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THE PUZZLING PICTURE OF MULTIPLE SCLEROSIS

by Margie Patlak

Neal Schmidtke of Waukesha, Wis., used to keep in shape by bounding up stairs two at a time and running to his appointments. But in January of 1987, when he was 31, Schmidtke started tiring quickly and feeling weak in the knees. By summer, clumsiness replaced his athletic prowess when he started having numbness in his hands and feet and frequent muscle twitches. Soon he could no longer shave or even stand in the shower. After blacking out a few times in August, Schmidtke embarked on a medical odyssey through four months of tests adding up to $20,000 in doctor bills and a near-certain diagnosis of multiple sclerosis.

Each year, 8,000 Americans are told they have multiple sclerosis, a debilitating ailment whose cause and cure are unknown. Even diagnosing multiple sclerosis is difficult and fraught with uncertainties. Symptoms vary greatly among patients and, over time, even within a single individual. This variability stems from the very nature of the disease.

The symptoms of multiple sclerosis are due to patchy destruction of the fatty sheath, called myelin, that envelops and insulates the nerves in the brain and spinal column. Scar tissue forms wherever the myelin jacket is lost, causing a hardening, or "sclerosis." The scar tissue slows or blocks the passage of messages along these nerves, which govern body movements and permit sensations of temperature and pain, among others. Because different nerves service different parts of the body, symptoms of multiple sclerosis vary according to which nerves have myelin destruction. A patient whose sclerosis is mainly limited to the nerves controlling the limbs, for example, will have numbness and, in extreme cases, paralysis of the extremities, whereas another patient may suffer more from vision problems because the optic nerves are affected.

Some common symptoms of multiple sclerosis are weakness, tingling, numbness, loss of coordination and balance, dizziness, fatigue, impotence, muscle spasms, slurred speech, burning or painful sensations, and blind spots in the center of vision. Blurred or double vision is often the first sign of the disease; a common late symptom is loss of bowel and bladder control. Patients are spared any mental disabilities, except in rare instances.

Usually symptoms come and go mysteriously. Attacks (the occurrence or worsening of symptoms) are considered by many doctors to be a sign of myelin destruction, while remissions (ces-

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Neal Schmidtke doesn't let his multiple sclerosis get in the way of sharing kitchen duty with his wife, Laurie, and daughter, Alissa.
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sation or lessening of symptoms) are thought by some doctors to signify myelin repair, although this remains to be proven.

Most patients initially have a series of attacks followed by periods of complete or partial recovery. As years go by, the attacks become more frequent and there is less improvement during remissions until, in the late stages of disease, patients usually experience a progressive decline with no remissions.

Multiple sclerosis is rarely fatal; however, the average life expectancy of a patient is 93 percent of that of the general population. Nor is the disease always disabling; 1 out of 5 patients only has one attack, with little to no progression thereafter. Studies show that two-thirds of patients are still able to walk with or without the assistance of walking aids 25 years after their disease was diagnosed. Of those, at least half can engage in most of the activities they performed before developing the disorder for as long as 15 to 20 years after its onset. In a small percentage of patients, the disease progresses very rapidly and leads to premature death from disease complications such as pneumonia and other infections.

Tricky to Diagnose

Most of the nearly 500,000 American men and women diagnosed with multiple sclerosis first get symptoms between the ages of 20 and 50. Diagnosis is difficult and often slow because so many neurologic and other disorders cause some of the same symptoms seen with multiple sclerosis. A person who is having trouble in only one part of the central nervous system, for example, often has to undergo special X-ray tests to rule out other causes, particularly tumors and strokes.

Unsuspected patches of myelin destruction are sometimes detected in sensory evoked potential tests. These painless tests use electrodes attached to the skin to measure how quickly nerve messages travel from the eye, ear or skin to the brain.

Magnetic resonance imaging (MRI) can also locate demyelinated areas in the brain and spinal cord. The patient lies still for about a half hour in a large doughnut-shaped magnet, while the tissues are pulsed with radio waves. Radio signals emitted by diseased tissue differ from those of healthy tissue.

Spinal taps—in which a small sample of spinal fluid is drawn for analysis—are often done to measure the levels of certain antibodies and cells that are usually elevated in patients with multiple sclerosis.

The sporadic nature of the disease also makes it difficult to diagnose. For example, a person may have vision problems typical of multiple sclerosis, but not have the disease. Most such people never experience the problem more than once. Those with recurrences usually have multiple sclerosis, but another episode of vision disturbance may not surface for months or even years after the first. Often multiple sclerosis cannot be firmly diagnosed until a person has had at least two episodes of dysfunction involving more than one area of the central nervous system that cannot be otherwise explained.

The cause of myelin destruction in multiple sclerosis eludes scientists. The myelin seems to be under attack by the body's own immune system cells. Some studies show that white blood cells, for example, help break down myelin in these patients. But what misdirects these cells to attack rather than defend the nervous system is not known. Over the past 10 or 15 years, however, researchers have concentrated on some clues that should hasten a better understanding of the disorder.

A visually striking clue is a map of the prevalence of multiple sclerosis. Certain regions of the world with a temperate climate, such as the northern United States, Canada and Europe, have almost 10 times the number of multiple sclerosis cases as tropical regions. Age also seems to be significant in terms of risk. Studies show that a person moving from a temperate climate to a tropical climate before the age of 15 tends to adopt the risk associated with the new area, whereas people who move after age 15 maintain the risk of their homeland.

Search for a Viral Cause

These findings suggest that some environmental factor could influence a person's risk for multiple sclerosis up to age 15. It could be a virus native to temperate regions that lies dormant in the body for years before some event triggers it. At least two other human neurological disorders are known to be caused by such "slow" viruses.

A virus could cause myelin loss by attacking the myelin or the cells that produce and maintain myelin. Or, if the molecular structure of the invading virus were identical to part of the molecular structure of myelin, the invader could provoke the immune system to attack both the virus and the myelin. Over the years, more than 20 different viruses have been suspected of being linked to multiple sclerosis.

Recently, the human T-lymphotropic virus (HTLV-I) has come to the forefront in the scientific search for the cause of multiple sclerosis. This virus has been linked to other nervous system disorders and to blood cancers. HTLV-I is a retrovirus, a kind of virus that uses an enzyme to convert its genetic material, RNA (ribonucleic acid), to DNA (deoxyribonucleic acid). The viral DNA then becomes integrated with the DNA of the host cell, where it may remain silent for years without causing symptoms. A research group at the Wistar Institute in Philadelphia has found pieces of genetic material nearly identical to that of HTLV-I in the blood cells of all six of the multiple sclerosis patients they've tested, but in only 1 of 20 people tested without the disorder. They also found particles that look like retroviruses under the electron microscope in tissue taken from one multiple sclerosis patient. Similar findings were generated by a research group at the National Cancer Institute in Bethesda, Md.

The presence of HTLV-I or a relative of it in the blood of multiple sclerosis patients doesn't necessarily mean the virus causes the disorder. "But before any of the retroviruses were found to cause disease in humans," says Dale McFarlin, M.D., a multiple sclerosis expert at the National Institute of Neurological and Communicative Disorders and Stroke, "we suspected that a retrovirus caused multiple sclerosis." Much more research is needed, he adds, however, before researchers will be able to conclude with certainty that HTLV-I or its relative sparks the development of the disease.

The Gene Scene

Meanwhile McFarlin and other researchers working on the genetic front have turned up two genes that, when inherited together, triple a person's risk of developing multiple sclerosis. Although multiple sclerosis is not considered an inherited disease, the chance of a parent or sibling of a patient also having the disorder is 10 to 15 times higher than that of the general population. The disease is thought to be caused, in part, by abnormalities in immune function, and scientists have been studying the genes that govern the immune system to find those that make a person more susceptible to the disease. One of the genes McFarlin has pinpointed prompts the production of a protein, called DR2, that juts out of the surface of white blood cells. DR2 is one of a myriad of proteins called HLA (human leukocyte antigen) molecules, whose various combinations give an individual "fingerprint" to each person's cells. Scientists suspect that the immune system relies on the HLA fingerprint to distinguish

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between cells that are "self" and not to be destroyed and cells that are foreign and subject to attack.

Researchers were particularly interested in finding the gene that prompts the production of the DR2 protein because studies have shown that multiple sclerosis patients are more likely to have this subtype of DR2 protein than others, although the presence of DR2 does not necessarily mean a person will develop multiple sclerosis.

The other gene known to heighten susceptibility to multiple sclerosis governs the production of a receptor protein on the surface of a type of white blood cell called a T cell. The receptor is essential for the functioning of T cells, which orchestrate immune defenses. Other genes also probably play a role, McFarlin says. "A person would have to have just the right combination of several genes," he says, "to be prone to multiple sclerosis, which would explain why the disease is so rare."

It's not known yet how the genes that code for DR2 and the T cell receptor proteins boost the risk of developing multiple sclerosis. One possible scenario is that in a person who inherits these two genes as well as certain others, multiple sclerosis begins when a virus damages some myelin. The body's scavenger cells (macrophages) then digest the damaged myelin and in the process display myelin protein fragments in the grooves of the DR2 molecules dotting their surfaces. Patrolling T cells that would not normally bind to these self proteins do so in someone with the right genetic makeup, and prompt the destruction of other cells bearing the same protein fragments as well.

Although scientists don't know what causes multiple sclerosis, some of the pieces to the puzzle they've uncovered so far have fostered a number of experimental treatments. Researchers are testing these treatments to see if they can stave off the myelin destruction that plagues patients with the disorder.

Experimental Treatments Show Promise

One treatment uses alpha interferon, an anti-viral compound produced by the immune system that also hampers production of the DR2 grooves on cell surfaces. In a preliminary study by Kenneth Johnson, M.D., of the University of Maryland in Baltimore, a small number of multiple sclerosis patients given regular injections of alpha interferon had progressively fewer attacks. And since the start of the program four years ago, Johnson has observed no worsening of overall neurologic function or degree of disability in the treated patients. No long-term adverse side effects were noted.

Radiation treatment designed to "knock off" T cells, McFarlin says, has also stabilized—for up to four years so far—disease progression in 18 of 27 patients treated with severe forms of multiple sclerosis. The patients, studied by Stuart Cook, M.D., of the New Jersey Medical School of Newark, were given total lymphoid irradiation intermittently over a five-week period. Radiation was directed to the spleen and to lymph nodes in the neck, armpit, chest, abdomen, and groin—tissues that produce T cells. The patients suffered no serious side effects from the treatment.

Research that clearly demonstrates the safety and effectiveness of these and other experimental therapies involving immune-suppressing drugs is needed, however, before the Food and Drug Administration can approve them for treatment of multiple sclerosis. Often a treatment that seems worthy in preliminary studies doesn't pan out in controlled trials with larger numbers of patients.

In the meantime, several drugs can be used to counter some of the symptoms of multiple sclerosis. Short-term administration of ACTH (adrenocorticotropic hormone) and steroids such as prednisone can shorten the duration of attacks. These immune suppressants don't impede the long-term progression of the disorder, however, and can cause mood changes, fluid retention with consequent weight gain, high blood pressure, and ulcers. Patients given ACTH often must be hospitalized for continual monitoring for side effects.

Aspirin, acetaminophen, and other painkillers may relieve the occasional pain some multiple sclerosis patients experience. If the pain stems from muscle spasms, an anticonvulsive such as carbamazepine or muscle relaxants such as diazepam and dantrolene sodium may also help. The constant pain that afflicts some people with severe multiple sclerosis is more difficult to relieve. Tricyclic antidepressants such as amitriptyline may be helpful. Drugs that relax the bladder, such as amitriptyline, can help alleviate urinary frequency and urgency in patients with these problems.

Preventive measures are also beneficial. Overexhaustion, emotional stress, viral infections, and a rise in body temperature (from a hot bath or hot and humid weather, for example) are thought to trigger or worsen symptoms and should therefore be avoided. Patients should also follow a well-balanced and nutritionally sound diet and maintain a desirable weight.

Patients with muscle stiffness may be aided by physical therapy, and moderate exercise can help keep limbs supple and maintain muscle function. Certain exercises can also alleviate spasms.

Occupational therapy can provide multiple sclerosis patients with techniques or devices that help them perform their normal daily tasks. For example, "reachers" that help open cabinet doors, devices that aid with opening plastic bags and boxes, and a swiveling wall mirror that enables a person to see into a pan while it is bubbling on the stove can allow a wheelchair-bound patient to continue to cook meals.

Counseling can help alleviate the emotional stresses felt by multiple sclerosis patients and their families. Many people feel depressed, angry and frustrated when first confronted with their diagnosis. Part of the difficulty in coping with the disease—both for patients and families—stems from the unpredictability of the severity and frequency of symptoms. Most local chapters of the National Multiple Sclerosis Society offer counseling referrals and support groups for people affected by the disease. ■

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For More Information

For more information, contact your local chapter of the National Multiple Sclerosis Society. This organization offers a variety of services designed to provide practical assistance, emotional support, and accurate information to multiple sclerosis patients and their families. Information on research advances in multiple sclerosis can also be obtained from the information office at the National Institute of Neurological and Communicative Disorders and Stroke, Building 31, Room 8A06, Bethesda, Md. 20892.