The Infection Connection

The controversial role of viruses in schizophrenia is being examined from new angles

By BRUCE BOWER

Michael Harrington, a neurologist at the National Institute of Mental Health (NIMH) in Bethesda, Md., knows that his slides of protein patterns taken from the spinal fluid of healthy and schizophrenic persons are not setting the scientific world on fire. "Many people have criticized our work and called it a fishing expedition," he says.

Yet the fish he and his colleagues recently netted — actually no more than tiny splotches on specially prepared, computer-analyzed strips of gel — may pan out nicely, leading to the identification of viruses that could contribute to some cases of schizophrenia.

Theories about a possible role for viral infections in schizophrenia have circulated in the psychiatric community for more than a century. But research attempting to demonstrate such a link "has provided only indirect evidence and is fraught with pitfalls," says psychiatrist Charles A. Kaufmann of St. Elizabeths Hospital in Washington, D.C. The "infectious disease theory" has traditionally stirred up controversy, a hallmark of much research on mental illness. The term schizophrenia encompasses a number of disorders that are caused, according to various schools of thought, by genes, stress, early family interactions, a biochemical imbalance, infections, nutrition or some combination of these factors. Symptoms are severe and include social withdrawal, incoherent speech, blunted emotions, delusions and hallucinations. At least 2 million people in the United States are estimated to have some form of schizophrenia.

In the past 10 years a number of brain diseases, such as multiple sclerosis (which also affects the spinal cord) and Alzheimer's disease, have been increasingly examined for evidence of viral infection. Viruses are of interest to schizophrenia researchers for a number of reasons, explains psychiatrist E. Fuller Torrey of St. Elizabeths Hospital. They often influence the nervous system, they may not flare up into active infections for 20 years or more, they wax and wane in their intensity and they can alter brain cell function without causing visible, surface changes.

One way to tell whether viruses are at work is to look for changes in protein production in spinal fluid, which closely reflects brain proteins, says Harrington. Only recently, however, have researchers developed techniques that detect trace amounts of protein. More than 300 proteins now can be separated by electrical charge and mass in gel preparations, illuminated through an advanced staining procedure and computer-analyzed.

"Viruses . . . often influence the nervous system, they may not flare up into active infections for 20 years or more, they wax and wane in their intensity and they can alter brain cell function without causing visible, surface changes."

When the spinal fluid of 54 hospitalized schizophrenics was examined in this way, two proteins appeared in 17 of the patients that did not turn up in any of 99 healthy volunteers, report Harrington, Torrey and Carl R. Merril of NIMH in the May CLINICAL CHEMISTRY. The same two proteins, always occurring together, also have been found in a majority of patients with herpes simplex encephalitis and Creutzfeldt-Jakob disease, as well as in some patients with Parkinson's disease and multiple sclerosis, although sample sizes are still relatively small. Viruses are believed to play a part in all of these neurological diseases, points out Harrington.

"We really don't know what the presence of these proteins in one-third of the schizophrenics means," he says. "The data suggest that their origin is within the nervous systems of individuals with primarily a brain disease."

But do the proteins represent a viral infection that precedes schizophrenia, or are they a result of nervous and immune system changes caused by the disorder? An answer to this thorny question, which has plagued the search for viral culprits, might be in sight, says Harrington, once the mystery proteins are "purified." If their chemical structure is unraveled through purification, scientists can make synthetic copies of the proteins, inject them in animals and trace the origins of antibodies that are produced. It will also be possible to locate the gene responsible for each protein.

Harrington hopes to have at least one of the proteins purified in the next year.

The "disease-associated" protein pair did not seem to identify certain types of schizophrenics, he adds, such as those with an early onset of the disorder, poor response to antipsychotic drugs or especially severe symptoms.

Another study, conducted by Torrey and Olivia T. Preble of the Uniformed Services University of the Health Sciences in Bethesda, has managed to link immunological changes with a couple of clinical features. Of 82 hospitalized psychiatric patients with psychosis — a gross impairment in evaluating thoughts and external events that characterizes schizophrenia and several other mental disorders — the researchers found

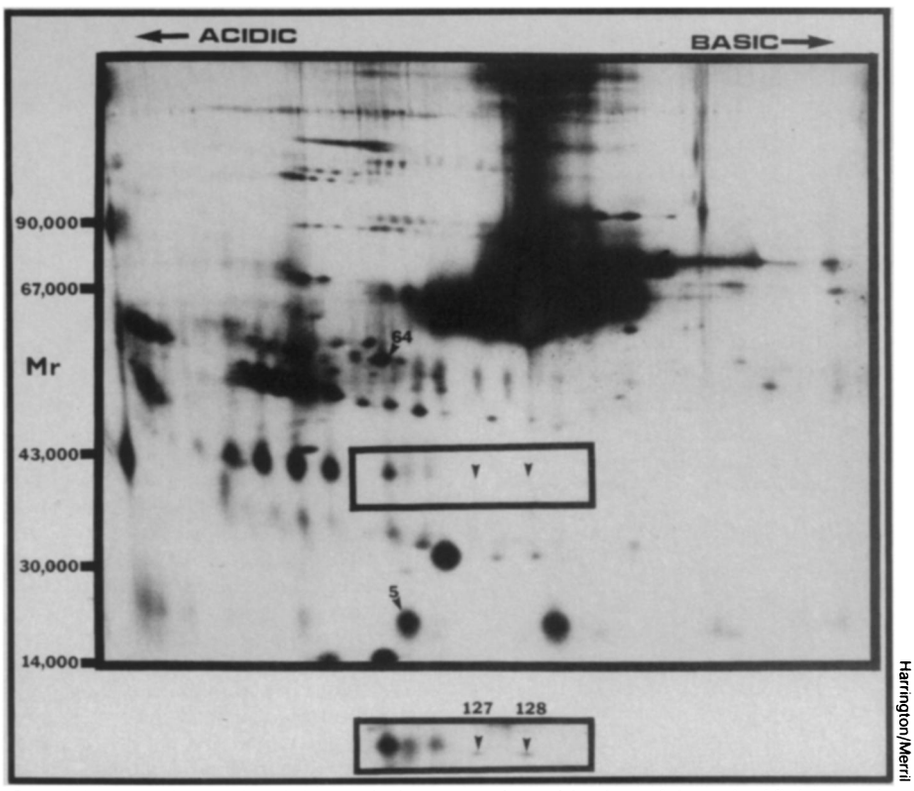
20 with markedly elevated interferon levels in their blood. Only two of 64 healthy subjects had an excess of interferon, a disease-fighting substance released by infected cells.

Patients who were "interferon-positive" were more likely to have had a recent onset or worsening of their psychotic symptoms and to be on low-dose or no medication, report Torrey and Preble in the October AMERICAN JOURNAL OF PSYCHIATRY. The immune system changes do not appear to be caused by drugs used to treat psychiatric disorders. In fact, says Torrey, the patient with the highest interferon level was admitted to the hospital the day before being tested and had never been treated before, although his blood contained as much of the substance as has been reported for patients with acquired immune deficiency syndrome (AIDS).

"Frequent prenatal and birth complications for babies who later become schizophrenic and their tendency to be born between January and April suggest that infections could affect a fetus or newborn child and lead to disease years later."

Again, however, it is not clear whether interferon is related to causes or effects of psychosis. A more extensive study of patients whose symptons recently flared up is now under way, according to Torrey.

Although a "smoking gun" in the form of a discrete virus that causes psychotic symptoms in some patients still eludes researchers, there is indirect evidence to spur them on, maintains Torrey. Studies of twins suggest that about half of all schizophrenic cases are strongly influenced by genetic makeup, and it is known that infectious agents can be transmitted across genes; there is also an inherited susceptibility to some infections. Frequent prenatal and birth complications for babies who later become schizophrenic and their tendency to be born between January and April suggest that infections could affect a fetus or newborn child and lead to disease years later. Many infectious agents, explains Torrey, appear seasonally. Some viruses cause changes in the chemicals that transmit messages across brain cells, such as dopamine, and this might account for biochemical changes in schizophrenia.



Harrington/Merril

Special separation and staining techniques produce this view of the spinal fluid protein pattern of a healthy volunteer. Arrows in the inner rectangle mark the position of two proteins found only in some schizophrenics. The lower rectangle shows the proteins (numbered 127 and 128) in the spinal fluid of a schizophrenic patient.

Yet tissue taken from schizophrenics' brains does not yield viruses, says Kaufmann (conventional viruses can be grown in culture). In addition, he and his colleagues injected bits of schizophrenics' brain tissue (collected shortly after death) into the brains of monkeys, but after six years there was no evidence the disorder was transmitted to the primates. "A normal slow-acting virus doesn't behave like that," he observes.

A host of studies looking at immunoglobulin and other markers of viral or immune involvement in schizophrenia are inconclusive and often at odds with one another. Researchers frequently have not used the same criteria to diagnose schizophrenia, points out psychiatrist Lynn E. DeLisi of NIMH. Control subjects, she adds, are not routinely screened for a family history of mental illness.

Even without these drawbacks, notes Torrey, "no laboratory currently has the technology to measure central nervous system antibodies unless they're overwhelmingly present."

Still, efforts are afoot to track antibodies more closely. In a study published early this year in BIOLOGICAL PSYCHIATRY, DeLisi, Richard J. Weber and Candace B. Pert of NIMH report that some schizophrenics appear to have antibodies in their blood that undermine the function of brain cells. For 13 of 69 psychotic patients, most of whom had schizophrenia, immunoglobulin binding to normal human brain tissue was elevated outside the range observed in 58 healthy volunteers.

"I'm sure we saw a signal of antibrain antibodies at work," says Pert. The internally produced antibodies may mimic or block brain cell receptors, and they may appear after viral or other damage to the central nervous system. Another possibility is that they are induced by antipsychotic drug use, not by psychosis.

Pert and her co-workers are developing new techniques with which they hope to pinpoint the aberrant antibodies.

Their quest is not new. Reports on the search for antibrain antibodies in schizophrenics first appeared in 1937. The findings since then have been inconsistent, and most attempts have relied on inadequate measures of antibody activity, says Pert.

"There's been so much bad work in this field that scientists are a little depressed about it and don't expect much from new studies," explains Pert. "But the theory for antibrain antibodies in schizophrenia is more viable than ever. The trick will be to get immunologists to start working with biological psychiatrists so the theory can be more rigorously tested." □