

Editors' Introduction: Schizophrenia and Toxoplasmosis

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This issue of *Schizophrenia Bulletin* includes articles on a possible infectious cause of schizophrenia. This approach follows a lead suggested by Emil Kraepelin and Eugen Bleuler a century ago. In the 1896 edition of his textbook, Kraepelin speculated that dementia praecox might be caused by a focal infection of bodily organs that then affected the brain as an autointoxication.¹ Fifteen years later, Bleuler, in his *Dementia Praecox, or The Group of Schizophrenias*, suggested that “the connection of the disease to infectious processes equally needs further study ... many writers assume that schizophrenia is caused by some physical weakness or possibly even by some infectious disease.”²

Toxoplasma gondii has emerged as an interesting candidate as a possible cause of some cases of schizophrenia. Past infectious research on schizophrenia has focused almost exclusively on bacteria and viruses, but *T. gondii* is a protozoa. Other protozoa known to chronically infect human brain tissue and cause behavioral changes include *Plasmodium* (malaria) and *Trypanosoma* (sleeping sickness).

The meta-analysis by Torrey et al provides an overview of studies of *T. gondii* antibodies in individuals with schizophrenia.³ The number of such studies that have been carried out surprised even the authors; even as this article was going to press, we became aware of additional studies, such as the one by Yazar et al that accompanies this special section.⁴ Since most of the studies have been published in languages other than English, they provide a sobering reminder of the limitations of MEDLINE and other search engines. The odds ratio of 2.73, although modest, exceeds that for most genetic studies and suggests that *T. gondii* may play some etiological role in a large number of cases. The fact that the studies were done in many geographical areas suggests that *T. gondii* may be associated with the disease worldwide.

Dickerson et al provide additional information on one of the cohorts included in the meta-analysis.⁵ The indi-

viduals with schizophrenia who have antibodies against *T. gondii* were more likely to be female but otherwise did not differ clinically on the Positive and Negative Syndrome Scale or cognitively on repeatable battery for the assessment of neuropsychological status from those who do not have antibodies, suggesting that cases associated with *T. gondii* do not form a clinical or cognitive subgroup. Of note, however, is the significantly increased mortality associated with seropositive antibody status. If this study can be replicated, it will be an important milestone in helping explain the 20% increase in premature mortality among individuals with schizophrenia.

T. gondii has a known pernicious effect on the developing fetal central nervous system (CNS) when it infects women early in pregnancy; that is why pregnant women are advised to not change the cat litter. Possible delayed CNS effects of *T. gondii* infection later in pregnancy have been the subject of much speculation but with no definitive resolution of this issue.^{6,7} In this regard, the review of two studies by Mortensen et al is of special interest.⁸ One study showed that mothers having antibodies to *T. gondii* late in pregnancy, even though the infection was not necessarily recent, had an increased risk of giving birth to offspring who later were diagnosed with a schizophrenia spectrum disorder. The other study revealed that newborns who have antibodies to *T. gondii* have an increased risk of later being diagnosed with schizophrenia. A much larger replication of this latter study is in progress.

Carruthers and Suzuki contribute an elegant summary of *T. gondii*'s life cycle and its ability to cause a chronic, latent infection in both neurons and glia.⁹ The outcome of such infections is determined by a variety of factors, including host genes and cytokine production. Of special interest are differences in *T. gondii* strains as well as the route of initial infection. Both these factors may contribute to the differences in levels of antibody observed by Hinze-Selch et al in the accompanying article in her large study of *T. gondii* in individuals with schizophrenia and major depression.¹⁰

The ability of *T. gondii* to alter rodent behavior has received considerable publicity. Much of this work has been carried out by Joanne Webster, who clearly summarizes it.¹¹ Webster describes how the *T. gondii* infection causes a rat to lose its innate avoidance of cats, thus increasing the chances that the rat will be eaten by a cat, thereby enabling the *T. gondii* to complete its life cycle.

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Noteworthy was Webster's experiment showing that haloperidol apparently suppressed the *T. gondii* and reversed its effect on the rat.

Finally, Jaroslav Flegr summarizes his pioneering research demonstrating the effects of *T. gondii* on the personality and behavior of university students and military recruits.¹² Such studies need to be replicated but are of great interest. Humans are reluctant to acknowledge the possibility that our behavior may be manipulated by infectious organisms; anyone who doubts that it is possible will no longer doubt, if they read Carl Zimmer's fascinating *Parasite Rex*¹³

Where do we go from here with this research? The facts that *T. gondii* is neurotrophic, affects neurotransmitters, is apparently suppressed by some antipsychotic drugs, and has predisposing genes make an etiological link between toxoplasmosis and schizophrenia inherently plausible. A major limitation of such a hypothesis is that it has been difficult to detect *Toxoplasma* organisms in the brains of individuals with schizophrenia. However, it is of note that *Toxoplasma* organisms can persist in very small numbers in the brains of immune competent individuals. It is also unclear why most individuals with *Toxoplasma* do not develop schizophrenia. Variables in terms of disease expression are likely to include the timing of infection, the strain of the infecting organism, and the genetic makeup of the infected individual.

If a causal relationship is to be established between toxoplasmosis and schizophrenia, it will most likely be established by treatment trials, specifically by demonstrating that medications that suppress *T. gondii* infections produce an improvement in the clinical symptoms of schizophrenia. This is the way in which the *Helicobacter pylori* bacteria was ultimately proven to cause gastric ulcers. Multiple treatment trials are in progress, and others are planned using various antitoxoplasmosis drugs as adjunct medication to treat individuals with schizophrenia. Combined with ongoing research on the neuropathology and strain differences in *T. gondii*, such research should help illuminate the validity of this approach to schizophrenia. And if a causal relationship can be established, it will open the door to new treatment approaches as well as to the ultimate possibility of prevention through vaccines.

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