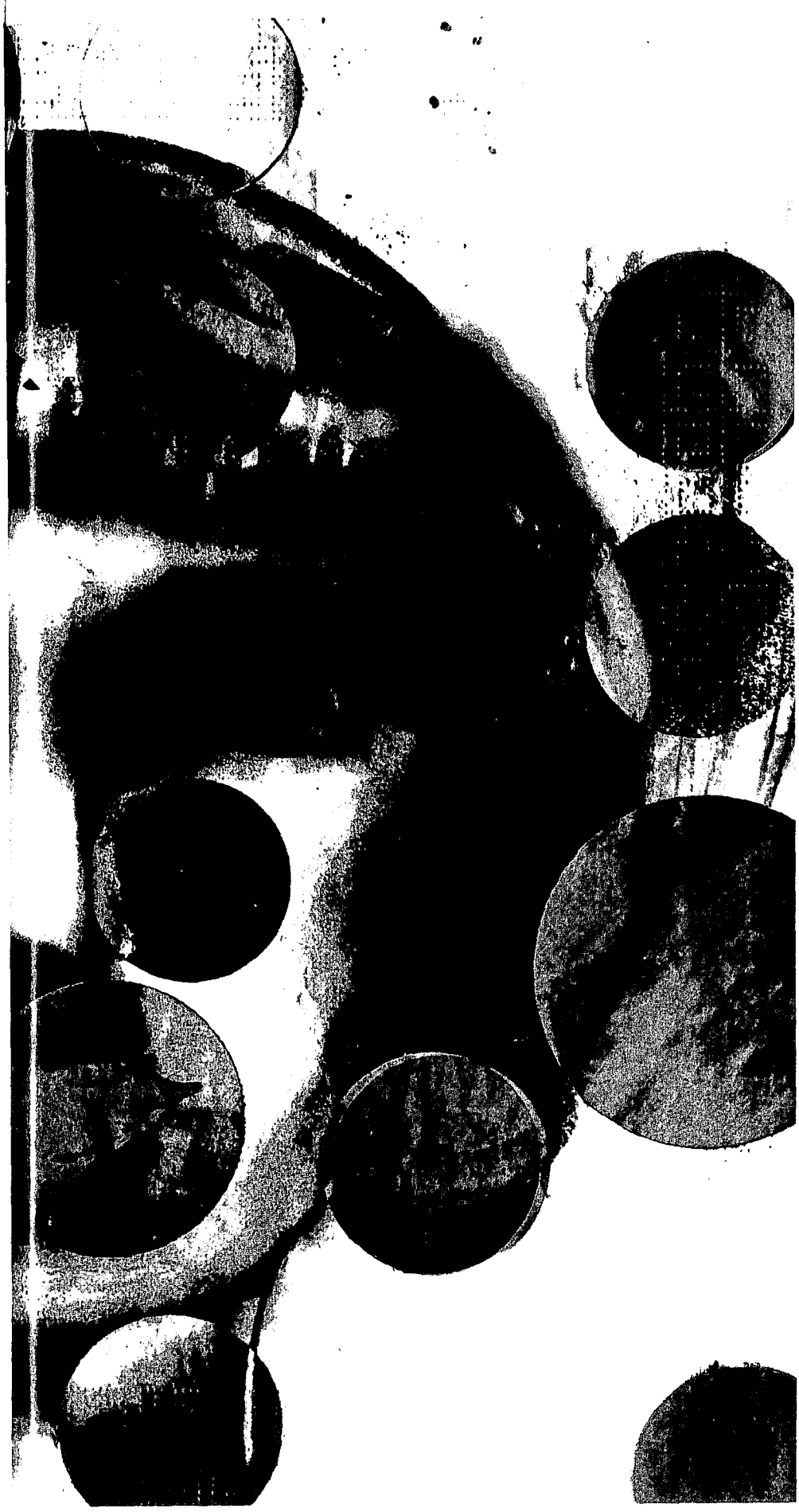

Steven and David Elmore were born identical twins, but their first days in this world could not have been more different. David came home from the hospital after a week. Steven, born four minutes later, stayed behind in the ICU. For a month he hovered near death in an incubator, wracked with fever from what doctors called a dangerous viral infection. Even after Steven recovered, he lagged behind his twin. He lay awake but rarely cried. When his mother smiled at him, he stared back with blank eyes rather than mirroring her smiles as David did. And for several years after the boys began walking, it was Steven who often lost his balance, falling against tables or smashing his lip. ¶ Those early differences might have faded into distant memory, but they gained new significance in light of the twins' subsequent lives. By the time Steven entered grade school, it appeared that he had hit his stride. The twins seemed to have equalized into the genetic carbon copies that they were: They wore the same shoulder-length, sandy-blond hair. They were both B+ students. They played basketball with the same friends. Steven Elmore had seemingly overcome his

rough start. But then, at the age of 17, he began hearing voices.

The voices called from passing cars as Steven drove to work. They ridiculed his failure to find a girlfriend. Rolling up the car windows and blasting the radio did nothing to silence them. Other voices pursued Steven at home. Three voices called through the windows of his house: two angry men and one woman who begged the men to stop arguing. Another voice thrummed out of the stereo speakers, giving a running commentary on the songs of Steely Dan or Led Zeppelin, which Steven played at night after work. His nerves frayed and he broke down. Within weeks his outbursts landed him in a psychiatric hospital, where doctors determined he had schizophrenia.

The story of Steven and his twin reflects a long-standing mystery in schizophrenia, one of the most common mental diseases on earth, affecting about 1 percent of humanity. For a long time schizophrenia was commonly blamed on cold mothers. More recently it has been attributed to bad genes. Yet many key facts seem to contradict both interpretations.

Schizophrenia is usually diagnosed between the ages of 15 and 25, but the person who becomes schizophrenic is sometimes recalled to have been different as a child or a toddler—more forgetful or shy or clumsy. Studies of family videos confirm this. Even more puzzling is the so-called birth-month effect: People born in winter or early spring are more likely than others to become schizophrenic later in life. It is a small increase, just 5 to 8 percent, but it is remarkably consistent, showing up in 250 studies. That same pattern is seen in people with bipolar disorder or multiple sclerosis.

"The birth-month effect is one of the most clearly established facts about schizophrenia," says Fuller Torrey, director of the Stanley Medical Research Institute in Chevy Chase, Maryland. "It's difficult to explain by genes, and it's certainly difficult to explain by bad mothers."

The facts of schizophrenia are so peculiar, in fact, that they have led Torrey and a growing number of other scientists to abandon the traditional explanations of the disease and embrace a startling alternative. Schizophrenia, they say, does not begin as a psychological disease. Schizophrenia begins with an infection.

The idea has sparked skepticism, but after decades of hunting, Torrey and his colleagues think they have finally found the infectious agent. You might call it an insanity virus. If Torrey is right, the culprit that triggers a lifetime of hallucinations—that tore apart the lives of writer Jack Kerouac, mathematician John Nash, and millions of others—is a virus that all of us carry in our bodies. "Some people laugh about the infection hypothesis," says Urs Meyer, a neuroimmunologist at the Swiss Federal Institute of Technology in Zurich. "But the impact that it has on researchers is much, much, much more than it was five years ago. And my prediction would be that it will gain even more impact in the future."

The implications are enormous. Torrey, Meyer, and others hold out hope that they can address the root cause of schizophrenia, perhaps even decades before the delusions begin. The first clinical trials of drug treatments are already under way. The results could lead to meaningful new treatments not only for schizophrenia but also for bipolar disorder and multiple sclerosis. Beyond that, the insanity virus (if such it proves) may challenge our basic views of human evolution, blurring the line between "us" and "them," between pathogen and host.

Torrey's connection to schizophrenia began in 1957. As summer drew to a close that year, his younger sister, Rhoda, grew agitated. She stood on the lawn of the family home in upstate New York, looking into the distance. She rambled as she spoke. "The British," she said. "The British are coming." Just days before Rhoda should have started college, she was given a diagnosis of schizophrenia. Doctors told the grieving family that dysfunctional household relationships had caused her meltdown. Because his father was no longer alive, it was Torrey, then in college, who shouldered much of the emotional burden.

Torrey, now 72, develops a troubled expression behind his steel-rimmed glasses as he remembers those years. "Schizophrenia was badly neglected," he says.

In 1970 Torrey arrived at the National Institute of Mental Health in Washington, D.C., having finished his training in psychiatric medicine. At the time, psychiatry remained under the thrall of Freudian psychoanalysis, an approach that offered little to people like Rhoda. Torrey began looking for research opportunities in schizophrenia. The more he learned, the more his views diverged from those of mainstream psychiatry.

A simple neurological exam showed Torrey that schizophrenics suffered from more than just mental disturbances. They often had trouble doing standard inebriation tests, like walking a straight line heel to toe. If Torrey simultaneously touched their face and hand while their eyes were closed, they often did not register being touched in two places. Schizophrenics also showed signs of inflammation in their infection-fighting white blood cells. "If you look at the blood of people with schizophrenia," Torrey says, "there are too many odd-looking lymphocytes, the kind that you find in mononucleosis." And when he performed CAT scans on pairs of identical twins with and without the disease—including Steven and David Elmore—he saw that schizophrenics' brains had less tissue and larger fluid-filled ventricles.

Subsequent studies confirmed those oddities. Many schizophrenics show chronic inflammation and lose brain tissue over time, and these changes correlate with the severity of their symptoms. These things "convinced me that this is a brain disease," Torrey says, "not a psychological problem."

By the 1980s he began working with Robert Yolken, an infectious-diseases specialist at Johns Hopkins University in

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Baltimore, to search for a pathogen that could account for these symptoms. The two researchers found that schizophrenics often carried antibodies for toxoplasma, a parasite spread by house cats; Epstein-Barr virus, which causes mononucleosis; and cytomegalovirus. These people had clearly been exposed to those infectious agents at some point, but Torrey and Yolken never found the pathogens themselves in the patients' bodies. The infection always seemed to have happened years before.

Torrey wondered if the moment of infection might in fact have occurred during early childhood. If schizophrenia was sparked by a disease that was more common during winter and early spring, that could explain the birth-month effect. "The psychiatrists thought I was psychotic myself," Torrey says. "Some of them still do."

While Torrey and Yolken were chasing their theory, another scientist unwittingly entered the fray. Hervé Perron, then a graduate student at Grenoble University in France, dropped his Ph.D. project in 1987 to pursue something more challenging and controversial: He wanted to learn if new ideas about retroviruses—a type of virus that converts RNA into DNA—could be relevant to multiple sclerosis.

Robert Gallo, the director of the Institute of Human Virology at the University of Maryland School of Medicine and codiscoverer of HIV, had speculated that a virus might trigger the paralytic brain lesions in MS. People had already looked at the herpes virus (HHV-6), cytomegalovirus, Epstein-Barr virus, and the retroviruses HTLV-1 and HTLV-2 as possible causes of the disease. But they always came up empty-handed.

Perron learned from their failures. "I decided that I should not have an a priori idea of what I would find," he says. Rather than looking for one virus, as others had done, he tried to detect any retrovirus, whether or not it was known to science. He extracted fluids from the spinal columns of MS patients and tested for an enzyme, called reverse transcriptase, that is carried by all retroviruses. Sure enough, Perron saw faint traces of retroviral activity. Soon he obtained fuzzy electron microscope images of the retrovirus itself.

His discovery was intriguing but far from conclusive. After confirming his find was not a fluke, Perron needed to sequence its genes. He moved to the National Center for Scientific Research in Lyon, France, where he labored days, nights, and weekends.

Rhoda Torrey and her brother Fuller, who would go on to research schizophrenia.

He cultured countless cells from people with MS to grow enough of his mystery virus for sequencing. MS is an incurable disease, so Perron had to do his research in a Level 3 biohazard lab. Working in this airtight catacomb, he lived his life in masks, gloves, and disposable scrubs.

After eight years of research, Perron finally completed his retrovirus's gene sequence. What he found on that day in 1997 no one could have predicted; it instantly explained why so many others had failed before him. We imagine viruses as mariners, sailing from person to person across oceans of saliva, snot, or semen—but Perron's bug was a homebody. It lives permanently in the human body at the very deepest level: inside our DNA. After years slaving away in a biohazard lab, Perron realized that everyone already carried the virus that causes multiple sclerosis.

Other scientists had previously glimpsed

Perron's retrovirus without fully grasping its significance. In the 1970s biologists studying pregnant baboons were shocked as they looked at electron microscope images of the placenta. They saw spherical retroviruses oozing from the cells of seemingly healthy animals. They soon found the virus in healthy humans, too. So began a strange chapter in evolutionary biology.

Viruses like influenza or measles kill cells when they infect them. But when retroviruses like HIV infect a cell, they often let the cell live and splice their genes into its DNA. When the cell divides, both of its progeny carry the retrovirus's genetic code in their DNA.

In the past few years, geneticists have pieced together an account of how Perron's retrovirus entered our DNA. Sixty million years ago, a lemurlike animal—an early ancestor of humans and monkeys—contracted an infection. It may not have made the lemur ill, but the retrovirus spread into the animal's testes (or perhaps its ovaries), and once there, it struck the jackpot: It slipped inside one of the rare germ line cells that produce sperm and eggs. When the lemur reproduced, that retrovirus rode into the next generation aboard the lucky sperm and then moved on from generation to generation, nestled in the DNA. "It's a rare, random event," says Robert Belshaw, an evolutionary biologist at the University of Oxford in England. "Over the last 100 million years, there have been only maybe 50 times when a retrovirus has gotten into our genome and proliferated."

But such genetic intrusions stick around a very long time, so humans are chockablock full of these embedded, or endogenous, retroviruses. Our DNA carries dozens of copies of Perron's virus, now called human endogenous retrovirus W, or HERV-W, at specific addresses on chromosomes 6 and 7.

If our DNA were an airplane carry-on bag (and essentially it is), it would be bursting at the seams. We lug around 100,000 retrovirus sequences inside us; all told, genetic parasites related to viruses account for more than 40 percent of all human DNA. Our body works hard to silence its viral stowaways by tying up those stretches of DNA in tight stacks of proteins, but sometimes they slip out. Now and then endogenous retroviruses switch on and start manufacturing proteins. They assemble themselves like Lego blocks into bulbous retroviral particles, which ooze from the cells producing them.

Endogenous retroviruses were long considered genetic fossils, incapable of doing anything interesting. But since Perron's revelation, at least a dozen studies have found that HERV-W is active in people with MS.

By the time Perron made his discovery, Torrey and Yolken had spent about 15 years looking for a pathogen that causes schizophrenia. They found lots of antibodies but never the bug itself. Then Håkan Karlsson, who was a postdoctoral fellow in Yolken's lab, became interested in studies showing that retroviruses sometimes triggered psychosis in AIDS patients. The team wondered if other retroviruses might cause these symptoms in separate diseases such as schizophrenia. So they used an experiment, similar to Perron's, that would detect any retrovirus (by finding sequences encoding reverse transcriptase enzyme)—even if it was one that had never been catalogued before. In 2001 they nabbed a possible culprit. It turned out to be HERV-W.

Several other studies have since found similar active elements of HERV-W in the blood or brain fluids of people with schizophrenia. One, published by Perron in 2008, found HERV-W in the blood of 49 percent of people with schizophrenia, compared with just 4 percent of healthy people. "The more HERV-W they had," Perron says, "the more inflammation they had." He now sees HERV-W as key to understanding many cases of both MS and schizophrenia. "I've been doubting for so many years," he says. "I'm convinced now."

Torrey, Yolken, and Sarven Sabunciyan, an epigeneticist at Johns Hopkins, are working to understand how endogenous retroviruses can wreak their havoc. Much of their research revolves around the contents of a nondescript brick building near Washington, D.C. This building, owned by the Stanley Medical Research Institute, maintains the world's largest library of schizophrenic and bipolar brains. Inside are hundreds of cadaver brains (donated to science by the deceased), numbered 1 through 653. Each brain is split into right and left hemispheres, one half frozen at about −103 degrees Fahrenheit, the other chilled in formaldehyde. Jacuzzi-size freezers fill the rooms. The roar of their fans cuts through the air as Torrey's team examines the brains to pinpoint where and when HERV-W awakens into schizophrenia.

New high-speed DNA sequencing is making the job possible. In a cramped room at Johns Hopkins Medical Center, a machine the size of a refrigerator hums 24/7 to read gene sequences from samples. Every few minutes the machine's electric eye scans a digital image of a stamp-size glass plate. Fixed to that plate are 300 million magnetic beads, and attached to each bead is a single molecule of DNA, which the machine is sequencing. In a week the machine churns out the equivalent of six human genomes—enough raw data to fill 40 computer hard drives.

One study found the HERV-W virus in 49 percent of people with schizophrenia, compared with just 4 percent of healthy people.

The hard part starts when those sequences arrive at Sabunciyan's desk. "We got these data right around New Year's 2009," Sabunciyan said one day last August as he scrolled through a file containing 2 billion letters of genetic code, equivalent to 2,000 John Grisham novels composed just of the letters G, A, T, and C (making the plot a great deal more confusing). "We're still looking at it."

Sabunciyan has found that an unexpectedly large amount of the RNA produced in the brain—about 5 percent—comes from seemingly "junk" DNA, which includes endogenous retroviruses. RNA is a messenger of DNA, a step in the path to making proteins, so its presence could mean that viral proteins are being manufactured in the body more frequently than had been thought.

Through this research, a rough account is emerging of how HERV-W could trigger diseases like schizophrenia, bipolar disorder, and MS. Although the body works hard to keep its ERVs under tight control, infections around the time of birth destabilize this tense standoff. Scribbled onto the marker board in Yolken's office is a list of infections that are now known to awaken HERV-W—including herpes, toxoplasma, cytomegalovirus, and a dozen others. The HERV-W viruses that pour into the newborn's blood and brain fluid during these

Better prenatal care or vaccinations could prevent the infections that put people on a path to schizophrenia, and early treatment might prevent psychosis from developing two decades later.

infections contain proteins that may enrage the infant immune system. White blood cells vomit forth inflammatory molecules called cytokines, attracting more immune cells like riot police to a prison break. The scene turns toxic.

In one experiment, Perron isolated HERV-W virus from people with MS and injected it into mice. The mice became clumsy, then paralyzed, then died of brain hemorrhages. But if Perron depleted the mice of immune cells known as T cells, the animals survived their encounter with HERV-W. It was an extreme experiment, but to Perron it made an important point. Whether people develop MS or schizophrenia may depend on how their immune system responds to HERV-W, he says. In MS the immune system directly attacks and kills brain cells, causing paralysis. In schizophrenia it may be that inflammation damages neurons indirectly by overstimulating them. "The neuron is discharging neurotransmitters, being excited by these inflammatory signals," Perron says. "This is when you develop hallucinations, delusions, paranoia, and hyper-suicidal tendencies."

The first, pivotal infection by toxoplasmosis or influenza (and subsequent flaring up of HERV-W) might happen shortly before or after birth. That would explain the birth-month effect: Flu infections happen more often in winter. The initial infection could then set off a lifelong pattern in which later infections reawaken HERV-W, causing more inflammation and eventually symptoms. This process explains why schizophrenics gradually lose brain tissue. It explains why the disease waxes and wanes like a chronic infection. And it could explain why some schizophrenics suffer their first psychosis after a mysterious, monolike illness.

The infection theory could also explain what little we know of the genetics of schizophrenia. One might expect that the disease would be associated with genes controlling our synapses or neurotransmitters. Three major studies published last year in the journal *Nature* tell a different story. They instead implicate immune genes called human leukocyte antigens (HLAs), which are central to our body's ability to detect invading pathogens. "That makes a lot of sense," Yolken says. "The response to an infectious agent may be why person A gets schizophrenia and person B doesn't."

Gene studies have failed to provide simple explanations for ailments like schizophrenia and MS. Torrey's theory may explain why. Genes may come into play only in conjunction with certain environmental kicks. Our genome's thousands of parasites might provide part of that kick.

"The 'genes' that can respond to environmental triggers or toxic pathogens are the dark side of the genome," Perron says. Retroviruses, including HIV, are known to be awakened by inflammation—possibly the result of infection, cigarette smoke, or pollutants in drinking water. (This stress response may be written into these parasites' basic evolutionary strategy, since stressed hosts may be more likely to spread or contract infections.) The era of writing off endogenous retroviruses and other seemingly inert parts of the genome as genetic fossils is drawing to an end, Perron says. "It's not completely junk DNA, it's not dead DNA," he asserts. "It's an incredible source of interaction with the environment." Those interactions may trigger disease in ways that we are only just beginning to imagine.

Torrey's sister has had a tough go of it. Schizophrenia treatments were limited when she fell ill. Early on she received electroshock therapy and insulin shock therapy, in which doctors induced a coma by lowering her blood sugar level. Rhoda Torrey has spent 40 years in state hospitals. The disease has left only one part of her untouched: Her memory of her brief life before becoming ill—of school dances and sleepovers half a century ago—remains as clear as ever.

Steven Elmore was more fortunate. Drug therapy was widely available when he fell ill, and although he still hears voices from time to time, he has done well. Now 50 years old, he is married, cares for an adopted son and stepson, and works full time. He has avoided common drug side effects like diabetes, although his medications initially caused him to gain 40 pounds.

Torrey and Yolken hope to add a new, more hopeful chapter to this story. Yolken's wife, Faith Dickerson, is a clinical psychologist at Sheppard Pratt Health System in Baltimore. She is running a clinical trial to examine whether adding an anti-infective agent called artemisinin to the drugs that patients are already taking can lessen the symptoms of schizophrenia. The drug would hit HERV-W indirectly by tamping down the infections that awaken it. "If we can treat the toxoplasmosis," Torrey says, "presumably we can get a better outcome than by treating [neurotransmitter] abnormalities that have occurred 14 steps down the line, which is what we're doing now."

Looking ahead, better prenatal care or vaccinations could prevent the first, early infections that put some people on a path to schizophrenia. For high-risk babies who do get sick, early treatment might prevent psychosis from developing two decades later. Recent work by Urs Meyer, the neuroimmunologist, and his colleague Joram Feldon at the Swiss Federal Institute of Technology drives this point home. When they injected pregnant mice with RNA molecules mimicking viral infections, the pups grew up to resemble schizophrenic adults. The animals' memory and learning were impaired, they overreacted to startling noises, and their brain atrophied. But this March, Meyer and Feldon reported that treating the baby mice with antipsychotic drugs prevented them from developing some of these abnormalities as adults.

Perron has founded a biotech start-up—GeNeuro, in Geneva, Switzerland—to develop treatments targeting HERV-W. The company has created an antibody that neutralizes a primary viral protein, and it works in lab mice with MS. "We have terrific effects," Perron says. "In animals that have demyelinating brain lesions induced by these HERV envelope proteins, we see a dramatic stop to this process when we inject this antibody." He is scheduled to begin a Phase 1 clinical trial in people with MS near the end of this year. A clinical trial with schizophrenics might follow in 2011.

Even after all that, many medical experts still question how much human disease can be traced to viral invasions that took place millions of years ago. If the upcoming human trials work as well as the animal experiments, the questions may be silenced—and so may the voices of schizophrenia.