Recent epidemiologic studies indicate that infectious agents may contribute to some cases of schizophrenia. In animals, infection with Toxoplasma gondii can alter behavior and neurotransmitter function. In humans, acute infection with T. gondii can produce psychotic symptoms similar to those displayed by persons with schizophrenia. Since 1953, a total of 19 studies of T. gondii antibodies in persons with schizophrenia and other severe psychiatric disorders and in controls have been reported; 18 reported a higher percentage of antibodies in the affected persons; in 11 studies the difference was statistically significant. Two other studies found that exposure to cats in childhood was a risk factor for the development of schizophrenia. Some medications used to treat schizophrenia inhibit the replication of T. gondii in cell culture. Establishing the role of T. gondii in the etiopathogenesis of schizophrenia might lead to new medications for its prevention and treatment.

Schizophrenia is a pervasive neuropsychiatric disease of uncertain cause that affects approximately 1% of the adult population in the United States and Europe. An increased occurrence of schizophrenia in family members of affected persons suggests that genetic factors play a role in its etiology, and some candidate predisposing genes have been identified. Environmental factors are also important. Epidemiologic studies, for example, have established that winter-spring birth, urban birth, and perinatal and postnatal infection are all risk factors for the disease developing in later life. These studies have rekindled an interest in the role of infectious agents in schizophrenia, a concept first proposed in 1896 (1). This review focuses on evidence specifically linking infection with Toxoplasma gondii to the etiology of some cases of schizophrenia.

T. gondii is an intracellular parasite in the phylum Apicomplexa. Its life cycle can be completed only in cats and other felids, which are the definitive hosts. However, T. gondii also infects a wide variety of intermediate hosts, including humans. In many mammals, T. gondii is known to be an important cause of abortions and stillbirths and to selectively infect muscle and brain tissue. A variety of neurologic symptoms, including incoordination, tremors, head-shaking, and seizures, have been described in sheep, pigs, cattle, rabbits, and monkeys infected with T. gondii (2).

Humans may become infected by contact with cat feces or by eating undercooked meat. The importance of these modes of transmission may vary in different populations (3). Individual response to Toxoplasma infection is determined by immune status, timing of infection, and the genetic composition of the host and the organism (4).

Toxoplasma organisms have also been shown to impair learning and memory in mice (5) and to produce behavioral changes in both mice and rats. Of special interest are studies showing that Toxoplasma-infected rats become less neophobic, leading to the diminution of their natural aversion to the odor of cats (6). These behavioral changes increase the chances that the rat will be eaten by a cat, thus enabling Toxoplasma to complete its life cycle, an example of evolutionarily driven manipulation of host behavior by the parasite.

In humans, Toxoplasma is an important cause of abortions and stillbirths after primary infection in pregnant women. The organism can also cross the placenta and infect the fetus. The symptoms of congenital toxoplasmosis include abnormal changes in head size (hydrocephaly or microcephaly), intracranial calcifications, deafness, seizures, cerebral palsy, damage to the retina, and mental retardation. Some sequelae of congenital toxoplasmosis are not apparent at birth and may not become apparent until the second or third decade of life. Hydrocephalus (7), increased ventricular size (8), and cognitive impairment (9) have also been noted in some persons with schizophrenia and other forms of psychosis.

Some cases of acute toxoplasmosis in adults are associated with psychiatric symptoms such as delusions and hallucinations. A review of 114 cases of acquired toxoplasmosis noted that “psychiatric disturbances were very frequent” in 24 of the case-patients (10). Case reports describe a 22-year-old woman who exhibited paranoid and
bizarre delusions (“she said she had no veins in her arms and legs”), disorganized speech, and flattened affect; a 32-year-old woman who had auditory and visual hallucinations; and a 34-year-old woman who experienced auditory hallucinations and a thought disorder (11). Schizophrenia was first diagnosed in all three patients, but later neurologic symptoms developed, which led to the correct diagnosis of Toxoplasma encephalitis.

Psychiatric manifestations of T. gondii are also prominent in immunocompromised persons with AIDS in whom latent infections have become reactivated. Reviews of such AIDS cases with toxoplasmosis have indicated that altered mental status may occur in as many as 60% of patients and that the symptoms may include delusions, auditory hallucinations, and thought disorders (12).

Additional studies have documented that persons with serologic evidence of Toxoplasma infection have evidence of psychiatric changes in the absence of a history of clinically apparent Toxoplasma infection. Studies in which personality questionnaires have been administered to healthy adults have indicated that serum antibodies to T. gondii are associated with alterations in behavior and psychomotor skills (13). Seropositivity to Toxoplasma has also been associated with “lack of energy or tiredness” in schoolchildren (14). In view of these findings, we decided to carry out serologic and other studies and to survey the literature for possible additional links between Toxoplasma infection and schizophrenia.

Serologic Studies of Patients with Schizophrenia

Studies Before 1980

In the course of doing our studies, we discovered that much research had been published in languages other than English and was not listed on searchable databases. Through direct contact with authors and by obtaining references listed on their papers, we identified 13 relevant studies published between 1953 and 1979 (15–27), as listed on the Table. Some publication bias is likely, since negative studies are less likely to have been submitted or published.

The 13 studies used a variety of immunologic methods for measuring antibodies, including the Sabin Feldman dye test, skin tests, and complement fixation (CF). One study used a test in which an alkaloid from T. gondii caused a tropical fish, Lebistes reticulatus, to change color (19). Some of the studies compared the relative efficacy of two different tests. Most of the studies defined Toxoplasma-positive results as the presence of a skin reaction or antibodies above a certain titer but often without specifying the precise details of the method; thus, comparing the older studies with each other was not possible. Most of these studies also did not specify what diagnostic criteria were used for schizophrenia, but since at least 12 of them used inpatients, the patients likely had a severe psychiatric disorder. Similarly, most of the studies did not specify the origin of their control group other than saying such things as “681 healthy persons working or studying in the city of Gdansk” (15).

Despite these limitations, 12 of the 13 studies found that the patient group had a higher percentage of antibodies to Toxoplasma than the control group. In eight of the studies, the increase was statistically significant by chi square at the level of p < 0.05. In the two largest studies, Kozar (15) in Poland reported antibodies in 495 (52%) of 961 psychiatric inpatients compared with 170 (25%) of 681 controls, and Roch and Varela (25) in Mexico found antibodies in 836 (86%) of 973 patients with schizophrenia compared with finding antibodies in 30% of the general population.

Studies Since 1999

We identified no studies that were done between 1979 and 1999. Since that time, six studies have been carried out, including our own (28–32). All used enzyme immunoassay methods for measuring antibodies to Toxoplasma. All of the studies also used modern diagnostic criteria for schizophrenia; three studies included patients with chronic disease, and three included patients who were in the first episode of the disease. All of the studies identified their control groups, and some attempts were made to match them to the patient groups.

The results of these studies are summarized in the Table. In all of the studies, the patients had more antibodies to Toxoplasma than the control groups, and in the three studies, carried out in China and Germany, of patients who were having their first-episode of schizophrenia, the differences were statistically significant. One of the first-episode studies, carried out in Cologne by Leweke et al. (32), divided the first-episode patients into those who had never received antipsychotic treatment and those who had received some treatment. The antibody levels for the treated group were intermediate between the levels of the never-treated group and those of the control group, suggesting that antipsychotic medication may have decreased the antibody levels. This conclusion is supported by a study that indicated that some antipsychotic medications inhibit the growth of T. gondii in cell culture (33).

The Leweke et al. study also collected cerebrospinal fluid (CSF) from the first-episode patients. The level of Toxoplasma antibody in the CSF of untreated patients was significantly higher than the normal controls (p < 0.0001) (32). Treated first-episode patients had CSF antibody levels intermediate between those of the untreated patients and the controls, just as was found for the sera.

In addition to these studies on adults with schizophrenia, a study was also conducted by analyzing serum samples from pregnant women, obtained shortly before deliv-
ery, who gave birth to children in whom schizophrenia or other psychoses developed. Preliminary analysis indicates an increased rate of immunoglobulin (Ig) M (but not IgG) class antibodies to *Toxoplasma gondii* in mothers with infants in whom schizophrenia developed later, suggesting that the mothers were experiencing an active infection or that they had persistent IgM antibodies, as described in other studies. Increased levels of IgM antibodies were not found to other perinatal pathogens such as rubella virus or cytomegalovirus (34).

Table. Toxoplasmosis antibody studies of psychiatric patients

| Year | Author and country | Test used | Patients | Controls | % Patients antibody positive | % Controls antibody positive | p value |
|------|-------------------|-----------|----------|----------|-----------------------------|-----------------------------|---------|
|      |                    |           |          |          |                             |                             | chi square |
| **Before 1980** |                |           |          |          |                             |                             |         |
| 1955 | Kozar (15) Poland  | Skin test | Psychiatric inpatients, all diagnoses | Healthy persons, ages 18–60 | 52 (495/961) | 25 (170/681) | <0.0001 |
| 1956 | Vojtechovská et al. (16) Czechoslovakia | Skin test | Inpatients with “psychosis” | General population | 59 (68/116) | 30 (not specified) | <0.0001 |
| 1956 | Wende (17) East Germany | Dye test | Inpatients with schizophrenia | Inpatients with neurologic disorders | 8 (3/38) | 5 (24/520) | 0.418 |
| 1957 | Jirovec et al. (18) Czechoslovakia | Skin test | Inpatients with schizophrenia | Normal population | 48 (238/501) | 29 (286/970) | <0.0001 |
| 1958 | Buentello (19) Mexico | Color change in fish | Inpatients with schizophrenia | Normal subjects | 69 (29/42) | 0 (0/60) | <0.0001 |
| 1958 | Caglieris (20) Italy | Dye test | Inpatients with schizophrenia | Normal subjects | 21 (13/61) | 15 (12/81) | 0.376 |
| 1961 | Cook & Derrick (21) Australia | Dye test | Inpatients with schizophrenia | General population | 36 (195/53) | 24 (182/760) | 0.053 |
| 1962 | Yegerov et al. (22) Russia | Skin test | Inpatients with schizophrenia | Hospital employees | 19 (7/37) | 4 (1/25) | 0.124 |
| 1962 | Avlavidov (23) Bulgaria | Skin test | Psychiatric inpatients, not specified | Female surgical patients | 26 (5/19) | 3 (1/35) | 0.017 |
| 1966 | Roch & Varela (25) Mexico | Dye test | Schizophrenia, hospital status not specified | General population | 86 (836/973) | 30 (4,411/14,689) | <0.0001 |
| 1968 | Garrido & Redondo (26) Spain | C.F. | Inpatients with schizophrenia | General population | 44 (17/39) | 29 (147/500) | 0.072 |
| 1979 | Garcia (27) Cuba | Skin test | Psychiatric inpatients | Normal persons | 60 (60/100) | 30 (30/100) | <0.0001 |
| **Since 1999** |                |           |          |          |                             |                             |         |
| 1999 | Qiuying et al. (28) China | EIA | Inpatients with schizophrenia | Normal persons from same region for routine physicals | 14 (22/152) | 10 (41/396) | 0.181 |
| 2001 | Gu et al. (29) China | EIA | First-episode schizophrenia | Normal controls matched for age, sex, birthplace | 33 (45/135) | 9 (4/43) | 0.002 |
| 2001 | Yolken et al. (30) Germany | EIA: IgG or IgM | First-episode schizophrenia | Normal controls matched for age, sex, SES | 42 (16/38) | 11 (3/27) | 0.007 |
| 2002 | Boronow et al. (31) United States | EIA | Outpatients with schizophrenia | Normal controls matched for age, sex, SES | 12 (28/229) | 7 (7/100) | 0.147 |
| 2003 | Leweke et al. (32) Germany | EIA | First-episode schizophrenia, never treated | Normal controls matched for age, sex, SES | 36 (13/36) | 14 (10/73) | <0.007 |
| 2003 | Torrey & Yolken (unpub. data) Ireland | EIA | Inpatients with schizophrenia | Hospital employees | 60 (31/52) | 45 (9/20) | 0.299 |

*C.F., complement fixation; EIA, enzyme immunoassay; Ig, immunoglobulin; SES, socioeconomic status.*
Discussion

Multiple studies have demonstrated that the brains of persons with schizophrenia show structural and functional changes and that these exist even in patients who have never been treated with antipsychotic medications (35). Thus, schizophrenia, like multiple sclerosis and Parkinson’s disease, is a chronic disease of the central nervous system; as with other such diseases, infectious agents should be considered as possible etiologic agents, perhaps in persons who also have an increased genetic susceptibility.

T. gondii is of special interest because of its known affinity for brain tissue and its capacity for long-term infection starting in early life. The effect of Toxoplasma infection on any given person may differ, depending on such factors as individual genetic predisposition, the state of the immune system, the dose, the virulence of the infecting strain, the timing (e.g., infections in the first trimester of pregnancy differ from those in the third trimester; prenatal and postnatal infections differ; etc.), and the part of the brain affected.

If Toxoplasma is involved in the etiology of schizophrenia, however, its synergy with genes may determine the person’s brain development, immune response to infections, and response to other infectious agents. The fact that T. gondii has been shown to activate retroviruses in animal model systems may be relevant (36). This property is consistent with the recent finding that many persons with schizophrenia exhibit increased retroviral activation within their central nervous systems (37).

Numerous studies indicate that, although the symptoms of schizophrenia generally do not manifest until late adolescence or early adulthood, the disease process has its origins in earlier stages of brain development. The ability of Toxoplasma organisms to infect the perinatal brain is thus consistent with this aspect of schizophrenia pathogenesis. However, prospective studies also support a possible role of postnatal infections in some cases of schizophrenia (38).

The potential effects of the transmission of Toxoplasma in early childhood or later in life should thus be considered.

Epidemiologically, two studies have reported that adults who have schizophrenia or bipolar disorder had a greater exposure to cats in childhood. In one study, 84 (51%) of the 165 affected versus 65 (38%) of the 165 matched controls had owned a house cat in childhood (p = 0.02) (39). In the other study, 136 (52%) of the 262 affected versus 219 (42%) of the 522 matched controls owned a cat between birth and age 13 (odds ratio 1.53; p < 0.007) (40). Whether any geographic association exists between the prevalence of toxoplasmosis and the prevalence of schizophrenia is unknown. France, which has a high prevalence of Toxoplasma-infected persons, was reported to have first-admission rates for schizophrenia approximately 50% higher than those in England (41). Ireland also has a high rate of Toxoplasma-infected persons in rural areas (42), confirmed by the high rate of infection in hospital personnel in our own study. The area of our study in Ireland has also been reported to have a high prevalence of schizophrenia (43).

Neuropathologically, studies of T. gondii in cell culture have shown that glial cells, especially astrocytes, are selectively affected (44,45). Postmortem studies of schizophrenic brains have also reported many glial abnormalities (46), including decreased numbers of astrocytes (47). Similarly, animal studies of Toxoplasma infections have demonstrated that this organism affects levels of dopamine, norepinephrine, and other neurotransmitters, which are well known to be affected in persons with schizophrenia.

Few data exist concerning the clinical correlates of Toxoplasma infection in persons with schizophrenia. A recent study found that persons with schizophrenia who have serologic evidence of Toxoplasma infection have increased levels of cognitive impairment compared to age-matched Toxoplasma-seronegative patients with similar degrees of psychotic symptoms (31). Additional studies are needed on the possible associations between Toxoplasma infections and the symptoms or clinical course of schizophrenia and other psychiatric diseases.

One limitation of studies of Toxoplasma infection and schizophrenia is that one cannot conclusively rule out disease-related differential exposure to the organism. Thus, hospitalized patients may be fed undercooked meat, thereby increasing their seropositivity. Alternatively, the authors of one of the studies speculated that the increased patient seropositivity might have been because the patients worked in the hospital gardens, which were also frequent-ed by cats (21). The possible effects of hospitalization, altered behavior, or other artifactual factors on seropositivity can be minimized by the analysis of persons with the recent onset of symptoms, as three studies described above have done.

Studies are ongoing in attempts to better define the relationship of Toxoplasma infection to schizophrenia. An initial study of the orbital frontal cortex of 14 persons with schizophrenia (48), in which primers to T. gondii were used, did not detect sequences. Studies should also include organisms such as Neospora caninum and Hammondia hammondi, which are closely related to T. gondii and which cross-react serologically (49); N. caninum has been detected in human specimens in our laboratory and by others (50). The use of organism-specific antigens generated from molecular cloning and the use of stage-specific antibodies should help elucidate both the specificity and the timing of the infection.

Finally, clinical trials are under way of antimicrobial drugs with anti-Toxoplasma activity, such as trimethoprim-sulfamethoxazole and azithromycin, as adjunctive treat-
ment for persons with schizophrenia in double-blind trials. These studies may lead to new methods for the treatment of schizophrenia and other psychiatric disorders that may be associated with Toxoplasma and related organisms.

Acknowledgments

We gratefully acknowledge the following persons for allowing us to use unpublished data: John Boronow, Faith Dickerson, Christoph Gerth, Joachim Klosterkötter, Dagmar Koethe, Beth Lee, Markus Leweke, Andrea Origoni, and Cassie Stallings.

Dr. Torrey is the associate director for laboratory research at the Stanley Medical Research Institute and professor of psychiatry at the Uniformed Services University of the Health Sciences, Bethesda, MD. Dr. Yolken is the director of the Stanley Laboratory of Developmental Neurovirology and the Stanley Distinguished Professor of Pediatrics at Johns Hopkins University Medical Center, Baltimore, MD. Their research focuses on the causes and treatment of schizophrenia and bipolar disorder.

References

1. Is insanity due to a microbe? [editorial] Sci Am 1896;75:303.
2. Wastling J, Heap S, Ferguson D. Toxoplasma gondii—keeping our guests under control. Biologist (London) 2000;47:234–8.
3. Tenter AM, Heckeroth AR, Weiss LM.
4. Witting PA. Learning capacity and memory of normal and Toxoplasma-infected laboratory rats and mice. Z Parasitenkd 1979;61:29–51.
5. Berdoy M, Webster JP, Macdonald DW. Fatal attraction in Toxoplasma-infected rats: a case of parasite manipulation of its mammalian host. Proc R Soc (Lond) 2000;267:1591–4.
6. Suzuki Y. Host resistance in the brain against Toxoplasma gondii. J Infect Dis 2002;185(Suppl 1):S58–65.
7. Kaiser GL, Burke CE. Schizophrenia like syndrome following chronic hydrocephalus in a teenager. Eur J Pediatr Surg 1996;6(Suppl 1):39–40.
8. Pearlson GD, Garbuz DJ, Moberg PJ, Ahn HS, DePaulo JR. Symptomatic, familial, perinatal, and social correlates of computerized axial tomography (CAT) changes in schizophrenics and bipolars. J Nerv Ment Dis 1985;173:42–50.
9. Eldevåg B, Goldberg TE. Cognitive impairment in schizophrenia is the core of the disorder. Crit Rev Neurobiol 2000;14:1–21.
10. Kramer W. Frontiers of neurological diagnosis in acquired toxoplasmosis. Psychiatria Clinica 1966:69:43–64.
11. Minto A, Roberts FJ. The psychiatric complications of toxoplasmosis. Lancet 1959;1:1180–2.
12. Israelski DM, Remington JS. Toxoplasmic encephalitis in patients with AIDS. Infect Dis Clin North Am 1988;2:429–45.
13. Haviček J, Gašová Z, Smith AP, Zvára K, Flger J. Decrease of psychomotor performance in subjects with latent ‘asymptomatic’ toxoplasmosis. Parasitology 2001;122:515–8.
14. Taylor MR, Lennon B, Holland CV, Cafferkey M. Community study of Toxoplasma antibodies in urban and rural schoolchildren aged 4 to 18 years. Arch Dis Child 1997;77:406–9.
15. Kožar Z. Badania nad toksoplasmozą wstępnym umysłowym chorych. Bull Inst Mar Trop Med Gdansk 1953;5:134–45.
16. Vojtechovská M, Vojtechovský M, Petru M. Nekteré parasitologické problémy u duševně nemocných. Cas Lek Ces 1956;95:559–66.
38. Rentakallio P, Jones P, Moring J, Von Wendt L. Association between central nervous system infections during childhood and adult onset schizophrenia and other psychoses: a 28-year follow-up. Int J Epidemiol 1997;26:837–43.
39. Torrey EF, Yolken RH. Could schizophrenia be a viral zoonosis transmitted from house cats? Schizophr Bull 1995;21:167–71.
40. Torrey EF, Rawlings R, Yolken RH. The antecedents of psychoses: a case-control study of selected risk factors. Schizophr Res 2000;46:17–23.
41. Van Os J, Galdos P, Lewis G, Bourgeois M, Mann A. Schizophrenia among French and British psychiatrists. Br Med J 1993;307:489–92.
42. Stanford CF, Connolly JH, Ellis WA, Smyth ETM, Coyle PV, Montgomery WI, Simpson DIH. Zoonotic infections in Northern Ireland farmers. Epidemiol Infect 1990;105:565–70.
43. Torrey EF, McGuire M, O’Hare A, Walsh D, Spellman MP. Endemic psychosis in western Ireland. Am J Psychiatry 1984;141:966–70.
44. Creuzet C, Robert F, Roisin MP, Van Tan H, Benes C, Dupouy-Camet J, et al. Neurons in primary cultures are less efficiently infected by Toxoplasma gondii than glial cells. Parasitol Res 1998;84:25–30.
45. Halonen SK, Lyman WD, Chiu FC. Growth and development of Toxoplasma gondii in human neurons and astrocytes. J Neuropathol Exp Neurol 1996;55:1150–6.
46. Cotter DR, Pariante CM, Everall IP. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. Brain Res Bull 2001;55:585–95.
47. Doyle C, Deakin JFW. Fewer astrocytes in frontal cortex in schizophrenia, depression and bipolar disorder [abstract]. Schizophr Res 2002;53:106.
48. Conejero-Goldberg C, Torrey EF, Yolken RH. Herpesviruses and Toxoplasma gondii in orbital frontal cortex of psychiatric patients. Schizophr Res 2003;60:65–69.
49. Nishikawa Y, Claveria FG, Fujisaki K, Nagasawa H. Studies on serological cross-reaction of Neospora caninum with Toxoplasma gondii and Hammondia heydorni. J Vet Med Sci 2002;64:161–4.
50. Transas J, Heinzen RA, Weiss LM, McAllister MM. Serological evidence of human infection with the protozoan Neospora caninum. Clin Diagn Lab Immunol 1999;6:765–7.