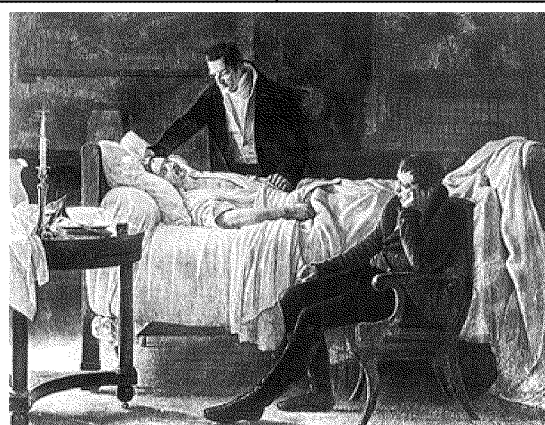


THE HISTORY OF MS

The history of multiple sclerosis (MS) is a detective story spanning more than a century. Many clues have been pieced together, but only now are answers emerging. To appreciate why the trail to a solution has been so long and hard, it is necessary to understand what we scientists now believe to be true about MS.

Multiple sclerosis is one of the most common diseases of the nervous system, afflicting people of virtually all ages around the world, although it has a special preference for young people, especially women, and for those who grew up in northern latitudes.

We believe MS involves a genetic susceptibility, but it is not directly inherited. It usually causes sudden neurologic symptoms including vision loss, paralysis, numbness, and walking difficulties. The symptoms can be diverse and confusing, often coming and going without any pattern, making it difficult to diagnose, even today.



In the 19th century, doctors could do little more than watch and wait when a patient was seriously ill. But as scientific medicine developed, physicians learned to recognize specific diseases through methodical observation, laying the groundwork for 20th-century advances. *New York Public Library, from Histoire Générale de la médecine, Paris: Albin Michel, © 1936.*

The symptoms appear because nerves in the brain and spinal cord lose their ability to transmit signals. Myelin, a complex substance that surrounds and insulates

nerve fibers, is essential for nerves to conduct electricity and carry out their function. Myelin is destroyed in MS.

In MS, cells and proteins of the body's immune system, which normally defend the body against infections, leave the blood vessels serving the central nervous system, pour into the brain and spinal cord, and destroy myelin. The specific triggering mechanism that causes an immune system to attack its own myelin remains unknown, although a viral infection on top of an inherited genetic susceptibility is a leading suspect.

The discovery of MS

Until the early years of the 19th century, physicians relied on superstition, hearsay, and the wisdom of the ancients to care for the sick. Medical ideas were not scientifically tested. Even so, physicians were sometimes good observers and we can identify people who undoubtedly had MS from descriptions written as long ago as the Middle Ages. MS has always been with us.

Once the scientific method took hold in medicine, MS was among the first diseases to be described scientifically. The 19th-century doctors did not understand what they saw and recorded, but drawings from autopsies done as early as 1838 clearly show what we today recognize as MS.

Then, in 1868, Jean-Martin Charcot, a professor of neurology at the University of Paris who has been called "the father of neurology," carefully exam-

ined a young woman with a tremor of a sort he had never seen before. He noted her other neurological problems including slurred speech and abnormal eye movements, and compared them to other patients he had seen. When she died, he examined her brain and found the characteristic scars or "plaques" of MS.

Dr. Charcot wrote a complete description of the disease and the changes in the brain that accompany it. However, he was baffled by its cause and frustrated by its resistance to all of his treatments. These included electrical stimulation and strychnine—because this poison is a nerve stimulant. He also tried injections of gold and silver, as they were somewhat helpful in the other major nerve disorder common at that time—syphilis.

A prisoner of biotechnology

In the last decades of the 19th century, the leading physicians of the world came to understand that MS was a specific disease. MS was recognized in England by Dr. William Moxon in 1873, and in the United States by Dr. Edward Seguin in 1878. By the end of the century, much of what can be learned about MS from careful observation was known: that the disease is more common in women than men, that it is not directly inherited, and that it can produce many different neurological symptoms.

But observation can go only so far. Knowledge of MS could not advance without deeper understanding of biology and better research tools. The very existence of the immune system was unknown. Doctors of the time assumed the same disease rarely struck the same person twice because a disease “used up” the materials in the body it needed to live, much the way crops use up soil nutrients and die unless they are rotated.

In the 19th century, scientists first learned that bacteria cause many diseases. As the 20th century began, they discovered even smaller organisms, viruses, and developed techniques for growing and studying bacteria and viruses in the laboratory.

In 1906, the Nobel Prize for Medicine was awarded to Dr. Camillo Golgi and Dr. Santiago Ramon y Cajal, who perfected new chemicals to enhance the visibility of nerve cells under the microscope. Equipped with this new technology, Dr. James Dawson at the University of Edinburgh in 1916 performed detailed microscopic examinations of the brains of patients who had died with MS.

Dr. Dawson wrote a description of the inflammation around blood vessels and the damage to the myelin with a clarity and thoroughness which has never been improved upon. But so little was known about the brain’s function that the meaning of these changes could only be guessed at.

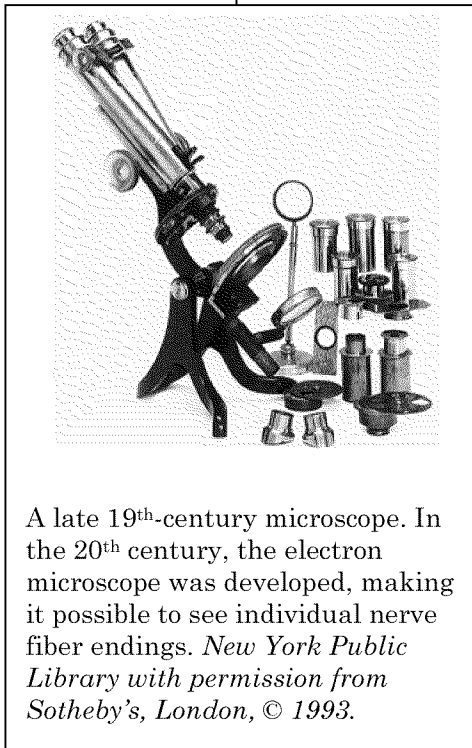
Complexities — and an unrecognized breakthrough

In the decade after World War I, MS research grew more sophisticated.

Abnormalities in spinal fluid were noted for the first time in 1919, though their significance was a puzzle. Myelin, which had been discovered in 1878 by Dr. Ranvier, was studied intensively under the microscope and the cell that makes myelin, the oligodendrocyte, was discovered in 1928.

The first electrical recording of nerve transmission, by Lord Edgar Douglas Adrian in

1925, established techniques needed to study the activity of nerves and launched a series of experiments to determine just how the nervous system works. Ultimately, six Nobel Prizes were awarded for these studies. The resulting knowledge included clarification of the role of myelin in



A late 19th-century microscope. In the 20th century, the electron microscope was developed, making it possible to see individual nerve fiber endings. *New York Public Library with permission from Sotheby's, London, © 1993.*

nerve conduction and a realization that demyelinated nerves cannot sustain electrical impulses.

At this time, scientists suspected that some form of toxin or poison caused MS. Because most MS damage occurs around blood vessels, it seemed reasonable that a toxin circulating in the bloodstream leaked out into the brain, even though no researcher could find a trace of it.

Just before World War II, an important breakthrough occurred. An animal model of MS was developed out of research on vaccines. It had been known that people vaccinated against viral illnesses, especially rabies, sometimes developed a disease resembling MS. It had been assumed that this occurred because the virus in the vaccines was not completely inactivated.

In 1935, Dr. Thomas Rivers at the Rockefeller Institute in New York City demonstrated that nerve tissue, not viruses, produced the MS-like illness. By injecting myelin he knew to be virus-free into laboratory animals under the proper conditions, he could induce their immune systems to attack their own myelin, producing a disease very similar to MS.

This laboratory animal form of MS, called experimental allergic encephalomyelitis, or EAE, would later become an important model for studying the

immunology and treatment of MS. In fact, it paved the way to modern theories of autoimmunity, for it demonstrated how the body can generate an immunologic attack against itself.

But most doctors in the 1930s were still analyzing toxins or checking blood circulation in MS. The importance of EAE to MS was virtually ignored.

Instead, a flurry of experiments in lab animals demonstrated that blocking the blood supply to the brain sometimes caused myelin to die. The damage looked a bit like MS. Doctors wondered if MS was caused by circulation problems, and they tried therapies to stimulate blood flow including blood thinners and drugs to dilate blood vessels. X-rays were also used to treat MS, although more for their novelty than for any sound scientific reason.

It would be many years before the essential similarity of EAE and MS was understood and a link between the immune system and MS was forged.

1940s: The coming of the National MS Society...

World War II focused the energies of the scientific world on new technologies. New methods and new understandings emerged from war-time research efforts in many areas.

In 1943, for example, the actual composition of myelin was determined. Then, when peace came, one of the most important catalysts in the fight against MS was created. The National Multiple Sclerosis Society was founded in 1946.

Sylvia Lawry, an extraordinary ordinary citizen whose brother suffered from the disease, placed a classified advertisement in *The New York Times* asking to hear from anyone who had recovered from MS. But all the letters she received came from others who also sought help and hope.

Instead of being discouraged, Ms. Lawry mobilized a group of friends and advisors, including some who had answered her ad. From this the National MS Society was formed to promote contacts among neurologists around the country who treated MS and to raise money to fund a search for answers.

A promising start

With remarkable foresight, the very first research grant from what was then called The Society for the Advancement of Multiple Sclerosis Research was awarded to study the immunology of MS—the relationship between the body’s immune defense system and the impact of MS on the central nervous system (the brain and spinal cord).

This 1947 grant went to Dr. Elvin Kabat at Columbia University. He subsequently identified abnormal immunologic proteins in the spinal fluid of people with MS. In lab tests, these proteins appeared as patterns known as oligoclonal bands. Oligoclonal bands not only proved to be a valuable diagnostic test for MS but also a major demonstration that MS and the immune system are connected.

A world-wide research effort begins

In the next few years, the renamed National Multiple Sclerosis Society awarded grants to scientists in 17 countries in all fields of medicine, pushing forward research that ranged from description to diagnosis and from finding a cause to searching for a cure.

Recipients of early National MS Society grants included Dr. Jonas Salk for studies on the immunology of MS and Dr. Rita Levi-Montalcini, who later won the Nobel Prize for describing proteins that help nerve cells grow and stay healthy.

A new major partner

In 1950, in a bold move, the new Society persuaded Congress to establish a special section of the National Institutes of Health. With the birth of what is now called the

