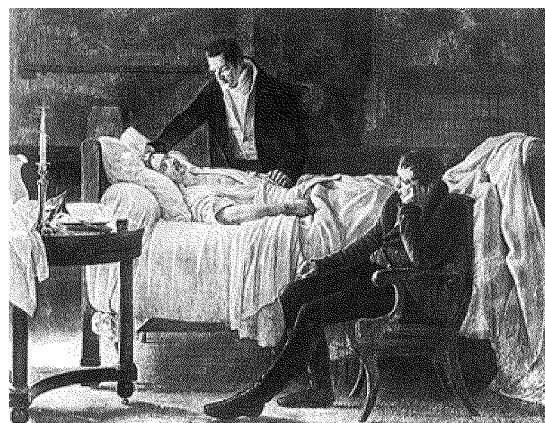


THE HISTORY OF MS

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.

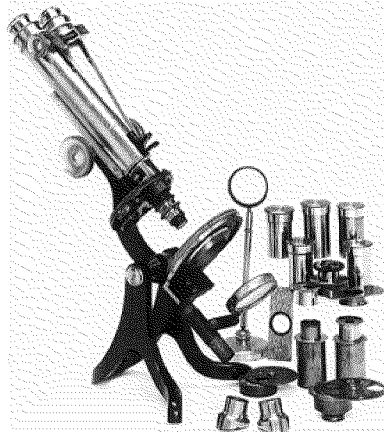
Complexities — and an unrecognized breakthrough

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

National Institute for Neurologic Disorders and Stroke (NINDS), the movement against MS gained one of its most essential partners. NINDS and the National MS Society—along with members of the International Federation of MS Societies, which was also founded by Sylvia Lawry in 1967—have supported virtually every major MS study from that day to this.

New research directions

An unforeseen consequence of World War II was the availability of medical information on a huge population of mostly young men who had served in the military. For the first time, the uneven distribution of MS was appreciated. A strong geographical gradient was apparent, showing that the incidence and prevalence of MS increased steadily as one moved northward or southward away from the equator.

Meanwhile, the immune system became an object of intense scientific study. Special white blood cells called B cells were discovered and shown to produce proteins called antibodies. It was soon learned that antibodies neutralize viruses and other infectious

agents. Antibodies are also capable of attacking the body's own tissues.

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

But, 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 dominated treatment. These therapies were used without controlled studies to track the results, studies called clinical trials, so no reproducible or

valid information could emerge about either safety or effectiveness.

Breakthroughs expand knowledge but increase confusion

In 1953, one of the major medical breakthroughs of the century occurred with the Nobel Prize-winning descrip-



Ms. Sylvia Lawry and her first board of advisors.

tion of the structure of DNA by Francis Crick and James Watson. The way in which genes control biologic functions became clearer—as did ideas about how viruses work and how the immune system is regulated.

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

This era saw scientists striking out on many different paths, testing many possibilities, and formulating many new theories, but without uncovering a clear unifying thread to direct MS treatment. Meanwhile, doctors continued to struggle with the challenge of diagnosing and treating people with MS. The emerging scientific complexity of MS confused rather than clarified their challenge. So while much was being learned, research could give doctors very little guidance on what was best for their patients.

Chaos addressed by the National MS Society

Some in the MS community were disaffected by this situation. They felt the MS movement should concentrate solely on services for people living with MS. Perhaps the mystery was too complex to be solved. The National MS Society, which by 1960 had esta-

blished 114 local 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, these standards are 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 refined by Dr. John Kurtzke.

Having standards helped doctors make earlier, more accurate diagnoses and allowed research on treatments to be conducted with greater reliability.

The first valid scientific trial

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 corticosteroids by the adrenal glands. Increased secretion of these natural steroids provides an anti-inflammatory and immune-suppressing effect. The experience of the ACTH group was compared to that of 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 corticosteroid therapy that is in use today for acute exacerbations.

This trial used the new rating scales and diagnostic standards to ensure that results seen in the treated and untreated groups could be compared accurately. The way to solid progress was now open.

1960-1970: Two big ideas

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

The first emerged from a finding about 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.

1970-1980: Laboratory advances

Understanding of immunology was enhanced as doctors learned to prevent the immune system from rejecting transplanted organs. Intensive studies of EAE further linked MS to the part of the immune system that makes tissues compatible with each other.

In 1978, the first CAT 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 tests called “evoked potentials” which measure nerve conduction.

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 and then humans with MS. The product was named copolymer 1 and is today an approved disease-modifying therapy under the name Copaxone.

1980-1990: Explosion in clinical trials

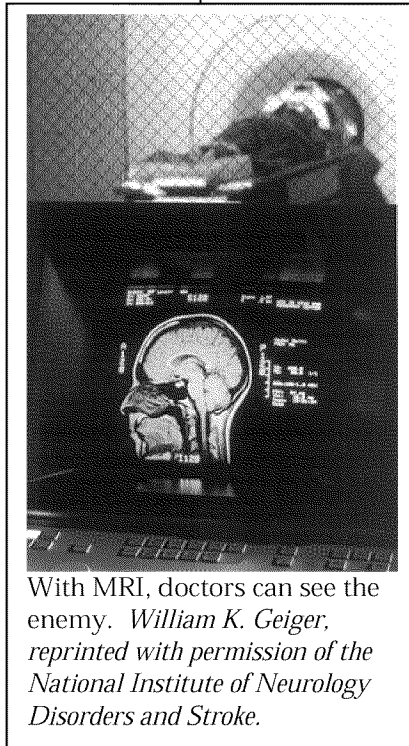
Scientists began to understand in more detail how white blood cells are activated by foreign substances to mount attacks. One activating trigger can be a virus. Scientists also learned that parts of some viruses look so much like normal human tissue that white blood cells will inadvertently attack them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

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. And psychosocial and mental-health issues, as well as the cognitive changes occasionally caused by MS, began receiving long overdue research attention.

CAT scanning was surpassed by a new technology, the MRI scan, which show 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 the MRI could actually see MS attacks within the brain, including many which did not cause any symptoms. By 1988 sequential MRI scans showed that MS is a constant, ongoing disease even though symptoms may appear only sporadically.



With MRI, doctors can see the enemy. *William K. Geiger, reprinted with permission of the National Institute of Neurology Disorders and Stroke.*

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

the National MS Society, scientists reached a consensus on the design and conduct of research for new treatments. For the first time the emphasis could shift away from palliation, where the aim is to help people with MS feel as good as possible for as long as possible, and go

instead toward attempts to control or cure the underlying MS.

Major clinical trials conducted during this decade led to approvals of 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.

MRI changed our picture of MS

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 (areas of scarring and damage in the brain or spinal cord) earlier and more accurately than ever. That led to more rapid definite diagnoses of the disease.

In 1970, the average time from a person’s first symptom of MS until a definite diagnosis was 7 years. This often meant 7 years of uncertainty, anxiety, and missed opportunities.

Now, the plaque that causes symptoms can often be seen immediately. The power of a rapid, painless MRI scan to provide information for the diagnosis is an incalculable blessing for doctors and patients alike.

MRI also changed MS treatment

Studies with a series of MRI scans over time showed how MS plaques actually develop and permitted researchers to track the “burden of disease” in individual patients. This clarified the nature of MS and forced us physicians to alter our fundamental concept of the disease. Serial MRI studies confirmed that the disease is often very active even when patients feel no symptoms. MS is not, as we once believed, a disease that flares up only intermittently with periodic attacks or exacerbations. Rather it is an almost constantly ongoing illness that can cause silent damage within the nervous system. These findings added urgency to the need for effective treatment to reduce this silent damage as early as possible.

At the same time, MRI scanning gave researchers faster and more sophisticated ways of testing drugs to treat MS. The disease is slow and often subtle. 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 protein substance 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. This may account for much of the permanent disability MS causes. Myelin might be repaired or restored by natural processes in the body, but not nerve cells. Once lost, their failure is permanent.

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 there is a genetic determinant to 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), which helps determine who will get MS. This is yet another clue to the cause of the disease.

The Information Age kicks in

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. We were able to identify characteristic patterns of MS. MS clinics and research laboratories are now linked. And MS research groups such as the Americas and European Committees for Treatment and Research in MS (ACTRIMS and ECTRIMS) share and evaluate new findings.

Computer technology now benefits not only researchers but also people affected by MS. Anyone with access to the Internet can tap into networks of information and support. The Internet

has become a marvelous window to the world, accessible to people at virtually every level of ability.

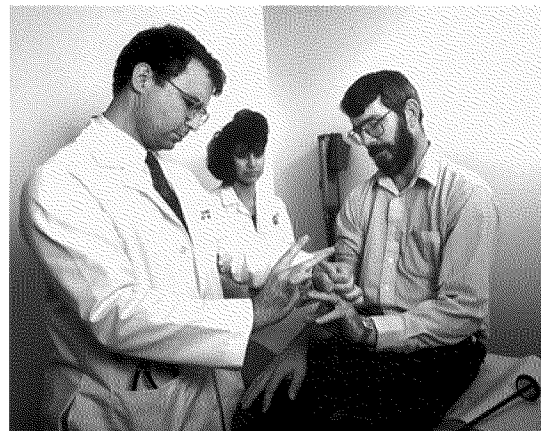
The treatment payoff—for symptoms

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 widespread. It delivers medication directly to the spinal cord to relieve intense muscle stiffness and spasms. Improvements were made in medications for bladder management (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). Gabapentin was introduced to treat many painful symptoms ranging from severe face pain (trigeminal neuralgia) to burning pains in the limbs.

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 we physicians can calm symptoms and improve the quality of life for our patients.



Clinical trials provide proof that treatments for MS work—or don't work. Dr. Jack Ownby and Dr. Milvia Pleitez examine Clayton Farr. *Reprinted with permission of Baylor College of Medicine.*

The treatment payoff—for MS

I've saved the most historic events of the "Decade of the Brain" for the last.

Years of research 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 for injection (Copaxone) arrived in late 1996. Two years into the new century, a variation of beta interferon 1-a (Rebif) was also introduced, giving U.S. patients four options. The course of MS can now be altered by reducing disease activity and preventing many attacks.

Subsequent research has confirmed and further demonstrated their benefits of these disease-modifying drugs, affirming their value. Before the 1990s, people had no power to change the course of their MS, but

today tens of thousands of people worldwide are benefiting from these drugs.

The battle in context

To appreciate these changes we need only to look back.

- MS was first described in 1838, but it was 30 years before doctors recognized it as a specific disease.
- In 1900, the life expectancy of a person with MS was just five years.
- At the start of World War II, 100 years after MS was first described, the standard therapy was blood thinners because of the mistaken belief that MS was a problem with circulation.
- The first demonstration of immune system changes in laboratory studies of MS took place in 1935, but it was not until after World War II that an immunologic cause of MS was seriously investigated.
- It was not until 1970 that the first positive results of treatment with an immunologic therapy (steroids) were published.

- In the 1990s, the disease-modifying drugs became the first line of medications that fight MS directly.

Since then, our understanding of MS has grown quickly. Indeed, more has been accomplished to fight MS in the last decade than in the preceding century. The new century will see our victory.

Written by Loren A. Rolak, MD.
Reviewed by the Client Education
Committee of the National MS
Society's Medical Advisory Board.

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