

Torrey on schizoviruses (interview)

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by Stephen Mihm

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"I THINK CATS ARE GREAT," says E. Fuller Torrey. His office decor would seem to confirm this statement: A cat poster hangs on one wall; a cat calendar sits on his desk; and a framed picture of a friend's cat leans against the windowsill. He even admits to having a "cat library" at home. But Torrey's interest in felines is a bit different from that of your typical cat lover. That's because Torrey, a psychiatry professor at the Uniformed Services University of Health Science and the enfant terrible of mental health research, believes that *Felis domestica* may carry infectious diseases that could cause schizophrenia and bipolar disorder. "My wife thinks I'm going to be assassinated by cat owners," says Torrey with a sigh. "In fact, I like cats. Unfortunately, if we are correct that they transmit infections..." Here his voice trails off, and he pensively fingers his closely cropped beard.

Torrey often speaks in a self-deprecating manner of his "delusional" notions, but he's dead serious about the cat connection. He thinks "typhoid tabbies" are passing along *Toxoplasma gondii*, a parasite that causes brain lesions and, if Torrey is right, schizophrenia. Torrey first made the argument nearly thirty years ago. "It was considered psychotic," he admits. But since then, his ideas, though still outside the mainstream, have attracted converts, most notably the Johns Hopkins virologist Robert Yolken, with whom he now collaborates. Together, they're trying to prove that toxoplasmosis is but one of several infectious diseases that cause most cases of schizophrenia and bipolar disorder. It helps their case that previous explanations -- bad mothering, bad genes -- have proven deficient to varying degrees. But Torrey and Yolken have also uncovered some hard evidence to support their claims, and they are about to put their theory to the test with clinical trials of drugs that are new to the psychopharmacological arsenal: antibiotics and antivirals similar to those used by AIDS patients. If the duo finds that such drugs alter the course of schizophrenia, Yolken observes, their results "would represent a major advance in the treatment of this devastating disease as well as in understanding its basic etiology."

"SCHIZOPHRENIA is a cruel disease," Torrey has written, with considerable understatement. Although it affects only 1 percent of the population, schizophrenia is among the most debilitating forms of mental illness. Trapped in a world of private delusions, a schizophrenic might cling, for example, to the belief that he is Jesus Christ, or that the government has implanted a monitoring device in his mouth during a routine dental procedure. Visual and auditory hallucinations can range from the terrifying to the merely strange: gigantic spiders, voices that insult or instruct. Some schizophrenics withdraw, becoming mute or catatonic; others remain communicative but incoherent, jumping from one topic to another without logical connections.

With little or no warning, schizophrenia usually manifests itself in patients between the ages of sixteen and thirty. From then on, the illness waxes and wanes, with symptoms generally becoming less severe as the patient ages. Psychotherapy is of little help to schizophrenics, but medication and constant medical care enable over 50 percent to make a full recovery. Still, relapses are common, and many patients spend their lives in halfway houses and institutions. Approximately 40 percent of schizophrenics don't get the help they need and end up on the streets or in prisons -- or committing suicide. There has never been a consensus on schizophrenia's etiology or cause. Many nineteenth-century psychiatrists thought it was a biological disorder; some speculated that it might have an infectious origin. As far back as 1845, the French neurologist Jean E. Esquirol wrote that "mental alienation is epidemic." He added: "It is certain that there are years when...insanity seems suddenly to extend to a great number of individuals." In 1874, the *American Journal of Insanity* published a lengthy brief titled "On the Germ-Theory of Disease." By the early twentieth century, doctors like Eugen Bleuler had suggested that "the connection of [schizophrenia] to infectious process equally needs further study." An outbreak of psychoses after the 1918 influenza epidemic and the discovery that syphilis could cause dementia lent further credence to such theories. In 1922, the psychiatrist Karl Menninger hypothesized that schizophrenia was "in most instances" the by-product of viral encephalitis.

Menninger later became a prominent Freudian psychoanalyst, following a career trajectory that mirrored a larger movement in American psychiatry away from biological explanations of mental illness. By the 1950s, Freudian thought had solidified its grip on the American psychiatric profession. That also happened to be the time when Torrey first began thinking of a career in psychiatry.

As he tells it, the formative event for him came between his second and third years at Princeton. His sister, who was due to start college that fall, began hallucinating and yelling, "The British are coming!" The diagnosis was acute schizophrenia. "My mother was told that it was because my father had died," Torrey says with disgust. "I thought, 'This is absurd -- a lot of people's fathers die and they don't develop schizophrenia.' There was this disconnect between what I was looking at and what I was being told."

As Torrey wrapped up his degree at Princeton and went on to medical school at McGill, he began seriously to contemplate a career in psychiatry. After two years as a Peace Corps doctor in Ethiopia and a year in the South Bronx helping to set up one of the area's first neighborhood health centers, Torrey began a psychiatry residency in Stamford, Connecticut. "It looked to me as if psychiatry was at least twenty years behind the rest of medicine," he recalls. "It was more likely to move and be exciting during my practicing lifetime." That wasn't what attracted most people to the field in the 1960s. Says Torrey, "Psychiatry was the thing you could do if you found yourself in medical school and realized that you had made a terrible mistake -- that giving people rectal exams was pretty unsavory and not what you

wanted to do. You could still be paid to be a doctor and talk to people about their problems." Those problems didn't include schizophrenia, Torrey remembers: "To specialize in schizophrenia was about the lowest form of psychiatric practice."

Torrey was undeterred. Not long after he went to work as a special assistant to the director of the National Institute of Mental Health (NIMH), he attracted controversy by publishing a bruising attack on Freudian psychoanalysis. In *The Death of Psychiatry* (Chilton, 1974), Torrey argued that psychiatry should either limit itself to the treatment of patients with severe brain disorders -- schizophrenia, bipolar disorders -- or abandon its medical pretensions altogether. In 1976, he moved from NIMH to St. Elizabeth's Hospital in Washington, D.C., where he achieved considerable renown as an advocate for the seriously mentally ill. He also helped found the National Alliance for the Mentally Ill, a nationwide patient advocacy group.

The turning point in Torrey's career came in 1983, when he published two books: *Surviving Schizophrenia*, which soon became the authoritative text for patients and families; and *The Roots of Treason*, a biography of Ezra Pound based on research conducted at St. Elizabeth's. The second book, which was nominated for an award by the National Book Critics Circle, was inspired by rumors that Pound had sought refuge at St. Elizabeth's after World War II to avoid standing trial for treason. When Torrey researched the case, he discovered that a hospital administrator had colluded to protect Pound by declaring him insane. It was a great piece of detective work, but the book earned Torrey a demotion at St. Elizabeth's. Disillusioned, he retired two years later and began pursuing his unorthodox theories of schizophrenia. That meant getting inside the brain of the schizophrenic -- literally.

"THE BRAIN is in a very inconvenient place," says Torrey, guiding me up the walkway to a boxy white building on the grounds of the Naval Hospital in Bethesda, Maryland. "People just don't like you opening up their heads and looking around while they're alive." This building, he tells me, houses a solution to that problem. He opens a door and we enter what looks and smells like the maintenance area of an indoor pool. "The Navy has a dive chamber here," says Torrey, pointing to something that looks like a beached bathysphere in the middle of a large warehouse. "We're sharing space with them for now."

This is home to the Stanley Foundation Brain Bank and Neuropathology Consortium's laboratories. Scattered throughout the building's corridors and storerooms are some fifty-five freezers containing the brains of about 385 people -- schizophrenics, manic depressives, people with severe depression, and so-called normal controls. The bank obtains the brains with the assistance of designated medical examiners and the permission of surviving family members. Each brain comes with a complete set of medical records, family medical histories, and other clinical information. The brains are then made available to mental illness researchers worldwide, including Torrey and his colleagues. The whole undertaking, along with a number of related projects, is funded by Theodore and Vada Stanley, wealthy philanthropists who made their money selling mail-order collectibles. (In

one of his many roles, Torrey is the executive director of the Stanley Foundation, an organization that dispensed some twenty-one million dollars in research funds last year.)

As we wind our way down hallways packed with gigantic freezers, Torrey stops to turn on the light in what looks like a storage closet. "Here are the brains," he says, pointing to countless plastic pails stacked on metal shelves. "We put half of each brain in formalin and half in the freezers." Torrey turns out the lights. "Sometimes I take a brain to show my students. They always enjoy that."

We enter the room where most of his staff work. Torrey is in his element, clapping pathologists on the shoulder, joking with them, seemingly oblivious (unlike me) to the business at hand: carving up brains with what looks disturbingly like the meat slicer used at the local deli. The staff are equally upbeat, even when describing the downside of the work. "It can be a little depressing at times," admits Dr. Maree Webster, who runs the bank. "Many of the brains are from suicides, that sort of thing. It's really tragic."

The Brain Bank is the culmination of Torrey's dream to study schizophrenia from the inside out. He hopes that the collection will ultimately lead researchers to the cause of the disease. As for himself, he's hoping that one day he and his colleagues will find their hypothetical virus, though, as Webster admits, "it's a little like trying to find a needle in a haystack. The brain is a big place." And viruses are pretty small.

TORREY DATES his obsession with infectious disease to the early 1970s. "I was becoming aware of proven cases of viral encephalitis that had been diagnosed as cases of schizophrenia or cases of manic depressive illness," he recalls. Torrey discovered some of the cases in the work of Menninger and others near the turn of the century. It was also during the 1970s that the future Nobel Prize winner Daniel Carleton Gajdusek published some of his first research on so-called slow viruses -- pathogens that lie quiescent for twenty or thirty years before emerging as full-blown infections.

Intrigued, Torrey met with Gajdusek. In conversation, the elder scientist mentioned a trip he had made to the highlands of Papua New Guinea to catalog neurological disorders. He told Torrey that he had never found a cut-and-dried case of schizophrenia there, despite the fact that the disease is supposed to afflict about 1 percent of the world's population. Torrey himself made several trips and confirmed as much. "But on the coast," he recounts, "where there had been missions and contact with outsiders for a hundred years, you found occasional cases." To Torrey, that raised the tantalizing possibility that some kind of infectious agent was at work.

Torrey's theory started to look even more plausible when he began to collaborate with Robert Yolken, who now runs the Stanley Division of Developmental Neurovirology, based at the Johns Hopkins Children's Center. Yolken, a summa cum laude graduate of Harvard who stayed on for a medical degree, is a study in contrasts with Torrey. Whereas Torrey

spins stories and lingers on words for effect, Yolken speaks without affect at an extraordinarily rapid rate, as though his tongue can barely keep pace with his brain. Pictures of ski vacations with his family and Torrey are taped to the shelves above his computer. When the two scientists began working together in the 1980s, genetic explanations had usurped traditional psychoanalytic theories about the cause of schizophrenia. The new biological paradigm held that it was only a matter of time before some hypothetical "schizophrenia gene" would be identified, solving the mystery. But Torrey and Yolken remained skeptical. There were some things that genetics couldn't explain. For starters, several studies had shown that children born in urban areas were more likely to develop schizophrenia than those born in rural regions. Household crowding, too, had been demonstrated to be a risk factor. And both urban living and household crowding increase exposure to infectious agents.

Schizophrenia also appeared to correlate with birthdays. More than 250 epidemiological studies, including some of Torrey's own, have demonstrated that both schizophrenic and manic depressive patients are between 5 and 15 percent more likely to have been born in the winter or spring months. Part of that statistical bump, in Torrey's opinion, could be attributed to the increased rate of viral infection in the colder months. "The seasonality data make the geneticists very uncomfortable," says Torrey.

Paul Ewald, a professor of biology at Amherst College and a specialist in infectious diseases, is a bit more blunt. "With schizophrenia, you have seasonal correlations, which is a telltale sign of infectious agents. There are not that many things that can explain that association," he says. "Unless you believe in astrology."

Ewald is little known in mental health circles, but his theories have already earned him considerable attention among infectious disease specialists. He and his collaborator, Gregory Cochran, believe that many diseases -- heart disease, various forms of cancer, multiple sclerosis, cerebral palsy, most major psychiatric diseases -- are often caused by infectious agents. Their reasoning is simple: Any gene that adversely affects an individual's ability to reproduce and care for offspring will ultimately fall victim to natural selection. Therefore, severe common diseases -- those having an incidence higher than one in a thousand -- can't be chalked up simply to bad genes. Some kind of environmental factor, either infectious or noninfectious, must play a role as well.

Schizophrenia, says Ewald, must be one of these diseases, because it seriously diminishes a person's reproductive fitness. At the same time, neither he nor Torrey and Yolken suggest that genetic factors are irrelevant. After all, there's plenty of evidence that genes play a role in schizophrenia. One measure of that is the monozygotic twin test, which yields the percentage of identical twins who both develop a particular disease. A concordance rate of 100 percent is evidence of a purely genetic disease, one that is little influenced by environmental factors like infection, nutrition, or toxins. Huntington's disease, for example, has a concordance rate of 100 percent. Similarly, Down's syndrome has a concordance rate

of 95 percent; autism, 82 percent. By contrast, a viral infection like polio has a concordance rate of only 36 percent among identical twins -- thus, genetics plays some role, but most of the blame lies with the polio virus. What about schizophrenia? According to Torrey's (controversial) calculations, the concordance rate averages approximately 28 percent. With a rate that low, says Ewald, "we have to look elsewhere."

For Torrey, Ewald, and others, that means looking for some kind of infectious agent that may exploit a genetic weakness when invading a host. This interplay of genetics and infectious disease is complex and has a lot to do with whether a faulty gene permits the virus, bacterium, or parasite in question to lock onto cells. As Yolken explains it, these "genetic determinants" are different from those involved in typical "genetic" diseases like Huntington's in that a person's genetic susceptibility doesn't surface unless he or she comes into contact with a particular environmental factor. In theory, that's why one identical twin and not the other will come down with schizophrenia: Only one is exposed to the "schizovirus."

Torrey says that these theories aren't news to most people in the medical profession, particularly those working with infectious diseases. "Psychiatrists," he notes in an exasperated tone, "are the only ones that are surprised by this."

TORRY IS talking about cats again. "I've given talks on the cat stuff and people's response is almost universal: 'I'm not surprised -- I've known my cat is schizophrenic for years!'" He chuckles. "One talk I gave at a department of psychiatry, a fellow came up to me and said, 'I don't want you to repeat this, but the former chairman of our department of psychiatry was convinced that his cat was hallucinating, so he gave him liquid Thorazine and it really seemed to help.'" Torrey looks at me and smiles. "People find cats strange, so they don't find this idea so odd."

Yolken, who owns two cats, is less critical of our feline friends, but he agrees that there may be a connection. "Cat feces are the biggest source of toxoplasma infections in the United States," he says, preparing to guide me through a PowerPoint presentation at his desk. Toxoplasma, Yolken informs me, is one of the more adaptable parasites, able to set up shop in any number of mammals. Although most humans can battle, or even carry, toxoplasma without ill effects, the parasite poses a special danger to people with compromised immune systems. It is also hazardous to pregnant mothers and their fetuses, causing serious brain lesions and retardation in infants when contracted during the first trimester of pregnancy. That's why doctors now forbid expectant mothers to clean litter boxes. Torrey and Yolken speculate that a toxoplasma infection contracted during pregnancy or infancy could lie dormant in some patients' central nervous system, only to be reactivated when the host's immune system is compromised by a secondary infection in late adolescence.

Cats, meanwhile, don't seem to suffer toxoplasma's ill effects. They pick up the parasite from eating infected rodents, typically rats or mice. In the rodents themselves, the parasite produces brain lesions and a host of rather odd behaviors. Infected rats, for example, lose their instinctive fear of cat urine, making them more likely to be caught and eaten by feline predators. As Ewald explains, "The parasite gets to the next host in its life cycle by messing up the rodents' minds." Once in the cat, the parasites infect the lining of the small intestine, reproduce asexually, and encase themselves in a sturdy membrane. These oocysts, or spores, are then shed in the cat's feces. The cycle begins anew when human beings and other mammals become infected from handling the feces or, in some cases, breathing and swallowing the airborne spores.

Torrey first postulated that toxoplasmosis might cause schizophrenia in the 1970s, when he read several articles attributing an outbreak of multiple sclerosis in the Faeroe Islands to the introduction of dogs there during World War II. Could indoor pets like cats, which had become widely popular only in the nineteenth century, also be reservoirs of infectious agents? Torrey, who had recently completed a book manuscript arguing that in the late nineteenth century schizophrenia and bipolar disorder went from being rare diseases to relatively common ones, became convinced that cats were central to that story. "The cat craze began with the cat shows in the late nineteenth century," he explains. "And when I went back and looked at what we know about cats as pets, it corresponded almost perfectly to what we know about the rise of psychosis."

Eager to test the theory, he and Yolken conducted a study in the early 1990s wherein parents of schizophrenics and nonschizophrenics were asked whether they owned a cat during pregnancy or when their offspring were young. That study revealed a higher incidence of cat ownership among the parents of children who developed schizophrenia (51 percent) versus those who did not (38 percent). A second study, much larger in scope, looked into nineteen different factors, including cat ownership, dog ownership, complications during pregnancy, breast feeding, and urban versus rural residence. Only five of the variables proved statistically significant, cat ownership among them (52 percent of those who developed schizophrenia had lived with cats versus 42 percent of the nonschizophrenics). Dog ownership, by contrast, was marginally more common among nonschizophrenics (78 percent) than among schizophrenics (73 percent).

Such epidemiological data are further supported by a recent study by Yolken and Stephen Buka of the Harvard School of Public Health. The two stumbled onto medical records and blood samples taken from some fifty-five thousand pregnant women taken between 1959 and 1966 as part of a study on the causes of cerebral palsy. Buka tracked down about twenty-five hundred families from Providence, Rhode Island, who took part in the study. Among these families, twenty-seven children had exhibited psychoses. Buka matched these with some fifty-four controls of the same age, sex, race, and month and year of birth. Yolken then subjected the blood samples of both groups to a battery of tests for different

antibodies. The mothers of the children who later developed psychoses were approximately 4.5 times more likely to have antibodies to toxoplasmosis than the mothers of the healthy controls.

"It's been known for a long time that toxo can get into the brain," says Yolken. But can it cause schizophrenia? One bit of evidence, he says, comes from the AIDS epidemic. "It turns out," he explains, "that about 30 percent of the adult population is toxo-positive" -- that is, has antibodies to toxoplasmosis -- "and that if you suppress our immune systems enough, we'll get toxoplasmosis. Most HIV patients who are toxo-positive will eventually show signs of toxoplasmosis." Today many such patients get medication to prevent this, but a decade ago, Yolken recalls, "we saw massive toxo." He thinks it was probably there all along, hibernating in the brain. So far, his and Torrey's attempts to find evidence of toxoplasma in the brains of schizophrenics have failed. "The brain is a big place," says Yolken with a sigh. "And it doesn't take much toxo to start an infection."

Of the other diseases that Yolken tried to correlate with schizophrenia -- rubella, influenza, cytomegalovirus, chlamydia, and herpes simplex 2 (HSV-2) -- only herpes was significant. Tests showed that mothers of schizophrenic children were 5.8 times more likely to have antibodies to HSV-2 than mothers of the healthy controls. How might a herpes infection contracted in the womb lead to mental illness years later? As Yolken sees it, the age when most schizophrenics first develop symptoms suggests exposure to some sort of "infectious agent which has a higher rate of transmission in late adolescence and early adulthood." Yolken hypothesizes that the herpes virus remains quiescent in the brain until adolescence, when it is triggered by the Epstein-Barr virus that causes mononucleosis, also known as the kissing disease. Another theory holds that it is reactivated by another version of itself picked up in sexual contact. How such an infection translates into schizophrenia is still a matter of considerable speculation. Yolken is wary of saying that herpes causes schizophrenia. "These represent complex disorders," he says. Adding to the complexity, Yolken thinks that other kinds of viruses also play a role in severe mental disorders. He and Torrey have just completed a study in which more than 17 percent of patients who recently manifested schizophrenia had antibodies to the multiple sclerosis retrovirus. Equally interesting to Yolken is evidence that in nearly 30 percent of recent-onset schizophrenics, endogenous retroviruses had made copies of themselves. In both cases, the rate for the controls was zero percent.

Endogenous retroviruses, admits Yolken, "are not well known in the scientific community." They are viruses that are incorporated into the human genome. In other words, he explains, at some point in evolutionary history, "progenitors of humans or primates got infected with a retrovirus, and the retrovirus got into the genome and stayed in the genome." As a consequence, foreign bits of genetic material are scattered through the human genome. "In most cases, they don't seem to do very much," Yolken says reassuringly. But it seems that in some cases they can be activated by other viruses. Then the little stowaways begin to make

copies of themselves, perhaps wreaking havoc on adjacent genes and, Yolken conjectures, triggering schizophrenia. If schizophrenia is caused by a virus, can it be cured? "What we don't know is whether the infection is reversible," says Yolken. "If the damage is done in childhood, then treating patients as adults may not work." Still, he and Torrey are going to try: They are administering acyclovir, an antiviral drug better known for its efficacy against herpes infections, to groups of schizophrenic patients. They're encouraged by several previous studies, including one of their own, which have shown that antipsychotic drugs like Thorazine, Haldol, and clozapine inhibit viral replication. Torrey and Yolken hypothesize that the drugs' efficacy may have something to do with their antiviral properties. In a subsequent trial, they will administer antibiotics customarily used to treat toxoplasmosis.

ALTHOUGH Torrey and Yolken's theory that an infectious disease causes schizophrenia has gained some acceptance, or at least respect, it is still far from the prevailing view. Torrey in particular has many critics, even among colleagues with whom he has collaborated. Take Irving Gottesman, a professor of psychology and clinical pediatrics at the University of Virginia and a major proponent of genetic explanations of schizophrenia. The two men maintain a friendly relationship despite their differences. "The thing that keeps us together," explains Gottesman, "is that we have common enemies: the Freudians, the sociologists, the cultural anthropologists" -- anyone, in other words, who wants to ascribe schizophrenia to nonbiological causes. They frequently co-author articles attacking what they perceive to be misallocations of mental health research funds. But when it comes to explaining schizophrenia, they part ways.

Gottesman casts doubt on Torrey's data for the rate of concordance for schizophrenia among identical twins. "He's always trying to lower the rates," claims Gottesman. "I'm just doing it the way geneticists have always done." Gottesman's statistical method, known among geneticists as probandwise concordance, samples admissions to a particular hospital. If one member of an identical-twin pair shows up with schizophrenia and the other member shows up at a different hospital with schizophrenia, too, then the twin pair counts as one concordant pair. But if one twin shows up at the hospital and the other twin shows up at the same hospital, each twin counts as a concordant pair, thus yielding two pairs instead of one. This method produces a concordance rate that's close to 50 percent. "Geneticists use probandwise to avoid errors when comparing rates with the general population rate," explains Gottesman.

"I call it a system of double counting," says Torrey of Gottesman's method. "I don't know of any other people outside of psychiatry who use the probandwise concordance rate." Paul Ewald agrees. In an e-mail, he notes that "proband concordance is vulnerable to overestimates on the basis of selection biases.... I trust Torrey's figures for schizophrenia," he writes. "They don't incorporate this bias."

Nonetheless, Gottesman is certain that genes play a bigger role than Torrey and his colleagues admit. In fact, Gottesman has helped formulate a multiple-gene theory of

schizophrenia, which holds that the disorder arises from a complex set of interactions between many different genes. He's also interested in what he calls epigenetics, the study of environmental factors -- drugs and other toxins, for example -- that control or trigger gene events.

"Viruses could be epigenetic contributors, too," concedes Gottesman. But he will accompany Torrey only so far down that road. Back in 1994, when Gottesman and Torrey published the findings of a landmark study of twins and schizophrenia, they offered their differing interpretations of the results not as a traditional conclusion but in the form of a fictional conversation among three experts. Gottesman, who spoke for the geneticists under the pseudonym Dr. Mendel M. Malgene, urged Torrey, who assumed the nom de plume Dr. Dena S. Daverus, not to dismiss or diminish the complex interplay of different genes. He also pointed out that the brain scans they had conducted in the course of their study revealed broad, scattered types of changes in the structure of schizophrenic brains. Infectious diseases like rabies or polio, by contrast, afflict very specific types of cells or regions of the brain. And anyhow, says Gottesman today, "If schizophrenia is caused by an infectious disease, why is it that psychiatric nurses and psychiatrists don't have higher rates?" He pauses. "Why don't spouses of schizophrenics have higher rates of the disease?"

JOINING Dr. Daverus and Dr. Malgene in the fictional schizophrenia debate was Dr. A. Dominic D'Velupmoni, modeled after Daniel Weinberger, who in real life represents what has since become the dominant school of thought about the disease. Weinberger, who is chief of the Clinical Brain Disorders Branch Intramural Research Program at the National Institute of Mental Health, is one of the most articulate spokesmen for what is known as the neurodevelopmental hypothesis. Writes Weinberger, "It has recently become de rigueur to refer to schizophrenia as a neurodevelopmental disorder in which the primary cerebral insult or pathological process occurs during brain development long before the illness is clinically manifest." In other words, as Weinberger explains it to me, something "disrupts the normal programs of brain development." That could be a faulty gene or an obstetric complication. Or something else: Like Gottesman, Weinberger is willing to consider that viruses might play a role. "Genetics can't explain it all," he says. "There have to be environmental factors, too, and viruses may be one of those." But though he describes Torrey's viral theory as "very provocative, very interesting," Weinberger argues that "it's been supported by very little credible scientific data."

The neurodevelopmental theory "is not a theory about a specific cause; it's a theory about timing," counters Torrey. "We have fashions in schizophrenia research, and the neurodevelopmental theory is very fashionable right now." As he sees it, Weinberger needs to explain what exactly causes the schizophrenic brain to develop in the way it does. Attributing some of that process to obstetric complications or malnutrition during pregnancy, as some proponents of the neurodevelopmental hypothesis do, doesn't add up.

Areas of the world that have the worst prenatal care, diet, and rates of obstetric complications do not have higher rates of schizophrenia; if anything, Torrey points out, the incidence of schizophrenia may be lower in such places.

Neurodevelopmental thinking nonetheless remains at the center of current psychiatric accounts of schizophrenia. And though Torrey and Yolken's views currently sit on the margins, Ewald does not think they will remain there. "Infectious causation has been seriously underestimated from the 1800s onward," he notes. "Many people who suggested infectious causes of diseases were dismissed but later proven right." Take gastric ulcers. Only in the last decade did researchers prove that *Helicobacter pylori* bacteria, not stress and hot food, cause most ulcers -- even though evidence for this had been accumulating for over a century. With a disease as complex and mysterious as schizophrenia, Ewald admonishes, researchers need to be careful not to reject infectious disease hypotheses out of hand. To be sure, the field is less divided today than it was when Torrey began his training some thirty years ago. Almost everyone in psychiatry now accepts the biological model of mental illness. No surprise, then, that Torrey, Yolken, Gottesman, and Weinberger all admit that their theories may well be compatible. At the same time, none shows much willingness to dilute a life's worth of research with such compromise. "The best theory of all would be one that integrates all of them without preconceptions," says Gottesman. "But," he says sadly, "who's going to do that?"

Stephen Mihm is the producer of *The New York Times Magazine* on the Web and a doctoral candidate in history at New York University. He lives in New York City with his three cats, all of whom declined to be interviewed for this story.

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See also "[Virus in DNA 'is cause of mental illness'](#)" in The Times, 10 April 2001 (external).



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