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Infected with Insanity

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The evidence is mounting: mental illness might be caused by microbes

Schizophrenia is a devastating illness. One percent of the world's population suffers from its symptoms of hallucinations, psychosis and impaired cognitive ability. The disease destroys relationships and renders many of its sufferers unable to hold down a job. What could cause such frightening damage to the brain? According to a growing body of research, the culprit is surprising: the flu.

If you are skeptical, you are not alone. Being condemned to a lifetime of harsh antipsychotic drugs seems a far cry from a runny nose and fever. And yet studies have repeatedly 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.

Doctors have known for many years that microbes such as syphilis and streptococcus can, if left untreated, lead to serious psychiatric problems. Now 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. The strongest evidence pertains to schizophrenia, but autism, bipolar disorder and obsessive-compulsive disorder have also been linked to bacterial, viral or parasitic infections in utero, in childhood or in maturity. Some of these infections can directly affect the brain, whereas others might trigger immune reactions that interfere with brain development or perhaps even attack our own brain cells in an autoimmune mistake.

As scientists tease out the link between infections and psychiatric disorders, they anticipate opening the door to a

Dots Recent studies have found links between a huge variety of infections and psychiatric ailments, from both prenatal and postnatal exposures. Here are some of the best-supported correlations:

8. (Further Reading)

new world of preventive measures. In the most immediate cases, a simple vaccine or regimen of antimicrobial drugs could rid the body of an infection before it damages the brain. And if our immune system is responsible, we might be able to develop drugs that stifle the effect of the immune response in the brain. The bottom line is, the more we know about the complex roots of mental illness, the better we can fight it.

What Causes Mental Illness?

In 1896 Scientific American published an editorial entitled "Is Insanity Due to a Microbe?" The question seemed logical, given that microbes were starting to be implicated in other diseases. In the editorial, two doctors described how they had injected cerebrospinal fluid of mentally ill patients into rabbits, which later got sick. The doctors concluded that "certain forms of insanity" could be caused by infectious agents, "similar to typhoid, diphtheria and others."

But when Freudian psychoanalysis became popular in the 1930s, the idea was more or less put to rest. Then, in the 1950s, the discovery of DNA as hereditary material sparked a rising interest in genetics as a cause of illness, including mental disorders. Several papers reported a clear hereditary component to diseases such as schizophrenia, but genes were obviously not the whole story — as a number of studies have found, the identical twin of someone with schizophrenia has only about a one-in-two chance of developing schizophrenia himself.

Certain environmental influences therefore probably interact with genes to trigger mental illness in a person with a genetic predisposition. Scientists began investigating everything from diet and lifestyle to parental nurturing and geographical location. In 1973 E. Fuller Torrey, now a research psychiatrist at the Stanley Medical Research Institute in Chevy Chase, Md., published an article in the British journal Lancet that revived an idea that had been set aside for decades — could microbial infection cause mental illness?

For the next 20 years, a few rogue scientists dominated the field, searching for connections between infections and psychiatric disorders — and the closer they looked, the more they found.

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.

In 2004 Alan S. Brown, a psychiatrist at Columbia University, analyzed blood samples collected from 1959 through 1966 from 189 pregnant women, 64 of whom had later given birth to children who became schizophrenic. The women had had their blood drawn multiple times during pregnancy, allowing Brown and his colleagues to compare if and when the women had been exposed to the flu. "We showed that if [flu] infection occurred in the early to middle part of pregnancy, the risk of schizophrenia was increased three times," Brown explains. "For first-trimester exposure, it was increased seven times."

Brown had also found in a 2001 study that children born to mothers who were exposed to the viral infection rubella, known as German measles, during the 1964 U.S. epidemic were 10 times more likely than other children to develop schizophrenia. Most people today are vaccinated against rubella during childhood, so the risk from this infection is now negligible. But Brown also showed a link between schizophrenia and Toxoplasma gondii, a single-celled parasite that infects about 40 percent of the human population through contaminated water and uncooked meat. One of his studies suggests that if T. gondii antibodies — the human immune system's soldier cells that are a sure sign of ongoing or previous infection — are elevated in a mother's blood, her child is 2.5 times more likely than other children to develop schizophrenia.

Although the case is strongest for schizophrenia, prenatal infections with rubella and several types of herpes have been linked less conclusively with psychiatric disorders, including autism, bipolar disorder and even Alzheimer's disease. To date, most of the correlations found between infections and psychiatric conditions are just that — correlations. There is no conclusive evidence that infections actually cause these diseases; it could be, for example, that carrying the genes for mental illness makes a person more likely to behave in a way that exposes him or her to a virus.

But animal studies lend powerful support to the idea that prenatal infections can affect an offspring's brain. In 2003 California Institute of Technology biologist Paul H. Patterson showed that mice born to mothers infected with flu during gestation are much more fearful than normal mice, reluctant to explore novel objects and interact with other mice. Neural development also appears to be disrupted in these animals: postmortem investigation reveals vast differences in the distribution of their neurons.

As the evidence mounts, many experts are beginning to think that a causal link indeed exists between prenatal infections and psychiatric disorders. Now a new question arises: What exactly are these infections doing to the fetal brain?

The Immune Factor

Although a developing fetus is protected by the placenta — the organ that transfers nutrients and waste between mother and fetus and prevents their blood from mixing — some microbes can cross this hurdle. T. gondii has this ability during its initial, or acute, infection of a pregnant woman. If an acute infection during early pregnancy is left untreated, it can cause severe birth defects or miscarriage. But the picture is less clear for acute infections in late pregnancy and dormant infections, in which the parasite hibernates quietly in the

body and does not cross the placenta. Brown's antibody study suggests that these types of infections, once thought to be harmless, may lead to schizophrenia.

T. gondii is also one of the few microbes that can cross the blood-brain barrier, a protective membrane separating brain cells from the rest of the body. Once in the brain, T. gondii affects its hosts' behavior. Infected rats and mice lose their fear of cats, making the rodents more likely to approach and be eaten by a cat, which is in the parasite's best interest — it can reproduce only in a feline. 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, for example, found that T. gondii increases the production of dopamine, an important neurotransmitter involved in a variety of brain processes, including motor activity, sleep, attention and reward. 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.

But a dormant T. gondii infection, which may also 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. Something else, then, may be at play.

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 and does the damage. "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, a psychologist at the University of Wisconsin-Madison who studies the effects of psychological and environmental factors on the immune system.

For example, recall how you typically feel the day before you come down with the flu. "You just don't feel right — you're more achy, you lose your appetite, you have a sense of fatigue," Coe says. It is not the flu making you feel that way — it is your immune response to it. "You're feeling cytokines," he says, referring to the small molecules produced by many cell types, including immune cells, for signaling purposes.

Cytokines are produced in large numbers during infection, but 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?"

It is possible, according to Coe; a pregnant mother's immune response may affect the way the placenta functions. The placenta's job is to pass hormones and nutrients to the fetus, but when the mother's body is fighting an infection the placenta likely behaves slightly differently. In some cases, 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.

Bolstering the idea that cytokines play a key role are a number of studies showing that the levels of certain cytokines, such as one called interleukin-8, were markedly increased in the blood of mothers who gave birth to schizophrenic children, based on blood samples taken from pregnant women decades ago and the psychiatric profiles of their adult children. Genetic research has uncovered two genes associated with schizophrenia that are also involved in cytokine function, and animal research has lent support as well. Patterson of Caltech recently performed an experiment in which he injected pregnant mice not with a flu virus but with a dose of synthetic double-stranded RNA. Although this molecule of viral 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. He found that the 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.

Defense on the Offense

The immune system may inadvertently harm the brain in another way, too — and not only in a fetus. Although current scientific evidence most strongly links mental illness to prenatal infections, many researchers are also investigating the possibility that childhood or even adult infections could cause psychiatric conditions by triggering an autoimmune reaction. Similar to the way the body attacks insulin-producing pancreas cells in type 1 diabetes, certain infections may trick the immune system into attacking brain cells.

One such infection may result from Streptococcus, the same organism that causes strep throat. In 1998 doctors who were performing long-term studies of children who had obsessive-compulsive disorder (OCD) noticed that a small percentage of the children had suddenly developed OCD and a tic disorder following an infection with group A beta-hemolytic Streptococcus. 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." In other words, these children literally woke up one day with OCD or serious tics.

Swedo and her colleagues named the new mental disorder PANDAS, for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. They believe PANDAS develops because the immune system begins attacking the brain after infection. The Streptococcus bacterium displays certain proteins on its surface that resemble proteins made by humans — a strategy that helps the bacterium evade detection by its host. Eventually, however, the body discovers the bacterium and attacks it. In that process of defense, 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. "We feel very strongly that the data support that infections will make tics worse but not cause them," says neurologist and pediatrician Harvey Singer of Johns Hopkins University. In 2005 Singer and his colleagues analyzed blood samples from similar numbers of PANDAS patients and healthy people and did not find any major antibody differences between the two groups.

Although PANDAS remains a subject of debate, many scientists consider it an important piece of the puzzle. Whether through an autoimmune reaction or the disruption of fetal brain development, if the immune system, rather than the infections themselves, is to blame for infection- related mental illness, it would surely simplify the problem. It would also explain why so many different infections seem to be implicated in mental illness. Flu, rubella, strep, herpes, T. gondii — these infections do quite different things to our bodies, yes. But they do have us in common.

Stopping Illness before It Starts

Researchers hope that as they continue to unravel the complex causes of mental illness, they will also keep moving closer to the ultimate prize: a cure. "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. "I think that this may just be the tip of the iceberg," he says.

Even the small body of work that now exists could have immediate policy implications. The Centers for Disease Control and Prevention currently recommend 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 don't think they have considered this risk. In fact, 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 also hope these new insights will help them develop preventive drug regimens, even perhaps 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, took this idea one step further. She wondered whether antipsychotics might be able to prevent schizophrenia — not just treat some of its symptoms. As Weiner explained at the 2007 conference of the International Brain Research Organization, 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. As 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.

Future drugs and vaccines may target the infections directly or go after the immune system, controlling its interference with the developing brain or preventing an autoimmune attack on brain cells. "There are many, many things that can be done," Brown says — the more we learn about the impact of infections on the brain, the better we will be able to prevent the damage that leads to mental illness. Last century scientists cured a broad range of physical diseases caused by infections; many hope that the 21st century will bring cures for the infections ailing our minds.

Up to one fifth of all schizophrenia cases are caused by prenatal infections, say Columbia University scientists.

When the immune system becomes active, it can influence the functioning of the brain.

These children literally wake up one day with obsessive-compulsive disorder (OCD) or serious tics.

FAST FACTS Bugs and the Brain

1. Mental illnesses once thought to be the result of neurological or psychological defects may be caused by viral or microbial infections.
2. The strongest evidence links schizophrenia to prenatal influenza infection; pregnant women who become ill with the flu are more likely to give birth to children who will develop schizophrenia.
3. The body's immune reaction, rather than the infections themselves, may be to blame for the resulting brain damage and psychiatric symptoms.

4. Understanding the relation between infections and psychiatric disorders may someday allow us to prevent mental illness using drugs or vaccines.

Connecting the Dots Recent studies have found links between a huge variety of infections and psychiatric ailments, from both prenatal and postnatal exposures. Here are some of the best-supported correlations:

Schizophrenia	Prenatal	Influenza, rubella, Toxoplasma gondii, herpes, Lyme disease, polio, measles
	Postnatal	T. gondii, Lyme disease, chlamydia, herpes
OCD/tic disorder	Prenatal	No links found
	Postnatal	Streptococcus
Bipolar disorder	Prenatal	Herpes, T. gondii
	Postnatal	Herpes, T. gondii
Autism	Prenatal	Rubella, herpes, Lyme disease
	Postnatal	Lyme disease, Mycoplasma (bacterium that causes "walking pneumonia"), Clostridium (bacterium that causes botulism)
Alzheimer's disease	Prenatal	Herpes
	Postnatal	No links found
Tourette's syndrome	Prenatal	No links found
	Postnatal	Mycoplasma

PHOTO (COLOR): When a woman gets sick during pregnancy, her baby is more likely to develop a psychiatric illness later in life.

PHOTO (COLOR): Mice infected with Toxoplasma gondii lose their fear of cats, the parasite's preferred breeding ground. In humans, T. gondii infections may be linked to schizophrenia and bipolar disorder.

PHOTO (COLOR): Vaccinating a pregnant woman may be risky if her immune response interferes with neuronal growth in her unborn baby's brain.

PHOTO (COLOR): Streptococcus, the same bacterium responsible for strep throat, may trick the body into attacking its own brain cells. Some scientists think this immune mistake causes childhood OCD.

PHOTO (COLOR): Streptococcus

PHOTO (COLOR)

(Further Reading)

• *Toxoplasma gondii and Schizophrenia. E. Fuller Torrey and Robert H. Yolken in Emerging Infectious Diseases, Vol. 9, No. 11, pages 1375-1380; November 2003.*

• *Neuropsychiatric Disorders and Infection. Edited by S. Hossein Fatemi. Taylor & Francis, 2005.*

• *Pregnancy, Immunity, Schizophrenia, and Autism. Paul H. Patterson in Engineering & Science, Vol. 69, No. 3, pages 10-21; 2006.*

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