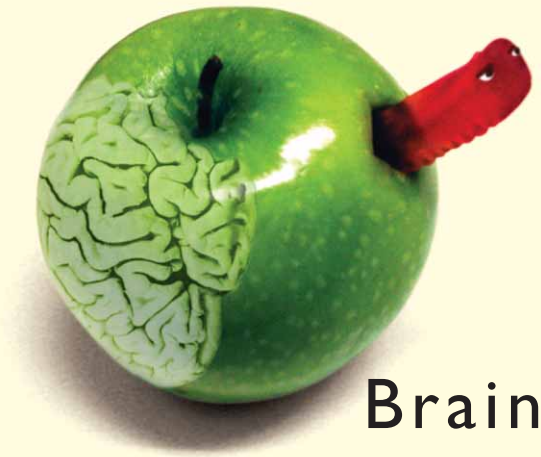


Brain Worms and Brain Amoebas: They Do Exist

by Andrea Manzo

The E&S *staff have selected this article from those written for the Core 1 Science Writing course, which is a requirement for all undergraduates so that they can gain experience in communicating science to the general public.*

Parasites in the Brain?

At a recent evening lecture at the California Institute of Technology, a neurologist was explaining the ins and outs of new brain-imaging technology to an audience composed of Caltech professors, students, and members of the general public. The audience was rather quiet, lulled by the technical tone of the lecture. But when the neurologist mentioned in passing that the disease afflicting one of his patients was caused by a brain parasite, the whole room sat up and made a collective noise of disgust and alarm. *Brain* parasites!

But, in fact, parasites infect us all the time. They live in our bodies, even in our cells, and most of the time we do not even know that they are there. The brain can provide a pleasant, nurturing environment for parasites, because it has structures that prevent many of the immune system's cells from entering, at least in the early stages of infection. Add to that plenty of oxygen and nutrients, and the brain seems like a rather nice place to live.

Despite its seemingly idyllic home, a brain parasite's life does have its hardships. To begin with, the parasite has to find a way into the brain. Invasion of any organ is difficult, but the brain is an especially tough nut to crack due to a protective barrier between the bloodstream and brain fluid, called the blood-brain barrier. This barrier is made up of cells that make a tight seal along any blood vessels so that most stuff from the bloodstream (including brain parasites) can't leak into the brain. If the parasite does manage to successfully enter the brain, it then has to deal with the attack of the immune system. The cells of the immune system act together to rid the body of any foreign organisms. In humans, the immune system is highly organized and efficient; parasites' evasion mechanisms have evolved to be good enough to thwart the immune system, at least for a little while. Unfortunately, the most effective parasites are the ones we really have to worry about.

In fact, millions of people worldwide are infected by these efficacious brain parasites. If you haven't heard about them before, it is probably because most infected people live in nonindustrialized countries, where living conditions are not very sanitary. Many of these brain parasites cause debilitating conditions and sometimes even death. So, in addition to being interesting biologically, brain parasites are also important in the context of human disease.

Two parasites with disease-causing capabilities are the pork tapeworm, *Taenia solium*, and the amoeba *Naegleria fowleri*. In addition to their medical importance, these two organisms illustrate the many ways that brain parasites are able to affect their hosts through their methods of invasion and survival.

Tapeworm: From Pork Chops to the Brain

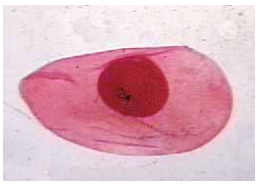
The pork tapeworm is one of the most common disease-causing brain parasites. This parasite infects over 50 million people worldwide, and is the leading cause of brain seizures. It is usually contracted from eating undercooked pork, and once in the gut, it attaches to the intestine, and then grows to be several feet long. Under certain circumstances, these worms can also invade the brain, where thankfully they don't grow to be quite so large.

Why does the worm sometimes attach to the intestine but at other times travel to the brain? It all depends on what stage of its life cycle the worm is in when it is swallowed. In its larval stage, the worm will hook onto the intestine; however, if eggs are swallowed, they hatch in the stomach. From there the larvae can enter the bloodstream and eventually travel to the brain. But in order to reach the brain from the bloodstream, the larvae must traverse the blood-brain

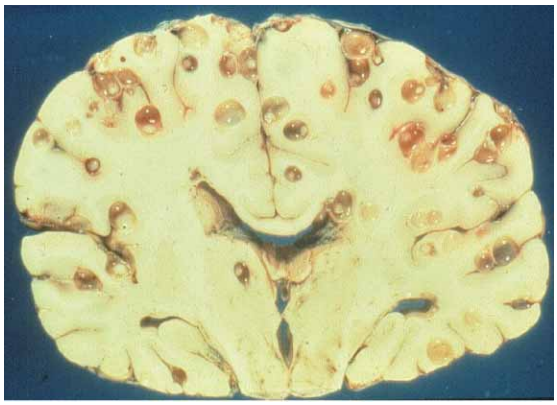
barrier. Unfortunately, researchers still don't know exactly how this happens. Many scientists think that the larvae can release enzymes that are able to dissolve a small portion of the blood-brain barrier to allow the parasite to get through into the brain.

Once the larvae reach the brain, they cause a disease called neurocysticercosis, by attaching to either the brain tissue itself, or to cavities through which brain fluid flows. (Brain fluid carries nutrients and waste to and from the brain, and acts as a cushion to protect the brain against physical impact.) Once attached, the larvae develop into cyst-like structures. The location of the cysts determines the symptoms exhibited by the host. If the larvae attach to the brain tissue, then the host often experiences seizures. This occurs partly because the presence of the larvae causes the activity of the brain to become wild and uncontrolled, thereby causing a seizure. On the other hand, if the larvae attach to the brain-fluid cavities, the host experiences headaches, nausea, dizziness, and altered mental states in addition to seizures. These additional symptoms occur because the flow of the brain fluid is blocked by the larvae. Often, the presence of the larvae also causes the lining of the brain-fluid cavities to become inflamed, further constricting the flow of the brain fluid. Since the cavities are a closed system, blockage of the cavities exerts pressure on the brain. This increased cranial pressure forces the heart to pump harder in order to deliver blood to the brain area, increasing the pressure on the brain even more. If the condition is not treated, the heart eventually cannot pump enough blood to the brain, neurons begin to die off, and major brain damage occurs.

It is interesting to note that some of these symptoms, such as seizures, are caused not only by the presence of the brain parasites, but also by the immune system. In general, parasites do not want to be detected by the immune system, because then they will most likely be eaten and killed. They try to do everything they can to avoid eliciting a strong immune response. Parasites also don't want to do anything that can kill the host. If the host dies, then the parasites die too. For this reason, people can have parasites for years and not show any symptoms at all. But then, as the larval defenses break down, the host immune system is able to have a greater effect, and the symptoms become more obvious. What does the host immune system do to defend against the parasites, and why do its actions elicit harmful effects on its own body?

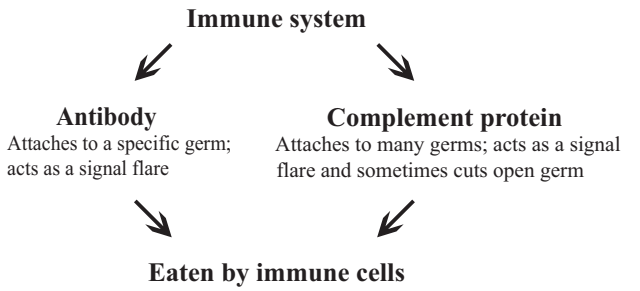


Left: A pork tapeworm (*Taenia solium*) cysticercus, the form in which the tapeworm is found in an infected brain. (Colorized image by P. W. Pappas and S. M. Wardrop, courtesy of P. W. Pappas, Ohio State University.)
Below: *T. solium* cysticerci in the brain of a nine-year-old girl who died during cerebrospinal fluid extraction to diagnose her headaches. This was in the 1970s—if it had happened 10 years later, noninvasive computerized tomography would have given an accurate diagnosis, and the parasites could have been killed with drugs. (Image courtesy of Dr. Ana Flisser, National Autonomous University of Mexico.)



Defending the Body from Invaders

The main function of the immune system is to make sure that any foreign object in the body is destroyed, including brain parasites. Many of the symptoms arising from brain parasite infection are due to the interactions between the immune system and the parasite. There are two main methods by which the immune system tries to rid the brain of the parasite. First, certain cells of the immune system make antibodies specifically against the parasite. Antibodies are molecules that can attach to a foreign organism and act like a signal flare, telling the rest of the immune cells that this organism is foreign and should be destroyed. There are also other immune cells, called phagocytes, which travel around the body eating anything that isn't recognized as belonging to that body. These cells are much more effective at destroying germs that are labeled by antibodies.



Second, there are proteins in the body that are able to recognize some general characteristics of many germs. These proteins make up the complement system. The complement proteins are able to attach to the germ and also act as signal flares to attract other immune cells that can destroy the germ. However, these proteins are sometimes also able to kill the germ themselves by forming a structure on the surface that can cut the germ open.

Why the Immune System Can't "See" Tapeworm Cysts

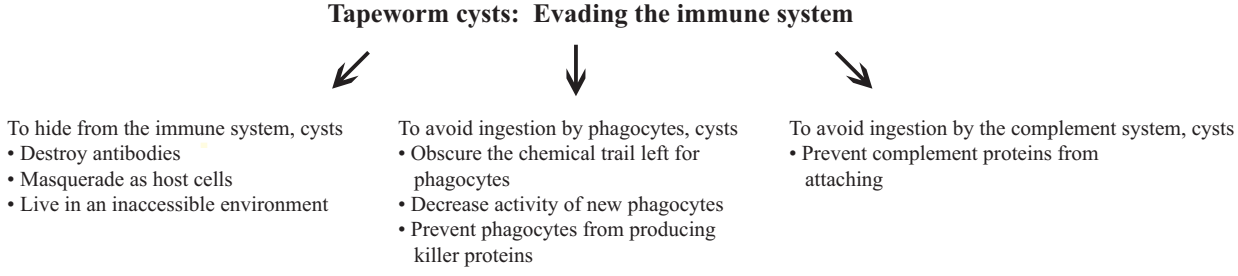
The interaction between the immune system and the cysts is quite amazing; it is a great example of how evolution can produce two complementary systems. The immune system is seeking to find and destroy the parasite, while the parasite is attempting to stay hidden and alive. One way that the cysts are able to "hide" from the immune system is by degrading the antibodies that attach to them. There is some evidence that the antibodies are used as a food source, and that the cysts are able to coax the immune system to make more antibodies. The cysts can even disguise themselves as part of the host's body by displaying proteins on their surfaces that identify them as part of the host—much as Wile E. Coyote hides from Sam Sheepdog in a herd of sheep by wearing a sheepskin. Finally, the location of the cysts is itself conducive to escaping detection by the immune system. The brain is not easily accessible to the cells of the immune system due to the presence of the blood-brain barrier, and so the parasites are partially protected from random encounters with the body's defenders. Only when the immune response is in full swing can the immune cells enter the brain in large numbers.

Besides hiding from the immune system, the tapeworm parasites are able to prevent the immune cells from killing them by using several strategies. For instance, the parasites are able to prevent the complement proteins from attaching to their surfaces. The tapeworms can even release molecules that act as decoys, tricking the killer proteins into leaving them alone. The cysts also release other proteins that are able to protect them from being eaten, although how exactly this is accomplished is still unknown. There is some evidence that these proteins are able to prevent phagocytes from accurately targeting the cysts. One of the ways that phagocytes are able to go to the right place in the body during an infection is by following a chemical trail. This trail is produced by other immune cells at the site of infection. Some of the proteins released by the cysts are able to obscure this chemical trail so that the phagocytes become lost on their way to the infection. Cysts are also thought to release a second set of proteins that decreases the activity of new phagocytes. These proteins affect another group of immune cells that control the activity of new phagocytes; these regulatory immune cells then decrease the number of active phagocytes. Finally, a third set of proteins released by the cysts is thought to be able to prevent phagocytes from producing the proteins necessary to kill the cysts.

Victory?

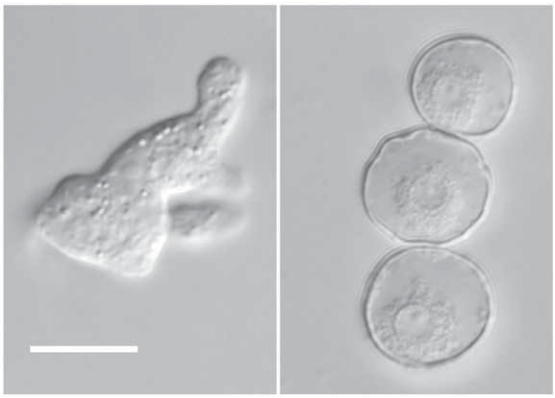
The cysts are very successful in evading the immune system, but they gradually become more and more vulnerable to attack. As the immune system response gains strength, the most common symptoms of infection become more and more obvious. At first, the parasites are simply unable to hide from the immune cells, and cannot pretend to be part of the host's body anymore. Then the full immune system response kicks in, and because the immune cells are able to detect the parasites, the parasites are doomed. More antibodies and complement proteins are released, more phagocytes are born, and more blood and immune cells rush to the parasitic sites. The areas where the

At top: The two main pathways of the immune system response. Below: How tapeworm cysts evade the immune response.



parasites are located become swollen, which often leads to seizures and compression of the surrounding brain tissue. As the response progresses, the cysts are replaced by scar tissue, and finally by calcium deposits. (Calcium deposition often occurs in the body due to the activity of bacteria living in the blood, rather than as a direct effect of the immune system's response.) The scar tissue and calcium deposits are also known to cause seizures. In addition, the immune response causes irreparable brain damage to the areas of the brain around the cyst as the phagocytes ingest the cells surrounding the cysts, which also contributes to the seizures.

In fact, more harm than good often comes out of the immune response to infection of the brain by tapeworms. Against most pathogens, however, the immune response is actually beneficial to the body.



***Naegleria fowleri* in the amoeboid form, near right, and in the cyst form, far right. The scale bar is 10 micrometers. Images courtesy of Bret Robinson, Australian Water Quality Centre and CRC for Water Quality Research.**

Foreign organisms often cause lots of damage, and it is important that they be destroyed as quickly and efficiently as possible. Furthermore, the immune system response is generally the same regardless of the identity of the foreign invader; and in most circumstances, the immune response does not have negative effects. Overall, the immune system is actually highly effective at defending the body from foreign organisms.

Of course, the effectiveness of the immune system is largely dependent on the ability of the body to mobilize its defenses. Some parasites act so quickly that the immune system is unable to react before the infection becomes fatal. One such brain parasite is *Naegleria fowleri*, a water-borne amoeba.

Danger in the Waters

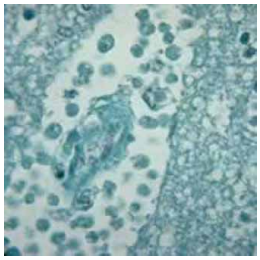
If you've never heard of *Naegleria fowleri*, don't be surprised. Unlike the pork tapeworm, *N. fowleri* has only infected about 175 people in the world, causing a disease called primary amoebic meningocephalitis. But out of those 175 people, only six have survived, giving a mortality rate of 97 percent. For this reason, it is quite an important parasite to study, as there are no current treatments that have proven effective against it.

Fortunately, natural infection by the parasite is very rare, although *N. fowleri* is ubiquitous in the wild. It lives mostly in warm freshwater lakes and ponds, but can even thrive in heated swimming pools. Furthermore, *N. fowleri* is actually a free-living organism, which means that it can survive without a host. This explains why *N. fowleri* attacks are so rapidly fatal—since hosts are not necessary to its survival, the parasite does not have to take pains to avoid killing them.

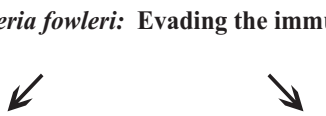
Part of the reason that *N. fowleri* can survive in such numbers and in so many different places is because it is an amoeba. Amoebas are single-celled creatures that resemble sacks of fluid gelatin surrounded by a greasy membrane. Because of their small size and few requisites for survival, these organisms are found everywhere. In addition, the amoebas can form cysts in harsh conditions like extreme cold; in this form, they are protected against the environment.

Attack of the Amoebas

When an amoeba invades a person, it is normally in its active, reproductive phase. Invasion occurs when the amoeba attaches to the inside of its host's nose and then travels up the nose to the brain. The amoeba follows the path laid out by the olfactory nerve, although sometimes it can also use the bloodstream. Several enzymes released by the amoeba are able to dissolve the host's tissues, giving access to the brain. Once in the brain, the amoeba causes damage by actually eating the nerve cells. As you can imagine, this is very harmful to the host, and is the main reason why infection by *N. fowleri* causes such rapid death. The amoeba is able to eat neurons because it has surface proteins that allow it to cut a hole in the covering of the cell. The contents of the neuron leak out, and the



Brain tissue infected by *Naegleria fowleri*. The dark dots are the amoebas. Notice the empty space around the dots; this space used to be tissue before the amoebas digested it. Image provided by the Division of Parasitic Diseases, Centers for Disease Control and Prevention.



How *Naegleria fowleri* amoebas evade the immune system.

amoeba can feed on the nutrients it contains. The amoeba even has proteins on its surface that tell it where the best food sources are. These proteins are able to sense the presence of certain nutrients, and then send signals to the rest of the cell indicating in which direction the amoeba should move to eat those nutrients. Finally, there are other proteins on the amoeba's surface that direct it to the most vulnerable areas of a neuron.

In addition to causing direct brain damage by ingesting neurons, the presence of *N. fowleri* amoebas can cause inflammation of the brain-fluid cavity linings. Similarly to infection by tapeworm, blocking the brain fluid can cause increased pressure on the brain. However, this effect is usually only secondary to the much more destructive digesting action of the amoebas.

Fighting the Invader

The immune system, however, is not completely idle while this invasion and destruction is occurring, although for the most part its efforts are in vain. The amoebas use several strategies to stave off the immune cells. Many of these strategies are similar to those used by tapeworm cysts. For example, the amoebas are able to internalize antibodies on their surfaces, although they don't need these antibodies as a food source. Other proteins on the amoeba's surface prevent the attachment of complement proteins. If the complement proteins are able to bypass these surface proteins, the amoeba is able to collect them in one area of its membrane. Afterwards, the amoeba can shed that piece of the membrane. The shed membrane acts as a decoy, attracting more complement proteins that would otherwise attack the amoeba.

Why are these strategies effective in shielding the amoebas, but not tapeworms, from the immune system? The reason is that an amoebal infection is rapidly fatal. The immune system does not have time to fully mobilize its immune cell armies before the brain damage is so extreme that the organism dies. Since these amoebas don't need the host to survive, it's not a big deal if they kill him or her off. Tapeworms, however, die when the host does, and so they try very hard to keep from being detected by the immune system. And in fact, they do a fairly good job at that, since most tapeworm infections aren't noticeable until many years after the tapeworms get into the brain. The immune system is only able to have a big effect on the infection when the tapeworms start to die, often from old age.

Parasite Evolution

These two parasites offer only an inkling of the many organisms that can infect the human brain. While the two seem to differ greatly, the molecular weapons they use for defense and invasion are really very similar. For instance, there is evidence that both parasites use enzymes to penetrate the blood-brain barrier, and both use a decoy strategy to deflect the attention of the immune system. This similarity results from evolution, which has slowly altered these parasites so that they are as effective as possible at survival. As new treatments and cures of brain-parasite-related diseases become available, it will be interesting (as well as medically useful) to see how the strategies of these parasites change. □

Andrea Manzo is a senior majoring in biology. She decided to find out more about brain parasites after attending the 2002 Biology Forum, "Gray Matters: Perception, Intention, Memory, and Dysfunction in the Brain," but is currently doing a research project on neural-crest cell development in chick embryos, a subject with a much lower yuk factor, in the lab of Ruddock Professor of Biology Marianne Bronner-Fraser. Andrea is also house secretary and webmaster of Ricketts. Her faculty mentor on the Core 1 paper was Jed Buchwald, the Dreyfuss Professor of History (see page 20), and the editor was Gillian Pierce.

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