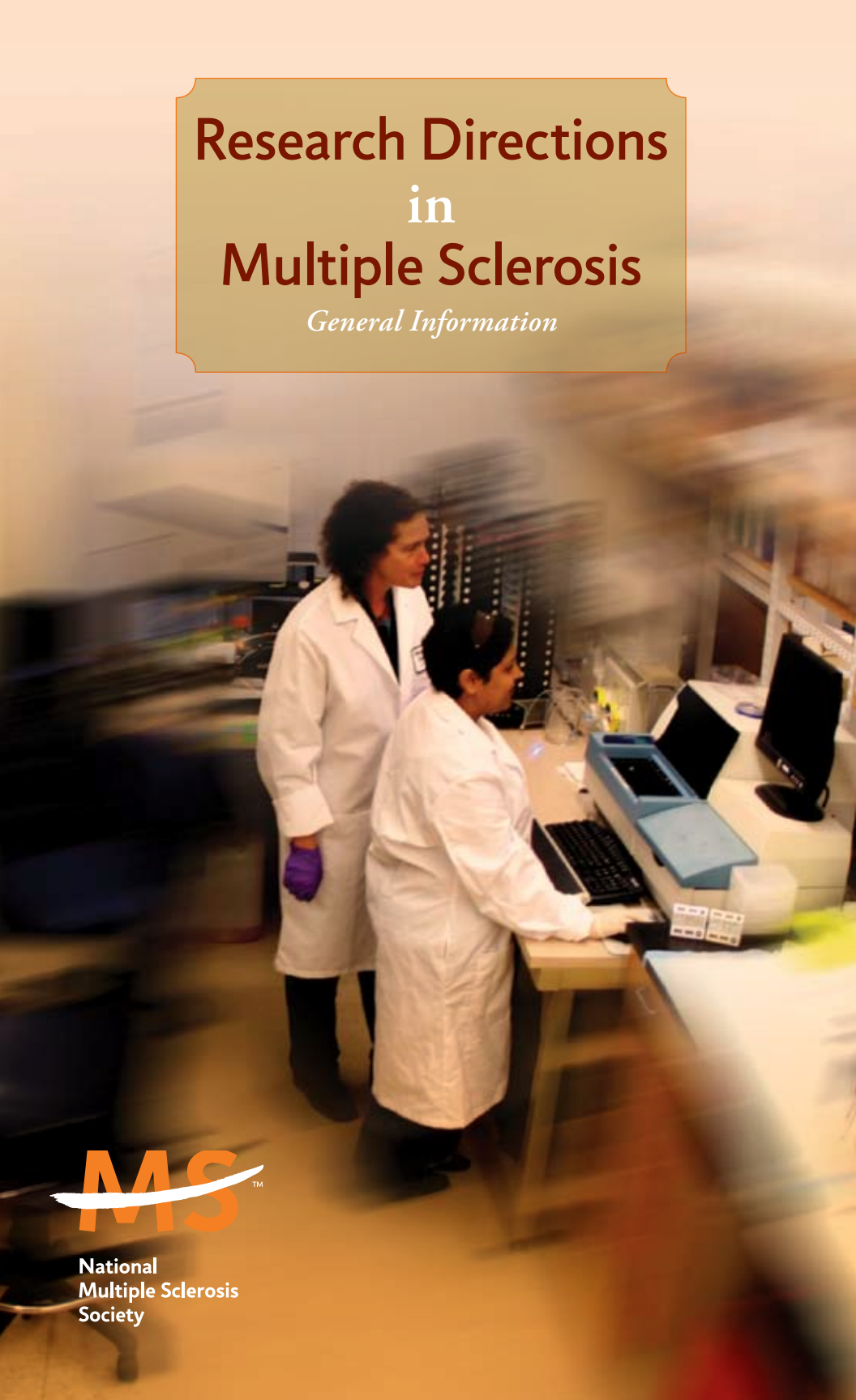
Research Directions in Multiple Sclerosis

General Information



National Multiple Sclerosis Society

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Cover: MS Researcher at Brookdale Center for Molecular Biology, Mt. Sinai School of Medicine, New York. Photograph by Bill Stanton.

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Research Directions in Multiple Sclerosis

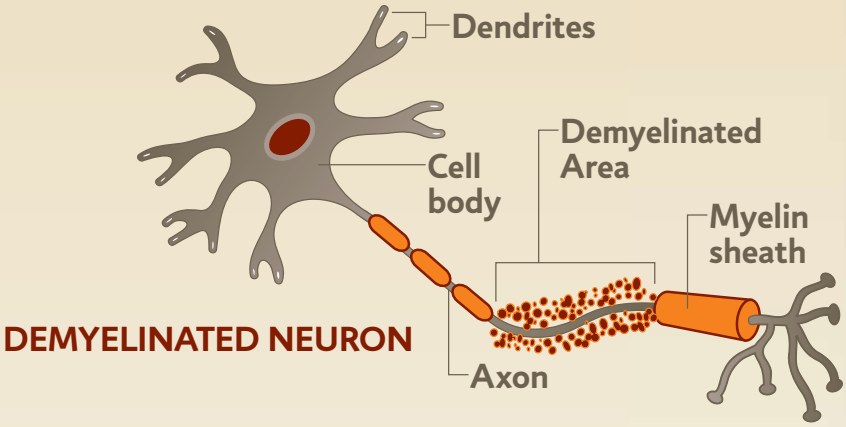
by John Richert, MD, and Diana M. Schneider, Ph.D.

Research Directions in Multiple Sclerosis

Multiple sclerosis (MS) is one of the most common neurologic disorders of young adults, affecting approximately 400,000 Americans and an estimated 2.5 million people worldwide. Advances in research have led to tremendous progress in the diagnosis and management of MS. Safe, effective treatments are now available to reduce disease activity for most forms of MS, and significant relief of many symptoms can be achieved. Research continues to accelerate, with new findings occurring virtually every month. Now, more than ever, there is hope that we will uncover the cause of MS and find its cure.

What Is Multiple Sclerosis?

The neurologic symptoms of MS are the result of inflammation and the breakdown of myelin that surrounds nerve fibers (*axons*) in the central nervous system (CNS, which includes the brain, spinal cord, and optic nerves), as well as the loss of the nerve fibers themselves. Nerve fibers function like electrical cables: the axon is analogous to the copper wire and the myelin serves as the insulation that surrounds it. Sensory organs such as the eyes, ears, or skin send information about the environment along these axons to the brain



and spinal cord, and signals are sent back to muscles with "instructions" in response. Other pathways are involved with cognition and other functions. In MS this transmission of information is slowed or interrupted.

Patterns of Multiple Sclerosis

In about 85% of people who develop MS, the disease begins with a "relapsing-remitting" course (RRMS) (Figure 1), characterized by acute attacks (relapses) with unpredictable timing and severity followed by periods of remission with complete or partial recovery. Over time, there tends to be a gradual accumulation of disability, all of which occurs during the relapses, and the periods between relapses are stable. Without treatment, over half of these individuals eventually develop "secondary-progressive" disease (SPMS) (Figure 2), characterized by a steady increase in disability with fewer or no clear attacks. It is

Disease Course Classifications in Multiple Sclerosis

Figure 1
Relapsing-Remitting

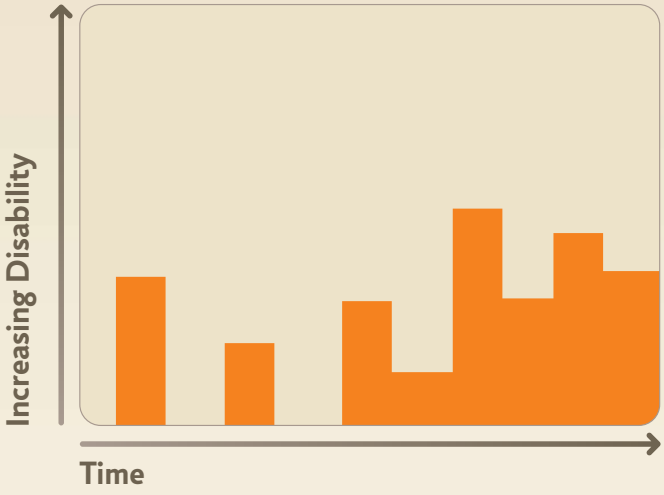


Figure 2
Secondary-Progressive

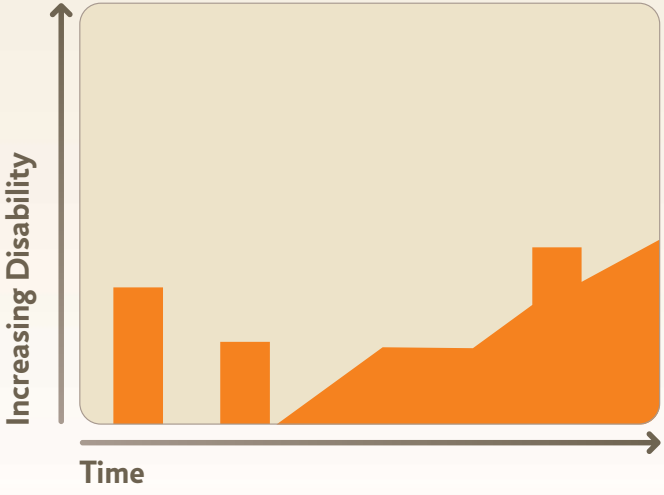


Figure 3
Primary-Progressive

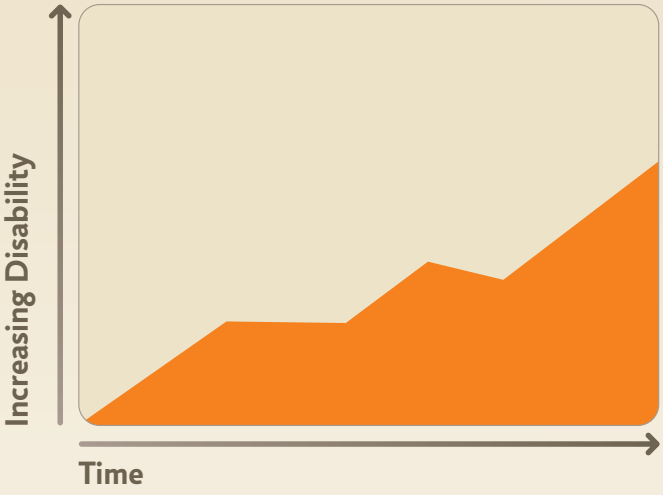
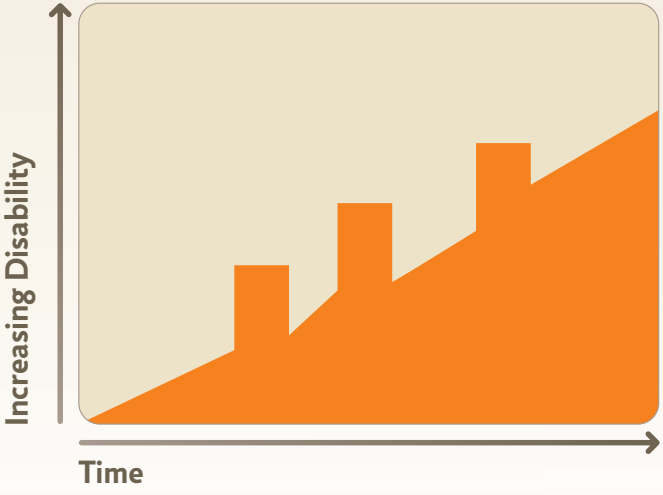


Figure 4
Progressive-Relapsing



too early to know if the disease-modifying treatments now available will decrease the number of people whose disease progresses in this fashion. However, preliminary data that point in this direction are encouraging.

About 10% of people with MS show steady progression of disability from disease onset, without recognizable attacks. This "primary-progressive" form of MS (PPMS) (Figure 3) is frequently diagnosed in individuals in their forties or fifties. Another relatively rare form, experienced by about 5% of people who develop MS, is progressive-relapsing MS (PRMS) (Figure 4). People with this type of MS experience steadily worsening disease from the onset but subsequently also have clear acute relapses, with or without recovery. In contrast to relapsing-remitting MS, the periods between relapses are characterized by continuing disease progression.

The Symptoms of Multiple Sclerosis

MS symptoms vary greatly, both for a given individual over time and from person to person. Many people initially experience problems that include double or blurred vision, numbness or tingling, or other unusual sensations. Other symptoms commonly affect mobility; these include weakness, spasticity, fatigue, and tremor. Bladder and bowel problems are common, as are difficulties with speech, thinking, and memory. In more severe situations, a substantial degree of paralysis may occur.

Most people with MS will have a normal lifespan, although they can expect to live with some uncertainty about the course of their disease. While MS is rarely fatal in and of itself, complications may contribute to a shortened life span in the most seriously affected individuals.

A History of Multiple Sclerosis Research

In the United States, the National Multiple Sclerosis Society and the National Institutes of Health (NIH, part of the federal government) provide the vast majority of MS research and training support in every conceivable biomedical research area. "To end the devastating effects of MS" is not just the Society's mission, but also the dream upon which it was founded. To this end, the Society has actively supported research since 1947. Thanks to the support of generous friends and donors, the Society has been able to allocate hundreds of millions of dollars to funding innovative research programs around the world, and it currently funds more research than any other MS organization.

Physicians and scientists funded by the Society, in collaboration with the NIH, other government agencies, and the pharmaceutical industry, have made enormous strides in understanding what causes MS. This knowledge is rapidly leading to the development of strategies to

treat and manage the disease and its symptoms. Current research efforts are also aimed at developing therapies to reverse damage and restore function.

Research in the 1960s and '70s strongly indicated that MS involves the immune system "turning against" the *myelin* that normally wraps around nerve fibers in the brain and spinal cord and serves as insulation for the nerves. This *myelin sheath* is necessary for normal nerve conduction and probably also for the normal health of the axon. In MS, the myelin breaks down and is replaced by scar tissue. This results in slowing and even complete blocking of conduction of the electrical impulses along the nerve. When this occurs, the body functions that are regulated by the now-damaged nerves become impaired or completely lost. With the loss of its protective myelin sheath, the underlying nerve fibers also become damaged and this probably also contributes to disability.

Increasing knowledge about the immune attacks that underlie MS has been the basis for the development of treatments that modify immune function. It has also led to current experimental therapies that show promise for actually protecting the brain and spinal cord tissue from damage caused by the abnormal immune responses involved in the disease.

Research on the immunology of MS, along with demographic information about who develops the disease, led to the idea that the immune attack in MS may be triggered by an environmental agent such as a virus or

bacterium. Society-funded researchers were among the first to report that the cells of the immune system that appear capable of attacking the nerve tissue in MS also react to certain viruses and bacteria. This suggested that infectious agents might be "triggers" for developing MS. It is clear, however, that MS is not a contagious disease; people do not "catch" MS from other people.

Although there is strong evidence for a genetic component in MS, genetic factors are not by themselves capable of causing the disease. Most likely, an individual's genetic blueprint determines whether she or he will respond to a triggering factor in the environment, as well as the patterns of the immune response that lead to the development of MS. In other words, a person who has inherited the multiple gene variations that are likely linked to MS has a *susceptibility* to develop MS, but will not necessarily do so.

The development of magnetic resonance imaging (MRI) in the 1980s made it possible to "see" the damage done by MS. This technology is now widely used to confirm the diagnosis of MS, and has shortened the time between the appearance of symptoms and diagnosis. As MRI technology has become more sophisticated, its ability to show damaged tissues in the brain and spinal cord has led to a better understanding of the disease process, as well as to the ability to demonstrate changes in tissue damage and slowed disease progression in response to disease-modifying therapies.

The 1990s brought about significant advances in symptom management, as well as the first drugs to slow the underlying disease process. Six drugs are now FDA-approved to treat relapses and MS progression: Avonex® (interferon beta-1a), Rebif® (interferon beta-1a), Betaseron® (interferon beta-1b), Copaxone® (glatiramer acetate), Tysabri® (natalizumab) and Novantrone® (mitoxantrone). Other drugs are now in advanced stages of testing.

We now know that myelin repair occurs naturally to some degree and that adult brains store early-stage cells that are capable of maturing into "oligodendrocytes," which can repair damaged myelin. This process seems to be inhibited in MS, for reasons that are not yet clear. This new understanding offers hope that myelin repair can be stimulated to improve function and protect nerve fibers.

Current research takes many directions, including: what causes MS; how can the disease be prevented; how can we better stop the immune attack on the nervous system; how can existing damage be reversed or its effects minimized; and how can we better deal with the social, psychological, and policy issues that result from living with the disease.

The Search for Solutions

As substantial as advances in MS research have been, much remains to be understood. The National MS Society—in collaboration with other research efforts—sponsors research to find solutions at every stage of the

disease. To understand how current research programs are structured, it helps to think of them as a search for "three cures": Stop, Repair, and Prevent.

The First Cure: Stop Disease Activity

Essentially all research that may help us learn how to stop disease activity ultimately requires a better understanding of the role that the immune system plays in MS. This system is involved both in the inflammatory attacks on myelin and, very possibly, in the axonal injury that appears to contribute to longer-term disability. This includes studies on components of the immune system such as T cells, B cells, and antibodies; understanding why women are affected by MS more than twice as often as men; determining whether differences in disease pattern hold a key to better therapies; identification of new targets for therapeutic intervention; and the identification of substances that are involved in producing axonal injury.

We especially need to know more about the molecules that the immune system uses to attack the nervous system, because each of these serves as a potential therapeutic target for new therapies, with the aim of treating the disease while leaving the rest of the immune system capable of fighting infections. Researchers are also identifying the body's natural immune messenger molecules that *dampen* abnormal immune activity

and that may therefore be used as therapies, as well as developing "decoys" to waylay attacking immune cells.

A few examples of the studies that the National MS Society is currently funding are discussed below.

The MS Lesion Project

- Because a treatment that helps a person with one MS lesion pattern may not help someone with a different pattern, the MS Lesion Project was designed to determine whether specific characteristics of *lesions*—areas of brain tissue in which myelin has been lost—will reveal why people experience the disease so differently. The goals of the MS Lesion Project are to better understand these patterns and to find ways to tell the difference among them with non-invasive tools such as MRI. The Project is centered at the Mayo Clinic, in collaboration with an international team. They are analyzing tissue specimens from people with active MS (obtained through brain biopsies—a rare procedure) or through tissue donation after death. Their research suggests that different lesion types may be related to differences in disease type and prognosis, and perhaps to different responses to treatment. If the lesion patterns can be distinguished on MRI, in the future it may be possible to determine patterns noninvasively and to use this information to direct treatment.

Immune System Function and Disease-Modifying Therapies

- No drug is as yet approved for the treatment of PPMS, and questions remain as to whether this type of MS might be an entirely different disease, rather than a variant of RRMS. Investigators at the University of Texas Southwestern Medical Center are analyzing blood samples from individuals with PPMS and RRMS, including people who participated in the glatiramer acetate PPMS clinical trial and those with RRMS who were treated with glatiramir acetate or interferon beta as part of their ongoing therapy. The investigators aim to shed light on the immune forces at work during the course of these various types of MS and how they may differ, including how they differ in their response to therapy.
- A Collaborative MS Research Center Award to Stanford University is applying new techniques in molecular biology to study the immune attack in MS, with the goal of identifying targets for therapies aimed at specific components of this attack. They have also identified a protein, called alpha B crystallin, that appears to play a significant protective role in the production of nervous system inflammation and which has the potential for being tested as a new therapeutic agent. The Stanford team is also zeroing in on other potential therapies through this Collaborative Center Award.

- Injecting a "foreign" protein into the body can produce antibodies that bind to it and block (neutralize) its action or lead to its destruction. If the foreign protein is part of an infectious agent, such as a virus, the antibody attacks the virus and neutralizes its ill effects. If the injected protein is a therapeutic agent, the antibody may block the drug's effectiveness. Investigators at the University of Medicine and Dentistry of New Jersey are measuring the levels of antibodies that attack interferons before and after interferon therapy. The purpose is to determine the extent to which the antibodies may block the clinical effects of interferon treatment, and whether this leads to a poorer outcome. These findings may lead to major changes in how interferon therapy is monitored, and help to identify people for whom further treatment may or may not be successful.
- Current FDA-approved disease-modifying agents are only partially effective; they reduce the frequency of relapses but don't eliminate them, and they slow the rate of disability progression but don't stop it completely. There is a clear need for new therapies that will target the specific immune system components that contribute to inflammation, as well as promote the protection and regeneration of myelin and nerve fibers. The Collaborative MS Research Center at the University of Rochester Medical Center is seeking to develop therapeutic vaccines and immune-modulating agents that adjust or modify how the immune system functions, in order to improve the treatment of MS and advance nervous tissue repair.

Cellular and Molecular Components of the Immune Response in MS

- Researchers at the University of Maryland Biotech Institute are attempting to design a drug that will stop T cells of the immune system from recognizing and attacking myelin. This work is the result of very sophisticated studies of the 3-dimensional structure of myelin-reactive and virus-reactive T cell receptors using X-ray crystallography techniques.
- Researchers at the Mayo Clinic are investigating the possible role in axonal injury of a molecule called perforin, which is secreted by cells of the immune system and perforates the outer skins or membranes of "foreign" or virus-infected cells, causing them to die. In mice with an MS-like disease, the axons of those that lack the gene for perforin remain uninjured. Identifying mediators of axonal injury, as perforin appears to be, may lead to therapies that will prevent such injury in people with MS
- B cells, a major component of the immune system, make antibodies that may play a key role in the development of MS. Investigators at Washington University in St Louis are testing the safety and preliminary measures of efficacy of Rituxan® (rituximab), a drug that depletes B cells from the immune system, when used in combination with existing therapies in people with relapsing-remitting MS. All participants have taken interferon beta or glatiramer acetate but continue to demonstrate MS disease activity. They will continue to take these

medications while receiving Rituxan by infusion. Three MRI scans are taken before infusion and three taken after treatment has been completed. These will be compared to assess the drug's impact on the number and size of MS brain lesions. If combining Rituxan with other drugs proves to be safe and shows possible signs of benefit, a larger trial will be warranted. Larger-scale studies of Rituxan alone are already underway, including a trial in people with primary-progressive MS.

Why Are More Women Than Men Affected by MS?

- The National MS Society's $10 million Gender Initiative, completed in 2005, was based on the fact that MS affects women two to three times more often than men, and also on the knowledge that pregnancy has a temporary beneficial effect on MS disease activity in women. Among the findings arising from its 50 funded projects was the possibility that the female hormone *estriol* may help protect against the immune attacks that underlie MS. Levels of this hormone rise significantly during pregnancy. A small, early-phase trial at the University of California at Los Angeles (UCLA) showed a decrease in disease activity during estriol treatment, and a two-year clinical trial involving 130 women with newly diagnosed relapsing-remitting MS is now ongoing. If successful, it will lay the groundwork for a larger trial that could lead to a new oral treatment option for women with MS. Although men aren't part of this study, researchers are

now looking to see whether testosterone might have a similar effect in men with MS. The rationale for this study is that the lesser frequency of MS in men (and therefore a potential protective effect related to male gender) may be related to testosterone.

The Second Cure: Repair the Nervous System

The aim of repairing the nervous system is to achieve an actual *reversal of* the damage caused by MS and to restore function. When myelin is damaged or destroyed, electrical conduction along the nerve fiber is impaired or stopped. For decades it was debated whether, once lost, central nervous system myelin could be regenerated. We now know that myelin *can* be repaired—axons *can* be "remyelinated." Remyelination occurs because cells within the brain and spinal cord are capable of forming new myelin, and because "immature" myelin-making cells begin to divide, multiply, and produce myelin in response to tissue damage. However, in MS, myelin loss proceeds more aggressively and quickly than remyelination. In addition, the ability to remyelinate decreases over a period of years. It is critically important that we develop therapies to restore nerve function by helping the body make new myelin and thus prevent or reverse tissue damage.

Regeneration of damaged axons is a more difficult matter. Until the past decade, it was generally believed that axons are spared in MS, and the concept of restoration of function was thought to rely solely on learning how

to better remyelinate the demyelinated axons. However, within the past decade, a much greater understanding of the MS disease process has led to the knowledge that substantial axonal loss also occurs in MS. Thus, a new additional research focus has emerged: in order to repair the nervous system, we must learn how to regenerate axons as well as myelin.

The question is this: although damaged axons in the *peripheral* nervous system (e.g., nerves in the arms and legs) are able to regenerate and regrow, damaged axons in the *central* nervous system (brain, spinal cord, and optic nerves) do not regenerate. The reasons for this are only now being clarified. For example, recent data indicate that there are proteins in normal mature myelin that inhibit the growth of axons. Although this mechanism makes sense for controlling the normal growth and development of the nervous system as one progresses through childhood into adulthood, it is counter-productive when it comes to repairing the damaged central nervous system. However, insights into these mechanisms now make it feasible to aggressively address the task of repairing axons as well as myelin in MS.

Approaches to repairing the nervous system are varied. Some are aimed at inducing the body's own cells to more adequately carry out the repair function. Another approach is to introduce replacement cells from a different source. Research into the potential of stem cell therapy is proceeding rapidly, using cells obtained from a variety of adult and non-adult sources. It is currently not clear which source of stem cells, if any, will be of value in treating

people with MS. Similarly, if more than one source proves to be valuable, it is not clear which will be best. The MS Society and the MS International Federation sponsored a Stem Cell Summit meeting in January 2007 to begin to determine how best to answer these questions. This is a field that is in its earliest stages of development, and the NMSS is funding research studies that will lead to significant advances in our knowledge on this front.

In conjunction with the efforts to repair axons are new efforts to protect them from degeneration in the first place. For example, it is not clear whether axonal degeneration in MS results from a direct attack on axons by the immune system or, alternatively, if the loss of myelin by itself is enough to cause axonal degeneration (i.e., whether myelin has a protective effect on axons that is lost in the MS disease process). The protection of axons from these and other insults are a new area of intense research efforts in MS.

The Nervous System Repair and Protection Initiative

Recent advances in many fields are coming together to bring the dream of protecting and repairing nervous system tissue and restoring function within our grasp. The National MS Society's new Nervous System Repair and Protection Initiative was developed to support the multidisciplinary study of tissue regeneration and repair, from basic research to human clinical trials, with the goal of making tissue repair and protection a reality.

Four teams in North America and Europe are laying the groundwork for clinical trials over the next four years. Their goals are to:

- move tissue repair and protection studies out of the test tube and laboratory mice into human testing;
- find ways to monitor tissue repair and protection in a non-invasive fashion to determine whether the treatment is working; and
- ensure that successfully repaired tissue is protected from the future ravages of the immune system.

Other National MS Society Research on Regeneration

- Researchers at the Johns Hopkins University, with collaborators in Israel, are working to improve the techniques involved in transplanting cells into areas of damage as a strategy for making new myelin and thus repairing tissue damage in MS. This research group is also working to develop a non-invasive way to track repair cells in future clinical trials.
- Oligodendrocytes, the cells that make myelin, appear to be naturally replaced to some extent during the course of MS, but it is generally felt that central nervous system nerve cells are not replaced after injury. A team at the Cleveland Clinic Foundation is searching for evidence that damaged nerve cells in the brain DO have some capacity to regenerate by studying tissue obtained from people with MS via autopsy. Results from this study could lead to the development of new

ways to repair tissue damage to restore function in people living with this disease.

- Investigators at Hunter College in New York have been studying myelin-associated glycoprotein (MAG), which inhibits nerve regeneration in MS. Reversing its action may lead to ways to re-grow nerve fibers. They are examining this process in nerve cells taken from mice, to understand the sequence of events that results in inhibition of regeneration and to identify treatments that can overcome this inhibition, which may lead to ways of repairing damaged nerve fibers in MS.

The Third Cure: Prevent the Disease

Because preventing MS will require an understanding of what causes the disease, areas of major research focus are to better understand the basic characteristics of the people who develop it and to identify the relevant environmental trigger(s). Understanding why and how the immune system malfunctions requires an improved understanding of epidemiology, genetics, and possible infectious triggers of the disease.

Epidemiology

Epidemiology is the study of disease patterns, including variations in geography, demographics, socioeconomic status, genetics, environmental risk factors, and exposure to infectious agents. It provides information about relationships among these factors, so that we can better

understand who gets MS and why, identify and explain areas with high or low rates of the disease, and assist in planning for health care and other services.

Epidemiologic studies have given us some important clues about who develops MS:

- The disease affects more than twice as many women as men.
- It is most common among people with a northern European heritage, but people of other backgrounds develop the disease as well.
- MS appears to be more prevalent in temperate regions of the world than in the tropics.
- It is diagnosed most often in people between the ages of 20 and 50, although it also can develop quite early or quite late in life.

Genetics

Genetics is an important research issue in MS because:

- It will provide key information regarding the cause of the disease and therefore how to prevent it.
- Genes that are associated with MS may be targets for the development of new therapies.
- If we could identify those people who have a strong genetic predisposition to the disease, we might be able to intervene at its earliest stages or before it appears.

Abnormalities or variations in single genes cause disorders such as Huntington's disease and cystic

fibrosis. The pattern in MS is different, however. Instead, variations in many separately inherited genes appear to contribute to a *susceptibility* to develop MS, which makes unraveling its genetic basis more complex. Much attention has been focused on genes that are important in determining immune system function and others that affect myelination.

Investigators are studying individuals with a variety of diseases and comparing them genetically with healthy individuals. Some investigators are working with families in which more than one member has MS, while others are studying ethnically diverse populations with MS or groups with restricted geography and gene mixture. Their goal is to identify genes that are inherited by people with a susceptibility to MS. Examples of these types of study are:

- The International MS Genetics Consortium, a group of MS genetics researchers that was organized through an MS Society Collaborative Research Center grant, recently identified variations in two genes that help regulate the immune system as clearly increasing genetic susceptibility to MS, as well as several other genes of newly suspected importance in MS, some of which have, as yet, no known function. These have now become targets of intense research interest by MS investigators.
- University of California at San Francisco (UCSF) researchers and an international team of genetics investigators have screened genetic material from hundreds of families with multiple members who have

MS in an additional search for MS susceptibility genes. They are now studying ethnically diverse families, both those with susceptibility that is lower (such as African-Americans) and higher (such as individuals of Northern European descent) than average, and searching for commonalities and differences that may help identify MS genes.

Infectious Triggers

There is some evidence that exposure to one or more viruses may be a "trigger" that causes MS in susceptible individuals, although no specific infectious agent has as yet been proven to cause MS. How could common infectious agents be involved with MS when relatively few people have the disease? This is where genetic susceptibility may have its impact: a common infectious agent may trigger MS, but *only* in susceptible individuals. Current evidence also suggests that this important exposure must occur within a particular time frame, probably within the mid-teenage years but perhaps even earlier in life.

Many investigators believe that no single infectious agent is "the" cause of MS. Rather, they are exploring how a susceptible person's immune system reacts to a variety of viral or other infections, and how immune function is linked to hormonal and other factors.

Examples of ongoing research on potential infectious triggers include:

- Researchers at the University of Utah are following up on evidence that colds caused by "picornoviruses" are associated with MS attacks, to detect specific viruses causing the colds that may be linked to MS attacks, and comparing MS attack rates in individuals whose colds are due to picornoviruses compared to other types of virus. This study may provide important clues to the specific viral triggers of some MS attacks, and new leads for preventing or treating those attacks.
- A research group led by investigators at Harvard recently provided evidence that exposure to Epstein-Barr virus (the same virus that causes infectious mononucleosis) may be important in the development of MS. This has stimulated considerable new effort to prove or disprove a causal role for this virus.

Helping People Now

Although we are making great strides toward understanding the cause of MS and finding more effective treatments, people with the disease continue to face daily challenges while coping with its unpredictable effects and symptoms. An important aspect of the Society's research program is the search for ways to improve symptom management, functional abilities, quality of life, and the treatment of relapses.

This includes the psychosocial aspects of MS—not only how it impacts people with the disease, but their family members and friends as well. Research in this area focuses on the impact that MS has on families and caregivers, and enhancing individual and family wellness.

Recently funded research projects related to helping people manage their MS include:

- improving learning and memory for everyday activities
- studying the effects of a home-based aerobic exercise program
- a study following a group of individuals with very mild cognitive deficits to determine to what extent these deficits change or progress over time, and at what rate
- comparing the time and accuracy of performing specific physical movements in patients who first practice the movements by mentally visualizing the task, compared to others who perform the task without prior visualization

The Management of Relapses

- Steroids affect the level of activity in the immune system, and the administration of steroids is the most common treatment to help speed recovery from MS relapses. Seven MS centers in the New York City area are studying the safety and benefit of oral as compared to intravenous steroids in the management of acute attacks in MS, starting within seven days of onset of the attack. Participants are randomly assigned to one of two treatment groups: high-dose

oral steroids and intravenous placebo for 5 days, or intravenous steroids and oral placebo for 5 days. If oral steroids are found to be as effective and safe as when administered by the intravenous route, this study may lead to a major change in the practice of medicine related to treating MS exacerbations.

Symptom Management and Rehabilitation

Some examples of research in this area include:

- Taking in and learning new information can be a difficult task for people with MS. Investigators at New York University are testing several learning techniques to determine whether they can improve performance of everyday tasks. The results are expected to provide information about the application of various learning strategies to real-life tasks, and may ultimately help people with MS to maintain their current lifestyles at home, at work, and in the community.
- The National MS Society's research programs go well beyond traditional biomedical research. Many complementary therapies have been, and are being, examined as prospective treatments in MS. The Society has recently supported research on reflexology in pain management, Ginkgo biloba for symptomatic treatment of cognitive problems in MS, the ability of cannabis and its derivatives to reduce MS spasticity, and the value of exercise programs and rehabilitation, including a robotics-based program to enhance walking abilities.

Health Care Delivery and Policy Research

Understanding how MS care is delivered and the barriers that exist to obtaining quality care is crucial if we want to change policy and service delivery. The Society is actively involved in such research, and uses the results to influence policy-makers. Recent topics pursued through our Health Care Delivery and Policy Research program include:

- the quality of health care and mental health care for people with MS
- the accessibility, impact, and cost effectiveness of disease-modifying therapies
- the delivery of health care in rural areas
- long-term care needs
- evaluating MS adult day programs
- unmet needs of older people with MS
- the health care experiences of people with MS from minority populations
- insurance issues of National MS Society members
- the use of rehabilitation services by people with MS
- financial aspects of MS medical care
- the development of quality indicators for medical care

Here are examples of studies related to this topic:

- The Sonya Slifka Longitudinal MS Study is seeking to understand the factors that influence the quality of life for people with MS. Participants provide information every six months about the disease's influence on their daily lives, the effectiveness and types of treatments they receive, and how they utilize health care. In addition to vital information about the disease's impact on individuals and families, the Study is providing the Society's advocacy efforts with the data it needs to inform policy makers about long-term care, prescription drug coverage, and other quality-of-life issues. For example, the study provided data for the Society's Long-Term Care Caucus suggesting that about 30% of people with MS need home care assistance. As with the general population, about 80% of this care is provided by unpaid helpers, usually family members.

  Information provided by this study will lead to a better understanding of the day-to-day issues faced by people with MS and their families, and to ways that can help to improve their quality of life. It has a special emphasis on how many people with MS actually receive the treatments they need, and the possible reasons they may not, including:

  - a lack of personal financial resources
  - insurance-related issues
  - a lack of knowledge about available treatments

- a lack of knowledge on their physicians' part about currently available treatments
- their doctors' reluctance to prescribe disease-modifying therapies, possibly due to the view that treatment should be initiated only when the disease worsens

- Despite the availability of a wide range of mobility aids—from canes and crutches to wheelchairs and scooters, people with MS may not use them, for a variety of reasons. Investigators at Beth Israel Deaconess Medical Center are exploring the extent, nature, and consequences of unmet needs for mobility aids, and are evaluating Medicare and Medicaid policies related to paying for them. This study will provide vital information to help improve the use of mobility aids by people with MS—a critical step toward improving their quality of life.

Summary

Research sponsored by the National Multiple Sclerosis Society and its many partners in government and the private sector has led to major advances in our understanding of the complex causes of MS. We now know that the neurologic signs and symptoms of the disease are caused by dysfunction in the conduction of nerve signals, and that this occurs as a result of damage to the insulation around nerve fibers and to the nerve

fibers themselves. This has led to new treatments that modify immune function as well as to experimental therapies that may protect brain and spinal cord tissues or enhance nerve fiber conduction even in the presence of existing damage.

Research focused on how damaged tissue may be repaired, replaced, and protected is leading to new possibilities for therapy. New strategies, such as new technologies in genetics and immunology, are allowing researchers to revisit long-standing questions about MS in exciting new ways, and may lead to answers that will allow physicians to stop the immune attack and, ultimately, to repair tissue damage and thus restore function in individuals with MS.

Finally, we are making significant advances in understanding the underlying causes of MS, which will eventually permit us to develop a way to prevent the disease—the ultimate cure and the ultimate goal of our research efforts.

The National MS Society addresses the challenges of each person affected by MS by funding cutting-edge research, driving change through advocacy, facilitating professional education, collaborating with MS organizations around the world, and providing programs and services designed to help people with MS and their families move their lives forward. The Society is a collective of passionate individuals committed to doing something about MS *now,* moving together with everyone in the MS movement toward a world free of multiple sclerosis.

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The National Multiple Sclerosis Society is proud to be a source of information about multiple sclerosis. Our comments are based on professional advice, published experience, and expert opinion, but do not represent individual therapeutic recommendations or prescription. For specific information and advice, consult your personal physician.

The Society publishes many other pamphlets and articles about various aspects of MS. To ask for these, or for other information, call the National MS Society at 1-800-344-4867.

All our publications are on our Web site, along with handouts called "Basic Facts" on various topics. For a list, click the bar on our home page called "Library." If you have no access to the Internet, just call your chapter and ask for a copy of the latest Publications List.

Some of our popular pamphlets include:

- Managing Progressive MS
- So You Have Progressive MS?
- Hiring Help at Home: The Basic Facts
- Managing MS Through Rehabilitation
- At Home with MS: Adapting Your Environment


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