Introduction

Although multiple sclerosis (MS) was first diagnosed in 1849, the earliest known description of a person with possible MS dates from fourteenth century Holland. An unpredictable disease of the central nervous system, MS can range from relatively benign to somewhat disabling to devastating as communication between the brain and other parts of the body is disrupted.

The vast majority of patients are mildly affected, but in the worst cases MS can render a person unable to write, speak, or walk. A physician can diagnose MS in some patients soon after the onset of the illness. In others, however, physicians may not be able to readily identify the cause of the symptoms, leading to years of uncertainty and multiple diagnoses punctuated by baffling symptoms that mysteriously wax and wane.

Once a diagnosis is made with confidence, patients must consider a profusion of information-and misinformation-associated with this complex disease. This brochure is designed to convey the latest information on the diagnosis, course, and possible treatment of MS, as well as highlights of current research. Although a pamphlet cannot substitute for the advice and expertise of a physician, it can provide

patients and their families with information to understand MS better so that they can actively participate in their care and treatment.

**What is Multiple Sclerosis?**

During an MS attack, inflammation occurs in areas of the white matter of the central nervous system in random patches called plaques. This process is followed by destruction of myelin, the fatty covering that insulates nerve cell fibers in the brain and spinal cord. Myelin facilitates the smooth, high-speed transmission of electrochemical messages between the brain, the spinal cord, and the rest of the body; when it is damaged, neurological transmission of messages may be slowed or blocked completely, leading to diminished or lost function. The name “multiple sclerosis” signifies both the number (multiple) and condition (sclerosis, from the Greek term for scarring or hardening) of the demyelinated areas in the central nervous system.

**How Many People Have MS?**

No one knows exactly how many people have MS. It is believed that, currently, there are approximately 250,000 to 350,000 people in the United States with MS diagnosed by a physician. This estimate suggests that approximately 200 new cases are diagnosed each week.

**Who Gets MS?**

Most people experience their first symptoms of MS between the ages of 20 and 40, but a diagnosis is often delayed. This is due to both the transitory nature of the disease and the lack of a specific diagnostic test-specific symptoms and changes in the brain must develop before the diagnosis is confirmed.

Although scientists have documented cases of MS in young children and elderly adults, symptoms rarely begin before age 15 or after age 60. Whites are more than twice as likely as other races to develop MS. In general, women are affected at almost twice the rate of men; however, among patients who develop the symptoms of MS at a later age, the gender ratio is more balanced.

MS is five times more prevalent in temperate climates—such as those found in the northern United States, Canada, and Europe—than in tropical regions. Furthermore, the age of 15 seems to be significant in terms of risk for developing the disease: some studies indicate that a person moving from a high-risk (temperate) to a low-risk (tropical) area before the age of 15 tends to adopt the risk (in this case, low) of the new area and vice versa. Other studies suggest that people moving after age 15 maintain the risk of the area where they grew up.

These findings indicate a strong role for an environmental factor in the cause of MS. It is possible that, at the time of or immediately following puberty, patients acquire an infection with a long latency period. Or, conversely, people in some areas may come in contact with an unknown protective agent during the time before puberty. Other studies suggest that the unknown geographic or climatic element may actually be simply a matter of genetic predilection and reflect racial and ethnic susceptibility factors.

Periodically, scientists receive reports of MS "clusters." The most famous of these MS "epidemics" took place in the Faeroe Islands north of Scotland in the years following the arrival of British troops during World War II. Despite intense study of this and other clusters, no direct environmental factor has been identified. Nor has any definitive evidence been found to link daily stress to MS attacks, although there is evidence that the risk of worsening is greater after acute viral illnesses.

**How Much Does MS Cost America?**

MS is a life-long chronic disease diagnosed primarily in young adults who have a virtually normal life expectancy. Consequently, the economic, social, and medical costs associated with the disease are significant. Estimates place the annual cost of MS in the United States in the billions of dollars.
What Causes MS?

Scientists have learned a great deal about MS in recent years; still, its cause remains elusive. Many investigators believe MS to be an autoimmune disease—one in which the body, through its immune system, launches a defensive attack against its own tissues. In the case of MS, it is the nerve-insulating myelin that comes under assault. Such assaults may be linked to an unknown environmental trigger, perhaps a virus.

The Immune System

To understand what is happening when a person has MS, it is first necessary to know a little about how the healthy immune system works. The immune system—a complex network of specialized cells and organs—defends the body against attacks by "foreign" invaders such as bacteria, viruses, fungi, and parasites. It does this by seeking out and destroying the interlopers as they enter the body. Substances capable of triggering an immune response are called antigens.

The immune system displays both enormous diversity and extraordinary specificity. It can recognize millions of distinctive foreign molecules and produce its own molecules and cells to match up with and counteract each of them. In order to have room for enough cells to match the millions of possible foreign invaders, the immune system stores just a few cells for each specific antigen. When an antigen appears, those few specifically matched cells are stimulated to multiply into a full-scale army. Later, to prevent this army from overexpanding, powerful mechanisms to suppress the immune response come into play.

T cells, so named because they are processed in the thymus, appear to play a particularly important role in MS. They travel widely and continuously throughout the body patrolling for foreign invaders. In order to recognize and respond to each specific antigen, each T cell's surface carries special receptor molecules for particular antigens.

T cells contribute to the body's defenses in two major ways. Regulatory T cells help orchestrate the elaborate immune system. For instance, they assist other cells to make antibodies, proteins programmed to match one specific antigen much as a key matches a lock. Antibodies typically interact with circulating antigens, such as bacteria, but are unable to penetrate living cells. Chief among the regulatory T cells are those known as helper (or inducer) cells. Helper T cells are essential for activating the body's defenses against foreign substances. Yet another subset of regulatory T cells acts to turn off, or suppress, various immune system cells when their job is done.

Killer T cells, on the other hand, directly attack diseased or damaged body cells by binding to them and bombarding them with lethal chemicals called cytokines. Since T cells can attack cells directly, they must be able to discriminate between "self" cells (those of the body) and "nonself" cells (foreign invaders). To enable the immune system to distinguish the self, each body cell carries identifying molecules on its surface. T cells likely to react against the self are usually eliminated before leaving the thymus; the remaining T cells recognize the molecular markers and coexist peaceably with body tissues in a state of self-tolerance.

In autoimmune diseases such as MS, the detente between the immune system and the body is disrupted when the immune system seems to wrongly identify self as nonself and declares war on the part of the body (myelin) it no longer recognizes. Through intensive research efforts, scientists are unraveling the complex secrets of the malfunctioning immune system of patients with MS.

Components of myelin such as myelin basic protein have been the focus of much research because, when injected into laboratory animals, they can precipitate experimental allergic encephalomyelitis (EAE), a chronic relapsing brain and spinal cord disease that resembles MS. The injected myelin probably stimulates the immune system to produce anti-myelin T cells that attack the animal's own myelin.

Investigators are also looking for abnormalities or malfunctions in the blood/brain barrier, a protective membrane that controls the passage of substances from the blood into the central nervous system. It is possible that, in MS, components of the immune system get through the barrier and cause nervous system damage.

Scientists have studied a number of infectious agents (such as viruses) that have been suspected of causing MS, but have been unable to implicate any one particular agent. Viral infections are usually
accompanied by inflammation and the production of gamma interferon, a naturally occurring body chemical that has been shown to worsen the clinical course of MS. It is possible that the immune response to viral infections may themselves precipitate an MS attack. There seems to be little doubt that something in the environment is involved in triggering MS.

**Genetics**

In addition, increasing scientific evidence suggests that genetics may play a role in determining a person’s susceptibility to MS. Some populations, such as Gypsies, Eskimos, and Bantus, never get MS. Native Indians of North and South America, the Japanese, and other Asian peoples have very low incidence rates. It is unclear whether this is due mostly to genetic or environmental factors.

In the population at large, the chance of developing MS is less than a tenth of one percent. However, if one person in a family has MS, that person’s first-degree relatives—parents, children, and siblings—have a one to three percent chance of getting the disease.

For identical twins, the likelihood that the second twin may develop MS if the first twin does is about 30 percent; for fraternal twins (who do not inherit identical gene pools), the likelihood is closer to that for non-twin siblings, or about 4 percent. The fact that the rate for identical twins both developing MS is significantly less than 100 percent suggests that the disease is not entirely genetically controlled. Some (but definitely not all) of this effect may be due to shared exposure to something in the environment, or to the fact that some people with MS lesions remain essentially asymptomatic throughout their lives.

Further indications that more than one gene is involved in MS susceptibility comes from studies of families in which more than one member has MS. Several research teams found that people with MS inherit certain regions on individual genes more frequently than people without MS. Of particular interest is the human leukocyte antigen (HLA) or major histocompatibility complex region on chromosome 6. HLAs are genetically determined proteins that influence the immune system.

The HLA patterns of MS patients tend to be different from those of people without the disease. Investigations in northern Europe and America have detected three HLAs that are more prevalent in people with MS than in the general population. Studies of American MS patients have shown that people with MS also tend to exhibit these HLAs in combination—that is, they have more than one of the three HLAs—more frequently than the rest of the population. Furthermore, there is evidence that different combinations of the HLAs may correspond to variations in disease severity and progression.

Studies of families with multiple cases of MS and research comparing genetic regions of humans to those of mice with EAE suggest that another area related to MS susceptibility may be located on chromosome 5. Other regions on chromosomes 2, 3, 7, 11, 17, 19, and X have also been identified as possibly containing genes involved in the development of MS.

These studies strengthen the theory that MS is the result of a number of factors rather than a single gene or other agent. Development of MS is likely to be influenced by the interactions of a number of genes, each of which (individually) has only a modest effect. Additional studies are needed to specifically pinpoint which genes are involved, determine their function, and learn how each gene’s interactions with other genes and with the environment make an individual susceptible to MS. In addition to leading to better ways to diagnose MS, such studies should yield clues to the underlying causes of MS and, eventually, to better treatments or a way to prevent the disease.

**What is the Course of MS?**

Each case of MS displays one of several patterns of presentation and subsequent course. Most commonly, MS first manifests itself as a series of attacks followed by complete or partial remissions as symptoms mysteriously lessen, only to return later after a period of stability. This is called relapsing-remitting (RR) MS. Primary-progressive (PP) MS is characterized by a gradual clinical decline with no distinct remissions, although there may be temporary plateaus or minor relief from symptoms. Secondary-progressive (SP) MS begins with a relapsing-remitting course followed by a later primary-progressive course. Rarely, patients may have a progressive-relapsing (PR) course in which the disease takes a progressive path punctuated by acute attacks. PP, SP, and PR are sometimes lumped together and called chronic progressive MS.
In addition, twenty percent of the MS population has a benign form of the disease in which symptoms show little or no progression after the initial attack; these patients remain fully functional. A few patients experience malignant MS, defined as a swift and relentless decline resulting in significant disability or even death shortly after disease onset. However, MS is very rarely fatal and most people with MS have a fairly normal life expectancy.

Studies throughout the world are causing investigators to redefine the natural course of the disease. These studies use a technique called magnetic resonance imaging (MRI) to visualize the evolution of MS lesions in the white matter of the brain. Bright spots on a T2 MRI scan indicate the presence of lesions, but do not provide information about when they developed.

Because investigators speculate that the breakdown of the blood/brain barrier is the first step in the development of MS lesions, it is important to distinguish new lesions from old. To do this, physicians give patients injections of gadolinium, a chemical contrast agent that normally does not cross the blood/brain barrier, before performing a scan. On this type of scan, called T1, the appearance of bright areas indicates periods of recent disease activity (when gadolinium is able to cross the barrier). The ability to estimate the age of lesions through MRI has allowed investigators to show that, in some patients, lesions occur frequently throughout the course of the disease even when no symptoms are present.

**Can Life Events Affect the Course of MS?**

While there is no good evidence that daily stress or trauma affects the course of MS, there is data on the influence of pregnancy. Since MS generally strikes during childbearing years, a common concern among women with the disease is whether or not to have a baby. Studies on the subject have shown that MS has no adverse effects on the course of pregnancy, labor, or delivery; in fact symptoms often stabilize or remit during pregnancy. This temporary improvement is thought to relate to changes in a woman's immune system that allow her body to carry a baby: because every fetus has genetic material from the father as well as the mother, the mother's body should identify the growing fetus as foreign tissue and try to reject it in much the same way the body seeks to reject a transplanted organ. To prevent this from happening, a natural process takes place to suppress the mother's immune system in the uterus during pregnancy.

However, women with MS who are considering pregnancy need to be aware that certain drugs used to treat MS should be avoided during pregnancy and while breast feeding. These drugs can cause birth defects and can be passed to the fetus via blood and to an infant via breast milk. Among them are prednisone, corticotropin, azathioprine, cyclophosphamide, diazepam, phenytoin, carbamazepine, and baclofen.

Unfortunately, between 20 and 40 percent of women with MS do have a relapse in the three months following delivery. However, there is no evidence that pregnancy and childbirth affect the overall course of the disease one way or the other. Also, while MS is not in itself a reason to avoid pregnancy and poses no significant risks to the fetus, physical limitations can make child care more difficult. It is therefore important that MS patients planning families discuss these issues with both their partner and physician.

**What are the Symptoms of MS?**

Symptoms of MS may be mild or severe, of long duration or short, and may appear in various combinations, depending on the area of the nervous system affected. Complete or partial remission of symptoms, especially in the early stages of the disease, occurs in approximately 70 percent of MS patients.

The initial symptom of MS is often blurred or double vision, red-green color distortion, or even blindness in one eye. Inexplicably, visual problems tend to clear up in the later stages of MS. Inflammatory problems of the optic nerve may be diagnosed as retrobulbar optic neuritis. Fifty-five percent of MS patients will have an attack of optic neuritis at some time or other and it will be the first symptom of MS in approximately 15 percent. This has led to general recognition of optic neuritis as an early sign of MS, especially if tests also reveal abnormalities in the patient's spinal fluid.

Most MS patients experience muscle weakness in their extremities and difficulty with coordination and balance at some time during the course of the disease. These symptoms may be severe enough to impair
walking or even standing. In the worst cases, MS can produce partial or complete paralysis. Spasticity—the involuntary increased tone of muscles leading to stiffness and spasms—is common, as is fatigue. Fatigue may be triggered by physical exertion and improve with rest, or it may take the form of a constant and persistent tiredness.

Most people with MS also exhibit paresthesias, transitory abnormal sensory feelings such as numbness, prickling, or "pins and needles" sensations; uncommonly, some may also experience pain. Loss of sensation sometimes occurs. Speech impediments, tremors, and dizziness are other frequent complaints. Occasionally, people with MS have hearing loss.

Approximately half of all people with MS experience cognitive impairments such as difficulties with concentration, attention, memory, and poor judgment, but such symptoms are usually mild and are frequently overlooked. In fact, they are often detectable only through comprehensive testing. Patients themselves may be unaware of their cognitive loss; it is often a family member or friend who first notices a deficit. Such impairments are usually mild, rarely disabling, and intellectual and language abilities are generally spared.

Cognitive symptoms occur when lesions develop in brain areas responsible for information processing. These deficits tend to become more apparent as the information to be processed becomes more complex. Fatigue may also add to processing difficulties. Scientists do not yet know whether altered cognition in MS reflects problems with information acquisition, retrieval, or a combination of both. Types of memory problems may differ depending on the individual's disease course (relapsing-remitting, primary-progressive, etc.), but there does not appear to be any direct correlation between duration of illness and severity of cognitive dysfunction.

Depression, which is unrelated to cognitive problems, is another common feature of MS. In addition, about 10 percent of patients suffer from more severe psychotic disorders such as manic-depression and paranoia. Five percent may experience episodes of inappropriate euphoria and despair-unrelated to the patient's actual emotional state-known as "laughing/weeping syndrome." This syndrome is thought to be due to demyelination in the brainstem, the area of the brain that controls facial expression and emotions, and is usually seen only in severe cases.

As the disease progresses, sexual dysfunction may become a problem. Bowel and bladder control may also be lost.

In about 60 percent of MS patients, heat—whether generated by temperatures outside the body or by exercise—may cause temporary worsening of many MS symptoms. In these cases, eradicating the heat eliminates the problem. Some temperature-sensitive patients find that a cold bath may temporarily relieve their symptoms. For the same reason, swimming is often a good exercise choice for people with MS.

The erratic symptoms of MS can affect the entire family as patients may become unable to work at the same time they are facing high medical bills and additional expenses for housekeeping assistance and modifications to homes and vehicles. The emotional drain on both patient and family is immeasurable. Support groups (listed on a card in the pocket at the back of this pamphlet) and counseling may help MS patients, their families, and friends find ways to cope with the many problems the disease can cause.

**Possible Symptoms of Multiple Sclerosis**

- Muscle weakness
- Spasticity
- Impairment of pain, temperature, touch senses
- Pain (moderate to severe)
- Ataxia
- Tremor
- Speech disturbances
Vision disturbances
Vertigo
Bladder dysfunction
Bowel dysfunction
Sexual dysfunction
Depression
Euphoria
Cognitive abnormalities
Fatigue

**How is MS Diagnosed?**

There is no single test that unequivocally detects MS. When faced with a patient whose symptoms, neurological exam results, and medical history suggest MS, physicians use a variety of tools to rule out other possible disorders and perform a series of laboratory tests which, if positive, confirm the diagnosis.

Imaging technologies such as MRI can help locate central nervous system lesions resulting from myelin loss. MRI is painless, noninvasive, and does not expose the body to radiation. It is often used in conjunction with the contrast agent gadolinium, which helps distinguish new plaques from old. However, since these lesions can also occur in several other neurological disorders, they are not absolute evidence of MS.

Several new MRI techniques may help quantify and characterize MS lesions that are too subtle to be detected using conventional MRI scans. While standard MRI provides an anatomical picture of lesions, *magnetic resonance spectroscopy* (MRS) yields information about the brain’s biochemistry; specifically, it can measure the brain chemical N-acetyl aspartate. Decreased levels of this chemical can indicate nerve damage.

*Magnetization transfer imaging* (MTI) is able to detect white matter abnormalities before lesions can be seen on standard MRI scans by calculating the amount of "free" water in tissues. Demyelinated tissues and damaged nerves show increased levels of free" (versus "bound") water particles.

*Diffusion-tensor magnetic resonance imaging* (DT-MRI or DTI) measures the random motion of water molecules. Individual water molecules are constantly in motion, colliding with each other at extremely high speeds. This causes them to spread out, or diffuse. DT-MRI maps this diffusion to produce intricate, three-dimensional images indicating the size and location of demyelinated areas of the brain. Changes in this process can then be measured and correlated with disease progression.

*Functional MRI* (fMRI) uses radio waves and a strong magnetic field to measures the correlation between physical changes in the brain (such as blood flow) and mental functioning during the performance of cognitive tasks.

In addition to helping scientists and physicians better understand how MS develops-an important first step in devising new treatments-these approaches offer earlier diagnosis and enhance efforts to monitor disease progression and the effects of treatment.

Other tests that may be used to diagnosis MS include visual evoked potential (VEP) tests and studies of *cerebrospinal fluid* (the colorless liquid that circulates through the brain and spinal cord). VEP tests measure the speed of the brain’s response to visual stimuli. VEP can sometimes detect lesions that the scanners miss and is particularly useful when abnormalities seen on MRI do not meet the specific criteria for MS. Auditory and sensory evoked potentials have also been used in the past, but are no longer believed to contribute significantly to the diagnosis of MS. Like imaging technologies, VEP is helpful but not
conclusive because it cannot identify the cause of lesions.

Examination of cerebrospinal fluid can show cellular and chemical abnormalities often associated with MS. These abnormalities include increased numbers of white blood cells and higher-than-average amounts of protein, especially myelin basic protein and an antibody called immunoglobulin G. Physicians can use several different laboratory techniques to separate and graph the various proteins in MS patients' cerebrospinal fluid. This process often identifies the presence of a characteristic pattern called oligoclonal bands.

While it can still be difficult for the physician to differentiate between an MS attack and symptoms that can follow a viral infection or even an immunization, our growing understanding of disease mechanisms and the expanded use of MRI is enabling physicians to diagnose MS with far more confidence than ever before. Today, most patients who undergo a diagnostic evaluation for MS will be classified as either having MS or not having MS, although there are still cases where a person may have the clinical symptoms of MS but not meet all the criteria to confirm a diagnosis of MS. In these cases, a diagnosis of "possible MS" is used.

A number of other diseases may produce symptoms similar to those seen in MS. Other conditions with an intermittent course and MS-like lesions of the brain's white matter include polyarteritis, lupus erythematosus, syringomyelia, tropical spastic paraparesis, some cancers, and certain tumors that compress the brainstem or spinal cord. Progressive multifocal leukoencephalopathy can mimic the acute stage of an MS attack. Physicians will also need to rule out stroke, neurosyphilis, spinocerebellar ataxias, pernicious anemia, diabetes, Sjogren's disease, and vitamin B12 deficiency. Acute transverse myelitis may signal the first attack of MS, or it may indicate other problems such as infection with the Epstein-Barr or herpes simplex B viruses. Recent reports suggest that the neurological problems associated with Lyme disease may present a clinical picture much like MS.

Investigators are continuing their search for a definitive test for MS. Until one is developed, however, evidence of both multiple attacks and central nervous system lesions must be found before a diagnosis of MS is given.

**Can MS be Treated?**

There is as yet no cure for MS. Many patients do well with no therapy at all, especially since many medications have serious side effects and some carry significant risks. Naturally occurring or spontaneous remissions make it difficult to determine therapeutic effects of experimental treatments; however, the emerging evidence that MRIs can chart the development of lesions is already helping scientists evaluate new therapies.

In the past, the principal medications physicians used to treat MS were steroids possessing anti-inflammatory properties; these include adrenocorticotropic hormone (better known as ACTH), prednisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone. Studies suggest that intravenous methylprednisolone may be superior to the more traditional intravenous ACTH for patients experiencing acute relapses; no strong evidence exists to support the use of these drugs to treat progressive forms of MS. Also, there is some indication that steroids may be more appropriate for people with movement, rather than sensory, symptoms.

While steroids do not affect the course of MS over time, they can reduce the duration and severity of attacks in some patients. The mechanism behind this effect is not known; one study suggests the medications work by restoring the effectiveness of the blood/brain barrier. Because steroids can produce numerous adverse side effects (acne, weight gain, seizures, psychosis), they are not recommended for long-term use.

One of the most promising MS research areas involves naturally occurring antiviral proteins known as interferons. Three forms of beta interferon (Avonex, Betaseron, and Rebif) have now been approved by the Food and Drug Administration for treatment of relapsing-remitting MS. Beta interferon has been shown to reduce the number of exacerbations and may slow the progression of physical disability. When attacks do occur, they tend to be shorter and less severe. In addition, MRI scans suggest that beta interferon can decrease myelin destruction.

Investigators speculate that the effects of beta interferon may be due to the drug’s ability to correct an MS-
related deficiency of certain white blood cells that suppress the immune system and/or its ability to inhibit gamma interferon, a substance believed to be involved in MS attacks. Alpha interferon is also being studied as a possible treatment for MS. Common side effects of interferons include fever, chills, sweating, muscle aches, fatigue, depression, and injection site reactions.

Scientists continue their extensive efforts to create new and better therapies for MS. Goals of therapy are threefold: to improve recovery from attacks, to prevent or lessen the number of relapses, and to halt disease progression. Some therapies currently under investigation are discussed below.

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**Immunotherapy**

As evidence of immune system involvement in the development of MS has grown, trials of various new treatments to alter or suppress immune response are being conducted. Most of these therapies are, at this time, still considered experimental.

Results of recent clinical trials have shown that immunosuppressive agents and techniques can positively (if temporarily) affect the course of MS; however, toxic side effects often preclude their widespread use. In addition, generalized immunosuppression leaves the patient open to a variety of viral, bacterial, and fungal infections.

Over the years, MS investigators have studied a number of immunosuppressant treatments. One such treatment, Novantrone (mitoxantrone), was approved by the FDA for the treatment of advanced or chronic MS. Other therapies being studied are cyclosporine (Sandimmune), cyclophosphamide (Cytoxan), methotrexate, azathioprine (Imuran), and total lymphoid irradiation (a process whereby the MS patient's lymph nodes are irradiated with x-rays in small doses over a few weeks to destroy lymphoid tissue, which is actively involved in tissue destruction in autoimmune diseases). Inconclusive and/or contradictory results of these trials, combined with the therapies' potentially dangerous side effects, dictate that further research is necessary to determine what, if any, role they should play in the management of MS. Studies are also being conducted with the immune system modulating drug cladribine (Leustatin).

Another potential treatment for MS is monoclonal antibodies, which are identical, laboratory-produced antibodies that are highly specific for a single antigen. They are injected into the patient in the hope that they will alter the patient's immune response. One monoclonal antibody, natalizumab (Tysabri), was shown in clinical trials to significantly reduce the frequency of attacks in people with relapsing forms of MS and was approved for marketing by the U.S. Food and Drug Administration (FDA) in 2004. However, in 2005 the drug's manufacturer voluntarily suspended marketing of the drug after several reports of significant adverse events. In 2006, the FDA again approved sale of the drug for MS but under strict treatment guidelines involving infusion centers where patients can be monitored by specially trained physicians.

Another experimental treatment for MS is plasma exchange, or plasmapheresis. Plasmapheresis is a procedure in which blood is removed from the patient and the blood plasma is separated from other blood substances that may contain antibodies and other immunologically active products. These other blood substances are discarded and the plasma is then transfused back into the patient. Because its worth as a treatment for MS has not yet been proven, this experimental treatment remains at the stage of clinical testing.

Bone marrow transplantation (a procedure in which bone marrow from a healthy donor is infused into patients who have undergone drug or radiation therapy to suppress their immune system so they will not reject the donated marrow) and injections of venom from honey bees are also being studied. Each of these therapies carries the risk of potentially severe side effects.

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**Therapy to Improve Nerve Impulse Conduction**

Because the transmission of electrochemical messages between the brain and body is disrupted in MS, medications to improve the conduction of nerve impulses are being investigated. Since demyelinated nerves show abnormalities of potassium activity, scientists are studying drugs that block the channels through which potassium moves, thereby restoring conduction of the nerve impulse. In several small experimental trials, derivatives of a drug called aminopyridine temporarily improved vision, coordination,
and strength when given to MS patients who suffered from both visual symptoms and heightened sensitivity to temperature. Possible side effects of these therapies include paresthesias (tingling sensations), dizziness, and seizures.

**Therapies Targeting an Antigen**

Trials of a synthetic form of myelin basic protein, called copolymer I (Copaxone), were successful, leading the FDA to approve the agent for the treatment of relapsing-remitting MS. Copolymer I, unlike so many drugs tested for the treatment of MS, has few side effects, and studies indicate that the agent can reduce the relapse rate by almost one third. In addition, patients given copolymer I are more likely to show neurologic improvement than those given a placebo.

Investigators are also looking at the possibility of developing an MS vaccine. Myelin-attacking T cells were removed, inactivated, and injected back into animals with experimental allergic encephalomyelitis (EAE). This procedure results in destruction of the immune system cells that were attacking myelin basic protein. In a couple of small trials scientists have tested a similar vaccine in humans. The product was well-tolerated and had no side effects, but the studies were too small to establish efficacy. Patients with progressive forms of MS did not appear to benefit, although relapsing-remitting patients showed some neurologic improvement and had fewer relapses and reduced numbers of lesions in one study. Unfortunately, the benefits did not last beyond two years.

A similar approach, known as peptide therapy, is based on evidence that the body can mount an immune response against the T cells that destroy myelin, but this response is not strong enough to overcome the disease. To induce this response, the investigator scans the myelin-attacking T cells for the myelin-recognizing receptors on the cells' surface. A fragment, or peptide, of those receptors is then injected into the body. The immune system "sees" the injected peptide as a foreign invader and launches an attack on any myelin-destroying T cells that carry the peptide. The injection of portions of T cell receptors may heighten the immune system reaction against the errant T cells much the same way a booster shot heightens immunity to tetanus. Or, peptide therapy may jam the errant cells' receptors, preventing the cells from attacking myelin.

Despite these promising early results, there are some major obstacles to developing vaccine and peptide therapies. Individual patients’ T cells vary so much that it may not be possible to develop a standard vaccine or peptide therapy beneficial to all, or even most, MS patients. At this time, each treatment involves extracting cells from each individual patient, purifying the cells, and then growing them in culture before inactivating and chemically altering them. This makes the production of quantities sufficient for therapy extremely time consuming, labor intensive, and expensive. Further studies are necessary to determine whether universal inoculations can be developed to induce suppression of MS patients’ overactive immune systems.

Protein antigen feeding is similar to peptide therapy, but is a potentially simpler means to the same end. Whenever we eat, the digestive system breaks each food or substance into its primary “non-antigenic” building blocks, thereby averting a potentially harmful immune attack. So, strange as it may seem, antigens that trigger an immune response when they are injected can encourage immune system tolerance when taken orally. Furthermore, this reaction is directed solely at the specific antigen being fed; wholesale immunosuppression, which can leave the body open to a variety of infections, does not occur. Studies have shown that when rodents with EAE are fed myelin protein antigens, they experience fewer relapses. Data from a small, preliminary trial of antigen feeding in humans found limited suggestion of improvement, but the results were not statistically significant. A multi-center trial is being conducted to determine whether protein antigen feeding is effective.

**Cytokines**

As our growing insight into the workings of the immune system gives us new knowledge about the function of cytokines, the powerful chemicals produced by T cells, the possibility of using them to manipulate the immune system becomes more attractive. Scientists are studying a variety of substances that may block harmful cytokines, such as those involved in inflammation, or that encourage the production of protective cytokines.
A drug that has been tested as a depression treatment, rolipram, has been shown to reduce levels of several destructive cytokines in animal models of MS. Its potential as a therapy for MS is not known at this time, but side effects seem modest. Protein antigen feeding, discussed above, may release transforming growth factor beta (TGF), a protective cytokine that inhibits or regulates the activity of certain immune cells. Preliminary tests indicate that it may reduce the number of immune cells commonly found in MS patients' spinal fluid. Side effects include anemia and altered kidney function.

Interleukin 4 (IL-4) is able to diminish demyelination and improve the clinical course of mice with EAE, apparently by influencing developing T cells to become protective rather than harmful. This also appears to be true of a group of chemicals called retinoids. When fed to rodents with EAE, retinoids increase levels of TGF and IL-4, which encourage protective T cells, while decreasing numbers of harmful T cells. This results in improvement of the animals' clinical symptoms.

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Remyelination

Some studies focus on strategies to reverse the damage to myelin and oligodendrocytes (the cells that make and maintain myelin in the central nervous system), both of which are destroyed during MS attacks. Scientists now know that oligodendrocytes may proliferate and form new myelin after an attack. Therefore, there is a great deal of interest in agents that may stimulate this reaction. To learn more about the process, investigators are looking at how drugs used in MS trials affect remyelination. Studies of animal models indicate that monoclonal antibodies and two immunosuppressant drugs, cyclophosphamide and azathioprine, may accelerate remyelination, while steroids may inhibit it. The ability of intravenous immunoglobulin (IVIg) to restore visual acuity and/or muscle strength is also being investigated.

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Diet

Over the years, many people have tried to implicate diet as a cause of or treatment for MS. Some physicians have advocated a diet low in saturated fats; others have suggested increasing the patient’s intake of linoleic acid, a polyunsaturated fat, via supplements of sunflower seed, safflower, or evening primrose oils. Other proposed dietary “remedies” include megavitamin therapy, including increased intake of vitamins B12 or C; various liquid diets; and sucrose-, tobacco-, or gluten-free diets. To date, clinical studies have not been able to confirm benefits from dietary changes; in the absence of any evidence that diet therapy is effective, patients are best advised to eat a balanced, wholesome diet.

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Unproven Therapies

MS is a disease with a natural tendency to remit spontaneously, and for which there is no universally effective treatment and no known cause. These factors open the door for an array of unsubstantiated claims of cures. At one time or another, many ineffective and even potentially dangerous therapies have been promoted as treatments for MS. A partial list of these “therapies” includes: injections of snake venom, electrical stimulation of the spinal cord's dorsal column, removal of the thymus gland, breathing pressurized (hyperbaric) oxygen in a special chamber, injections of beef heart and hog pancreas extracts, intravenous or oral calcium citrate, hysterectomy, removal of dental fillings containing silver or mercury amalgams, and surgical implantation of pig brain into the patient's abdomen. None of these treatments is an effective therapy for MS or any of its symptoms.

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Are Any MS Symptoms Treatable?

While some scientists look for therapies that will affect the overall course of the disease, others are searching for new and better medications to control the symptoms of MS without triggering intolerable side effects.

Many people with MS have problems with spasticity, a condition that primarily affects the lower limbs. Spasticity can occur either as a sustained stiffness caused by increased muscle tone or as spasms that come and go, especially at night. It is usually treated with muscle relaxants and tranquilizers. Baclofen (Lioresal), the most commonly prescribed medication for this symptom, may be taken orally or, in severe
cases, injected into the spinal cord. Tizanidine (Zanaflex), used for years in Europe and now approved in the United States, appears to function similarly to baclofen. Diazepam (Valium), clonazepam (Klonopin), and dantrolene (Dantrium) can also reduce spasticity. Although its beneficial effect is temporary, physical therapy may also be useful and can help prevent the irreversible shortening of muscles known as contractures. Surgery to reduce spasticity is rarely appropriate in MS.

Weakness and ataxia (incoordination) are also characteristic of MS. When weakness is a problem, some spasticity can actually be beneficial by lending support to weak limbs. In such cases, medication levels that alleviate spasticity completely may be inappropriate. Physical therapy and exercise can also help preserve remaining function, and patients may find that various aids-such as foot braces, canes, and walkers-can help them remain independent and mobile. Occasionally, physicians can provide temporary relief from weakness, spasms, and pain by injecting a drug called phenol into the spinal cord, muscles, or nerves in the arms or legs. Further research is needed to find or develop effective treatments for MS-related weakness and ataxia.

Although improvement of optic symptoms usually occurs even without treatment, a short course of treatment with intravenous methylprednisolone (Solu-Medrol) followed by treatment with oral steroids is sometimes used. A trial of oral prednisone in patients with visual problems suggests that this steroid is not only ineffective in speeding recovery but may also increase patients' risk for future MS attacks. Curiously, prednisone injected directly into the veins-at ten times the oral dose-did seem to produce short-term recovery. Because of the link between optic neuritis and MS, the study's investigators believe these findings may hold true for the treatment of MS as well. A follow-up study of optic neuritis patients will address this and other questions.

Fatigue, especially in the legs, is a common symptom of MS and may be both physical and psychological. Avoiding excessive activity and heat are probably the most important measures patients can take to counter physiological fatigue. If psychological aspects of fatigue such as depression or apathy are evident, antidepressant medications may help. Other drugs that may reduce fatigue in some, but not all, patients include amantadine (Symmetrel), pemoline (Cylert), and the still-experimental drug aminopyridine. People with MS may experience several types of pain. Muscle and back pain can be helped by aspirin or acetaminophen and physical therapy to correct faulty posture and strengthen and stretch muscles. The sharp, stabbing facial pain known as trigeminal neuralgia is commonly treated with carbamazepine or other anticonvulsant drugs or, occasionally, surgery. Intense tingling and burning sensations are harder to treat. Some people get relief with antidepressant drugs; others may respond to electrical stimulation of the nerves in the affected area. In some cases, the physician may recommend codeine.

As the disease progresses, some patients develop bladder malfunctions. Urinary problems are often the result of infections that can be treated with antibiotics. The physician may recommend that patients take vitamin C supplements or drink cranberry juice, as these measures acidify urine and may reduce the risk of further infections. Several medications are also available. The most common bladder problems encountered by MS patients are urinary frequency, urgency, or incontinence. A small number of patients, however, retain large amounts of urine. In these patients, catheterization may be necessary. In this procedure, a catheter or drainage tube is temporarily inserted (by the patient or a caretaker) into the urethra several times a day to drain urine from the bladder. Surgery may be indicated in severe, intractable cases. Scientists have developed a "bladder pacemaker" that has helped people with urinary incontinence in preliminary trials. The pacemaker, which is surgically implanted, is controlled by a hand-held unit that allows the patient to electrically stimulate the nerves that control bladder function.

MS patients with urinary problems may be reluctant to drink enough fluids, leading to constipation. Drinking more water and adding fiber to the diet usually alleviates this condition. Sexual dysfunction may also occur, especially in patients with urinary problems. Men may experience occasional failure to attain an erection. Penile implants, injection of the drug papaverine, and electrostimulation are techniques used to resolve the problem. Women may experience insufficient lubrication or have difficulty reaching orgasm; in these cases, vaginal gels and vibrating devices may be helpful. Counseling is also beneficial, especially in the absence of urinary problems, since psychological factors can also cause these symptoms. For instance, depression can intensify symptoms of fatigue, pain, and sexual dysfunction. In addition to counseling, the physician may prescribe antidepressant or antianxiety medications. Amitriptyline is used to treat laughing/weeping syndrome.

Tremors are often resistant to therapy, but can sometimes be treated with drugs or, in extreme cases,
Drugs Used to Treat Symptoms of Multiple Sclerosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug</th>
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<tr>
<td>Spasticity</td>
<td>Baclofen (Lioresal)</td>
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<tr>
<td></td>
<td>Tizanidine (Zanaflex)</td>
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<td>Diazepam (Valium)</td>
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<td>Clonazepam (Klonopin)</td>
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<td>Dantrolene (Dantrium)</td>
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<tr>
<td>Optic neuritis</td>
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<td></td>
<td>Oral steroids</td>
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<tr>
<td>Fatigue</td>
<td>Antidepressants</td>
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<tr>
<td></td>
<td>Amantadine (Symmetrel)</td>
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<td></td>
<td>Pemoline (Cylert)</td>
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<tr>
<td>Pain</td>
<td>Aspirin or acetaminophen</td>
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<td></td>
<td>Antidepressants</td>
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<td></td>
<td>Codeine</td>
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<tr>
<td>Trigeminal neuralgia</td>
<td>Carbamazepine, other anticonvulsant</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Papaverine injections(in men)</td>
</tr>
</tbody>
</table>

What Recent Advances Have Been Made in MS Research?

Many advances, on several fronts, have been made in the war against MS. Each advance interacts with the others, adding greater depth and meaning to each new discovery. Four areas, in particular, stand out.

Over the last decade, our knowledge about how the immune system works has grown at an amazing rate. Major gains have been made in recognizing and defining the role of this system in the development of MS lesions, giving scientists the ability to devise ways to alter the immune response. Such work is expected to yield a variety of new potential therapies that may ameliorate MS without harmful side effects.

New tools such as MRI have redefined the natural history of MS and are proving invaluable in monitoring disease activity. Scientists are now able to visualize and follow the development of MS lesions in the brain and spinal cord using MRI; this ability is a tremendous aid in the assessment of new therapies and can speed the process of evaluating new treatments.

Other tools have been developed that make the painstaking work of teasing out the disease’s genetic secrets possible. Such studies have strengthened scientists’ conviction that MS is a disease with many genetic components, none of which is dominant. Immune system-related genetic factors that predispose an individual to the development of MS have been identified, and may lead to new ways to treat or prevent the disease.

In fact, a treatment that may actually slow the course of the disease has been found and a growing number of therapies are now available that effectively treat some MS symptoms. In addition, there are a number of treatments under investigation that may curtail attacks or improve function of demyelinated nerve fibers.
Over a dozen clinical trials testing potential therapies are under way, and additional new treatments are being devised and tested in animal models.

**What Research Remains to be Done?**

The role of genetic risk factors, and how they can be modified, must be more clearly defined. Environmental triggers, such as viruses or toxins, need to be investigated further. The specific cellular and subcellular targets of immune attack in the brain and spinal cord, and the subsets of T cells involved in that attack, need to be identified. Knowledge of these aspects of the disease will enable scientists to develop new methods for halting—or reversing and repairing—the destruction of myelin that causes the symptoms of MS.

**What is the Outlook for People With MS?**

The 1990s—proclaimed the "Decade of the Brain" in 1989 by President Bush and Congress—have seen an unparalleled explosion of knowledge about neurological disorders. New technologies are forcing even complex diseases like MS to yield up their secrets. These burgeoning opportunities in the field of neurological research have prompted the National Advisory Neurological Disorders and Stroke Council to suggest that an effective treatment for and the cause of MS may be found during the Decade of the Brain. The former has already been achieved; scientists continue to diligently search for the latter. Their dedication is the best hope for a cure, or, better yet, a way to prevent MS altogether.

**How Can I Help Research?**

The NINDS contributes to the support of the Human Brain and Spinal Fluid Resource Center in Los Angeles. This bank supplies investigators around the world with tissue from patients with neurological and other disorders. Tissue from individuals with MS is needed to enable scientists to study this disorder more intensely. Prospective donors may contact:

**Human Brain and Spinal Fluid Resource Center**
Neurology Research (127A)
W. Los Angeles Healthcare Center
11301 Wilshire Blvd. Bldg. 212
Los Angeles, CA 90073
310-268-3536
24-hour pager: 310-636-5199
Email: RMMnbank@ucla.edu
[http://www.loni.ucla.edu/~nnrsb/NNRSB](http://www.loni.ucla.edu/~nnrsb/NNRSB)

**Where can I get more information?**

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
(800) 352-9424

Information also is available from the following organizations:

**Multiple Sclerosis Association of America**
706 Haddonfield Road
Cherry Hill, NJ 08002
webmaster@msaa.com

**Multiple Sclerosis Foundation**
6350 North Andrews Avenue
Ft. Lauderdale, FL 33309-2130
support@msfocus.org
American Autoimmune Related Diseases Association
22100 Gratiot Avenue
Eastpointe, MI 48201-2227
aarda@aarda.org
http://www.aarda.org
Tel: 586-776-3900 800-598-4668
Fax: 586-776-3903
National organization that works to alleviate suffering and the socioeconomic impact of autoimmunity. Dedicated to the eradication of autoimmune diseases through fostering and facilitating collaboration in the areas of education, research, and patient services.

Clearinghouse on Disability Information
Special Education & Rehabilitative Services Communications & Customer Service Team
550 12th Street, SW, Rm. 5133
Washington, DC 20202-2550
http://www.ed.gov/about/offices/list/osers
Tel: 202-245-7307 202-205-5637 (TDD)
Fax: 292024507636

National Organization for Rare Disorders (NORD)
P.O. Box 1968
(55 Kenosia Avenue)
Danbury, CT 06813-1968
orphan@rarediseases.org
http://www.rarediseases.org
Tel: 203-744-0100 Voice Mail 800-999-NORD (6673)
Fax: 203-798-2291
Federation of voluntary health organizations dedicated to helping people with rare “orphan” diseases and assisting the organizations that serve them. Committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service.

Paralyzed Veterans of America (PVA)
801 18th Street, NW
Washington, DC 20006-3517
info@pva.org
http://www.pva.org
Tel: 202-USA-1300 (872-1300) 800-424-8200
Fax: 202-785-4452
Non-profit organization dedicated to serving the needs of its members with spinal cord injuries.
Glossary

**antibodies** - proteins made by the immune system that bind to structures (antigens) they recognize as foreign to the body.

**antigen** - a structure foreign to the body, such as a virus. The body usually responds to antigens by producing antibodies.

**ataxia** - a condition in which the muscles fail to function in a coordinated manner.

**autoimmune disease** - a disease in which the body’s defense system malfunctions and attacks a part of the body itself rather than foreign matter.

**blood/brain barrier** - a membrane that controls the passage of substances from the blood into the central nervous system.

**cerebrospinal fluid** - the colorless liquid, consisting partially of substances filtered from blood and partially by secretions released by brain cells, that circulates around and through the cavities of the brain and spinal cord. Physicians use a variety of tests—electrophoresis, isoelectric focusing, capillary isotachophoresis, and radioimmunoassay—to study cerebrospinal fluid for abnormalities often associated with MS.

**cytokines** - powerful chemical substances secreted by T cells. Cytokines are an important factor in the production of inflammation and show promise as treatments for MS.

**demyelination** - damage caused to myelin by recurrent attacks of inflammation. Demyelination ultimately results in nervous system scars, called plaques, which interrupt communications between the nerves and the rest of the body.

**experimental allergic encephalomyelitis (EAE)** - a chronic brain and spinal cord disease similar to MS which is induced by injecting myelin basic protein into laboratory animals.

**fatigue** - tiredness that may accompany activity or may persist even without exertion.

**gadolinium** - a chemical compound given during MRI scans that helps distinguish new lesions from old.

**human leukocyte antigens (HLAs)** - antigens, tolerated by the body, that correspond to genes that govern immune responses. Also known as **major histocompatibility complex.**

**immunoglobulin G (IgG)** - an antibody-containing substance produced by human plasma cells in diseased central nervous system plaques. Levels of IgG are increased in the cerebrospinal fluid of most MS patients.

**immunosuppression** - suppression of immune system functions. Many medications under investigation for the treatment of MS are immunosuppressants.

**interferons** - cytokines belonging to a family of antiviral proteins that occur naturally in the body. Gamma interferon is produced by immune system cells, enhances T-cell recognition of antigens, and causes worsening of MS symptoms. Alpha and beta interferon probably exert a suppressive effect on the immune system and may be beneficial in the treatment of MS.

**lesion** - an abnormal change in the structure of an organ due to disease or injury.

**magnetic resonance imaging (MRI)** - a non-invasive scanning technique that enables investigators to see and track MS lesions as they evolve.
myelin - a fatty covering insulating nerve cell fibers in the brain and spinal cord, myelin facilitates the smooth, high-speed transmission of electrochemical messages between these components of the central nervous system and the rest of the body. In MS, myelin is damaged through a process known as demyelination, which results in distorted or blocked signals.

myelin basic protein (MBP) - a major component of myelin. When myelin breakdown occurs (as in MS), MBP can often be found in abnormally high levels in the patient's cerebrospinal fluid. When injected into laboratory animals, MBP induces experimental allergic encephalomyelitis, a chronic brain and spinal cord disease similar to MS.

oligodendrocytes - cells that make and maintain myelin.

optic neuritis - an inflammatory disorder of the optic nerve that usually occurs in only one eye and causes visual loss and sometimes blindness. It is generally temporary.

paresthesias - abnormal sensations such as numbness, prickling, or "pins and needles."

plaques - patchy areas of inflammation and demyelination typical of MS, plaques disrupt or block nerve signals that would normally pass through the regions affected by the plaques.

receptor - a protein on a cell's surface that allows the cell to identify antigens.

retrobulbar neuritis - an inflammatory disorder of the optic nerve that is usually temporary. It causes rapid loss of vision and may cause pain upon moving the eye.

spasticity - involuntary muscle contractions leading to spasms and stiffness or rigidity. In MS, this condition primarily affects the lower limbs.

T cells - immune system cells that develop in the thymus gland. Findings suggest that T cells are implicated in myelin destruction.

transverse myelitis - an acute spinal cord disorder causing sudden low back pain and muscle weakness and abnormal sensory sensations in the lower extremities. Transverse myelitis often remits spontaneously; however, severe or long-lasting cases may lead to permanent disability.

white matter - nerve fibers that are the site of MS lesions and underlie the gray matter of the brain and spinal cord.

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See a list of all NINDS Disorders

Prepared by:
Office of Communications and Public Liaison
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD 20892

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