Transmission of T. gondii

Although *Toxoplasma gondii*, the protozoan parasite that causes toxoplasmosis, was identified in 1908, it took more than half a century to identify felines as its primary host. By 1959 it was alleged that "dogs and cats have been most frequently suspected"[1] but it was the work of William Hutchinson in the 1960s that convincingly demonstrated the importance of oocysts shed in cat feces in the transmission of *T. gondii*[2-3] This was followed in 1969 by Gordon Wallace's report showing an absence of *T. gondii* on remote Pacific islands where there were no cats.[4] Therefore, in 1971, the United States Public Health Service recommended that pregnant women should avoid contact with cat feces to avoid becoming infected.

T. gondii can be acquired by humans in several different ways. It may be transmitted as a tissue cyst, usually by eating undercooked meat from an infected animal, or as an **oocyst**.

Ingestion of Tissue cysts

The infection of mammals with *T. gondii* is widespread. Such infections occur when farm animals ingest feed containing cat feces; when grazing animals inhale or ingest dried cat feces deposited on the ground; and when an animal eats a smaller animal, such as a mouse or rat that is infected. *T. gondii* then invades many parts of the body, especially muscles, where it becomes tissue cysts and remains for life. When the muscle is eaten as meat, especially if it has not been thoroughly cooked, the person becomes infected.

Lamb and pork are thought to be the most common source of *T. gondii* tissue cysts for humans, although cysts also occur in beef, chicken, and wild animal meat (e.g., deer, moose, bear). There have even been epidemics of adult toxoplasmosis among individuals who ate undercooked meat, such as hamburger, from a common source.[5]

Ingestion or Inhalation of Oocysts

As previously noted, approximately 1.5 million cats (1 percent of 150 million) in the United States are excreting oocysts on any given day; they may excrete up to 20 million oocysts per day, and the oocysts may live for a year or longer. Thus, wherever cats defecate is likely to be a source of contamination. Children's play areas and sandboxes are common places for cats to defecate because they can use the area's loose soil or sand to bury their feces. Children may become infected by **putting dirty hands, including oocysts, in their mouths**. One study of young children reported that children who are under three years of age put their hands or other objects in their mouths every 2 to 3 minutes[6] Another study, which included 64 children between one and four years old, carried out in a Massachusetts day care center reported that the children ingested a median of 40 mg of soil per day; furthermore, one child consumed 5 to 8 g of soil per day on average.[7] A family epidemic was described as having occurred this way.[8]

As the cat feces dry, the oocysts may become aerosolized. **They can thus be inhaled** by a person changing cat litter or just walking in an area where cats have defecated.[49] An outbreak of toxoplasmosis among patrons of a riding stable was thought to have occurred in this manner.[9]

Sandboxes (also called sandpits) are of special interest. Studies of sandboxes in public parks have been carried out in Japan. In one study, 12 of the 13 sandboxes were contaminated with animal feces; the "mean number of feces found in 1 square meter of the sandpits was 35"[10] In another study of three public sandboxes observed over 140 days, an average of 2.3 cat defecations occurred each day in each sandbox.[11]

Assuming that 1 percent of the cats were infected, that each infected cat excreted 10 million oocysts each time it defecated, and that the oocysts remained viable for one year, each sandbox would contain approximately 85 million viable oocysts at any given time. **For children playing in such a sandbox,** the chances of inhaling or ingesting (e.g., by putting fingers in mouth) *T. gondii* oocysts would appear to be high. This mode of transmission should not surprise us; as early as 1981 Frenkel and Ruiz, based on their studies in Costa Rica, speculated that "children start to become infected when they play in soil and sand, at an age when they are particularly prone to place their (soiled) fingers in their mouths".[12]

Gardens are also commonly used by cats for defecation and are also thought to be a common source of infection by inhalation for gardeners. **Unwashed vegetables** from gardens can also carry oocysts. Studies have also shown that cockroaches and flies can carry oocysts from cat feces to fruits and vegetables.[13-14] Another possible mode of transmission is by dogs that roll in cat feces. One study reported that 23 percent of dogs did this, suggesting "the contamination of fur, after rolling in cat feces containing oocysts, might make these accessible to children who pet dogs".[15]

Water infected with *T. gondii* oocysts is increasingly suspected of being a major source of transmission.[16] The water is thought to become contaminated by runoff from areas where cats defecate. Several epidemics of toxoplasmosis have been reported due to contaminated water, most notably a 1995 epidemic in Victoria, British Columbia, due to the contamination of the city water supply by cat feces.[17]

Finally, in a disturbing finding, researchers reported that you may even become infected with *T. gondii* oocysts by touching the keypad of an ATM. Presumably the previous user had been gardening and had oocysts on their fingers.[18]

The **relative importance of different modes of *T. gondii* transmission** has been widely debated but minimally studied. In countries like France, which has a high rate of *T. gondii* -infected individuals, the most important source of transmission is thought to be cysts in undercooked meat. Studies of pregnant women in Europe have identified the eating of raw or undercooked meat as the most likely source of transmission.[19-20] In countries like the United States, in which meat is generally well cooked, direct transmission of oocysts from cats especially via water, and contaminated fruits and vegetables, is thought to be more important.[22] Recent studies have reported that the majority of congenital infections[23] and postnatal acute infections[24] in the United States are from oocysts.

The question has been raised **whether the clinical outcome is different if a human becomes infected by a tissue cyst or an oocyst**. In mice, infection by oocysts appears to be more pathogenic. In humans, "circumstantial evidence suggests that oocyst-induced infections…are clinically more severe than tissue cyst-acquired infections".[25] There are also suggestions that **reinfection can occur with different strains of *T. gondii.*[26]** (see also reference #50 in previous section)

Vertical Transmission from Infected Mother to Offspring

In humans, it is well known that if a previously uninfected woman is infected with *T. gondii* while pregnant, the *T. gondii* may cross the placenta and cause brain damage (e.g., cysts, seizures, mental retardation) in the offspring. This is why women are cautioned to not change cat litter while they are pregnant.

In female mice, it is known that a mouse which has been infected with *T. gondii, even before becoming pregnant*, may pass along the *T. gondii* to their offspring. This is known to also occur in women.[50] In one documented case, a woman who had been infected with *T. gondii* 20 years earlier passed the infection to a newborn.[51] This may occur in subsequent litters as well so that the infected mouse mother may infect many

offspring.[27] More surprising is the vertical transmission of *T. gondii* from an infected mouse to its offspring, then from this offspring to its offspring, and on for up to five generations.[28] This would give the appearance of being a genetic disease with maternal inheritance, but in reality, would simply be the vertical transmission of an infectious agent.

A nice summary of the studies supporting the vertical transmission of *T. gondii* was published in 2016.[29]

Sexual Transmission of T. gondii

A study in dogs demonstrated that *T. gondii* can be transmitted sexually in that species. Male dogs were infected by *T. gondii* ; it was then found in their semen. The infected semen was then used to artificially inseminate four uninfected female dogs. Seven days after insemination, all four dogs had antibodies to *T. gondii*. Two of the pregnant dogs had miscarriages; the other two delivered four puppies, none of whom lived longer than three weeks and all of which had cysts containing *T. gondii* in their brains.[30] Another study demonstrated that *T. gondii* can be sexually transmitted in rats; 43 of 69 rat pup offspring, following sexual transmission, were found to be infected.[31] Most recently, it was demonstrated that *T. gondii* can be sexually transmitted in sheep; infected males were able to infect previously-uninfected females and the infection was then transmitted vertically to their lambs.[32]

There is also evidence that *T. gondii* can be sexually transmitted in humans. How often this actually happens and its clinical importance are unknown. A study in Germany examined semen collected from 125 men who were being examined for possible infertility. Among the 125, 3 men had evidence of *T. gondii* in their semen. Two of the men also had blood antibodies to *T. gondii*, but the third did not. One man had urethritis and another had gonorrhea.[33]

An American study examined the testes of 10 men who had died from AIDS and *T. gondii* opportunistic infection. In 6 of the 10 cases bradyzoite-filled cysts were identified in the testes. In 4 of these 6 cases, the only other organ in which *T. gondii* was found was the brain.[34] In another study 22% of the semen of male sheep was infected with *T. gondii*.[35]

Timing of Infection by T. Gondii

Since many people are infected by *T. gondii* who show no apparent effects of the infection, the question is why. It is known that humans differ in susceptibility genes to *T. gondii*[52], and genetic differences and strain differences are likely explanations. Another possible explanation is difference in the timing of the infection since the human brain is undergoing constant change during childhood and adolescence.

To test this hypothesis Kannan et. al. at Johns Hopkins infected juvenile mice (33 days) and adult mice with *T. gondii* and assessed differences in outcomes. Significant differences were seen on several measures including prepulse inhibition; immune response; and the distribution in brain areas of several neurotransmitters (GABA, glutamate, dopamine, serotonin, norepinephrine).[36]

Do people with close cat contact have a greater chance of being infected with *T. gondii*?

As noted previously, *T. gondii* can be transmitted from cats to humans in many different ways. Being bitten by a cat, however, apparently does not cause the transmission of *T. gondii*.[37] Some of the means of transmission require no contact whatever between cats and humans, e.g., through tissue

cysts in undercooked lamb, drinking water infected with oocysts, oocysts deposited by a neighborhood cat in your garden. For this reason, attempts to show a correlation between having antibodies to *T. gondii* and past contact with cats have yielded very inconsistent results.

A review of 30 such studies reported that half of them found a correlation, but half did not.[38] Those studies that were negative were more likely to have been studies of adults, e.g., pregnant women who were asked if they presently owned a cat. Those studies that were positive were more likely to have included children and teenagers, such as studies done in Costa Rica and Panama.[39-40] The results varied depending on how the question was asked, with cat ownership in childhood more likely to yield a positive correlation with *T. gondii* antibodies than cat ownership in adulthood. The complexity of studying human–cat contact was also illustrated by a Norwegian study that asked about cat contact in great detail. Becoming infected with *T. gondii* was not statistically related to "living in a neighborhood with a cat" (p=0.71) or "living in a household with a cat" (p=0.13) but was statistically significantly related to "living in a household with a kitten less than 1 year old" (p=0.04).[41] An American study reported that living in a household with one or two kittens was not a significant risk factor for becoming infected with *T. gondii*, but living in a household with three or more kittens was a highly significant risk factor (OR 35.4).[42]

Assessing the transmission from cats to humans is made even more complex by the fact that some breeds of cats are more likely to carry T. gondii than other breeds are; a study of 8 cat breeds reported that *T. gondii* seropositivity varied widely from a low of 16-18% among Korats and Burmese to 60% among Persians.[43]

Do children with close cat contact have a greater chance of developing schizophrenia?

Summary:

- Seven studies have assessed cat ownership in childhood and the subsequent development of schizophrenia. Three studies with large samples (number 2-4) reported highly significant associations (n=264, p=0.007; n=300; p=0.001; n=2,125; p=0.0001).
- Among the 4 negative studies, 3 had smaller samples (n=55, 68 and 141). One of these (number 7) asked about cat ownership prior to age 7 but the strongest findings in the positive studies have been between ages 6 and 10. Another one (number 1) was statistically significant (p=0.02) until corrected for number of questions asked.
- Three studies (numbers 1, 5 and 8) suggest that bipolar disorder may also be associated with cat ownership in childhood.
- One study (number 8) suggests that dog ownership in childhood may be a protective factor against developing schizophrenia.
- Two studies assessed cat ownership in childhood and the subsequent development of schizotypal traits in adulthood. A large study in Finland (n=4,866) (number 7)was positive (p=0.026). A study in the US (n=354) (number 9) was negative. However, in the latter study individuals who had been bitten by a cat in childhood were statistically more likely to have schizotypal traits.
- Finally, one study (number 6) assessed cat ownership in childhood and having psychotic-like experiences at ages 13 and 18. The authors reported it as negative. However, the results were statistically significant before being inappropriately corrected for causally related factors.

(1) US 165 Cases (141 schiz/schizo	Cat ownership before age 10	Cases 51% Controls 39%

affective and 24 bipolar) 165 individually matched controls		p=0.02 but n.s. when Bonferroni corrected max effect ages 6 to 10 association strongest in bipolars
(2) US 264 cases of schiz, schizoaffective and bipolar 528 matched controls	Cat ownership before age 13	Cases 52% controls 42% p = 0.007
(3) US 2,125 cases of schiz or schizoaffective 4,087 controls not well matched	Cat ownership before age 17	Cases 51% Controls 438 p<0.0001 OR 1.34 (1.24-1.53)
(4) Turkey 300 inpatients with schizophrenia 300 nonpsychotic psychiatric outpatients and blood donors as controls	Cat ownership before age 13	Cases 59% Controls 8%P < 0.001
(5) Czech Republic 68 schiz 178 bipolar Facebook solicited, self-reported	Cat ownership before age 13	Negative for both diagnoses
(6) England Self reported psychotic-like experiences at age 13 and 18	Cat ownership at ages 4 and 10	Initial result significant for cat at 4 (OR1.23) and 10 (OR 1.19) (p< 0.05). However, multivariable analysis using questionable “confounders” reported study as negative
(7) Finland a. 55 schizb. 4,866 who completed schizotypal trait scales at age 31	Cat ownership before age 7	(a) Negative(b) Positive for Social Anhedonia schizotypal scale (p=0.026)
(8) U.S. 396 schizophrenia 381 bipolar 594 controls	Cat ownership before age 13	Cat ownership and schiz trend for ages 9-12 (p=0.04) cat ownership and bipolar trend for ages 0-3 (p<0.026) dog ownership inversely associated with schiz. (p=0.02)
(9) U.S.	Cat ownership before age 13	Cat ownership and schizotypal

354 university students who completed schizotypal trait questionnaire	negative cat bites and schizotypal significantly associated (p=0.03)

1. In 1992 165 parents attending the annual NAMI convention agreed to fill out a questionnaire for their affected son or daughter and to then take a duplicate questionnaire home to be filled out by a age and sex matched non-mentally ill friend of the affected son/daughter as a control. The affected individuals were diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder. The questionnaire included 15 questions regarding family history, developmental milestones, and childhood social development. One question asked whether there was a cat living in the house during any one of four periods: during pregnancy, birth to age one; ages 1 to 5; and ages 6 to 10. Dog ownership was not included in this study. Overall 84 of the 165 cases (51%) had had a cat during childhood compared to 65 of the 165 controls (39%). The chi square was p = 0.02; however, using a Bonferroni correction for the number of questions asked would require p<0.01 to achieve true statistical significance. Among the four time periods, all the difference between cases and controls was in the ages 6-10 period.

   Torrey, EF, Yolken, RH. Could schizophrenia be a viral zoonosis transmitted from house cats? *Schiz Bull.* 1995; 21: 167-171.

   Several years after the publication of this study, as the results of other studies became available, we re-analyzed the questionnaires by diagnosis. Among the 141 individuals diagnosed with schizophrenia or schizoaffective disorder 46% of the cases and 37% of the controls had owned a cat in childhood. However, among the 24 individuals diagnosed with bipolar disorder 79% of the cases and 42% of the controls had owned a cat in childhood. Thus, cat ownership was more strongly associated with a diagnosis of bipolar disorder than schizophrenia.

2. In 1997, in an effort to replicate the first study, a telephone survey was done by the Survey Research Center at the University of Maryland. A total of 264 randomly selected NAMI families were interviewed along with 528 matched controls. The index cases were diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder. In addition to detailed questions on pet ownership between birth and age 13 there were questions on complications during pregnancy and developmental milestones. Between birth and age 13, 52% of the cases compared to 42% of the controls owned a cat (p=0.0007). Regarding dog ownership, 73% of the cases compared to 78% of the controls owned a dog, not significant.

   Torrey EF, Rawlings R, Yolken RH. The antecedents of psychoses: A case- control study of selected risk factors. *Schiz Bull* 2000; 46: 17-23.

3. Given the results of these two surveys, we then went back to look at data that had been collected in 1982 from 2,125 families attending the NAMI annual convention. As part of a large questionnaire cat and dog ownership between birth and age 17 was obtained for individuals diagnosed with schizophrenia or schizoaffective disorder. However, no controls had been collected for this 1982 questionnaire so we used a subset of data from a 1991 survey of 55,143 households by the American Veterinary Medical Association. The use of these controls has been

criticized (Wolf and Hamilton, *Schiz Res* (2015); 168: 596.) Among the cases 1075/2125 (51%) had owned a cat compared to 2065/4087 (43%) of the controls (p< 0.0001; OR 1.34. (1.24-1.53).

Torrey EF, Simmons W, Yolken RH. Is childhood cat ownership a risk factor for schizophrenia later in life? *Schiz Res* 2015; 165:1-2.

4. In 2007 in Turkey researchers compared 300 inpatients diagnosed with schizophrenia with two groups of controls: 150 psychiatric outpatients with non-psychotic diagnoses (anxiety, depression, OCD, etc) and 150 blood donors, matched for age, gender and residence. All completed a questionnaire that included cat and dog ownership in childhood up to age 13. The results were as follows:

	Cat ownership	Dog ownership
Schizophrenia	59%	8%
Psychiatric outpatients	6%	3%
Blood donors	9%	4%

The schizophrenia group differed significantly from the psychiatric outpatient group and blood donors (p<0.001).

Yuksel P et al. The role of latent toxoplasmosis in the aetiopathogenesis of schizophrenia—the risk factor or an indication of a contact with a cat. *Folia Parasitolgica* 2010; 57: 121-128.

5. In 2017 in the Czech Republic researchers used Facebook to solicit information from self-selected individuals regarding cat and dog contact and 24 neuropsychiatric conditions from which they might suffer. A total of 68 individuals self-reported to have schizophrenia and 178 with bipolar disorder responded. Years of keeping cats or dogs before age 13 was not significantly associated with schizophrenia or bipolar disorder. Number of cats currently in the person's house were significantly associated with bipolar disorder (OR 2.66) but not with schizophrenia.

Flegr J, Vedralova M. Specificity and nature of the association of twenty-four neuropsychiatric disorder with contacts with cats and dogs. Letter *Schiz Res.* 2017; 189: 219-220.

6. In England researchers examined the cat ownership question by using the Avon Longitudinal Study (n=6705). Since the participants were not yet to an age of peak schizophrenia onset, they used instead the childrens' self-reports of having psychotic like experiences at age 13 and 18; some of these are likely to later develop schizophrenia. Cat ownership was assessed at ages 4 and 10. Initial univariable analysis reported a statistically significant (p<0.05) relationship between cat ownership at age 4 (OR1.23) and 10 (OR 1.19) and psychotic-like experiences at age 13 but not 18. However, after multivariable adjustment for possible "confounders" the ORs decreased to 1.18 and 1.12 and were no longer significant. Two of the "confounders" corrected for by the researchers were social class and household crowding, both known to be strong risk factors for the transmission of *Toxoplasma gondii* (Jones JL et al, *Am J Trop Med Hyg* 2018; 98: 551-557). Therefore the researchers were adjusting for "confounders" that are known to be in the causation pathway of how people become infected with *gondii*, i.e. people living with cats in crowded households are more likely to become infected with *T. gondii* then people living with cats in non-crowded households.

Solmi F et al., Curiosity killed the cat: no evidence of an association between cat ownership and psychotic symptoms at ages 13 and 18 in a UK general population cohort. *Psychol Med* 2017; 47: 1659-1667.
Torrey EF, Yolken RH. How statistics killed the cat. Letter. *Psychol Med* 2017; 48: 175.

7. In Finland information on cat ownership in childhood prior to age 7 was collected at the 31- year follow-up (n=5,713) for the 1966 Northern Finland Birth Cohort. In addition, schizotypal trait scales were completed by 4,866 participants. Among the 55 participants who had developed schizophrenia, there was no association with cat ownership in childhood. However, among the 4,866 who completed the schizotypal trait scaled there was a significant association between cat ownership in childhood and the scale for Social Anhedonia (p=0.026).

   Palomaki J et al. Cat ownership in childhood and the development of schizophrenia. Letter. *Schiz Res*. 2019; 206: 444-445.

8. In Baltimore a carefully diagnosed group of 396 individuals with schizophrenia, 381 with bipolar disorder, and 594 non-psychiatrically ill matched community controls were asked whether their family owned a cat or dog during their childhood prior to age 13. There was a clear negative association between dog ownership in childhood and schizophrenia; thus having a dog was a protective factor (p=0.002). There was no significant relationship between cat exposure and schizophrenia or bipolar disorder overall but there was a trend for specific periods of exposure (schizophrenia ages 9-12; p = 0.04) (bipolar disorder ages 0-3; p< 0.026).

   This report is being submitted for publication.

9. In Florida 354 university students completed online the Schizotypal Personality Questionnaires as well as questions regarding cat ownership and being bitten by a cat prior to age 13. Forty-two percent acknowledged owning a cat, consistent with the controls in two of the NAMI series. Cat ownership was not associated with higher schizotypy scores. However, being bitten by a cat was significantly associated with higher schizotypy scores (p=0.03).

   Kolpakova J, Bedwall JS. Childhood cat bits and disorganized symptoms of schizotypy in adulthood. *Schiz Res*. 2013; 146: 370-391.

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