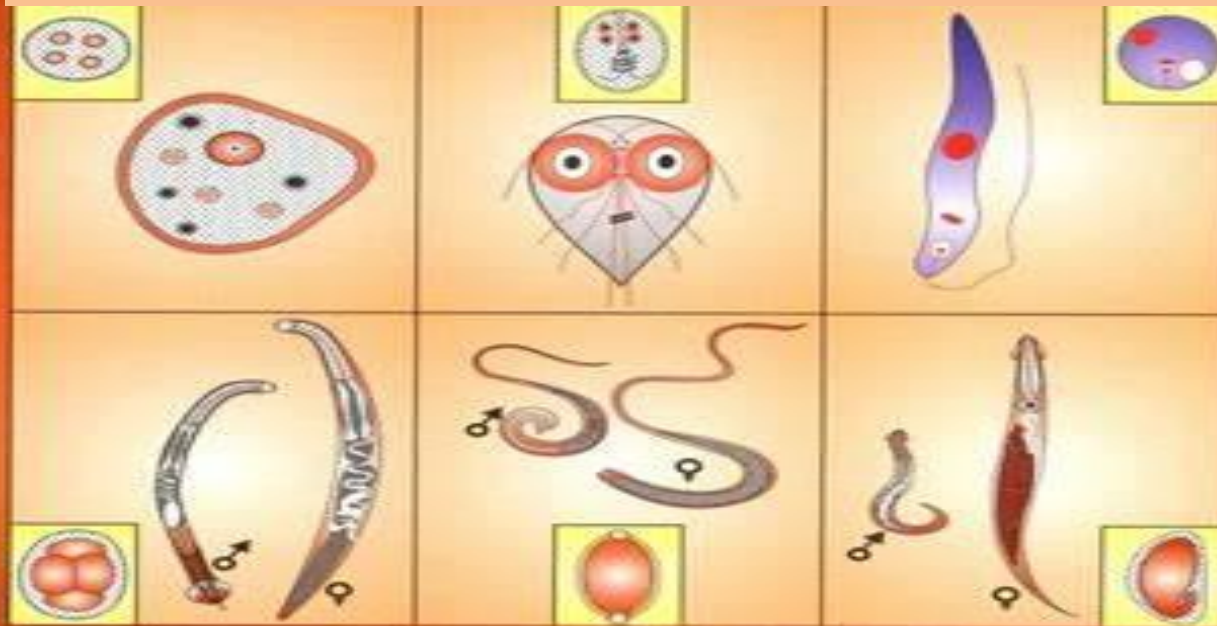# MEDICAL PARASITOLOGY

lec.7: Sporozoa

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Sporozoa

Sporozoa belong to the **phylum Apicomplexa**. This phylum contains two classes namely **Haematozoea** and **Coccidia**. The parasites of **class Haematozoea** occur in the blood of their vertebrate hosts; it contains two orders: **Haemosporida**, containing the genus *Plasmodium* which causes **malaria**, and Piroplasmida, containing the genus *Babesia* which is rare and accidental parasite of man, they complete their life cycle in two hosts.

PLASMODIUM

Malaria is caused by four plasmodia: *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae*, and *Plasmodium falciparum. P. vivax* and *P. falciparum* are more common causes of malaria than are *P. ovale* and *P. malariae*. Worldwide, malaria is one of the most common infectious diseases and a leading cause of deathOf the four species that infect humans, *P. vivax* and *P. falciparum* are responsible for 95% of infections. *P. vivax* has widest distribution, extending throughout the tropics, subtropics and temperate zones. *P. falciparum* is generally confined to (limited to) the tropics, *P. malariae* is sporadically distributed and *P. ovale* is confined mainly to central West Africa and some South Pacific Islands.
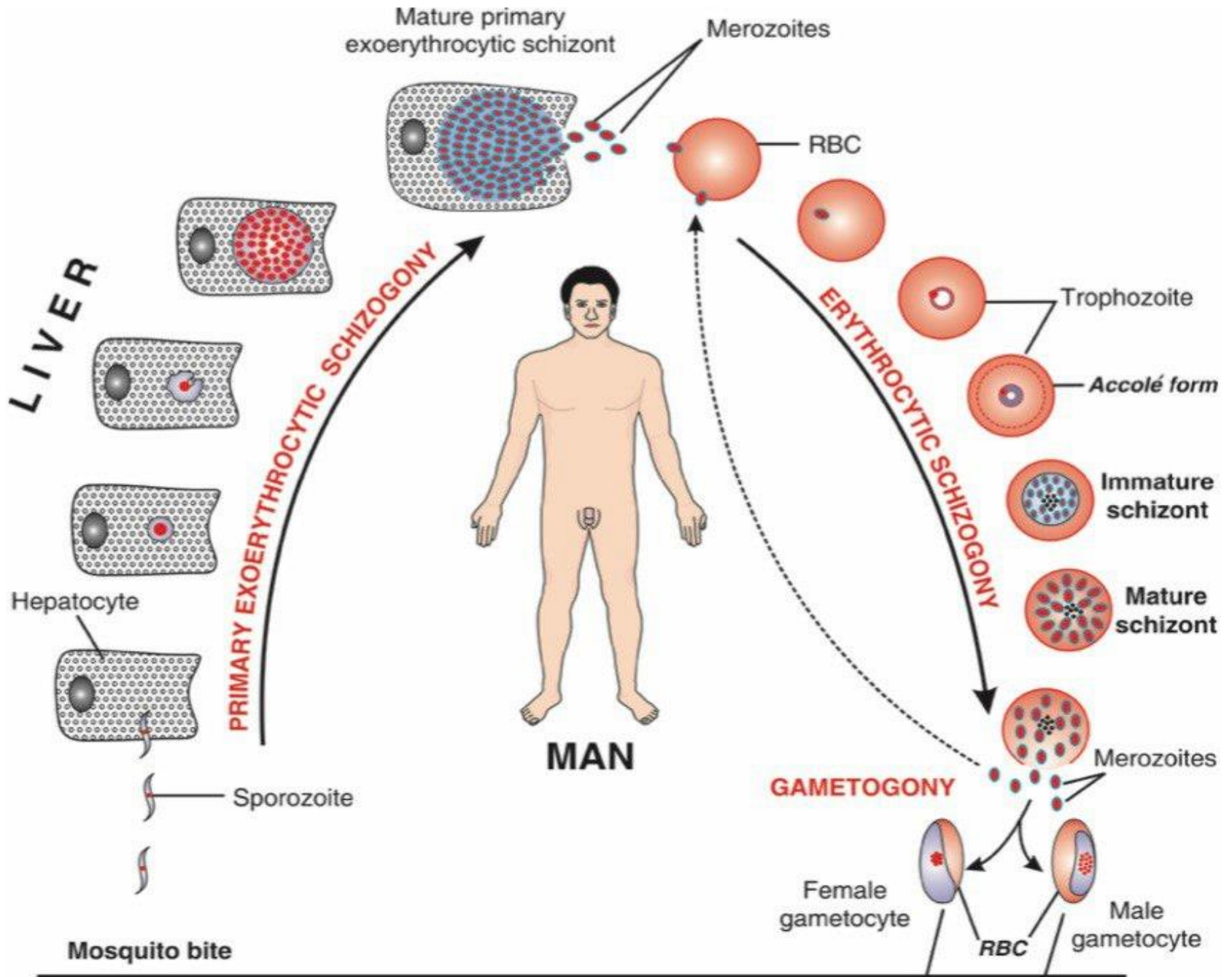
Life cycle

The vector and definitive host for plasmodia is the **female *Anopheles* mosquito** (only the female takes a blood meal). There are two phases in the life cycle: the sexual cycle, which occurs primarily in mosquitoes, and the asexual cycle, which occurs in humans, the intermediate hosts. The sexual cycle is called **sporogony** because sporozoites are produced, and the asexual cycle is called **schizogony** because schizonts are made.

The life cycle in humans begins with the introduction of sporozoites into the blood from the saliva of the biting mosquito. The sporozoites are taken up by hepatocytes within 30 minutes.

This "exoerythrocytic" phase consists of cell multiplication and differentiation into **merozoites**. *P. vivax* and *P. ovale* produce a latent form (**hypnozoite**) in the liver; this form is the cause of relapses seen with vivax and ovale malaria. Merozoites are released from the liver cells and infect red blood cells. During the erythrocytic phase, the organism differentiates into a ring-shaped trophozoite . The ring form grows into an ameboid form and then differentiates into a schizont filled with merozoites. After release, the merozoites infect other erythrocytes . This cycle in the red blood cell repeats at regular intervals typical for each species.

The periodic release of merozoites causes the typical recurrent symptoms of chills, fever, and sweats seen in malaria patients. The sexual cycle begins in the human red blood cells when some merozoites develop into male and others into female gametocytes.

The gametocyte-containing red blood cells are ingested by the female *Anopheles* mosquito and, within her gut, produce a female macrogamete and eight spermlike male microgametes. After fertilization, the diploid zygote differentiates into a motile ookinete that burrows into the gut wall, where it grows into an oocyst within which many haploid sporozoites are produced. The sporozoites are released and migrate to the salivary glands, ready to complete the cycle when the mosquito takes her next blood meal.
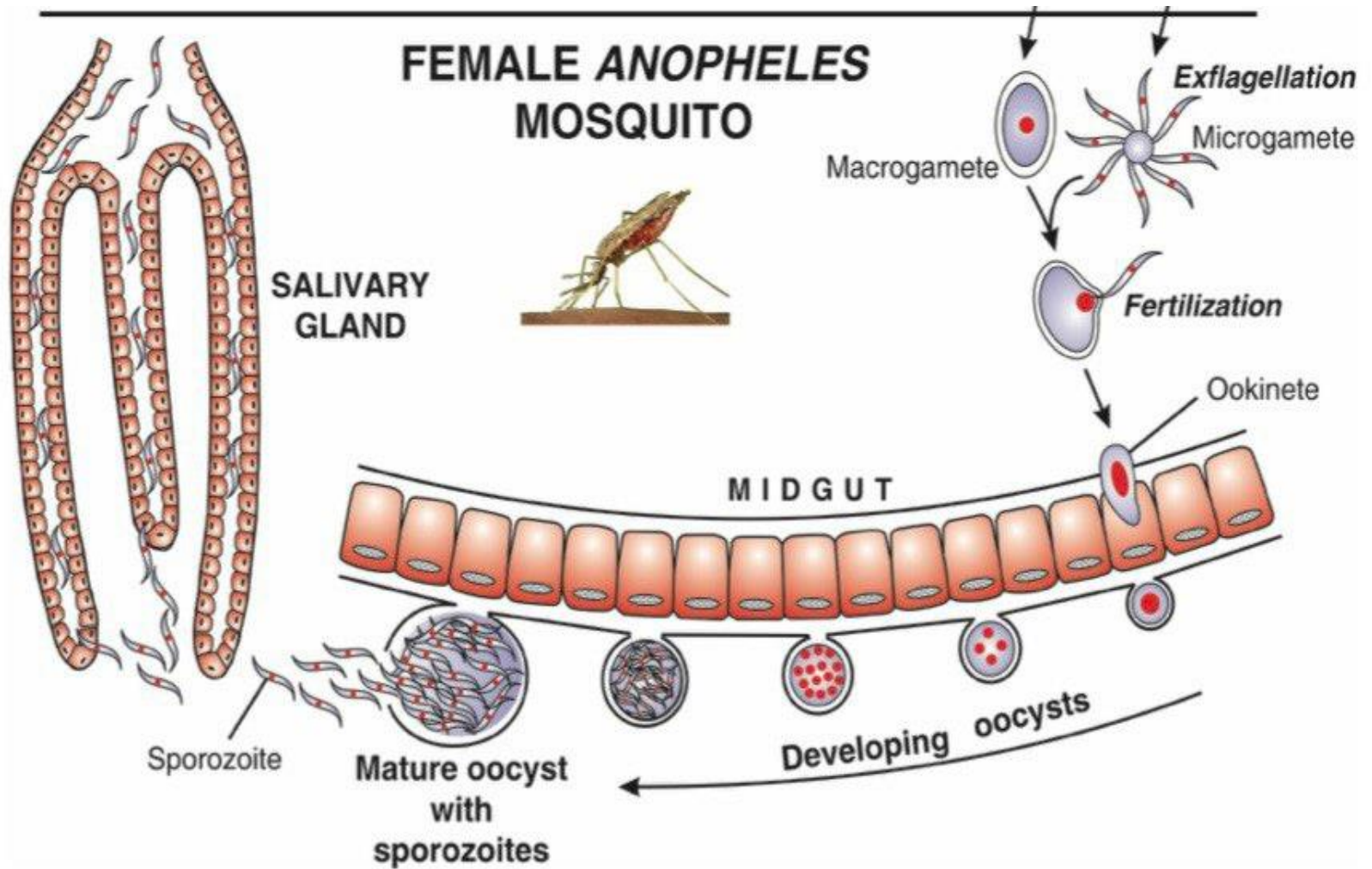
Mature primary
exoerythrocytic schizont

Merozoites

RBC

Trophozoite

Accolé form

Immature
schizont

Mature
schizont

LIVER

PRIMARY EXOERYTHROCYTIC SCHIZOGONY

ERYTHROCYTIC SCHIZOGONY

Hepatocyte

Sporozoite

MAN

GAMETOGONY

Merozoites

Female
gametocyte

RBC

Male
gametocyte

Mosquito bite

Fig. 5.1. Life cycle of malaria parasite.

Pathogenesis & Epidemiology

Most of the pathologic findings of malaria result from the **destruction of red blood cells**. Red cells are destroyed both by the release of the merozoites and by the action of the spleen to first sequester the infected red cells and then to lyse them. The enlarged spleen characteristic of malaria is due to congestion of sinusoids with erythrocytes, coupled with hyperplasia of lymphocytes and macrophages.

Malaria caused by *P. falciparum* is **more severe** than that caused by other plasmodia. It is characterized by infection of far more red cells than the other malarial species and by occlusion of the capillaries with aggregates of parasitized red cells. This leads to life-threatening hemorrhage and necrosis, particularly in the brain (cerebral malaria).

Furthermore, extensive hemolysis and kidney damage occur, with resulting hemoglobinuria. The dark color of the patient's urine has given rise to the term "blackwater fever." The hemoglobinuria can lead to acute renal failure. The timing of the fever cycle is 72 hours for *P. malariae* and 48 hours for the other plasmodia. Disease caused by *P. malariae* is called quartan malaria because it recurs every fourth day, whereas malaria caused by the other plasmodia is called tertian malaria because it recurs every third day.

Tertian malaria is subdivided into malignant malaria, caused by *P. falciparum*, and benign malaria, caused by *P. vivax* and *P. ovale*. *P. falciparum* causes a high level of parasitemia because it can infect red cells of all ages. In contrast, *P. vivax* infects only reticulocytes and *P. malariae* infects only mature red cells; therefore, they produce much lower levels of parasites in the blood.

Individuals with sickle cell trait (heterozygotes) are protected against malaria because their red cells have too little ATPase activity and cannot produce sufficient energy to support the growth of the parasite. People with homozygous sickle cell anemia are also protected but rarely live long enough to obtain much benefit.

The receptor for *P. vivax* is the Duffy blood group antigen. People who are homozygous recessive for the genes that encode this protein are resistant to infection by *P. vivax*. More than 90% of black West Africans and many of their American descendants do not produce the Duffy antigen and are thereby resistant to vivax malaria.

People with glucose-6-phosphate dehydrogenase (G6PD) deficiency are also protected against the severe effects of falciparum malaria. G6PD deficiency is an Xlinked hemoglobinopathy found in high frequency in tropical areas where malaria is endemic. Both male and female carriers of the mutated gene are protected against malaria. Malaria is transmitted primarily by mosquito bites, but transmission across the placenta, in blood transfusions, and by intravenous drug use also occurs.

Partial immunity based on humoral antibodies that block merozoites from invading the red cells occurs in infected individuals. A low level of parasitemia and low-grade symptoms result; this condition is known as **premunition**. In contrast, a nonimmune person, such as a first-time traveler to an area where falciparum malaria is endemic, is at risk of severe, life-threatening disease.

Clinical Findings

Malaria presents with abrupt onset of fever and chills, accompanied by headache, myalgias, and arthralgias, about 2 weeks after the mosquito bite. Fever may be continuous early in the disease; the typical periodic cycle does not develop for several days after onset. The fever spike, which can reach 41°C, is frequently accompanied by shaking chills, nausea, vomiting, and abdominal pain. The fever is followed by drenching sweats. Patients usually feel well between the febrile episodes. Splenomegaly is seen in most patients, and hepatomegaly occurs in roughly one-third. Anemia is prominent. Untreated malaria caused by *P. falciparum* is potentially life-threatening as a result of extensive brain (cerebral malaria) and kidney (blackwater fever) damage.

Malaria caused by the other three plasmodia is usually self-limited, with a low mortality rate. However, relapses of *P. vivax* and *P. ovale* malaria can occur up to several years after the initial illness as a result of hypnozoites latent in the liver.

Laboratory Diagnosis

Diagnosis rests on microscopic examination of blood, using both **thick** and **thin** Giemsa-stained smears. The thick smear is used to screen for the presence of organisms, and the thin smear is used for species identification. It is important to identify the species because the treatment of different species can differ. Ringshaped trophozoites can be seen within infected red blood cells . The gametocytes of *P. falciparum* are **crescent-shaped** ("banana-shaped"), whereas those of the other plasmodia are spherical . If more than 5% of red blood cells are parasitized, the diagnosis is usually *P. falciparum* malaria.

If blood smears do not reveal the diagnosis, then a polymerase chain reaction (PCR)-based test for *Plasmodium* nucleic acids or an enzyme-linked immunosorbent assay (ELISA) test for a protein specific for *P. falciparum* can be useful.

Treatment

Chloroquine was the standard treatment for acute malaria for many years. However, resistance to this drug in *P. falciparum* is widespread. Less commonly *P. vivax* may also be chloroquine-resistant. **Quinine** is the most reliable alternative to chloroquine for the treatment of malaria caused by chloroquine-resistant strains. **Tetracycline** and **clindamycin** exhibit some antimalarial activity and are used as an adjunct to quinine therapy. **Mefloquine** and **halofantrine** are also active against chloroquine-resistant strains, but resistance to these drugs has also been reported.
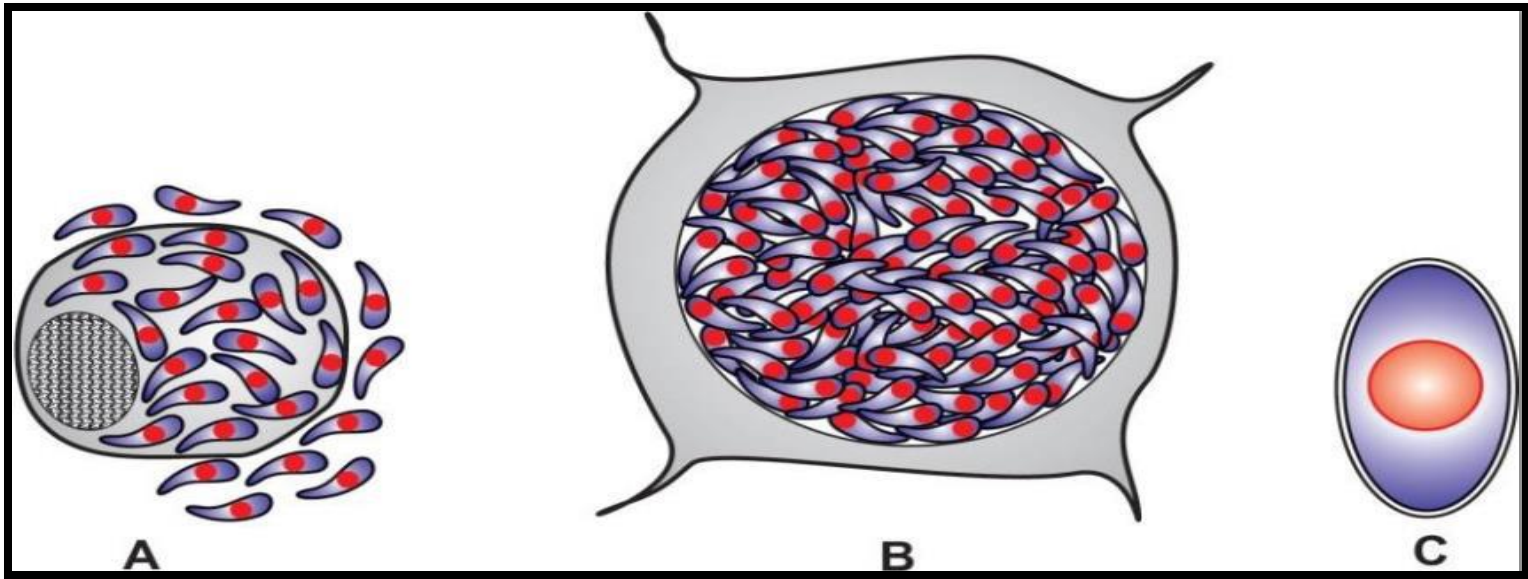
TOXOPLASMA

Disease

Toxoplasma gondii causes toxoplasmosis, including congenital toxoplasmosis.

Important Properties

The definitive host is the **domestic cat** and other felines; humans and other mammals are intermediate hosts. Infection of humans begins with the **ingestion of cysts** in undercooked meat or from accidental contact with cysts in cat feces. In the small intestine, the cysts rupture and release forms that invade the gut wall, where they are ingested by macrophages and differentiate into rapidly multiplying trophozoites (**tachyzoites**), which kill the cells and infect other cells

A: Tachyzoites seen within and outside a cell, B: tissue cyst, and C: oocyst of *Toxoplasma gondii*.

Cell-mediated immunity usually limits the spread of tachyzoites, and the parasites enter host cells in the brain, muscle, and other tissues, where they develop into cysts in which the parasites multiply slowly. These forms are called **bradyzoites**. These tissue cysts are both an important diagnostic feature and a source of organisms when the tissue cyst breaks in an immunocompromised patient. The cycle within the cat begins with the ingestion of cysts in raw meat (e.g., mice). Bradyzoites are released from the cysts in the small intestine, infect the mucosal cells, and differentiate into male and female gametocytes, whose gametes fuse to form oocysts that are excreted in cat feces. The cycle is completed when soil contaminated with cat feces is accidentally ingested. Human infection usually occurs from eating undercooked meat (e.g., lamb and pork) from animals that grazed in soil contaminated with infected cat feces.

Toxoplasmosis
(*Toxoplasma gondii*)

1

▲**i** Fecal Oocysts
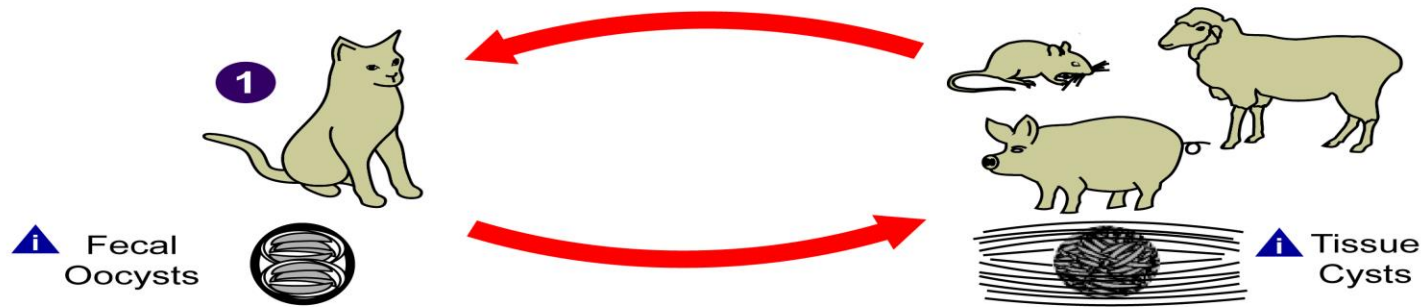
▲**i** Tissue Cysts

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.

3

2

▲**i** = Infective Stage
▲**d** = Diagnostic Stage

▲**d**

▲**d**
Serum, CSF
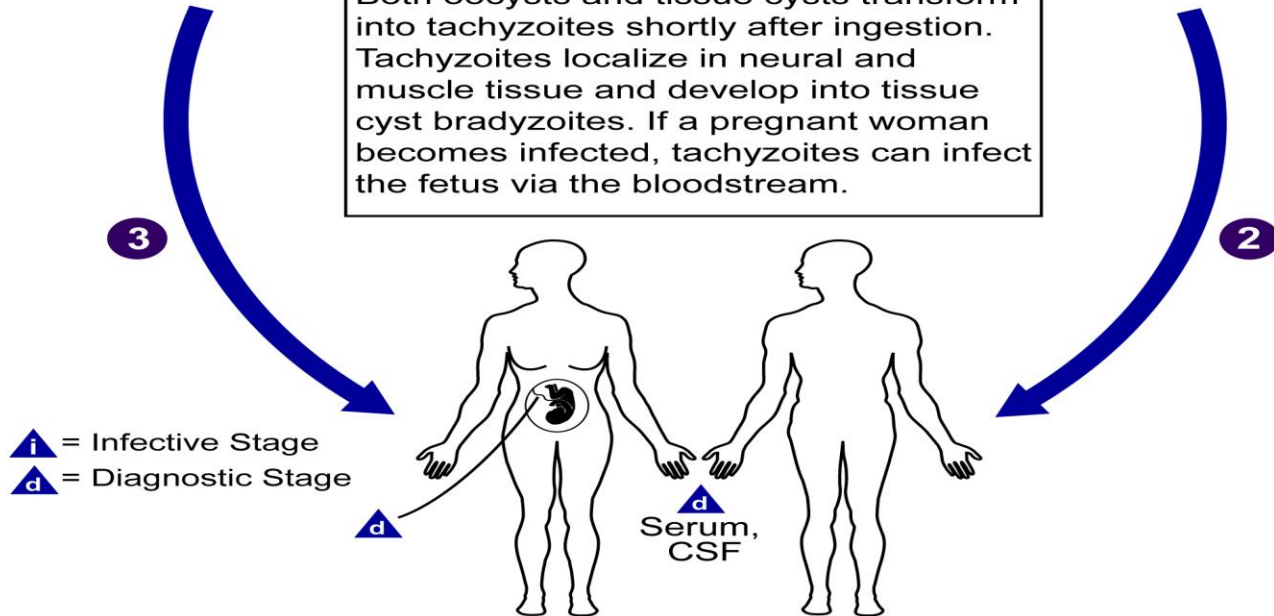
▲**d** Diagnostic Stage
1) Serological diagnosis.
or
2) Direct identification of the parasite from peripheral blood, amniotic fluid, or in tissue sections.

Pathogenesis & Epidemiology

T. gondii is usually acquired by **ingestion** of cysts in uncooked meat or cat feces. **Transplacental transmission** from an infected mother to the fetus occurs also. Human-to-human transmission, other than transplacental transmission, does not occur. After infection of the intestinal epithelium, the organisms spread to other organs, especially the brain, lungs, liver, and eyes. Progression of the infection is usually limited by a competent immune system.

Cell-mediated immunity plays the major role, but circulating antibody enhances killing of the organism. Most initial infections are asymptomatic. When contained, the organisms persist as cysts within tissues. There is no inflammation, and the individual remains well unless immunosuppression allows activation of organisms in the cysts.

Congenital infection of the fetus occurs *only* when the mother is infected during pregnancy. If she is infected before the pregnancy, the organism will be in the cyst form and there will be no trophozoites to pass through the placenta. The mother who is reinfected during pregnancy but who has immunity from a previous infection will not transmit the organism to her child. Roughly one-third of mothers infected during pregnancy give birth to infected infants, but only 10% of these infants are symptomatic. Infection by *T. gondii* occurs worldwide. Serologic surveys reveal that in the United States antibodies are found in 5% to 50% of people in various regions. Infection is usually sporadic, but outbreaks associated with ingestion of raw meat or contaminated water occur. Approximately 1% of domestic cats in the United States shed *Toxoplasma* cysts.

Clinical Findings

Most primary infections in immunocompetent adults are asymptomatic, but some resemble infectious mononucleosis, except that the heterophil antibody test is negative. Congenital infection can result in abortion, stillbirth, or neonatal disease with encephalitis, **chorioretinitis,** and hepatosplenomegaly. Fever, jaundice, and **intracranial calcifications** are also seen. Most infected newborns are asymptomatic, but chorioretinitis or mental retardation will develop in some children months or years later. Congenital infection with *Toxoplasma* is one of the leading causes of blindness in children. In patients with reduced cell-mediated immunity (e.g., patients with acquired immunodeficiency syndrome [AIDS]), life-threatening disseminated disease, primarily encephalitis, occurs.

Laboratory Diagnosis

For the diagnosis of acute and congenital infections, an immunofluorescence assay for **IgM antibody** is used. IgM is used to diagnose congenital infection, because IgG can be maternal in origin. Tests of IgG antibody can be used to diagnose acute infections if a significant rise in antibody titer in paired sera is observed. Microscopic examination of Giemsa-stained preparations shows crescent-shaped trophozoites during acute infections. Cysts may be seen in the tissue. The organism can be grown in cell culture. Inoculation into mice can confirm the diagnosis.

Treatment

Congenital toxoplasmosis, whether symptomatic or asymptomatic, should be treated with a combination of sulfadiazine and pyrimethamine. These drugs also constitute the treatment of choice for disseminated disease in immunocompromised patients.