SPECIAL **25th Anniversary Issue**

Discover

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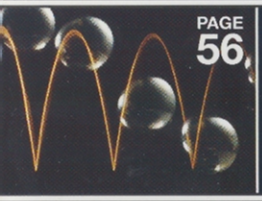

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BY JILL NEIMARK / GRAPHIC BY DAN DELORENZO

CAN THE FLU BRING ON PSYCHOSIS?

A risk for unborn children

LAST JULY FOOTBALL FANS WERE STUNNED BY newspaper stories that police had been called to check on Florida State University quarterback Wyatt Sexton, who was found doing push-ups in the street, half clothed and reportedly saying he was the "son of God." Medical exams later found that Sexton was suffering from advanced Lyme disease. His physician, S. Chandra Swami, reported that the infection caused both neuropsychiatric and cardiovascular defects. Sexton's treatment required months of high-dose antibiotics.

"Lyme-induced psychiatric illness is sometimes indistinguishable from other psychiatric diagnoses," says Kenneth Liegner, an Armonk, New York, physician who specializes in treating tickborne diseases. In 1982 only 491 cases of Lyme disease were reported to the Centers for Disease Control and Prevention; by 2002 the official count was almost 24,000. Liegner vividly recalls one young man who had been treated for Lyme disease whose physician recommended hospitalizing him for long-term psychiatric care. "He was so stuporous he couldn't recognize primary colors or identify his mother's name," says Liegner. "A brain scan showed hypoperfusion [reduced blood flow]. I put him on intravenous antibiotics for six months, and then switched him to oral antibiotics for several years. Today he is working full time and doing fine."

This young man's story is not an isolated case. Ten weeks of intravenous antibiotics improved cognitive functioning in Lyme disease patients in a 2004 study funded by the National Institutes of Health and carried out by psychiatrist Brian Fallon at Columbia University. Fallon is comparing brain scans of Lyme patients as well as those of anxious and depressed individuals and healthy control subjects, to ferret out differences. He notes that infection with *Borrelia burgdorferi*, the spirochete that causes Lyme disease, can lead to "severe sensory hyperarousal, depression, impatience, irritability, and prolonged panic attacks that can go on for hours, cognitive problems with attention and processing speed, and fatigue. We know that the spirochete can penetrate the blood-brain barrier, and we know it attaches to brain cells called glia in a test tube, but we don't know whether active, living spirochetes or the patient's inflammatory response is causing the symptoms."

Recent research has shown that the cascade of signals in the proinflammatory immune response tend to cause the amino acid tryptophan to break down into kynurenic acid rather than serotonin, a brain chemical that influences mood. "That's extremely interesting," says Fallon, "because serotonin depletion seems to be involved in depression. So you can see a very clear mechanism whereby people with chronic immune

DIALOGUE

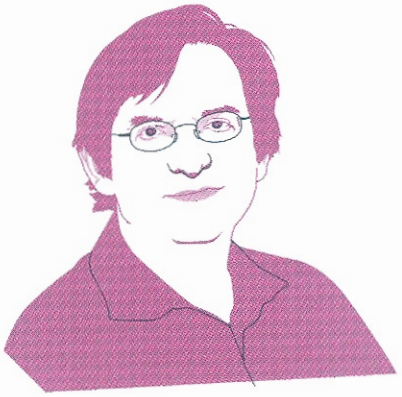
FETAL BRAIN TRIGGERS

W. IAN LIPKIN, director of the Jerome L. and Dawn Greene Infectious Disease Laboratory at the Mailman School of Public Health at Columbia University, led the scientific team that identified the first U.S. outbreak of West Nile virus in 1999. He and his colleagues have recently begun a large study of common infections and their impact on the cognitive development of young children.

Can a mother's flu render her unborn baby vulnerable to mental illness years later?
L: We think that a wide variety of triggers might interact with the developing brain. If you look back at epidemics of flu or rubella, famine, earthquakes, or any stressor, you'll find an association downstream with schizophrenia. However, the model is not about a single organism causing a single disease. Many different triggers may alter a common pathway, depending on the genetics of the patient. Once you create an abnormality in the circuit of the developing brain, or in its sensitivity, it can smolder there quietly and may not be obvious until many years later, perhaps when another virus or toxin is encountered that impairs it even further.

At that point, might you see an illness such as schizophrenia?
L: Yes, and we are only now starting to examine the mechanisms. It's possible that a mother's immune response to a virus regulates gene activity and pathways while the brain is still developing.

What are some of the practical outcomes of this research?
L: Someday we may have some worldwide low-tech solutions for mental disorders that could have an incredible impact. We may be able to say to a mother with a certain genetic profile, "If you get a fever in this trimester, take Tylenol, because it will bring down the fever and impact the same pathways that increase oxidative stress in susceptible animals we've studied." And we may be able to help her protect her child from certain disorders for the rest of his or her life.



'If you look back at epidemics of flu or rubella, famine, earthquakes, or any stressor, you'll find an association downstream with schizophrenia'

activation can become depressed."

Although most patients with Lyme recover health and sanity after extended treatment, other infections may leave a devastating imprint—permanent disruption of the developing brain. Using sophisticated new assays and technology, researchers are examining the impact of common infections such as herpes, streptococcus, and flu. A study in *Current Opinion in Microbiology,* by W. Ian Lipkin and Mady Hornig at the Mailman School of Public Health at Columbia University, notes that prenatal exposure to a wide range of viruses has been repeatedly suggested as a risk factor for the subsequent development of neuropsychiatric disorders. For instance, flu in the first half of a pregnancy seems to be linked to schizophrenia, while cytomegalovirus infection may be correlated with autism. A genetic vulnerability may also explain why some people are affected by prenatal exposure to infections.

"It's a whole different way of looking at the world that is still controversial," Hornig says. "We're examining the long-lasting effect of immune challenge on the nervous system."

One of the big questions to be answered: Are mentally ill children experiencing ongoing infection, or is a pathogen like a hit-and-run driver who continues to wreak damage even after he's gone? Perhaps the most controversial theory about ongoing infection stems from the work of Susan Swedo, a pediatrician and researcher at the National Institutes of Mental Health. In 1998 Swedo published a landmark paper, "Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections," in the *American Journal of Psychiatry.* She speculates that childhood outbreaks of obsessive-compulsive disorder follow strep throat infections in genetically susceptible kids. These children generate antibodies to molecules on streptococcal bacteria, and the antibodies may mistakenly target the child's basal ganglia, a cluster of neurons in the brain that regulate movement, thought, and emotion. When treated with antibiotics, either prophylactically before an infection or repeatedly after one, some children seem to get better.

Lipkin, the director of the Jerome L. and Dawn Greene Infectious Disease Laboratory at Columbia University, has discovered that susceptible mice react to strep bacteria with behavioral abnormalities: "We took a strain of mouse that is very prone to autoimmunity and exposed the mice to killed strep bacteria, and they developed repetitive behaviors and hyperlocomotion," says Lipkin. "And we found they had antibodies that reacted with parts of the brain. We have now created an assay from this experiment that we can use to test human serum from children. It's not conclusive, but it's exciting."

Lipkin is also working with the Norwegian government on an extensive, groundbreaking study of how maternal infections may influence vulnerability to autism. "It's the only study of its type in the world," he says. "Norway has recruited 100,000 pregnant women at their first ultrasound, and they are going to be followed for 72 months. We will do blood draws and a genetic analysis of both the mother and father, as well as cord blood from the children. There will be screening questionnaires and interviews at 6, 18, 36, and 72 months. We'll be able to look back in time and see, for instance, that this particular mom generated antibodies to this particular virus at the 17th week, and now her kid is autistic."

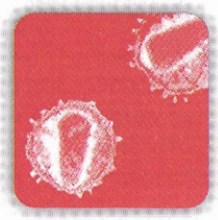
Lipkin believes studies in this new frontier of biology are long overdue. Mental illness, he adds, has too long been regarded as simply mental: "Identifying the biological markers and risk for mental illness in early childhood may ultimately have a huge impact on human and economic health. We're finally getting the funding to ask the right questions." ☒

Mind-Altering Infections

Even common infections can sometimes alter behavior. Some correlations between pathogens and behavior are well established, while others are under investigation.

Strength of evidence linking infection to neurological or psychological symptoms

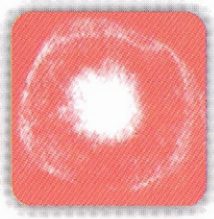
Weak — Strong



Human immunodeficiency virus

HIV/Dementia and psychosis

- Occurs in advanced infection
- Can affect all ages
- Advanced infection is thought to cause loss of neurons
- Many traditional anti-HIV drugs don't work in the brain because they can't cross the blood-brain barrier



Human herpesvirus

Herpes/Psychosis

- Affects all ages
- In rare cases, advanced infection causes inflammation in the brain's temporal lobes



Borrelia burgdorferi, spirochete

Lyme disease/Irritability and depression

- Affects all ages
- May infect membranes surrounding the brain
- Can be treated with antibiotics



Streptococcus pneumoniae, bacterium

Strep throat/Obsessive-compulsive disorder

- Childhood infection may cause immune reactions affecting the basal ganglia, a movement-planning center
- Antibiotics sometimes eliminate symptoms
- Suspected genetic vulnerability



Influenza A virus

Flu/Schizophrenia

- In utero exposure in the first half of pregnancy has been linked to schizophrenia later in life
- May alter brain development
- Suspected genetic vulnerability