Toxoplasmosis
By Amanda Baugh

Toxoplasmosis
Etiological agent: protozoan parasite *Toxoplasma gondii* (1).
Domain: Eukaryota
  (unranked): Sar
  (unranked): Alveolata
Phylum: Apicomplexa
Class: Conoidasida
Order: Eucoccidiorida
Family: Sarcocystidae
Subfamily: Toxoplasmatinae
Genus: Toxoplasma (7).

Toxoplasma is an obligate intracellular pathogen. Intracellular parasites have polarized cell structures, an organellar arrangement at their apical end that contain a number of regulated secretory organelles and a complex cytoskeleton. The secretory organelles include the apical micronemes and rhoptries and the more localized dense granules. Proteins contained in these compartments each have a function consistent with the timing of their release. The micronemes are released during the attachment-invasion process, the rhoptries are released throughout the invasion phase, and finally the dense granules release over the end of the invasion. The cytoskeleton is made up of a complex combination of microtubules and other macromolecular structures that provide structural integrity, direct polarized secretion, and enable *T. gondii* to glide across surfaces to access host cells. Immunoelectron microscopy of intracellular tachyzoites shows that actin has been detected in the conoid, preconoidal rings, and subpellicular microtubule. *T. gondii* has an actin-binding protein, referred to as “toxofilin”, sequesters G-actin and plays a key role in the creation and function actin filaments. The mechanoprotein, Myosin, colocalizes with the actin in the anterior portion of the parasite and along the inner membrane complex (7).
History:
In 1908, Nicolle and Manceaux in North Africa and Splendore in Brazil first described *Toxoplasma gondii*. The Greek word *toxon* meaning “bow” refers to the crescent shape of the organism. It wasn’t until 1937 that Sabin and Olitsky determined *T. gondii* to be an obligate intracellular parasite, and just two years later discovered during the autopsy of a child’s brain by Abner Wolf, determining it to have been spread congenitally (7).

Transmission:
*T. gondii* has a high virulence factor because of its capability of infecting and replicating within virtually any nucleated mammalian or avian cell. More research is also being done on the parasites ability to modify host behavior. *T. gondii* has the ability to release proteins throughout its lifecycle to increase uptake and propagation of parasite (7).

Foodborne – humans can become infected by ingesting the tissue form of the parasite in undercooked or contaminated meat (1). The rapidly multiplying forms called tachyzoites or the quiescent bradyzoites that occupy cysts in infected tissue spread to humans and to cats restarting the parasitic cycle (4).

Zoonotic (animal-to-human) – Cats become infected by ingesting rodents, birds or other small animals already infected by the parasite. They then pass through the cats’ stool in the microscopic oocyst form. Accidental ingestion of oocysts by touching a cat’s feces, contaminated soils, or drinking water.

Congenital (mother-to-child) – Toxoplasmosis can be passed during pregnancy from mother to child.

Rare Instance of Transmission – Organ transplant recipients of Toxoplasmosis positive organs, receiving infected blood via transfusions, or accidental inoculation by laboratory workers (1).

Reservoir:
The main reservoir for *Toxoplasma* is the domestic cat. Both wild and domestic cats can initially shed millions of oocysts in their feces for as long as 3 weeks after infection and then periodically throughout their lives (1).

General Information:
*Toxoplasma gondii* (*T. gondii*) is a single-celled parasitic organism that can infect animals and birds. (2) *Toxoplasma gondii* is an intestinal coccidia that infect domestic and wild cats as their parasitic host. Most infections are asymptomatic, but deadly disease and birth defects can occur (1). The prevalence of *Toxoplasma* is estimated to infect 22.5% of the population over 12 years of age in the United States and in some places of the world may infect up to 95% (2). Populations in Central and Southern Europe, Africa, South America and Asia may have an infection rate of more than 50%. *It is believed that the prevalence in France may be even higher due to their preference of minimally cooked and raw meat* (6). Diagnosis of toxoplasmosis is based off of examination of tissue and serologic examination. The most reliable serologic test to detect antibodies of *T. gondii* is the Sabin-Feldman dye test. Unfortunately, the test’s high cost
and the use of using living tissue are disadvantages. As another option, the indirect fluorescent antibody test (IFAT) can be utilized. The disadvantages of this test are the use of UV light needs and false-positive titers may occur (4). Although the reliability of other serological tests are not as high, there are others available such as the latex agglutination test, modified agglutination test, indirect hemagglutination test, and the enzyme-linked immunosorbent assay (ELISA). A positive result of a single serum sample only proves that the host has been infected at some point in the past. Acute acquired infections can only be detected when antibodies rise by a factor of 4 to 16 in serum taken 2 to 4 weeks from when the IgM antibody is detected. Tissue samples are dried and fixed with methyl alcohol and stained with Giemsa stain or the Romanowsky stains. Well preserved *T. gondii* organisms are crescent-shaped and become more oval as they degenerate and lose their ability to retain stain in their cytoplasm. Tachyzoites or tissue cysts can be identified using immunohistochemically staining and polymerase chain reaction (PCR). Tissue cysts are usually spherical and react strongly when periodic acid-Schiff stain come in contact with the bradyzoites. Computed tomography techniques may be one of the least invasive diagnostic tools for *T. gondii* but is only useful in the diagnosis of human cerebral toxoplasmosis (4).

Symptoms:

As stated above, most of those infected with *T. gondii* are asymptomatic. Some people may experience flu-like symptoms. Infants born to infected mothers and patients with weakened immune systems may experience more serious complications (2). Encephalitis is one of the most severe manifestations of toxoplasmosis. Symptoms of encephalitis include headache, dizziness, drowsiness, disorientation, hemiparesis, reflex delay, and convulsions. Coma and death may follow. Pneumonia, hepatitis and encephalitis due to toxoplasmosis have caused cats, dogs, and other animals with toxoplasmosis (4).
Fetuses are most at risk of contracting toxoplasmosis in the third trimester of pregnancy. However, the earlier the infection occurs during the pregnancy, the more serious the side effects. Many early infections end in stillbirth or miscarriages while babies that survive may suffer from seizures, enlarged spleens and livers, jaundice, and infections of the eyes (2).

**Life Cycle of Toxoplasmosis gondii**

![Diagram of the life cycle of Toxoplasmosis gondii](image)

After a cat has ingested meat containing Toxoplasmosis cysts, the cyst wall dissolves in the stomach and small intestines, releasing bradyzoites. Through a slow multiplying stage, the bradyzoites penetrate the epithelial cells and initiates the formation of numerous asexual generations before the gametogony. After fertilization, two walls are laid down around the zygote to form the oocyst which is excreted in the feces. The oocysts measure approximately 10X12µm and become infectious between 1 to 5 days after excretion. Each oocyst contains two sporocysts, which each contain four sporozoites, and are remarkably resistant, surviving in the soil for several months (4). Once the tachyzoites enter a new host cell they begin to multiply. This may result in microfoci of tissue necrosis, but the host usually overcomes this initial phase of infection. The parasite then enters the resting stage, forming bradyzoite clusters most commonly in the brain, liver, and muscles (4).

**Treatment/Control:**
Sulfonamides and pyrimethamine (Daraprim) are two drugs widely used to treat toxoplasmosis in humans. The mechanism of action of each medication are that they block the metabolic pathway involving p-aminobenzoic acid and the folic-folinic acid cycle, respectively. These two drugs usually are well tolerated by the patient, however, especially in immunocompromised patients sometimes thrombocytopenia, leukopenia, or both may develop. Although both drugs can be useful during the acute stage of the disease, they will not eradicate infections when a higher number of parasite multiplication has occurred. Spiramycin may be given to pregnant mothers that have been infected with toxoplasmosis. If the fetus has already contracted the disease, treatment with pyrimethamine and sulfadiazine and folic acid is recommended. Strict monitoring of the baby is recommended throughout the pregnancy and after birth (2).

Unfortunately, there is no killed vaccine currently available to help prevent congenital infections in humans or animals. Europe and New Zealand have produced a live vaccine using a nonpersistent T. gondii strain to reduce abortion in sheep (4). The CDC has targeted Toxoplasmosis as one of the Neglected Parasitic Infections along with a group of five parasitic diseases (1).

Control of T. gondii relies on ingesting properly cooked meat and food preparation, washing hands after contact with soils that may be contaminated with fecal matter and after cleaning litter boxes (1). Screening tissues for transplants and transfusions may also help to limit contaminated tissues especially for immunocompromised patients. (2).

More Information:

Toxoplasmosis gondii is most commonly associated and recognized as a risk during pregnancy. However, the American Pregnancy Association acknowledges that if you have owned cats for a while, then there is a limited chance of contracting the parasite as you have already developed an immunity to it (6).

Jaroslav Flegr is a 53-year-old evolutionary biologist in Prague that has focused much of his research of the effects T. gondii may have on their hosts during the latent stage of the parasite in the body. When Flegr first joined the biology faculty of Charles University in 1990, his new colleagues were searching for infected individuals to test improved diagnostic kits. He discovered that he himself carried the parasite, and wondered if this was possibly the connection to his self-destructive streak of behavior. He believed that T. gondii may be tweaking the connections between our neurons while in its "latent" stage, changing our responses to frightening situations, trust, extrovert/introvert behavior, and ever preference for scents. Due to these adjustments to our neural responses, he also believes he may have found a link between Toxoplasma and suicides, car crashes, and mental disorders such as schizophrenia.

Fortunately for Flegr, 30-40% of Czechs carry the latent form of the disease, allowing for many test subjects. He began with standard personality tests to see if there were any deviations within the groups. A computer-based test was also used to assess the participants’ reaction times by pressing a button as soon as a white square popped up anywhere on a dark monitor. Surprisingly, many correlations were seen between T. gondii positive subjects with delayed reaction times and many sex-specific changes within personality traits. Affected males were more introverted,
suspicious, oblivious to other's opinions of them, and included to disregard rules. Infected women presented the exact opposite way being more outgoing, trusting, image-conscious, and rule-abiding. So surprising were the results that Flegr repeated the examines with civilian and military personnel, only to have the same results. Later in his testing, Flegr suggested that infected males may have elevated testosterone levels. Women shown photos of these men rated them as more masculine that the pictures of uninfected men.

Ajai Vyas, a neurobiologist working with Robert Sapolsky at Stanford, inspected the infected rats' testicles for signs of cysts and found them there as well as the animals' semen. Thus, when the animals copulated, Vyas discovered, the protozoan was transmitted into the female's womb, typically infecting 60% of her pups before traveling up to her own brain. Sapolsky's lab also showed that T. gondii also boosted the dopamine levels in the reward processing part of the brain when the animal caught the scent of feline urine.

Joanne Webster, a parasitologist at Imperial College London, continued the research with infected rats by treating one corner of each rat's enclosure with the animal's own odor, a second with water, a third with cat urine, and the last corner with the urine of a rabbit (a non-predatory creature). Not only did the parasite not reduce the rats' aversion to feline predators, but it actually increased their attraction. She and other scientists repeated the experiment with the urine of dogs and minks, which also prey on rodents but the effect was so specific to cat urine, that “they began to call it the ‘fatal feline attraction’ (5). It is important to note that infected mice still avoid food if it smells different, an aversion that generally protects rodents from the potential for poison. The infected mice also respond appropriately to the smell of their littermates (3).

Rats and mice have been thoroughly researched with their correspondence with Toxoplasmosis. Their innate behavioral traits for self-preservation against feline predators makes them a prime subject for this reversal to fatal attraction. Spray cat urine in the corner of an enclosure, and the rat/mouse should avoid the corner. However, infected mice and rats were doing just the opposite (3). Between all of the studies that were conducted using infected and non-infected rats, all studies concluded that most of the rats appeared happy, healthy and asymptomatic of parasitic disease. Nonetheless the latent cyst forms of the disease were most abundant in the part of the brain that relates to pleasure and the amygdala, the area's that involve fear and anxiety. Parasitologist Glenn McConkey, at the University of Leeds, were probing the protozoan's genome for signs of what it might be doing and came upon a striking talent: it has two genes that allow it to crank up the production of the neurotransmitter dopamine in the host's brain. These findings meant that the parasite was creating the healthiest host, that is happy to go towards the prey needed to continue its own lifecycle (5). The parasite is now leading the cat into its own game of cat and mouse where the mouse is a happy martyr to pass on the infectious cycle.

Also following Flegr's research there were two Turkish studies replicating the linkage between T. gondii and traffic accidents. They believe because the parasite lowers the normal fear response, driver's reaction times are delayed and therefore cause more traffic accidents.

Continued tests in patients diagnosed with schizophrenia are also showing a possibility of a link between those that have contracted T. gondii. Twelve of 44 patients that were diagnosed with schizophrenia underwent MRI scans and showed reduced grey matter in the brains, almost exclusively in those who tested positive for T. gondii (5). It has been known by scientists for a long time that schizophrenic patients are two to three times more likely to carry antibodies to T. gondii than controls without the schizophrenic diagnosis. Furthermore, antipsychotic drugs that block the action of dopamine, that are commonly used to treat schizophrenic patients also have shown effective in combating toxoplasmosis in both rats and people (3)
Works Cited: