kupffer cells</td>
<td>Liver</td>
</tr>
<tr>
<td>Microglia</td>
<td>Neural tissue</td>
</tr>
<tr>
<td>Epithelioid cells</td>
<td>Granulomas</td>
</tr>
<tr>
<td>Osteoclasts</td>
<td>Bone</td>
</tr>
<tr>
<td>Hofbauer cell</td>
<td>Placenta</td>
</tr>
<tr>
<td>Sinusoidal lining cells</td>
<td>Spleen</td>
</tr>
<tr>
<td>Giant cells</td>
<td>Connective tissue</td>
</tr>
<tr>
<td>Peritoneal macrophages</td>
<td>Peritoneal cavity</td>
</tr>
</tbody>
</table>
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

- CMP
- CFU-GM
- CFU-M

Tissue macrophage

- Alveolar macrophage
- Osteoclast
- Histiocyte

- Kupffer cell
- Microglia
- Intestinal macrophage
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, lump 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**: riduvid bug
  - **Route of infection**: skin or placenta or transplantation.
  - **Infective stage**: metacyclic trypommasigote
- **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*
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 if 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 shaving, rigor last 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 МФ which phagocytized both infected and non-infected RBC.
When the mature schizont rupture releasing red cells fragments, merozoites, malaria pigments and other parasite debris which phagocytes 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

**Symptoms of Malaria**

- **Central**
  - Headache
- **Systemic**
  - Fever
- **Muscular**
  - Fatigue
  - Pain
- **Back**
  - Pain
- **Skin**
  - Chills
  - Sweating
- **Respiratory**
  - Dry cough
- **Spleen**
  - Enlargement
- **Stomach**
  - Nausea
  - Vomiting
Global Malaria Prevention and Control

- Most deaths 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 the 2000s.
- Diagnosis and prompt treatment to prevent complication.
- Avoidance of exposure to mosquitoes at their 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
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.
**THE LIFE CYCLE OF TOXOPLASMA GONDII (TOXOPLASMOSIS)**

- This phase of the life cycle occurs in all animals, including "cats."

  - The resulting tachyzoites reproduce asexually rapidly, liberating more tachyzoites and causing cell death.
  - Bradyzoites or sporozoites infect cells (macrophages) in the mucosa of the small intestine.
  - Tachyzoites are distributed throughout the host's body.
  - After several weeks, the parasites divide slower, producing zoitocysts filled with bradyzoites.

- The host is infected by ingesting oocysts or eating bradyzoites in the tissues of a reservoir.

- Bradyzoites or sporozoites from the oocyst penetrate the cells of the small intestine.

- Oocysts become infective (sporulate) in about 24 hours.

- The parasite undergoes asexual and sexual reproduction, and oocysts are produced.

- Asexual reproduction in the intestinal epithelium is self-limiting, so oocysts are passed by cats for only a few weeks.

- Oocysts are passed in the "cat's" feces.

- This phase of the life cycle occurs only in "cats."

(Parasites and Parasitological Resources)
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.

**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 (toxon 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 secretary 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

---

Reviewed in Molecular Medicine © 2001 Cambridge University Press
The life cycle of Toxoplasma involves several stages:

1. **Fecal Oocysts**
   - Oocysts are shed in the feces of infected cats.

2. **Tissue Cysts**
   - Tissue cysts develop in the tissues of intermediate hosts like sheep and pigs. If a pregnant woman becomes infected, tachyzoites can infect the fetus via the bloodstream.

Both oocysts and tissue cysts transform into tachyzoites shortly after ingestion. Tachyzoites localize in neural and muscle tissue and develop into tissue cyst bradyzoites. If a pregnant woman becomes infected, tachyzoites can infect the fetus via the bloodstream.

**Diagnostic Stage**

- Serological diagnosis.
- Direct identification of the parasite from peripheral blood, amniotic fluid, or in tissue sections.
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 from of the parasite found during the **acute face 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, **taczyzoite** differentiate in to **brayzoite** 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 within parent cells.
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 (blooob or body fluid) by enzyme-linked immunosorbent assay (ELISA).

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

ALGORITHM FOR SERODIAGNOSIS OF TOXOPLASMOSIS

Test for toxoplasma-specific IgG antibodies

- IgG negative
  - Not infected
- IgG positive
  - Infected at some time

  IgM negative
  - Infected over 2 years ago

  IgM low positive
  - 1. False positive
  - 2. Infection in past 2 years
  - 3. New infection

  Draw second sample
  - 2 weeks later and retest both together

  IgM high positive
  - Infected within past 3–6 months
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.