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Toxoplasmosis, a never-ending story

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Keep the cat away and serve only well-cooked meat or my husband might become jealous… This may sound a little strange and incongruous but behind it lurks the fear of a disease and its mysterious effects : toxoplasmosis. Toxoplasmosis is widely known for its high risk factor during pregnancy. And many of us associate it with our much loved pet cats. Cats do indeed occupy a central position in the transmission of toxoplasmosis and it is with reason that the illness is nicknamed "the litter disease". The pathogen is *Toxoplasma gondii* which – in order to survive – has devised a highly sophisticated strategy in conjunction with proteins that are just as efficient.

Toxoplasma gondii (*T. gondii*) is found worldwide. Depending on which continent it is rife, toxoplasmosis affects 20 to 80% of the population, which directly reflects the divergence in standards of living and eating habits. Unlike South America and Europe, the United States and Britain are little exposed to the parasite. France, on the other hand, is particularly affected. The French like their meat 'rare' and appreciate raw steak in the form of "steak tartare". The parasite survives precisely in raw or rare meat and is widely disseminated in cats' excrements.

The frailty of the fetus

T.gondii is more often than not ingested unknowingly. Occasionally, certain symptoms which hint a possible infection may develop. They are similar to those caused by the flu, i.e. a swelling of the glands, a temperature, a general feeling of tiredness, a sore throat, headaches and muscular pains. Which are all troubles that can be relieved by an antiparasitic treatment.

But it is a different matter when a pregnant woman is infected for the first time. This can be dangerous, not for the mother but for her unborn child. It is a rare occurrence, but out of 1'000 births, 1 to 3 children suffer from the after-effects of toxoplasmosis. How is the fetus infected? To understand, we must take a look at the reaction caused by the intrusion of the parasite in our organism. Once alerted, our immune system releases a myriad of proteins called antibodies. With their help, *T.gondii* is neutralized and the infection checked. And it will not get a second chance... Our organism keeps track of the first infection by stocking just enough antibodies to discourage it in the event of a second invasion. As a result, we are said to be immune to *T.gondii*.

What happens to a pregnant woman if she is exposed to the parasite? If she is already immune to it, she will have nothing to worry about. If she is not, the parasite will spread unhindered and even venture to cross the placenta. The placenta acts as a filter to protect the fetus. However, it

is not completely impermeable and can let some pathogens through, in particular *T.gondii*. The fetus' immune system is still too immature to react and as a result the repercussions on the infant's health can be severe. The risk of fetal contamination during the first months of pregnancy is small, but it increases towards the end of pregnancy as the placenta becomes more tolerant in its exchanges between mother and child. Conversely, the seriousness of the after-effects decreases as the months go by, the main reason being that the mother's antibodies are diffused into the bloodstream of the fetus after the sixth month.

Most toxoplasmosis after-effects become apparent a few months after birth only – sometimes even only in adulthood. The most common are ocular anomalies which can lead to loss of sight. Children infected in utero are liable to suffer from convulsions, hydrocephalus, calcification of the skull and mental retardation; more drastic manifestations can even be fatal to the fetus. A mother who is not immune to toxoplasmosis at the beginning of her pregnancy will have to undergo regular blood tests; if the infection is detected, antiparasitic treatment will be given taking into account the stage of her pregnancy.

Proteins to the aid of the intruder

Toxoplasma gondii was discovered in the beginning of the century, in a laboratory at the Institut Pasteur in Tunisia, following an epidemic among small rodents called *Ctenodactylus gundi*. C. Nicolle and L. Manceaux isolated a parasite giving it the name of *Toxoplasma* - from the Greek *toxon* meaning 'bow', and *plasma* meaning 'shaped' – and *gondii* in memory of the unfortunate rodents.

T.gondii is part of a large family of parasites of which *Plasmodium*, which is responsible for malaria, is a well-known member. As all the other members of the family, it is microscopic and consists of a single cell only.

Being a parasite means living on and at the expense of another organism. *T.gondii* goes a step further by squarely squatting the cells of its host. And the choice is unlimited: all mammals – humans included – as well as birds can be hosts to the parasite. Once inside an organism, *T.gondii* can invade any organ though it has a clear preference for the eyes, the brain and muscles. It then infiltrates the cells by use of an ingenious mechanism quite distinct from other pathogens. For this, it has two assets at its disposal: the adhesin proteins and MPP1.

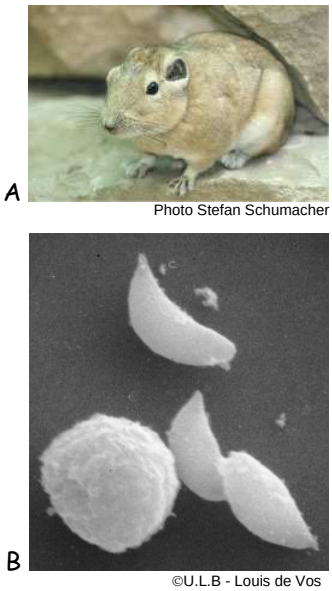

Fig.1 *A, The rodent Ctenodactylus gundii. By authorization of www.rodent-info.net. B, T.gondii and an immune cell. Size of parasite: 5-10µm x 3-4µm (1um = 0,001mm)*

Adhesins are "adhesive" proteins, stocked in small cavities called micronemes, which is why they have been nicknamed MICs. MICs are essential for the parasite to dock to the membrane of the cell it is about to infect. One of them – AMA1 – seems to play a decisive role in the completion of docking. Just before this protein is required, it is transferred from a vesicle onto the parasite's membrane where it is attached by way of a segment. It is still not known on which molecule AMA1 comes to rest in order to reinforce the adhesion. Nevertheless, this protein has aroused a great deal of interest among scientists for quite some time: it could be at the root of an anti-malarial vaccine since AMA1 is also present in Plasmodium. Such a vaccine would stimulate anti-AMA1 antibodies which would place themselves between the parasite and the cell to be invaded - in this case red blood cells. Preliminary experiments have been encouraging.

Once docked to the cell's surface, *T.gondii* injects various lipid compounds and proteins that contribute to form an envelope, which blows up like a balloon and takes in the contents of the parasite. *T.gondii* then marshals its second proteic asset: MPP1, which remains on the parasite's surface and whose chain of amino acids penetrates the membrane at least six times in succession. MPP1 is a protease, i.e. it severs proteins. Its position on the membrane keeps it in the vicinity of both AMA1 and the other adhesins. This is no coincidence since it has to sever the segment attaching the "adhesive" proteins to the parasite's membrane. As a consequence, the

docking sites are released. The parasite is then freed and can float in the cell unhindered. Its new envelope protects it from any cellular mechanism put forward to combat an unwanted host. And from then on the importunate microorganism is free to multiply and proliferate.

What cats do

Besides intruding cells, *T.gondii* travels from one animal to another - regardless of whether it is a mammal or a bird - until it comes across a cat or, more generally, an individual of the feline species.

The stage in the cat's system is essential for the parasite's reproductive cycle; humans and other animals are only intermediaries. Approximately 50% of the cat population is a carrier, but only 1% is contagious. And yet it is in cats that *T.gondii* is most active, since it is in their intestines that they unite to produce eggs. Each egg will produce and later harbor many parasites. The eggs are then literally "laid" by the million in cats' excrements in a period of one to two weeks. And since their 'skin' is extremely tough, they can survive for months in the environment.

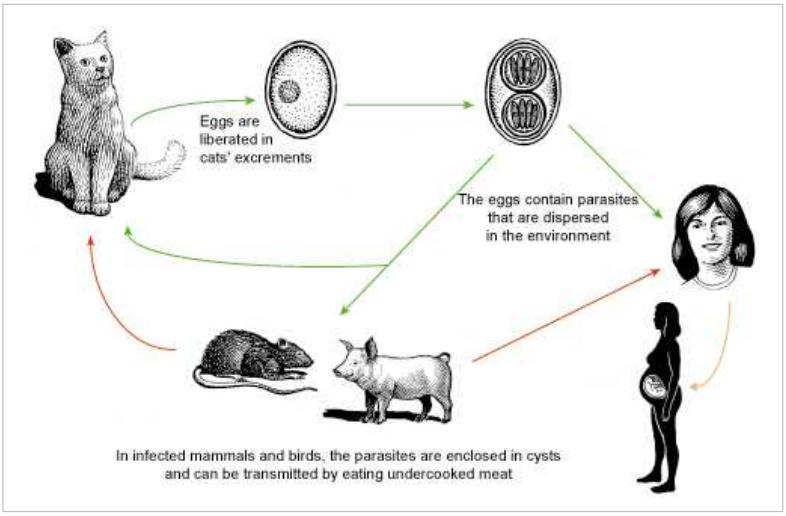

Fig.2 *The transmission of Toxoplasma gondii*

The eggs are not only scattered in the cat's bedding but also in soil and water, where they will inevitably be ingested by other animals such as rats, pigs, sheep, and even humans. The eggs hatch in the digestive system thereby liberating the parasites which then penetrate into the host's cells where they speedily proliferate. This phase – during which the cells burst and spill out parasites – lasts about ten days. The immune system reacts accordingly, but the result is double-edged: it checks the infection but favors the metamorphosis of *T.gondii* into a slow proliferating form. This form takes refuge in cysts within the cells and in so doing successfully hides from the immune system. Tucked away in the brain, eyes or muscles especially, *T.gondii* "hibernates" so to speak until better times.

How are cats infected in the first place? Like other hosts, they can swallow *T.gondii* eggs that have been excreted by other cats. Cats are also carnivores, and enjoy a rat or a bird for a juicy meal…raw naturally… And so we have come round in a full circle. The cysts burst, release the parasites into the cats' intestines and the cycle continues *ad vitam aeternam*.

The reason *T.gondii* favors cats is that it can produce its eggs in their system. To what end? Eggs are the result of a fusion of two individuals, and hence the mingling of two genotypes, which is crucial for the survival of the species.

A parasite for life

In the animal world, *T.gondii* is propagated by the accidental absorption of eggs scattered on the ground, on fruit or on vegetables, or by eating undercooked meat that contains cysts. It is an effective method of transmission since the eggs survive over a long period. *T.gondii* cysts are even more hardy, and can last for years – even as long as the host itself without bringing on any symptoms of infection. The infection – or toxoplasmosis – is what is termed latent.

If the parasite remains attached and hidden in an organ, it is under the control of the immune

system. What happens if the system fails? At the least sign of immune weakness, *T.gondii* is aroused from its dormant state and propagates rapidly in the organism. It is the start of a new acute infection and can be a real risk for some patients. Such is the case for those who have had an organ transplant, which is infected, or who are themselves carriers of cysts. Why? After a transplant, patients are treated with immunodepressive drugs that reduce the immune system's action, the object being to avoid any rejection of the foreign organ, but it also opens the way to parasites. In the same manner, patients with AIDS – acquired immunodeficiency syndrome – are extremely exposed to toxoplasmosis since their immune system deteriorates progressively. Infection of the brain in immunodepressive patients is frequent, and they frequently suffer from severe headaches, mental confusion or lethargy. The infection can cause a coma and fatal encephalitis[1]. In Europe, it is estimated that 30% of AIDS patients succumb to toxoplasmosis. Unfortunately, to date there is no way of checking the transition from cysts to active parasites, nor eliminating the cysts in order to spare patients the terrible consequences of a reactivation of toxoplasmosis.

Manipulation as a strategy

Besides the tragic cases of immunodepressive patients and fetuses, *T.gondii* is almost no threat to the health of its many hosts. However, it may influence the behavior of infected animals – a trick that hides a very subtle stratagem. Experiments carried out on rats and cats have given astonishing results. For small animals like rats, it is vital to detect the presence of a predator such as a cat. A cat's smell is sufficient for them to run for their lives and keep their distance. It so happens that rats that are carriers of *T.gondii* are oblivious to their predators – they trespass fearlessly onto the cat's territory, thus making an easy prey. Some of them even show a fatal attraction for cats! Incongruous though it may seem, such a behavior is all to the advantage of the parasite since it must get to a cat to reproduce and thus ensure the survival of its species.

T.gondii is not the only manipulative parasite. The worm *Euhaplorchis californiensis* infects the cranium of the seafish *Fundulus parvipennis*, for example. As a result, the fish swim to the surface of the water, leaping in and out of the sea and making a perfect prey for the sea birds. Infected fish are 30 times more likely to be snatched than healthy ones! *Dicrocoelium dendriticum* – another worm also known as the liver fluke – infects an ant's nervous system. As a consequence, the insects climb to the tip of a blade of grass and calmly wait to be devoured by a passing herbivore. The secret here is that *D.dendriticum* favors vegetarian animals for its reproduction in the same way that *T.gondii* seeks out cats…

And what of human beings? Experiments carried out on animals infected by *T.gondii* give an alarming insight into the parasite's stratagem for survival. It also gives a hint as to the mechanisms underlying changes in behavior. Indeed, *T.gondii* modifies the number of certain neurotransmittors[2], in particular of dopamine. What influence could this parasite have on human behavior, where dopamine variations are associated with neuronal disturbances? Though rare, it has been shown that certain patients suffer from hallucinations and various psychiatric symptoms that are very similar to schizophrenia. What is more, several studies have revealed that patients diagnosed as schizophrenic were also carriers of the parasite. Just as interesting are the observations that drugs used in the treatment of schizophrenia slow down the proliferation of *T.gondii*, and that toxoplasmosis worsens the state of schizophrenic patients.

Could toxoplasmosis be at the root of certain forms of schizophrenia? Undoubtedly, there seems to be a parallel between toxoplasmosis and schizophrenia, but the exact role of *T.gondii* in the causes of the psychiatric illness is yet to be defined. Cases of toxoplasmosis related to schizophrenia remain exceptional. In general, behavioral changes seem to be discrete. A few psychological studies have revealed that *T.gondii* carriers seem to suffer from a more pronounced lack of self-confidence than normal. Women tend to become more friendly and sociable, whereas men tend to become distrustful and jealous. And these distortions in personality intensify with time. These are unsettling findings which deserve to be studied more closely but they do raise the question of the role parasites play in our behavior. If behavioral changes in some animals are clearly to the parasites' advantage, to what extent could these microorganisms influence our personality? Could we be manipulated by parasites that "squat" our organism? It is mind-shattering to imagine the possible psychological impact – even social and cultural – that these miniature creatures could have on us... Enough to unbridle the most fertile imagination...

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*Translation: Geneviève Baillie

[1] Inflammation of the brain.

[2] Neurotransmittors are molecules which ensure communication between neurons.

For further information

On the Internet (in French):

- Symptoms, treatment and prevention: http://www.mediresource.com/sdm/sdm/french/disease_detail.asp?disease_id=130
- Toxoplasmosis: http://www.chambon.ac-versailles.fr/science/sante/immu/toxopl.htm
- Security at work: http://www.cchst.ca/reponsessst/diseases/toxoplasmosis.html

A little more advanced:

- About the toxoplasmosis: http://en.wikipedia.org/wiki/Toxoplasmosis

Illustrations:

- Fig.1 B, Adaptation : http://www.ulb.ac.be/sciences/biodic/
- Fig.2, Adaptation : http://www.omafra.gov.on.ca/english/livestock/swine/facts/04-055.htm

At UniProtKB/Swiss-Prot:

- Apical membrane antigen 1 homolog (AMA1), Toxoplasma gondii : O15681 (under annotation)
- Rhomboid-like protease 5 (MPP1), Toxoplasma gondii : Q6GV23

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