

The Basic Facts

The History of MS

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THE HISTORY OF MS

The history of multiple sclerosis (MS) is a detective story spanning more than a century. Multiple sclerosis is one of the most common diseases of the nervous system, affecting people of almost all ages in many parts of the world, although it has a special preference for young people, for women, and for those in northern latitudes. MS has a genetic susceptibility, but it is not directly inherited. It usually causes attacks of neurologic symptoms including vision loss, paralysis, numbness, and walking difficulties. These symptoms can be diverse and confusing, often coming and going without any pattern—making it difficult to diagnose, even today. These 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 damaged in MS, as well as some of the nerve fibers themselves.

The attacks strike when 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 releases the immune system to attack its own healthy tissue remains unknown, however, and the cause of MS is still its biggest mystery. How its other puzzles have been solved is a fascinating story.

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 often good observers and we can look back today and identify people who undoubtedly had MS from descriptions written as long ago as the Middle Ages.

Once doctors began to analyze illnesses scientifically, MS was among the first diseases to be described.

Drawings from autopsies done as early as 1838 clearly show what we now recognize as MS. Then, in 1868, Jean-Martin



**National
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Charcot, a professor at the University of Paris who has been called “the father of neurology,” carefully examined 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, including strychnine, a deadly poison that in small doses can stimulate nerves. He also tried injections of gold and silver, as they were standard treatments for 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. Walter 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.

Further knowledge of MS could not advance without better understanding of biology and better research tools. For example, MS could not be considered an immune disease because the very existence of the immune system was still unknown (doctors of the time assumed a disease rarely struck the same person twice because the 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. This later led to research on viral causes of MS.

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. With this new technology now available, 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 described the inflammation around blood vessels and the damage to the myelin with a clarity and thoroughness that 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. Louis Ranvier, was studied intensively under the microscope and the cells that make myelin (the oligodendrocytes) were 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 nerve conduction and a realization that demyelinated nerves cannot transmit impulses efficiently.

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, and so it attacked the myelin. In 1935, Dr. Thomas Rivers at the Rockefeller Institute in New York City, demonstrated that immune cells, 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 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”—the process by which the body generates an immunologic attack against itself. But most doctors in the 1930s were still analyzing toxins in MS and the importance of EAE was overlooked. It would be many years before the similarity of EAE and MS was understood and a link between the immune system and MS was forged.

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 abandoned their search

for toxins and instead wondered if MS was caused by circulation problems. So 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.

1940s: THE COMING OF THE NATIONAL MS SOCIETY

World War II focused the energies of the scientific world on new technologies, and research continued despite the global upheaval. 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 when the National Multiple Sclerosis Society was founded in 1946.

Sylvia Lawry, an extraordinary woman 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 system and 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. These proteins appeared in patterns known as oligoclonal bands. Oligoclonal bands not only proved to be valuable in diagnosing 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 dozens of scientists in 17 countries in all fields of medicine, pushing forward research that ranged over every aspect of MS from description to diagnosis to causes to cures. Recipients of early National MS Society grants included Nobel Prize winners such as Dr. Jonas Salk, who studied the immunology of MS, and Dr. Rita Levi-Montalcini, who described proteins that help nerve cells grow and stay healthy.

A NEW MAJOR PARTNER

In 1950, the new Society helped persuade Congress to establish a special section of the National Institutes of Health. With the birth of what is now called the National Institute for Neurologic Disorders and Stroke (NINDS), the movement against MS gained one of its strongest partners. NINDS and the National MS Society—along with members of the International Federation of MS Societies (founded by Sylvia Lawry in 1967)—have provided support for virtually every major MS researcher from that day to this.

NEW RESEARCH DIRECTIONS

An unforeseen consequence of World War II was the availability of medical information on the huge population of young men who had served in the military. Studying their MS, doctors discovered the uneven distribution of the disease. A strong geographical gradient was apparent, showing that the incidence and prevalence of MS increased steadily as one moved northward away from the equator.

Meanwhile, the immune system became an object of intense scientific study. Special immunological white blood cells called B cells were discovered and shown to produce proteins called antibodies. It was soon learned that antibodies neutralize viruses but are also capable of attacking the body's own tissues. It seemed that B cells also

produced the oligoclonal bands in MS spinal fluid.

There were more studies of EAE. Experiments showed that EAE could be transmitted by transferring T cells (another type of immunological white blood cell) from an affected animal to a well one, showing that EAE was an immune disease. And at last, scientists recognized that EAE was in many ways a model of human MS.

However, beyond the world of research, doctors who treated people with MS in the 1950s continued to suspect the cause lay in impaired blood flow, so circulation stimulators still dominated treatment. Nevertheless, doctors had not yet thought to analyze these therapies with controlled studies to track the results, so no reproducible or valid information could emerge about their safety or effectiveness. Treatments were still based more on opinions than facts.

BREAKTHROUGHS EXPAND KNOWLEDGE BUT INCREASE CONFUSION

In 1953, one of the major medical breakthroughs of the century occurred with the Nobel Prize-winning description of the structure of DNA by Francis Crick and James Watson. The way in which genes control biologic functions became clearer, including how the immune system is regulated by sequences of genes.

Additional studies on nerve conduction showed how chemicals generate electricity as they flow through channels in the nerve fiber membranes. And myelin was further broken down into its components, isolating the basic protein suspected to be the target of the MS attack.

Scientists studied B-cells, T-cells, genes, and myelin but without uncovering a clear unifying thread to direct MS treatment. The emerging scientific complexity of MS confused rather than clarified, and research gave doctors very little guidance on what was best for their patients.

CHAOS ADDRESSED BY THE NATIONAL MS SOCIETY

The National MS Society, which by 1960 had established 114 chapters to provide services for individuals and families, kept up the scientific assault. To bring order to the medical management of MS, the Society funded a panel of experts, headed by Dr. George Schumacher, to draw up standard guidelines for MS diagnosis. Although they have been refined since, the basic concept of these standards is still in use today. At the same time, a rating scale for determining the level of disability and the parts of the nervous system affected by MS was developed by Dr. John Kurtzke. These tools allowed doctors to make earlier, more accurate diagnoses and permitted research on treatments that would otherwise have been impossible.

THE FIRST VALID SCIENTIFIC TRIAL

With the ability now to make an accurate diagnosis and measure how therapies affected disability, it was possible to begin scientifically testing MS treatments. A group of patients who were having exacerbations—or acute attacks of their MS—were given adrenocorticotrophic hormone (ACTH), which is a hormone normally produced by the pituitary gland. It stimulates production of steroids by the adrenal glands. Increased secretion of these natural steroids provides an anti-inflammatory and immune-suppressing effect. The ACTH group was compared to a similar group that received a placebo (an inactive look-alike substance). The ACTH proved superior in speeding recovery. In subsequent years, treatment with ACTH was replaced by the high-dose, intravenous steroid therapy that is in use today for acute exacerbations. This 1969 study was the first to prove that a therapy could be developed that would improve the symptoms of MS. For the first time, there was a scientific treatment for MS.

1960–1970: TWO BIG IDEAS

During the 1960s, scientific research into the cause of MS came to focus on two main lines of inquiry that are still being explored today.

The first emerged from analysis of the immune system. White blood cells that react against myelin, specifically against a

component called myelin basic protein, were discovered in both EAE and human MS. This led scientists to consider the possibility that MS involves a direct immune-system attack on myelin.

The second idea came from studies that showed that people with MS have altered antibodies against viruses. This revived the older thinking that MS could be caused by a virus. But rather than a viral infection directly damaging the central nervous system, viruses involved in MS were now thought to alter the immune system and trigger it to damage myelin.

These two ideas remain closely mingled today: MS may combine features of both an infectious and an autoimmune disease. The treatments that were later developed for MS all targeted either an infectious or an immune mechanism.

1970–1980: LABORATORY ADVANCES

In 1978, the first CAT (Computed Axial Tomography) scans were performed on people with MS. And, in 1979, a Nobel Prize was awarded for development of this powerful new tool. CAT scans use a computer to link a circular array of x-ray images to create detailed pictures of the human brain. The diagnosis of MS was further improved with the introduction of brain wave tests called “evoked potentials” which measure nerve conduction throughout the optic nerves, brain and

spinal cord and often detect hidden areas of scarring and damage.

Scientific research began to yield direct therapeutic dividends as well. Steroids to suppress immune activity were now widely used to treat MS attacks, and the first small studies were performed using interferons (substances that modulate the immune system). The first studies of beta interferon for MS began at the end of the 1970s.

In 1970, scientists studying EAE in lab animals suspected that some myelin protein fragments prevented the disease and actually seemed to protect the animals. Spurred by this finding, they synthesized a mix of protein fragments and used it to treat first animals with EAE and then humans with MS. The product was named copolymer1 and is today an approved disease-modifying therapy under the new name glatiramer, or Copaxone®.

1980–1990: TREATMENT TRIALS BEGIN IN ERNEST

Scientists began to understand in more detail how white blood cells are activated by foreign substances to mount attacks. One activating trigger can be a virus. Scientists also learned that parts of some viruses look so much like normal human tissue that white blood cells will inadvertently attack that tissue when they attack the virus. This is yet another mechanism by which viral infections could lead indirectly to destruction of myelin—when immune

attacks on myelin-like viruses spill over onto the myelin itself.

At about the same time, the white blood cell type that causes the actual damage to myelin in MS was finally identified. It is the macrophage (or “Big Eater” in Greek).

The first studies of identical and fraternal twins begun in this decade extended knowledge about the genetics of MS. The twin of a person with MS often does not develop the disease, proving that genes determine only part of the MS risk, though their influence is important. Meanwhile, psychosocial and mental-health issues, as well as the cognitive changes that can be caused by MS, began receiving long overdue research attention.

CAT scanning technology was refined to produce the MRI (Magnetic Resonance Imaging) scan, which shows the brain in greater detail. The first MRI scans of people with MS were performed in 1981 by Dr. I R Young, in England. By 1984, it became apparent that MRI could actually see MS attacks within the brain, including many which did not cause any symptoms. By 1988 sequential MRI scans changed the entire concept of MS by showing that it is a constant, ongoing disease even though relapses with symptoms may appear only sporadically.

The 1980s may legitimately be called the “treatment decade” in MS. There was an explosion of new drug trials. Guided by

the National MS Society, scientists reached a consensus on the design and conduct of research for new treatments, and dozens of different therapies were tested in attempts to control or cure MS. Major clinical trials conducted during this decade finally found the first drugs in history shown to affect the course of this disease.

1990–2000: DECADE OF THE BRAIN

As the final decade of the 20th century approached, the Congress of the United States made a special effort to accelerate medical research. Recognizing the paramount importance of neurological disease, they designated the 1990s as the “Decade of the Brain” and purposefully funneled funds, time, and talent into the treatment of illnesses that affect the nervous system. Multiple sclerosis benefited enormously from these efforts, and an explosion of drug trials occurred during this period.

MRI TECHNOLOGY

Many of the decade’s advances sprang from the incredible power of new technology. Sophisticated techniques added to MRI allowed it to detect MS plaques earlier and more accurately than ever. That led to more rapid diagnosis of the disease. In 1970, the average time from a person’s first symptom of MS until a definite diagnosis was 7 years, but use of MRI technology reduced

the time to six months. Now the plaque that causes symptoms could often be seen immediately. The power of a rapid, painless MRI scan to provide information is an incalculable blessing for doctors and patients alike. Studies with a series of MRI scans over time showed how MS plaques actually develop and permitted researchers to track the “burden of disease” (total plaque area) in individual patients. At the same time, MRI scanning gave researchers faster and more sophisticated ways of testing drugs to treat MS. The benefits of a new drug can be seen on MRI scans before they can be seen in patients themselves. Research on the treatment of MS was thus greatly accelerated.

HIGH-TECH LABORATORY DISCOVERIES

Most diseases yield their secrets only through the painstaking laboratory work of research scientists. Laboratory work on MS showed us many essential aspects of the disease. A key culprit in MS is the white blood cell called a T cell. Although many details about the sequence of events in the process still remain to be learned, we know that T cells become activated, leave the bloodstream, and enter brain tissue to damage myelin, the fatty tissue that insulates and protects nerve fibers. This T cell has now been identified and characterized in detail. Recent discoveries also emphasize that myelin is not the only target for destruction in MS. Often the

underlying nerve cells, the neurons and their axons, are damaged as well, which is thought to account for some of the permanent disability MS causes.

GENE RESEARCH OFFERS CLUES

During the 1990s, the American-led project to discover and decode all the genes in the human body focused attention on the role of genes in many diseases. A monumental study of 15,000 people with MS, including some identical twins who were reared miles apart in different families, clearly demonstrated that genes play a role in determining who gets MS and who does not. Although there does not appear to be any single “MS gene,” there does seem to be something fundamental to each of us (i.e., something in our genes) that makes one person susceptible to developing MS and another not. This is yet another clue for the cause of the disease.

THE INFORMATION AGE

Of course, the sophisticated technology of the 1990s was not limited to medicine. There were quantum leaps in computers as well. During the “Decade of the Brain” computer scientists built the information superhighway and wove the Internet. Faster, better communications and data analysis brought MS doctors and researchers from all over the world together in increasingly powerful coalitions. Large databases were assembled to track and analyze thousands

of patient histories to clarify their disease variations and their responses to treatment. Characteristic patterns of MS began to emerge. MS clinics and research laboratories are now linked and share and evaluate new findings.

THE TREATMENT PAYOFF IN THE NEW MILLENNIUM

The symptoms of MS have never been as amenable to therapy as they are now. Tizanidine was introduced for management of spasticity. Use of the intrathecal baclofen pump for severe spasticity became more widely available. It delivers medication directly to the spinal cord to relieve intense muscle stiffness and spasms. Improvements were made in medications for bladder management (e.g., tolterodine) and for fatigue (modafinil). Treatment of sexual problems, a long-neglected aspect of MS, took a major leap forward with the introduction of sildenafil (better known as Viagra®) and other similar medications. Gabapentin was introduced to treat many painful symptoms ranging from severe face pain (trigeminal neuralgia) to burning pains in the limbs. Other drugs are being developed at a rapid pace.

Research also revealed many ways in which MS can alter the mind, slowing down thinking and affecting memory. New drugs, such as donepezil, used to treat these problems in Alzheimer's disease, are now being tested in MS. Refinements in

rehabilitation, exercise, and physical therapy also benefited people with MS. These and many other new treatments have markedly enhanced the ways physicians can calm symptoms and improve the quality of life.

Years of research with drugs to treat the actual disease—and not just its symptoms—came to fruition when beta interferon 1-b (Betaseron®) was introduced in 1993. Beta interferon 1-a (Avonex®) was introduced in mid-1996, and glatiramer acetate (Copaxone®) arrived in late 1996. Two years into the new century, a variation of beta interferon 1-a (Rebif®) was also introduced. The course of MS could now be altered by reducing disease activity and preventing many attacks.

In 1999 mitoxantrone (Novantrone®) was approved for treating MS and was especially useful against the slow chronic progressive forms of the disease, which none of the other therapies had been able to retard.

Nataluzimab (Tysabri®), the first of a whole new class of drugs called monoclonal antibodies, significantly suppressed relapses of MS in several large trials. Treatments began in 2004, but widespread use was delayed while procedures were developed to minimize the serious infections some patients developed during treatment with the drug.

Progress has thus been remarkable. Throughout history MS was an untreatable disease. Then in one decade (1993–2004)

researchers developed 6 drugs that suppress attacks and alter the course of MS. Many more drugs are being tested. These include oral cladribine, which may well be the first oral disease-modifying therapy to be approved for MS; two new monoclonal antibodies, rituximab (Rituxan®) and alemtuzumab (Campath®), which destroy the immune cells regulating MS attacks; and Fingolimod, a drug that blocks those cells from entering the nervous system. Further studies will clarify the value of these treatments, but whatever their ultimate role, there are nearly 100 more drugs being tested now.

The history of MS is still being written, but more has been accomplished to fight MS in the last decade than in the preceding century. Let us hope the new century will see our victory.

Written by Loren A. Rolak, MD.

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