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Infected with Insanity: Could Microbes Cause Mental Illness?

The following is excerpted from an article by Melinda Wenner that appeared in Scientific American Mind - April 17, 2008

Studies have linked schizophrenia to prenatal infections with influenza virus and other microbes, showing that the children of mothers who suffer these infections during pregnancy are more likely to be diagnosed with schizophrenia later in life. In 2006 scientists at Columbia University asserted that up to one fifth of all schizophrenia cases are caused by prenatal infections.

A growing number of scientists are proposing that microbes are to blame for several mental illnesses once thought to have neurological or psychological defects at their roots. Some infections can directly affect the brain, whereas others might trigger immune reactions that interfere with brain development or perhaps attack our own brain cells in an autoimmune mistake.

The most compelling evidence is for schizophrenia. More than 200 studies have suggested that schizophrenia occurs between 5 and 8 percent more frequently than average in children born in the winter or spring. Scientists realized that viruses, which are most prevalent in the cold, dry winter months, could be one of the factors influencing this correlation.

Alan Brown analyzed blood samples from 189 pregnant women, 64 of whom had later given birth to children who became schizophrenic. The women had their blood drawn multiple times during pregnancy, allowing comparison if and when the women had been exposed to the flu. They showed that if infection occurred in the early to middle part of pregnancy, the risk of schizophrenia was increased three times. For first-trimester exposure, it was increased seven times.

Brown found that children born to mothers who were exposed to rubella during the 1964 U.S. epidemic were 10 times more likely than other children to develop schizophrenia. Brown also showed a link between schizophrenia and *Toxoplasma gondii*. If *T. gondii* antibodies are elevated in a mother's blood, her child is 2.5 times more likely than other children to develop schizophrenia.

Although a developing fetus is protected by the placenta some microbes can cross. An acute [*T. gondii*] infection during early pregnancy can cause severe birth defects or miscarriage. The picture is less clear for acute infections in late pregnancy and dormant infections. Brown's antibody study suggests that these types of infections may lead to schizophrenia. Once in the brain, *T. gondii* affects its hosts' behavior. In people, *T. gondii* appears to subtly alter personality, making its hosts more neurotic and insecure and making men more cautious and women more kind and openhearted.

The parasite probably instigates these behavioral changes by affecting the levels of certain brain chemicals. One study found that *T. gondii* increases the production of dopamine. In a fetus, changes in dopamine levels can wreak havoc on normal brain development, and scientists have long known that schizophrenia is associated with an overabundance of dopamine in specific parts of the brain.

A dormant *T. gondii* infection, which may be correlated with an increased risk of schizophrenia in the fetus, does not cross the placenta and therefore cannot directly affect the fetal brain. The influenza link is equally difficult to understand, because flu does not usually infect the fetus.

Some studies suggest that infections per se are not responsible for disrupting brain development; rather the body's immune response to infection affects the nervous system. "When the immune system becomes activated, it can influence the functioning of the brain and, in turn, emotional and behavioral responses," explains Christopher L. Coe who studies the effects of psychological and environmental factors on the immune system.

Cytokines are produced in large numbers during infection. Their functions are not limited to the immune system—they are also important for brain development. When scientists culture neurons in the lab and then add cytokines to them, the neurons do not grow properly. "We know that high levels of cytokines interfere with growth and connections of neurons", Coe says. "A maternal infection—could that affect the immature brain in a way that sets the stage for mental illness?"

A pregnant mother's immune response may affect the way the placenta functions. When the mother's body is fighting an infection the placenta likely behaves slightly differently. It may prompt the fetus to produce its own cytokines; in other

cases, the mother's cytokines will cross the placenta themselves. "There's sort of a reverberation, a harmonic—so as the mother is responding, it causes the baby to respond, even though there's no virus there," Coe explains.

A number of studies show that the levels of certain cytokines, such as interleukin-8, were markedly increased in the blood of mothers who gave birth to schizophrenic children. Genetic research has uncovered two genes associated with schizophrenia that are also involved in cytokine function. Patterson of Caltech injected pregnant mice with a dose of synthetic double-stranded [flu] RNA. Although this genetic material does not behave like a virus on its own, it is recognized as foreign by the body, eliciting an immune response without other infection-related effects. Mice born of mothers injected with RNA behaved exactly like the offspring of flu-infected mothers—suggesting that the immune response, not the virus, is what actually affects the brain.

The immune system may inadvertently harm the brain in another way. Many researchers are investigating the possibility that childhood or even adult infections could cause psychiatric conditions by triggering an autoimmune reaction. Certain infections may trick the immune system into attacking brain cells.

In 1998 doctors noticed that a small percentage of children had suddenly developed obsessive-compulsive disorder (OCD) and a tic disorder following an infection with [Group A β -hemolytic streptococci]. Typical OCD will "just kind of come on gradually," says Susan E. Swedo, a senior neuroscience investigator at the National Institute of Mental Health. "But with these kids, it was 24 to 36 hours between absolutely no symptoms and peak."

Swedo and her colleagues named the new mental disorder PANDAS, for *p*ediatric *a*utoimmune *n*europsychiatric *d*isorders associated with streptococcal infections. They believe PANDAS develops because the immune system begins attacking the brain after infection. [Like rheumatic fever] the body also may begin attacking its own proteins. Some studies have found antibrain antibodies in PANDAS patients, and other studies have found temporal associations between a strep diagnosis and OCD onset. Other research, however, has failed to replicate these findings, and PANDAS is still a highly controversial diagnosis. Many experts doubt that such a clear cause-and-effect relation exists between strep infection and OCD.

[If] an autoimmune reaction or the disruption of fetal brain development [via] the immune system is to blame for infection-related mental illness, it would simplify the problem. It would explain why so many different infections seem to be implicated in mental illness.

"The most important thing, if you want to deal with mental disorders, is to prevent them from happening in the first place," Columbia's Brown says. If infections do play a causal role, then we have a number of new solutions at our fingertips.

Even the small body of work that now exists could have immediate policy implications. The CDC currently recommend [s] that all pregnant women get flu shots—a dangerous proposition if immune response, rather than infection itself, is responsible for harming the fetal brain. "I know they haven't considered this risk," Patterson says, referring to the CDC. "If you take it seriously and vaccinate everybody, then what's going to happen?" Researchers cannot yet predict how often a prenatal immune response might lead to fetal brain damage, but even if it happens less than 1 percent of the time, vaccinating an entire population of pregnant women could affect thousands of children.*

Scientists hope these new insights will help them develop preventive drug regimens, even using medications that exist today. A handful of studies have suggested that antipsychotic drugs have subtle effects on the immune system; Ina Weiner, a psychologist at Tel Aviv University, wondered whether antipsychotics might be able to prevent schizophrenia—not just treat some of its symptoms. She exposed mice in utero to an immune chemical that caused many of them to develop symptoms and brain abnormalities resembling schizophrenia's effects in humans. The mice showed early signs of cognitive decline around the age of puberty, before developing full-blown schizophrenia. Administering antipsychotic medication as soon as these early symptoms appeared not only prevented future schizophrenic behavior but also protected the brain from the physical changes, such as a shrinking hippocampus, that accompany schizophrenia.

There are at least two issues that should be kept in mind when considering the content of the above article:

- There does not appear to be any evidence supporting the concern of an adverse effect of vaccinating women during pregnancy.
- Recent articles in **Nature** describe the presence of deletions in the genomes of schizophrenic patients that appear to correlate with the disease. The articles are: 1. 'Large recurrent micro-deletions associated with schizophrenia', *Nature*, Digital Object identifier (DOI) number – 10.1038/nature07229; 2. 'Rare chromosomal deletions and duplications increase risk of schizophrenia', *Nature*, DOI number – 10.1038/nature07239.