# STILL STALKING MS

## Of unknown cause and cure, multiple sclerosis has researchers following both old and new trails of discovery

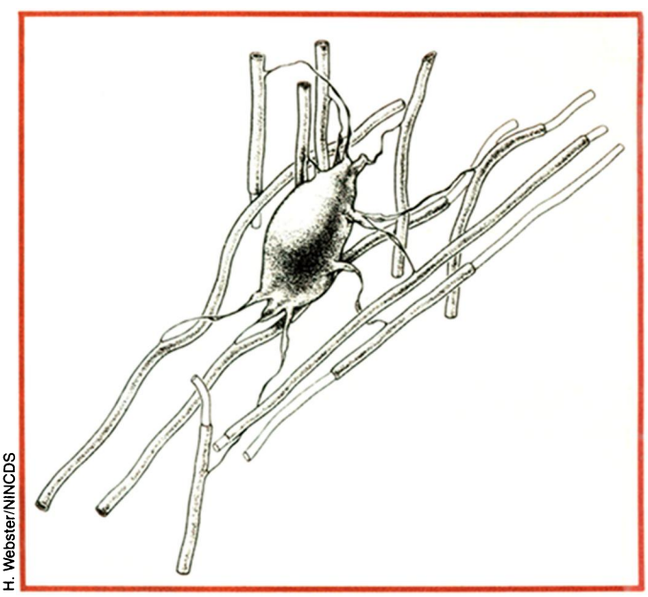
By DIANE D. EDWARDS

It comes like a thief. By attacking the nervous system, it steals mobility and independence from many of its victims. And it cheats by mimicking other neurological diseases. Many decades after medical science first noticed the disease, multiple sclerosis still eludes "capture" by those seeking causes and hunting possible cures for a disease that preys on some 2 million people worldwide.

Added to this evasive trickery is increasing concern that the focus on a relative newcomer called AIDS will dilute efforts to fight disorders like multiple sclerosis. Yet scientists at last month's meeting in Washington, D.C., of the International Federation of Multiple Sclerosis Societies discussed their varied research results in hopeful terms, convinced that data on other diseases will also bolster knowledge about multiple sclerosis. Tying together results from diverse research projects, however, may prove as challenging as solving the mysteries of multiple sclerosis has been in the past.

It is well established that certain cellular changes in the brain and spinal cord result in the many faces of multiple sclerosis. Nerve-cell extensions called axons are coated with a fatty sheath of myelin, produced by cells called oligodendrocytes (see drawing). These large cells send out thin fingers of myelin that wrap around axons in concentric circles to form the sheaths – which are conduits for messages between the central nervous system and the rest of the body.

But if the myelin sheath is destroyed by scavenging cells from the immune system, scar-like areas called plaques are formed (see photos). With their demyelinated nerve cells, the plaques disrupt proper nerve transmission. This short-circuiting phenomenon leads to a broad range of symptoms in multiple sclerosis, the most common of the demyelinating disorders. Symptoms like weakness, tremors and impaired vision usually first appear between the ages of 20 and 40 years of age, with twice as many women as men developing the disease. The complex course of the disease ranges from mild to severe, and is either progressive or chronic with relapses and remissions – sometimes changing from one form to the other.



H. Webster/NINCDS

*Cells in the brain called oligodendrocytes (center) send out multiple processes that wrap around nerve fibers to form the myelin sheath, along which electrical messages are carried. One cell can provide myelin for 50 sheets. Researchers say that abnormal oligodendrocyte activity may contribute to multiple sclerosis.*

Among the experimental treatments being tested now for multiple sclerosis are transplanting myelin-producing oligodendrocytes into animals' brains and using drugs that "fiddle with" electrical impulses in the brain so messages can be transmitted without myelin, according to Byron Waksman of the New York-based National Multiple Sclerosis Society. He says the ultimate goal is a vaccine for those at risk of developing multiple sclerosis. But it is doubtful that this goal will be achieved by taking a straight-and-narrow approach to research.

Scientific discovery in multiple sclerosis has followed a convoluted route, passing through the fields of genetics, virology and immunology. On the basis of data from this research, many now believe that viral infection serves as an environmental "trigger" in the disease, activating a malfunctioning immune system in those already genetically predisposed to it. At last month's meeting, scientists presented recent data supporting this multifaceted theory.

Early evidence for a genetic component in multiple sclerosis came from family and twin studies done by federal agencies. Among those early results was the observation that there is a higher frequency of the disease among identical twins than among nonidentical twins. Also supporting genetics as a factor was a series of epidemiologic surveys showing that the disease is concentrated in certain parts of the world. It is very rare among those living near the equator, for example, and most common in the temperate zones of Canada, the United States, South America and Europe.

There also are unexplained pockets of both the disease and resistance to it. On the Shetland and Orkney Islands near Scotland, the percentage of the population with the disease at any given time is three times the prevalence seen in nearby countries. Yet Hungarian gypsies, Canadian Hutterites and American blacks and Hispanics, for instance, are resistant to the disease, despite living in countries with relatively high incidence.

Traditionally, children of multiple sclerosis patients have not been considered at higher risk than the general population. Dessa Sadovnick of the University of

British Columbia in Vancouver, however, suggests that a patient's relatives may have a higher risk of developing multiple sclerosis than previously reported in the medical literature. Her recent study – of 815 patients and more than 11,000 relatives – found that nearly 20 percent of the 815 cases had at least one relative with the disease. Relatives of female patients have a slightly higher risk than relatives of male patients, says Sadovnick. She calculates that daughters of patients have the highest risk – 50 times greater than the general population.

"People have been reluctant to accept any genetic influence in [multiple sclerosis]," says George C. Ebers of University Hospital in London, Ontario. "Of course, a higher risk in a family doesn't necessarily mean [a disease] is genetic. Tuberculosis was once thought to be a genetic disease."

Determining whether the major factor is environmental or genetic can be difficult, he says. For example, is the higher incidence seen in the northwestern United States due to something inherent in the area, or because certain groups of people are more likely to settle there?

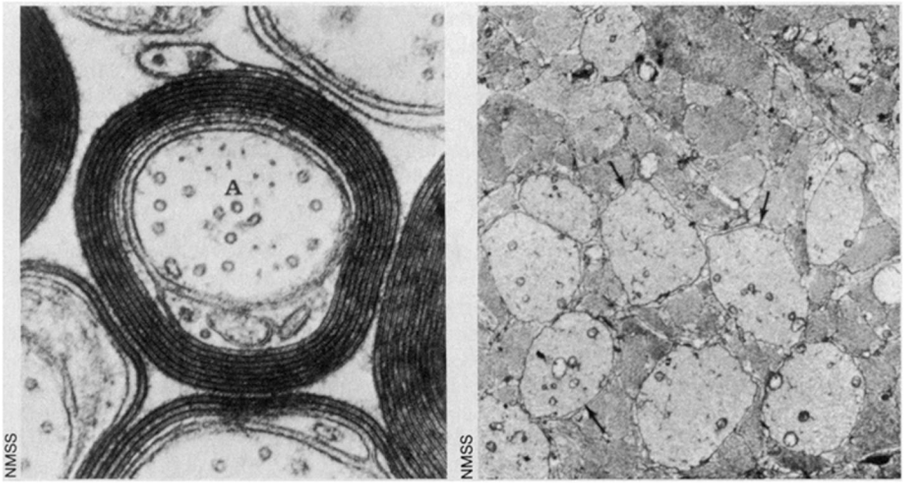
In order to solve the genetic question, Ebers and others, including John Bell of John Radcliffe Hospital in Oxford, England, are dissecting various components of heredity. Ebers feels that three or four yet-unidentified genes may be involved in the predisposition to multiple sclerosis, making a complicated puzzle for researchers to solve. Bell – who studies the relationship between autoimmune diseases and specific genes called histocompatibility loci – said at the meeting that the presence of a locus called DR2 in 60 percent of Caucasian multiple sclerosis patients is attracting the attention of geneticists. But, although his recently completed assay of DR2 found subtypes of the locus, Bell says it failed to pinpoint a specific gene that somehow causes the disease.

Despite evidence that genes participate in multiple sclerosis, many feel that it is the body's own immune system that ultimately attacks myelin. The single most convincing argument for an immune component, says Dale McFarlin of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), is the observation that injection with the immune-system-boosting gamma interferon exacerbates a patient's condition.

Finding the reasons why the body turns on itself will require what McFarlin calls "a safari through the immunology of multiple sclerosis." His own work concentrates on the possible role of T-cell lymphocytes and, most recently, on whether a soluble receptor for this group of immune cells is present on myelin.

Such soluble substances could be primarily responsible for demyelination, according to McFarlin, who predicts that "in the next few years, a number of these factors will be shown to have direct effects on myelin." The latest results supporting this optimism are new data indicating that scavenger cells called macrophages secrete a chemical that disintegrates other cells and McFarlin's preliminary discovery that multiple sclerosis patients have a "peculiar pattern of T-cell receptor gene." It is also possible, says McFarlin, that several genes responsible for regulation of the immune system are defective in multiple sclerosis.

Several studies suggest that certain types of T cells also are defective, particularly natural killer cells, which attack foreign matter like viruses. Henry F. McFarland of NINCDS reported at the meeting that multiple sclerosis patients have an impaired capacity to generate these killer cells against the measles virus, but apparently not against the mumps virus. This mysterious abnormality, says McFarland, could mean that viruses are more likely to persist in the body of a multiple sclerosis patient – allowing repeated viral activation of other cells, like macrophages, that ultimately attack myelin.




*Photos of brain tissue taken through an electron microscope show normal tissue (left) and tissue with the abnormal cellular appearance characteristic of multiple sclerosis (right). In the unaffected brain, myelin sheaths wrap around nerve fibers called axons (seen in cross-section and labeled A) to form an insulating spiral. But in the patient with multiple sclerosis, lesions called plaques contain many axons (arrows) that have lost their myelin.*

Viruses have been suspected as a causative agent in multiple sclerosis for more than a century. Geographic clustering of the disease, the fact that many viral infections are known to cause demyelination, and the disease's long duration punctuated with attacks all support a viral cause. A study of measles in Peru over the past six years by scientists at Johns Hopkins University in Baltimore showed that those attacked by the virus exhibit "immunosuppression of an unusual type," in which patients do not respond to some antigens and overrespond to others. Richard T. Johnson of Johns Hopkins says a similar situation may be at work in multiple sclerosis.

Also of interest, says Johnson, are the similarities between multiple sclerosis and AIDS. In AIDS, plaques similar to those in multiple sclerosis appear in the brain and are deficient in oligodendrocytes. The virus causing AIDS is a member of the same subfamily of viruses as that causing a sheep disease that researchers use as a natural model for multiple sclerosis. "It may be with the new emphasis on [brain] disease in AIDS that we very likely will get new insights into the causes of multiple sclerosis," says Johnson.

To study the viral connection in a controlled setting, Johns Hopkins' Bruce Trapp has custom-designed a mouse model that may help explain multiple sclerosis. Using a virus that causes a type of demyelinating disorder, Trapp created so-called transgenic mice with viral DNA incorporated into their genetic material. The viral DNA injected into these mice as embryos included genes for T antigens, which Trapp says are primarily expressed in the oligodendrocytes of the offspring. Although the nerve cells themselves are intact, their myelin sheaths are not – suggesting that the viral T antigens adversely affect myelin protein production by the oligodendrocytes.

Despite a parade of viruses that have been isolated from multiple sclerosis patients, none has been confirmed as a cause of the disease. No gene has been isolated, and no basic immune defect has been identified. There is, therefore, no unified theory of what causes multiple sclerosis.

But those involved with multiple sclerosis are aware that medical science has conquered villains before. "The first polio virus was isolated in 1909, but that wasn't a breakthrough in the disease," says Johnson. "Polio was just as confusing in the 1950s as multiple sclerosis is now, and [understanding it] was like laying bricks in a house." Scientists are hoping to build a similar structure of understanding in multiple sclerosis. □