Toxoplasmosis

- Like most of the Apicomplexa, *Toxoplasma* is an obligate intracellular parasite. Its life cycle includes two phases called the intestinal-enteric and Extraintestinal phases.
- Infects a wide range of animals, birds but does not appear to cause disease in them
- The intestinal phase occurs in cats only (wild as well as domesticated cats) and produces "oocysts."
- The extraintestinal phase occurs in all infected animals produces "tachyzoites" and, eventually, "bradyzoites" or “tissue cysts.“
- The disease toxoplasmosis can be transmitted by ingestion of oocysts (in cat feces) or bradyzoites (in raw or undercooked meat).
- A disease of the blood and lymphatic system.
- Primary problem is a congenital infection of fetus, resulting in either a stillbirth or a child with severe brain damage or vision problems.

Transmission

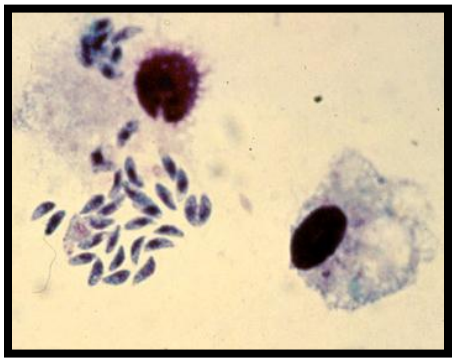
- Eating undercooked, contaminated meat (especially pork, lamb, and venison).
- Accidental ingestion of undercooked, contaminated meat after handling it and not washing hands thoroughly (*Toxoplasma* cannot be absorbed through intact skin).
- Eating food that was contaminated by knives, utensils, cutting boards and other foods that have had contact with raw, contaminated meat.
- Drinking water contaminated with *Toxoplasma gondii*.

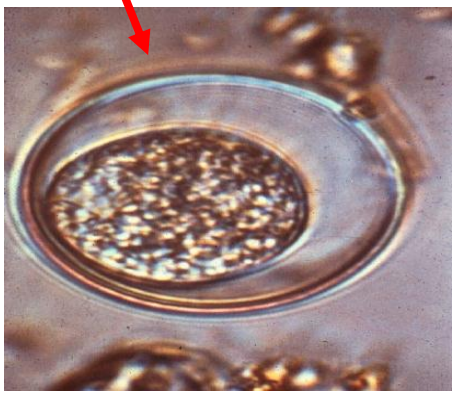
- Accidentally swallowing the parasite through contact with cat feces that contain *Toxoplasma*. This might happen by
  - cleaning a cat's litter box when the cat has shed *Toxoplasma* in its feces
  - touching or ingesting anything that has come into contact with cat feces that contain *Toxoplasma*
  - accidentally ingesting contaminated soil (e.g., not washing hands after gardening or eating unwashed fruits or vegetables from a garden)
- Mother-to-child (congenital) transmission.
- Receiving an infected organ transplant or infected blood via transfusion, though this is rare.

Morphology

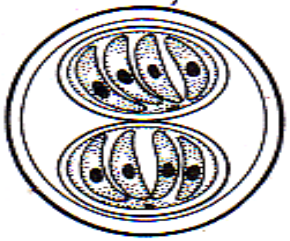
Toxoplasma gondii exists in three forms:

1. tachyzoites (trophozoites).
2. tissue cysts (bradyzoites).
3. oocyst.

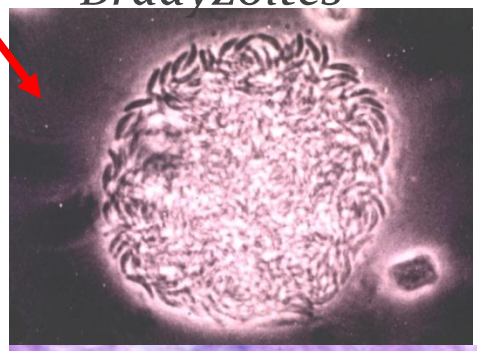


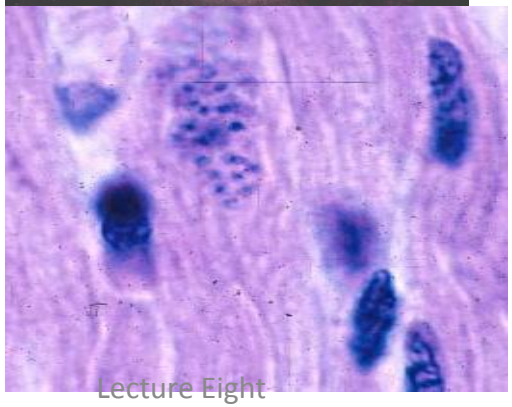


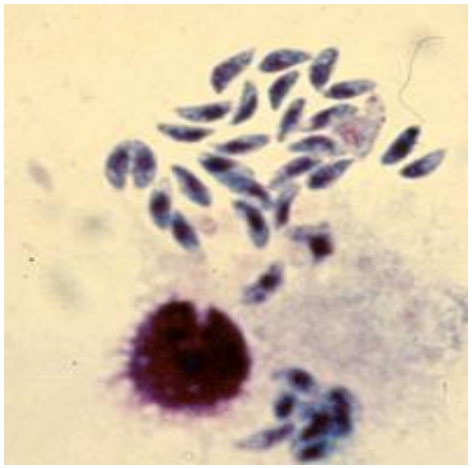
Sporulated oocyst



Bradyzoites



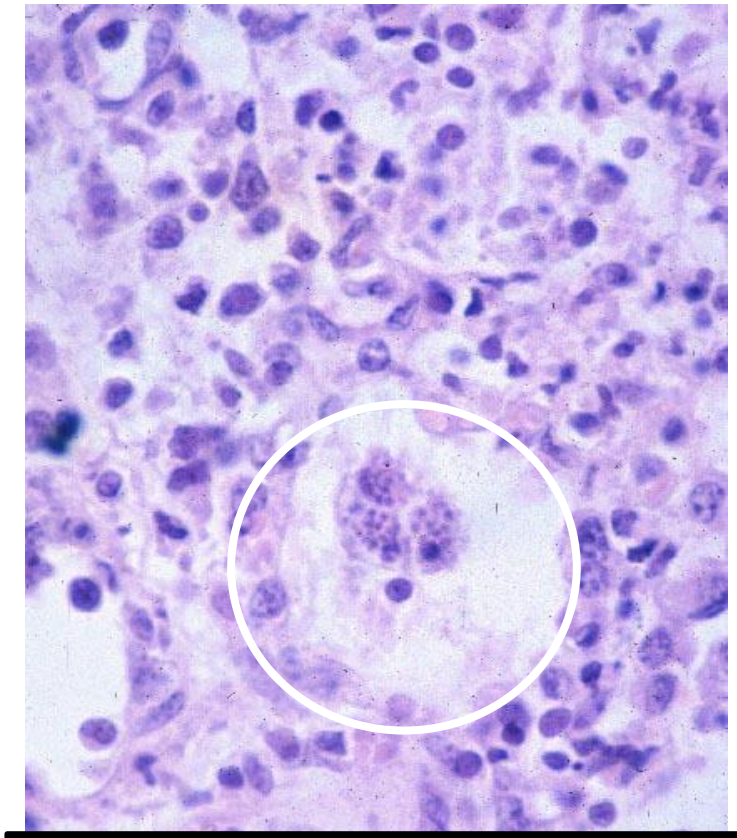


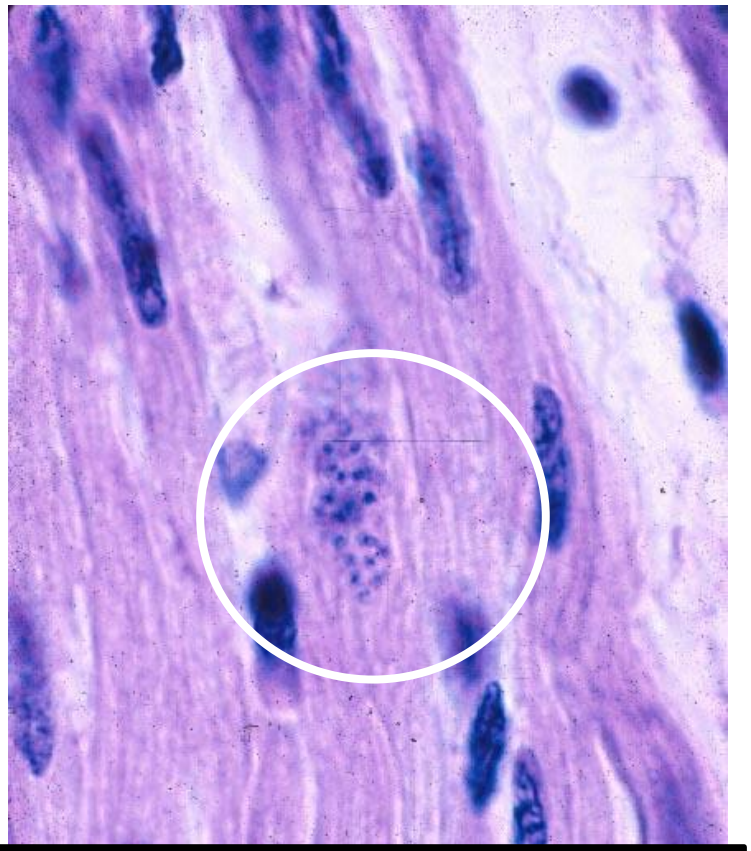


Morphologically different stages:

- **Trophozoite**: or Tachyzoite is crescent or banana shaped with a pointed end and a bluntly round end.
- In the acute stage of the disease, trophozoites are usually scattered in the blood, cerebrospinal fluid and various pathological exudates arranged in pairs or singly.
- The trophozoite community is within a host cell parasitophorous vacuole not surrounded by a cystic wall. Hence they are also known as a pseudocyst (usually a swelling macrophage with a several parasites).
- The trophozoites within a pseudocyst are Tachyzoites.

- **Tissue cyst**: is round and oval in appearance and the cystic wall created by the parasite is thin, but firm and elastic.
- The protozoa multiply in the tissue cyst slowly and repeatedly.
- The trophozoites in the cyst are called Bradyzoites, which are similar to the Tachyzoites, but smaller than them.





Tissue cysts of *Toxoplasma gondii* filled with bradyzoites

As host resistance develops, usually around 3 weeks post infection, tissue cysts may form in many organs, primarily in brain and muscle

- **Schizont:** can be found in the small intestinal mucosa of the infected cat.
- Schizonts contain about 4-40 merozoites.

- **Gametocytes** are also found in the small intestinal mucosa of the cat.
- Male gametocytes produce 12-32 male gametes, crescent in shape.
- The female gametocyte develops into a female gamete.
- Male and female gametes fertilize to form a zygote that develops into an oocyst.
- **oocyst** is round or elleptic and covered with a smooth transparent cystic wall consisting of two layers.
- Each mature oocyst contains two sporocysts with each sporocyst containing 4 sporozoites.

- Two different kinds of host are needed in the sexual and asexual generations present in the life cycle of *T. gondii*.
- Sexual development or Gametogony occurs in the epithelial cells of the small intestine of cats(intra-intestinal phase).
- The binary fission and endodyogeny (process of internal budding in which two daughter cells are formed within the body of the mother cell that dies when the progeny are released) of the asexual development takes place in various nucleated cells outside the intestine of many spp. Of mammals and birds.

Life Cycle

The life cycle of the parasite consists of 3 stages as follows

(a)Tachyzoites, the multiplying that which invade and multiply within cells,

(b)Bradyzoites,the slowly multiplying inside tisssue cysts, seen during latent and chronic infection.

(c)Sporozoites inside oocysts, which are shed in cat feces and remain in the environment.

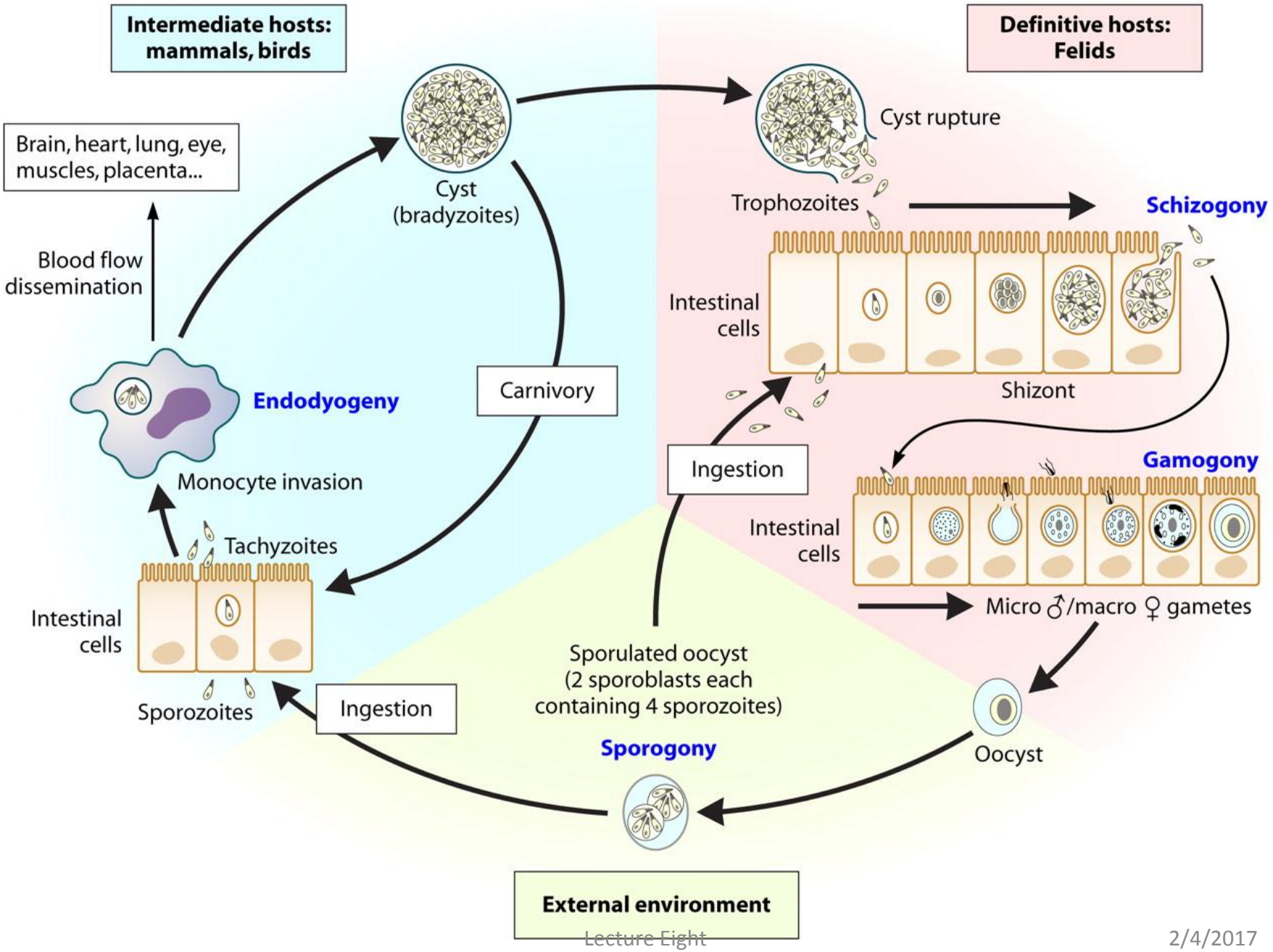
In cats, which are definitive hosts. both schizogony and gametogony takeplace in the epithelial cells of the small intestine (*enteric cycle).* Cat is infected either by ingestion of oocyst shed in its faeces or by eating flesh of other animals or birds containing tissue cysts

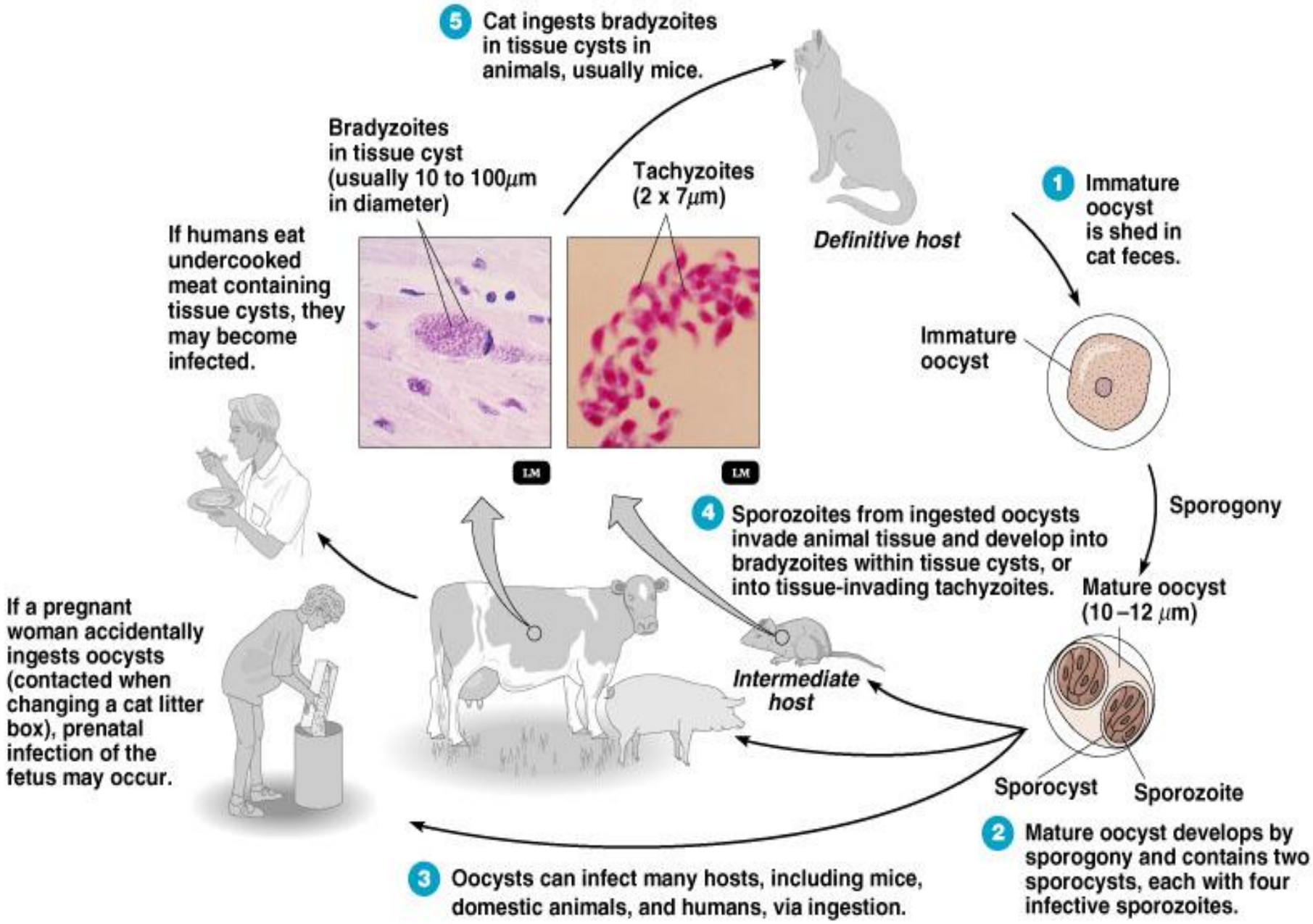
The oocysts produced by gametogony are shed in faeces. They develop into infective forms in soil or water.

When ingested by other animals, birds or human. which are intermediate hosts. The oocysts release sporozoites which infect the intestinal epithelial cells. Here, they multiply by endodyogeny to form tachyzoites. The host cell ruptures releasing numerous trophozoites which spread through blood and lymph infecting any type of nucleated cell in various tissues and organs. This is known as the *exoenteric cycle.*

Primary infection with the parasite may be asymptomatic, acute or chronic. In chronic infections tissue cysts are produced within muscles and other tissues.

- When other intermediate hosts ingest these tissue cysts, the asexual cycle is repeated. When cats ingest the tissue cysts they become infected and in them both asexual and sexual cycles are repeated
- Artificial methods of human infection are laboratory contamination, blood transfusion and organ transplantation. Congenital infection also occurs. When food or water contaminated with *T.gondii* oocyst or animal body containing cysts, pseudocyst ingested by a feline, sporozoites, bradyoites or Tachyzoites are released in the small intestine. These parasites invade the epithelial cells.


Intermediate hosts: mammals, birds
Definitive hosts: Felids
Brain, heart, lung, eye, muscles, placenta...
Cyst (bradyzoites)
Cyst rupture
Trophozoites
Schizogony
Blood flow dissemination
Intestinal cells
Shizont
Endodyogeny
Carnivory
Monocyte invasion
Ingestion
Gamogony
Tachyzoites
Intestinal cells
Micro ♂/macro ♀ gametes
Intestinal cells
Sporulated oocyst (2 sporoblasts each containing 4 sporozoites)
Sporozoites
Ingestion
Oocyst
Sporogony
External environment



Pathogenesis

- The Tacyzoites have predilection for parenchymal cells and Reticulo endothelial system and directly destroys the cells.
- Humans are relatively resistant to infection
- But low grade infection of lymph node persists
- When tissue cysts ruptures – releases number of Bradyzoites
- Local hypersensitivity reaction may cause inflammation.
- Causes blocking of blood vessels
- Causes death of cells near damaged area

Clinical Features

Most human infections are asymptomatic. Clinical toxoplasmosis may be congenital or acquired.

Congenital Toxoplasmosis

Congenital toxoplasmosis results when infection is transmitted transplacentally from mother to fetus. The risk of fetal infection rises with the progress of gestation, from 25 per cent when the mother acquires primary infection in the first trimester, to 65 per cent in the third trimester. Conversely the severity of foetal damage is highest when infection is transmitted in early pregnancy. Mothers with chronic or latent Toxoplasma infection acquired earlier do not ordinarily infect their babies, but in some women with latent or chronic infection may be to babies.

the tissue cyst may be reactivated during pregnancy and liberate trophozoites which may reach the fetus *in utero.*
Most infected newborns are asymptomatic at birth and may remain so throughout. Some develop clinical manifestations of toxoplasmosis weeks, months or even years after birth. The manifestations may be chorioretinitis, strabismus, blindness, deafness, epilepsy or mental retardation. A few are born with manifestations of acute toxoplasmosis, which may include fever, jaundice, diarrhoea, hydrocephalus, microcephaly,cerebralcalcifications,cataract,glaucoma,chori oretinitis, optic atrophy, lymphadenitis, pneumonitis, myocarditis and hepatosplenomegaly.

Acquired Toxoplasmosis

Infection acquired postnatally is mostly asymptomatic. The most common manifestation of acute acquired toxoplasmosis is lymphadenopathy, Fever, headache, myalgia and splenomegaly. The illness may resemble mild 'flu' or infectious mononucleosis lymphadenopathy may persist. In some there may be a typhus-like,with pneumonitis, myocarditis and meningoencephalitis, which may be fatal.

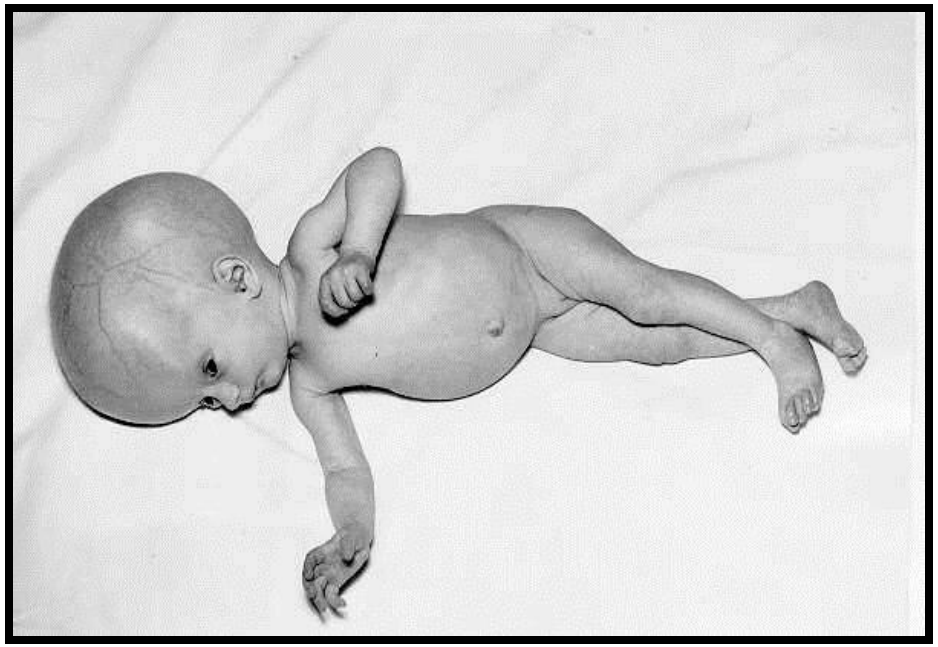
Another type of toxoplasmosis is **ocular**. Approximately 35 per cent of cases of chorioretinitis .

Toxoplasmosis primarily involving the central nervous system is usually fatal and often found in AIDS, severely in the immunodeficient, brain involvement is common.

Host defense against *Toxoplasma* infection involves both humoral and cellular responses. Specific IgG antibody can lyse extracellular trophozoites. But activated T cells and natural killer cells appear to be more important in containing the infection and preventing clinical disease.

Congenital Toxoplasmosis

1. **Intracerebral calcification.** toxoplasmic encephalitis
2. **Chorioretinitis .** Ocular toxoplasmosis
3. **Hydrocephaly.** } Congenital disease
4. **Microcephaly .** }
5. **Convulsions.**
6. **Mental retardation .**
7. **Cardiomegaly .**



Congenital toxoplasmosis is a problem in 1-5/1000 pregnancies

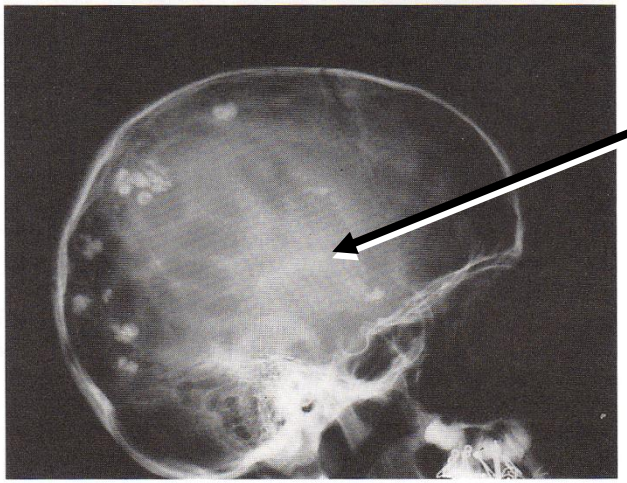


Fig. 16.10 Intracerebral calcification discovered fortuitously in a 10 year old girl, on a dental panoramic radiograph asked for by a dentist. The girl had unilateral retinochoroiditis and an IQ of 80. (Courtesy of Dr J. Couvreur).

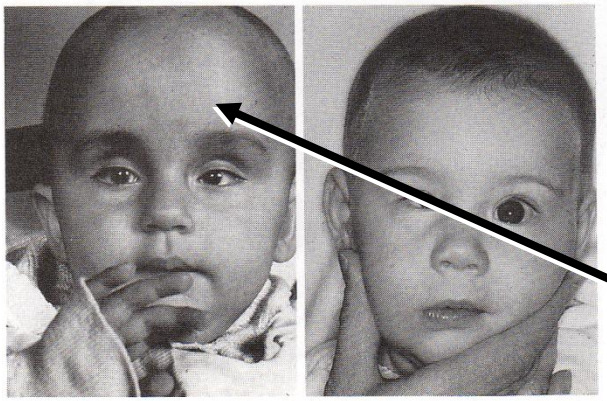


Fig. 16.9 Congenital toxoplasmosis in children. Hydrocephalus with bulging forehead (left) and microophthalmia of the left eye (right). (Courtesy of Dr J. Couvreur).

*** <u>Intracerebral calcification</u>.**

- If a woman is infected for the **first** time during pregnancy the parasite can cross the placenta and cause fetal disease.
- Both the* **probability** and **severity** of the disease depend on when the infection takes place during pregnancy.
- **<u>Early</u>:** low transmission, but severe disease
- **<u>Late</u>:** high transmission, more benign symptoms.
- **Hydrocephaly.**

Diagnosis

Laboratory diagnosis may be made by microscopic demonstration of the parasite, by its isolation or by serological tests. Giemsa stained impression smears of lymphnodes, bone marrow, spleen or brain may occasionally show the trophozoites, which can be readily identified by their morphology.

Inoculation of tissue culture and animal :

T. gondii can also be isolated by inoculation of tissue, also can be isolated by intraperitoneal inoculation of body fluids or ground tissues into young laboratory mice that are free from infection. If no death occurs, the mice are observed for about six weeks ,and tail or heart blood is then tested for specific antibody. The diagnosis is confirmed by demonstration of tissue cysts in the brain of inoculated mice.

Polymerase chain reaction :Toxoplasmal DNA can be detected in the specimens by PCR.

Skin test results showing delayed skin hypersensitivity to *Toxoplasma gondii* antigens.

Serology:

1. Sabin –Feldman dye test:

This test depends upon the appearance in 2-3 weeks of antibodies that render the membrane of laboratory –cultured living *T. gondii* impermeable to alkaline methylen blue, so that organisms are unstained in the presence of positive serum. It is one of the first methods used to diagnose toxoplasmosis. This highly sensitive and specific test is a complement – mediated neutralizing antigen –antibody reaction. It is performed in reference laboratories.

2-Latex agglutination test:

It is a simple test. It shows 94 % agreement with the dye test. The latex particles are coated with inactivated *T. gondii* soluble antigen. This test does not require heat inactivation of serum samples.

3 – Other tests :

The most common method of laboratory diagnosis is by serology. Several serological tests are available. Indirect immunofluorescence, indirect haemagglutination, complement fixation ,ELISA.

The standard test used now is ELISA, separately for IgM and IgG antibodies. The presence of IgM antibody in the absence of IgG denotes current infection, IgM antibody with high titre IgG suggests infection in the recent past; Negative IgM with positive IgG indicates past infection. This is subject to individual variation.

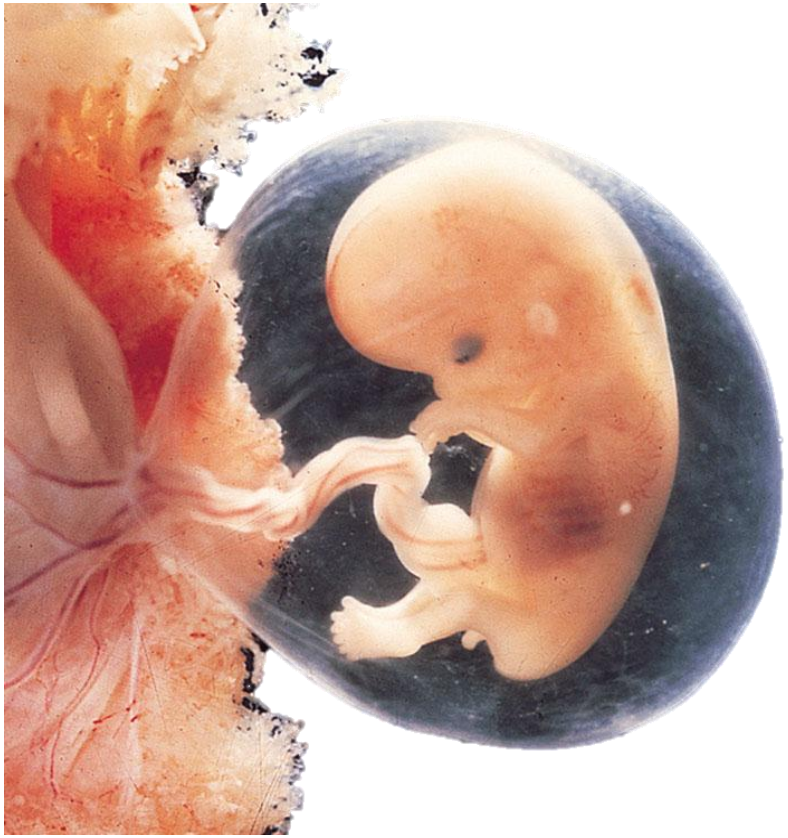
In some cases IgM antibody may persist up to 18 months. Serial ELISA provides better information than a single test.

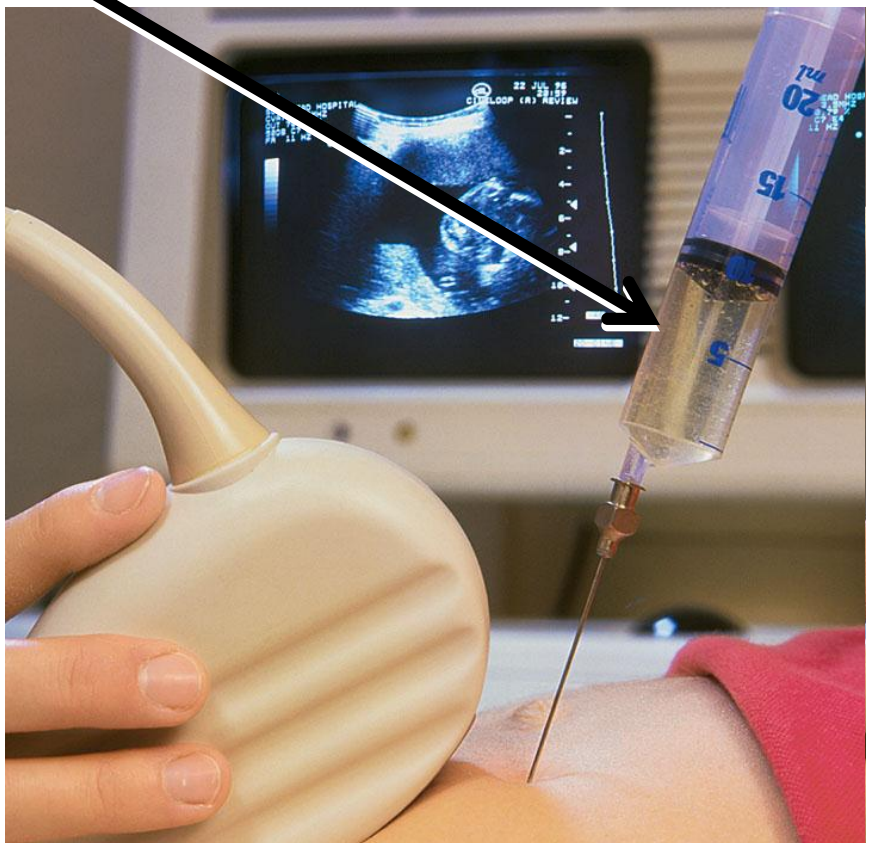
Diagnosis of congenital toxoplasmosis can be established by:

- PCR: PCR of the amniotic fluid to detect the B1 gene of the parasite.
- Serology: The presence of IgM (which dose not cross the placenta) in the infant's circulation is diagnostic but often this is not found . Specific IgG in the infant's circulation may be maternal origin or due to infection. Testing of infant's blood at 2 monthly intervals will show whether the IgG antibody level is decreasing . At 6- 10 months the infant's circulation should not contain maternal IgG and therefore persistence of IgG beyond this time is indicative of infection in the infant.

Amniocentesis

- Done around 16th week of pregnancy
- A long needle is inserted into the Amniotic sac and amniotic fluid is drawn.





Treatment

- Combination of Pyramethamine and Sulphadiazine or Trisulfapyramidines
- Other alternative Drugs

Spiramycin

Clindamycin

Trimethoprim – Sulphmethoxazole

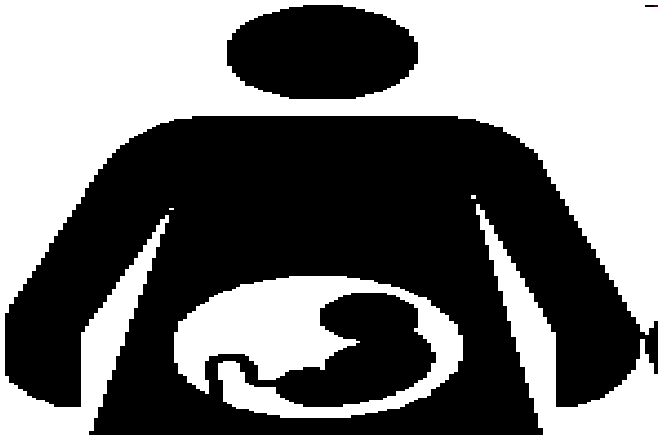
In pregnancy – Spriamycin is recommended drug

Control of Toxoplasmosis

- **Avoidance of human contact with Cat feces is highly important measure.**
- **Changing of Cat litter and safe disposal can prevent transmission**
- **Pregnant women should avoid contact with kittens**

Screening of pregnant women

- Periodic screening of pregnant women with high risk for IgG and IgM antibodies to Toxoplasmosis is recommended



Care of the Meat

- Avoid eating raw or undercooked meat.
- Freezing < -20^{0}c
- Heating at 50^{0}c for 4-6 minutes destroys the cysts and sterilizes the meat.