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MULTIPLE SCLEROSIS

ABSTRACT.—Multiple sclerosis is a chronic disease that begins in late adolescence or adulthood. It is highly variable in its expression and severity. It is believed to be autoimmune in nature. The cause is unknown; both genetic and environmental factors have been implicated in the pathogenesis. MS generally presents with the acute or subacute onset of neurologic abnormalities that may wax and wane over many years. Diagnosis is generally made by means of observation of the clinical course in conjunction with a neurologic examination and laboratory tests. These tests may include magnetic resonance imaging of the head and spine, lumbar puncture, and evoked potentials. Treatment is based on general supportive care, the use of corticosteroids for relapses, and symptomatic management of ongoing problems. The frequency of relapses can be reduced with interferon-β (Betaseron). Copolymer 1 and interferon-β la are being evaluated by the U.S. Food and Drug Administration for approval for use for reduction in the frequency of relapses in relapsing-remitting MS. Treatment of chronic progression is often attempted with immunosuppressive agents such as corticosteroids, azathioprine, and cyclophosphamide. Use of other agents is being investigated.

IN BRIEF

Multiple sclerosis (MS) is a chronic disease of the central nervous system that typically begins in late adolescence or early adulthood. The cause is unknown, although the disease is believed to be autoimmune in nature. Both genetic and environmental factors have been implicated in the pathogenesis of MS. A viral cause has been postulated, but no single virus has been confirmed to be associated with MS.

The pathologic features of MS include the presence of demyelinating areas in the white matter of the brain with perivascular in-
flammation and relative sparing of the axons. Plaques are commonly found in the periventricular areas of the cerebral hemispheres, in the optic nerves, the brainstem, the cerebellum, and the spinal cord.

The presence of inflammation in MS plaques and the presence of oligoclonal immunoglobulin bands suggest an autoimmune basis of the disease. Characterization of the inflammatory cells in the plaques and in the cerebrospinal fluid has revealed a predominance of T cells. This finding has focused a great deal of attention on the trimolecular complex, which consists of the major histocompatibility complex, the T-cell receptor, and the antigen. Consistent associations with DR2, DRb1501, DQb602, and the DW2 haplotypes have been identified in white persons. Studies of restricted use of specific T-cell receptor regions in the immune process have not revealed a specific receptor in this disease. The antigen remains unknown, although many investigators are working with myelin basic protein and other proteins associated with myelin.

Two animal models, experimental allergic encephalomyelitis and Theiler murine encephalomyelitis, are valuable in testing experimental immunotherapies and other aspects of autoimmune mediated demyelination.

MS generally appears with the acute or subacute onset of neurologic abnormalities that may wax and wane over many years. Common early symptoms include numbness, double vision, paraparesis, monoparesis, bladder control problems, optic neuritis, ataxia, or tremor. Common ongoing symptoms include those just mentioned, vertigo, increasing spasticity, depression, emotional lability, gait abnormalities, fatigue, dysarthria, quadriparesis, constipation, incoordination, fatigue, and pain.

Diagnosis is made by means of observation of the clinical course in conjunction with the neurologic examination and laboratory tests. Magnetic resonance imaging of the head and spine can be valuable in the evaluation of suspected MS. The presence of an elevated immunoglobulin G (IgG) index or oligoclonal bands in the spinal fluid also can be helpful. Evoked potentials can help confirm subclinical involvement of the eyes, vestibular function, or sensory tracts.

The differential diagnosis of MS includes other demyelinating syndromes, particularly the monophasic syndromes, such as postinfectious encephalomyelitis, postinfectious transverse myelitis, and isolated optic neuritis. Some infectious diseases, such as Lyme disease, syphilis, and HTLV-1 myelopathy, can be confused with MS. Other autoimmune conditions, such as systemic lupus erythematosus, Behçet's syndrome, sarcoidosis, and Sjögren's syndrome, can cause symptoms similar to those of MS. Some leukodystrophies and hereditary degenerative syndromes can be confused with MS.

MS is often classified by its clinical course. Benign MS is charac-
characterized by mild intermittent relapses with nearly complete resolution. Relapsing-remitting MS is the most common form of the disease. It is characterized by episodes of acute or subacute neurologic dysfunction followed by periods of improvement and stabilization. Secondary progressive MS begins with a relapsing-remitting course, but the disease gradually worsens, causing slow accumulation of neurologic signs and symptoms. MS that never has a relapsing-remitting course but begins with a slow progression of signs and symptoms is classified as primary progressive MS.

Treatment of MS is based on the progression of an individual case. General health measures include exercise, physical and occupational therapy, a balanced diet, and aggressive treatment of fever and overheating. Treatment of relapses is recommended for moderate to severe relapses. Corticosteroids are choice of treatment of relapses. Steroids should be used with caution because of the large number of side effects associated with long-term use.

The frequency of relapses can be reduced with interferon-β1b (Betaseron). Copolymer 1 and interferon-β1a are being evaluated by the U.S. Food and Drug Administration for approval for use in reduction of the frequency of relapses in relapsing-remitting MS. These drugs soon may be available for clinical use.

Treatment of chronic progression is often attempted with immunosuppressive agents such as corticosteroids, azathioprine, methotrexate, and cyclophosphamide (Cytoxan). Other agents under investigation are cladribine and intravenous immunoglobulin.

Symptomatic treatment of the chronic symptoms of MS is important. Treatment of symptoms can help patients remain functional and comfortable even with relatively severe chronic problems.

Fatigue can be treated with rest breaks during the day, exercise, and energy-conservation techniques. Medications that may help are amantadine hydrochloride and pemoline.

Spasticity is a severe problem that causes contractures, pain, insomnia, and increased fatigue. It can be treated conservatively with physical therapy, particularly stretching exercises. Baclofen and diazepam can also be useful and are often used alone or in combination. In patients with severe spasticity, baclofen can be administered with an intrathecal pump.

Urinary dysfunction is a common problem. A urologist usually is needed to define the type of dysfunction present. A hypertonic, spastic bladder can be treated with anticholinergic agents. A hypotonic bladder may require intermittent or long-term catheterization. Detrusor-sphincter dyssynergia may require a combination of anticholinergic agents and intermittent catheterization. Urinary retention, which causes frequent bladder infections, may require acidification of the urine or long-term administration of antibiotics. Patients with severe retention may require urinary diversion.

DM, January 1996
Sexual dysfunction often requires a multidisciplinary approach, including counseling, modification of sexual techniques, medication, or prosthetic devices for men.

Tremor can be a severe, intractable problem. Medications include clonazepam, propranolol, acetazolamide, or diazepam.

Emotional problems are common in patients with MS. Emotional lability may respond to tricyclic antidepressant medications. Depression is treated with antidepressant agents and counseling.

Pain is a prominent concern in many patients with MS. Dysesthetic pain can often be managed with tricyclic antidepressants, carbamazepine, phenytoin (Dilantin), or valproic acid. Musculoskeletal pain is treated with antiinflammatory medications and physical therapy.

Cognitive dysfunction can be a disabling and distressing component of MS. Documentation with neuropsychiatric testing may be helpful in managing these problems.

Current investigations of MS center on the concept of autoimmunity, possibly mediated by a viral illness. Studies designed to define the role of the immune system in MS may be useful. Medications designed to reduce a specific autoimmune response and medications that assist in stimulation of remyelination or improvements in quality of life are being developed.

Over the past few years, great strides have been made in understanding the role of the immune system, in improving diagnostic capabilities, and in managing the problems associated with MS. As this trend continues, we may have more diverse and effective therapies for the management of MS.
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John W. Rose, MD, was born in Oakland, California, and attended Johns Hopkins University. He entered medical school at the University of Maryland in 1971 and upon graduation received the Alexander Hammond Award for excellence in neurology. Dr. Rose entered the neurology residency at the University of Maryland and served as chief resident from 1978 to 1979. He was a fellow in neuromuscular diseases at the National Institutes of Health and later a medical staff fellow in the neuroimmunology branch at that institution. Dr. Rose moved to the Department of Neurology at the University of Utah in 1985. He is associate professor of neurology at the University of Utah and assistant chief of neurology at the Veterans Administration Medical Center in Salt Lake City.

Dr. Rose conducts clinical and basic research on multiple sclerosis. These investigations include clinical trials in the treatment of MS, experimental immunotherapy in disease models, and the search for genetic factors in MS. Dr. Rose serves on the fellowship advisory board for the National Multiple Sclerosis Society.
MULTIPLE SCLEROSIS

INTRODUCTION

Multiple sclerosis (MS) is a chronic disease with highly variable expression. The disease has many different clinical courses. It affects persons in late adolescence or adulthood. It is estimated that 300,000 Americans have MS. Because the disorder affects persons during their active years, it has a profound social and economic impact. Within a few years of clinical diagnosis, patients are partially or completely disabled. The disability results from the involvement of one or multiple neurologic deficits. Common symptoms are listed in Table 1.

Jean Martin Charcot’s description of the clinical and pathologic features of MS is the foundation of our knowledge of the disease.\(^1\) The historical aspects of MS are reviewed in previous publications.\(^2^,^3\) We are now entering a new phase of understanding brought about by careful clinical trials and the capability of monitoring the disorder with longitudinal magnetic resonance imaging (MRI). In an individual patient, MS can be described by means of clinical observation. Current concepts of the clinical courses, their relative frequencies, and MRI characteristics of MS are portrayed in Table 2.

Investigations with MRI have changed the concept of MS by demonstrating more evidence of disease activity than is expected from clinical examination. Disease activity, as measured with MRI, is particularly high among patients with chronic progressive disease.\(^4\)

The acute lesions of MS can now be demonstrated with gadolinium-enhanced MRI. The initial event is associated with local disruption of the blood-brain barrier (Fig. 1). As the abnormality evolves, increased signal intensity becomes evident on T2-weighted images (Figs. 2 and 3). The lesion may grow larger over a few days and then the areas of high signal intensity may begin to recede. Over time, the lesions may completely resolve on T2-weighted images. With each relapse, which is defined by new or newly enhancing lesions on MR images, the older areas of involvement may be reactivated. Reactivation is associated with the development of permanent lesions on MR images.\(^5\)

Clinical correlation is frequently observed with areas of contrast enhancement or abnormal signal intensity in the cerebellum,
| Common initial symptoms | Common chronic problems | Important uncommon problems |
|-------------------------|-------------------------|-----------------------------|
| Weakness: monoparesis or paraparesis | Motor weakness: monoparesis, paraparesis, hemiparesis, or quadriparesis | Seizures |
| Optic neuritis | Paresthesia | Altered level of consciousness |
| Paresthesia and numbness | Urinary frequency, incontinence, incomplete emptying | Mimicking brain tumor |
| Diplopia | Optic atrophy, blurred vision, or central scotomata | Trigeminal neuralgia |
| Vertigo | Diplopia | Hearing loss |
| Urinary frequency, urgency, or incontinence | Lhermitte’s sign | Narcolepsy |
| Unsteady gait or balance difficulties | Pain and dysesthesia | Involuntary movements |
| Incoordination and loss of balance | Cognitive abnormalities | |
| Cognitive abnormalities | Sexual dysfunction | |
| Fatigue | Depression | |
| Depression | Spasticity | |
| Spasticity | Vertigo and oscillopsia | |
**TABLE 2.** Clinical types of MS and related disorders and MRI findings

| Type                          | Characteristics                                      | Frequency* | MRI findings                                      |
|-------------------------------|------------------------------------------------------|------------|--------------------------------------------------|
| Benign MS                     | Mild relapses with little permanent disability       | 10%-20%    | Brain or spinal cord abnormality                 |
| Relapsing-remitting MS        | Intermittent attacks with complete or incomplete recovery | 30%-40%    | Brain or spinal cord abnormality                 |
| Primary progressive MS        | Slow progression of neurologic deficits from the beginning | 10%-20%    | Brain or spinal cord abnormality, often mild with few enhancing lesions |
| Secondary progressive MS      | Relapsing-remitting course that worsens develops gradually | 20%-30%    | Brain or spinal cord abnormality, usually many lesions with enhancement |
| Relapsing progressive MS      | Intermittent attacks with no clinically significant recovery | 10%-20%    | Brain or spinal cord abnormality                 |
| Optic neuritis                | Isolated inflammation of the optic nerve             | May be isolated or lead to MS | Optic nerve lesions Abnormality in brain suggests increased likelihood of future MS attacks |
| Transverse myelitis           | Inflammation of the spinal cord                      | May be isolated or lead to MS | Spinal cord lesion often present Abnormality in brain suggests increased likelihood of future MS attacks |
| Neuromyelitis optica          | Inflammation of spinal cord and optic nerves         | Infrequent | Isolated optic nerve and spinal cord lesions     |
| Postinfectious encephalomyelitis | Subacute onset of global demyelination             | Infrequent | Multiple brain lesions                           |

*Values are percentage of patients with MS.*
brainstem, or spinal cord. Abnormalities in the cerebral hemispheres are frequently periventricular in distribution and only occasionally correlate with specific symptoms or signs. The accumulation of lesions in the frontal lobes is associated with a decline in memory. In addition, a change in the number of lesions on cranial MR images correlates with a change in overall clinical status as measured with standard scales.

Observations made with MRI are having a marked impact on both our basic knowledge of MS and on therapeutic trials. MRI studies will provide considerable insight into the natural history of the disease and will be an excellent independent variable in future clinical trials.

**EPIDEMIOLOGY**

Traditionally MS is thought to have a relatively high incidence in the northernmost latitudes of the northern hemisphere. This theory is based on the incidence of the disease in Scandinavia and the northern United States. A similar association is documented in the southern hemisphere in Australia and New Zealand. These observations are supplemented by data from migration studies, which demonstrate a relation between age at migration and assumption of disease risk for the location. Risk is conferred by exposure to an environ-
FIG. 2. MR image of the cerebrum in a patient with multiple sclerosis demonstrates one large lesion and several smaller lesions in the white matter.

ment during adolescence. Thus environmental factors are important in the pathogenesis of MS.

Certain populations are susceptible to MS, and certain populations are resistant to MS. For example, Lapps in Scandinavia have a very low incidence of MS, even though they reside predominantly in the far northern latitudes. In North America the disease is infrequent among Hutterites and Native Americans. MS is uncommon in Japan. The incidence of the disease in first-degree relatives of patients with MS is 20 times that of the general population, suggesting that genetic factors influence disease expression.

The results of population-based studies of twins offer evidence that environmental and genetic factors contribute to the development of MS. These investigations show that the concordance in monozygotic twins is greater than 30%. It is less than 5% in dizyg-
FIG. 3. T2-weighted MR image of the cerebellum and brainstem shows a prominent lesion in the white matter of the left cerebellum.

gotic twins, suggesting that although genetic factors are important, environmental exposure also is important for disease expression.

It is now commonly accepted that multiple genes influence autoimmune diseases in both animals and human beings. Therefore polygenic inheritance is postulated for MS. Like other autoimmune diseases, MS is more frequent in women, with a ratio of 2:1.

PATHOLOGY

The pathologic features of multiple sclerosis were first described by Charcot, who recognized plaques in the white matter (scleroses en plaque) during pathologic examination of brain sections. These plaques were demonstrated to lack myelin and to contain perivascular inflammation. These features were established as the pathologic
hallmarks of MS. The following discussion centers on the typical findings in MS. Comparisons are made between MS and other forms of inflammatory demyelinating disease.

The distribution of plaques within the white matter is restricted to the central nervous system (CNS). Plaques are found frequently in a periventricular distribution in the cerebral hemispheres. Some of these plaques may be associated with the distribution of terminal veins. Plaques may occur anywhere within the white matter. When plaques are near the cortex, sparing of the subcortical myelinated fibers is often observed. Plaques adjacent to gray matter may at times spread into the gray matter, including the cortex and deeper nuclei. Plaques are frequently found in the white matter of the optic nerves, the brainstem, the cerebellum, and the spinal cord. Plaques in these locations more frequently correlate with symptoms. Within a plaque, axons are frequently preserved.

The evolution of a plaque is not known. MRI investigations show that the blood-brain barrier is locally disrupted at the onset of symptoms. Pathologists disagree as to whether demyelination precedes inflammation or is secondary to inflammation. At present the latter view predominates. In acute plaques, the inflammatory response of lymphocytes, plasma cells, and macrophages is capable of producing or augmenting demyelination by direct and indirect mechanisms. The inflammatory response is predominantly perivenular, with a lesser response at the edges of or within plaques. The macrophages associated with acute plaques characteristically contain myelin fragments or myelin breakdown products.

Lymphocytes may contribute to the pathologic process by means of direct or indirect pathways. Direct mechanisms include antibody- and cell-mediated immunity. T-cell–mediated reactivity is favored because most inflammatory cells are T cells. Indirect mechanisms include the secretion of lymphokines and cytokines. The ability of molecules such as tumor necrosis factor to damage myelin or oligodendrocytes is the focus of ongoing research. Cytokines may influence macrophage activation, stimulating the phagocytosis of myelin. In addition, the release of heat shock proteins may result in stimulation of T cells, resulting in increased cytotoxicity.

The CNS lesions of MS can be classified as early active, active, inactive, early remyelinating, and late remyelinating, according to histologic criteria. The features of these lesions are detailed in Table 3.

Studies of oligodendrocytes early in the course of MS have demonstrated relative preservation of these cells in some patients, and remyelination is possible in these patients. Other patients have a striking loss of oligodendrocytes, making remyelination unlikely. These differences may reflect the severity of the injury at a specific site of demyelination, or they may indicate that the pathogenesis of demyelination varies among patients with MS. This may imply that
TABLE 3. Histologic criteria for staging demyelinating lesions in MS

| Type of lesion                  | Criteria                                                                 |
|---------------------------------|---------------------------------------------------------------------------|
| Early active                    | Perivascular cuffing                                                     |
|                                 | Indistinct edge                                                          |
|                                 | Numerous macrophages present                                             |
|                                 | Extracellular myelin debris                                              |
|                                 | Myelin debris stains for myelin basic protein                            |
| Late active                     | Demyelinated area with shelving of edge                                  |
|                                 | Lipid-laden foamy macrophages                                            |
|                                 | Increased astrocytes                                                     |
|                                 | Lymphocytes and plasma cells at lesion margin                            |
|                                 | Myelin breakdown products no longer reactive for myelin basic protein    |
| Early remyelinating             | Small number of inflammatory cells at lesion edge                        |
|                                 | Fibrillary gliosis                                                       |
|                                 | Fields of thinly remyelinated axons                                      |
| Late remyelinating              | Fibrillary gliosis                                                       |
|                                 | Rare inflammatory cells                                                  |
|                                 | Nerve fibers with sheaths slightly thinner than normal                   |
| Inactive                        | Field of demyelinated axons                                              |
|                                 | Rare macrophages                                                         |
|                                 | Some loss of axons                                                       |
|                                 | Few oligodendrocytes                                                    |

heterogeneous mechanisms exist for the induction of MS. Ultrastructural findings frequently observed in the lesions of MS include the following: (1) separation of the outer lamellae of the myelin sheath, (2) degenerative changes in myelin (vesiculation, thinning, loss of periodic structure), and (3) infiltration with macrophages or microglia with phagocytosis of myelin.\(^ {17} \)

ETIOLOGY

AUTOIMMUNE CAUSES

An autoimmune basis for MS has long been suspected because of the inflammation in the CNS and the presence of oligoclonal bands in the cerebrospinal fluid (CSF). The inflammatory response is primarily lymphocytic and mononuclear.\(^ {2,3} \) The predominance of T cells among the lymphocytes has led investigators to evaluate the role of the T-cell receptor and its recognition of antigen combined with major histocompatibility antigens (MHC). This has been named the trimolecular complex.\(^ {23} \)

The T-cell receptor recognizes antigen in the context of the MHC molecule. In the case of MHC class II molecules such as DR2, the antigen fragments are bound in a cleft, which is presented to the T-cell receptor for recognition. With regard to the components of the
FIG. 4. Electrophoresis strip of CSF and serum shows oligoclinal immunoglobulin bands in the CSF but not in the serum of a patient with MS.

trimolecular complex, investigators have examined the response of T lymphocytes from patients with MS for reactivity with myelin antigens, especially myelin basic protein (MBP). These investiga-
tions demonstrated reactivity to MBP both in patients with MS and in healthy persons who served as controls. Initially, oligoclonality of responding lymphocytes and restricted T-cell receptor utilization were believed to differentiate patients with MS. Findings of more recent investigations suggest that the response to MBP in patients with MS is heterogeneous. It is important to consider that myelin proteins such as proteolipid protein, myelin oligodendrocyte glycoprotein, myelin-associated glycoprotein, or other myelin antigens may be important in the pathogenesis of MS.

In the context of the trimolecular complex, it is important to note that MS has been associated with certain MHC or human leukocyte antigen (HLA) markers. A consistent observation is the association of DR2, DRb1501, DQb602, and the Du2 haplotype with MS. Different HLA associations are reported within ethnic groups. The MHC molecules may contribute to genetic susceptibility to the disorder, but they are only one of a number of factors that confer risk for the disease.

The presence of oligoclonal bands in the CSF of patients with MS is frequently observed (Fig. 4). These abnormal immunoglobulins are identified in a high percentage of patients with clinically definite MS, and they are present in approximately 60% of patients at the clinical onset of the disease. The oligoclonal bands in MS are of unknown specificity. Small percentages may bind to known viral antigens in some patients. Consistent binding of these antibodies to specific viral polypeptides or viral oligopeptides with homology to myelin components has yet to be demonstrated.

The oligoclonal bands are not specific to MS and can be observed in patients with CNS infections such as syphilis, subacute sclerosing panencephalitis, viral encephalitis, or meningitis. If the infection is self-limited, the oligoclonal bands may be a transitory abnormality. In comparison, chronic infections of the CNS are associated with persistence of the oligoclonal bands. In these settings, the antibodies that compose the oligoclonal bands have pathogen specificity. Oligoclonal bands can be observed in patients with autoimmune diseases such as systemic lupus erythematosus.

**VIRAL CAUSES**

The probability that an environmental factor is involved in the pathogenesis of MS has stimulated interest in a viral cause. Although viral isolates are reported from the CNS of patients with MS, there are no consistent observations. Attempts to detect viral nucleic acids by means of in situ hybridization and polymerase chain reaction (PCR) are in progress. These techniques are extremely sensitive and require rigorous controls. Careful confirmation of any future viral isolates or viral nucleic acids by multiple laboratories is required.
Recent studies of tropical spastic paraparesis demonstrate that the retrovirus human T-cell lymphotropic virus type I (HTLV-I) is involved in the pathogenesis of this disorder, which shares some clinical features with MS. It is clear, however, that HTLV-I is not a pathogen in MS. There remains the possibility that a retrovirus or endogenous retrovirus could contribute to the pathogenesis of MS.

There is considerable interest in the possibility that exposure to a virus may lead to an immunopathologic condition that results in MS. Of particular note are investigations that demonstrate the potential of molecular mimicry to produce autoimmunity. The term molecular mimicry arises from the demonstration of shared homology between normal human myelin proteins and viral polypeptides. If an immune response is mounted to such a viral epitope, then it may be perpetuated by exposure of the shared region on the normal human protein. In MS, homology between myelin antigens and viral peptides is established. Thus this mechanism could result in CNS demyelination after viral infection.

Autoimmunity could also result from superantigenic stimulation of T cells by viral or bacterial proteins. Superantigens are capable of binding to specific T-cell receptor proteins, producing nonspecific stimulation of relatively large numbers of T cells, which might cause clonal expansion of T cells reactive to myelin or oligodendrocyte antigens.

ANIMAL MODELS OF DEMYELINATING DISEASE

CNS demyelination associated with inflammation is present in animal models of experimental allergic encephalomyelitis (EAE) and Theiler murine encephalomyelitis (TME). These models provide an opportunity for the investigation of autoimmune and virus-associated disease, respectively. EAE is an autoimmune disease of the CNS and a model for immunotherapy. A CD4+ T-cell population specific for a myelin antigen, either MBP or proteolipid protein, is required for initiation EAE. EAE and MS share characteristics that include CNS demyelination, perivascular T cells, association with MHC class II antigens, and possibly restricted TCR V-gene utilization. The murine adoptive transfer model has another important feature of MS: the chronic relapsing clinical course. This clinical course is useful for investigations of the immune response and immunotherapy not only during onset of the disease but also during relapse. The pathologic features of this murine transfer model are inflammation and prominent demyelination. EAE is not associated with an environmental factor.

The TME model of immune mediated demyelination is of particular interest because it has important parallels with postinfectious encephalomyelitis and MS. In this model, antecedent mild or even
subclinical viral encephalitis is followed by a period of quiescence and the eventual onset of demyelination.\textsuperscript{50} The virus is persistent during the demyelinating phase of the disease. This implies that either low-level expression of viral polypeptides or immunologic cross-reactivity between virus and myelin antigens is crucial for initiating demyelination. The demyelination in the TME virus model is mediated by T lymphocytes. These T cells may have viral specificity but produce demyelination. This mechanism would be relevant to MS if the suspected environmental factor were one or several viruses. As in MS and EAE, T cells appear to initiate immune-mediated demyelination in TME.\textsuperscript{51,52}

Experimental immunotherapies are evaluated in these animal models and provide a basis for clinical trials in human beings. Examples of these investigational treatments include cytokine transforming growth factor-\(\beta\), (TGF\(\beta\)),\textsuperscript{53} lymphokine-toxin,\textsuperscript{54} anti-T-cell receptor V\(b\)-specific monoclonal antibody,\textsuperscript{55,56} T-cell vaccination,\textsuperscript{57} blocking peptides,\textsuperscript{58} anti-adhesion molecule specific monoclonal antibodies,\textsuperscript{59} and nitric oxide synthetase inhibition.\textsuperscript{60}

These experimental models provide an invaluable resource for the study of immunotherapy. Although these experimental models are not likely to mirror the pathogenesis of MS, they are extremely useful in the study of CNS inflammation and demyelination.

**CLINICAL MANIFESTATIONS**

MS is primarily a disease of young adults. Most patients report their first symptoms between the ages of 20 and 45 years. The disorder rarely appears before the age of 15 years or after the age of 50 years, although it has been reported to occur in both children and the elderly. The symptoms of MS in children are essentially the same as those in adults; ataxia, numbness, and visual disturbance are the most common presenting symptoms. In elderly persons, a progressive onset is more common.

MS is characterized by episodes of neurologic dysfunction, followed by periods of stabilization or remission. Symptoms, once they appear, may partially or completely resolve or may be permanent. These episodes tend to develop over hours or days. Sometimes the symptoms occur with almost strokelike suddenness, or they may develop slowly over a few weeks. Once the symptoms have developed, resolution generally occurs over weeks or months.

**INITIAL SYMPTOMS**

Certain signs and symptoms are more common in the early stages of MS. These include numbness, double vision, monoparesis, paraparesis, bladder control problems, optic neuritis, ataxia, or tremor (Table 1).
Numbness can be difficult to evaluate. Numbness that suggests early MS includes an ascending numbness beginning at the feet. This may be a sign of transverse myelitis. Hemiparesthesia, bilateral hand numbness, and dysesthesia in both hands, both feet, or on one side of the body, also are early symptoms of MS. The numbness is usually present for days, weeks, or months. Many patients describe numbness or paresthesia with no objective abnormalities. If objective sensory abnormalities occur, they are more commonly reduction of vibration, proprioception, or stereognosis rather than pain or fever.

The diplopia that occurs with MS is frequently partial or complete internuclear ophthalmoplegia, which is often bilateral. A small percentage of patients have sixth nerve palsy or, more rarely, third or fourth nerve palsy. Sometimes monocular diplopia is a symptom of optic neuritis.

Optic neuritis is usually characterized by monocular blurred vision, sometimes with scotomata and often with alteration of color vision. Retroorbital pain or headache is common in patients with active optic neuritis. The pain may intensify with eye movement.

Motor weakness is usually accompanied by upper motor neuron signs, such as hyperreflexia or the Babinski sign. Paraparesis is the most common early symptom, but the weakness also can occur as hemiparesis or monoparesis. Spasticity can be a later manifestation.

**ONGOING SYMPTOMS**

Signs and symptoms that commonly occur as MS progresses include vertigo, tremor, incoordination, increasing spasticity, depression, mood swings, cognitive abnormalities, impotence or other sexual dysfunction, weakness, Lhermitte's sign, gait abnormalities, constipation, urinary incontinence, optic nerve pallor, fatigue, quadriparesis, dysarthria, loss of upper extremity coordination, and dysesthetic pain (Table 1).

Uncommon but important problems include seizures, atypical facial pain or tic douloureux (trigeminal neuralgia), bowel incontinence, swallowing problems, hearing loss, and dystonia. Bell's palsy is sometimes seen in patients with MS (Table 1).

**CLASSIC COURSE**

The classic course of MS is one of intermittent neurologic signs and symptoms over many years. As time progresses, chronic problems accumulate. The amount of total disability varies from patient to patient. After a number of years, a patient's condition may stabilize permanently, but this does not always occur.
SUBTYPES OF DISEASE

MS can be divided into subtypes according to the course of the disease. There is a continuum among the various subtypes, and the disease in some patients does not fit into a pattern.

Benign MS accounts for 10% to 20% of cases and occurs more often in young women. In this type of MS, symptoms are mild and often sensory. Resolution of neurologic problems is nearly complete. Over the years, these patients rarely experience considerable disability.

Relapsing-remitting MS is the most common form of the disease. It is characterized by episodes of neurologic dysfunction (variably called exacerbations, relapses, or attacks) followed by periods of improvement and stabilization (called remissions). During a remission, not all symptoms resolve completely. The patient may be left with permanent disabilities, which may vary in severity.

The condition of 30% to 50% of patients with an initial relapsing-remitting course begins to worsen gradually over time, and neurologic signs and symptoms accumulate. This form of the disease is classified as secondary chronic progressive MS or relapsing-progressive MS. The latter term is also used to describe disease in patients who have sudden deteriorations in a stepwise manner without clinically significant recovery.

Primary progressive MS occurs in 10% to 20% of patients. Disease in these patients begins with a slow progression of neurologic deficits with no history of relapse and may also have periods of stabilization or subacute worsening. Common problems that appear and gradually worsen with time include spastic paraparesis, cerebellar ataxia, and urinary incontinence.

CLINICAL FINDINGS

Although no neurologic findings are pathognomonic for MS, certain abnormalities found during a physical examination can be helpful in providing a clue to the diagnosis of MS. These include internuclear ophthalmoplegia, which is rarely seen in other diseases and is especially rare in young adults.

Hyperreflexia and the Babinski sign are common in early MS. Optic nerve pallor can provide a clue to subclinical or resolved optic neuritis. Altered color vision in one eye and a Marcus-Gunn pupil also are signs of optic neuritis. Nystagmus is a common finding in patients with MS. Many types of nystagmus are identified, including pendular nystagmus, small-amplitude nystagmus, or gaze-evoke nystagmus. Absent abdominal reflexes in a slender patient who has not undergone an abdominal operation may be a helpful sign. A mild intention tremor with or without past-pointing is also an early sign, as is a positive Romberg sign or difficulty with balance with
tandem gait. Subtle motor weakness or spasticity may also be found. Loss of vibratory or proprioceptive sensation in the lower extremities is common early in the course of the disease.

MS should be strongly suspected in young or middle-aged adults who describe symptoms consistent with the Lhermitte sign in the absence of obvious cervical cord abnormalities. The Lhermitte sign consists of paresthesia or an electric shock-like sensation that radiates up the head or down the spine on neck flexion or extension. Other important abnormalities are gait disturbances, persistent binocular double vision when looking in a particular direction, or a history of optic neuritis or transverse myelitis. Fatigue and depression are not criteria for the diagnosis of MS.

LABORATORY TESTING

No laboratory test is universally diagnostic for MS. Certain studies can be helpful in confirming the presence of separation of lesions in space and time.

SPINAL FLUID STUDIES

Examination of the CSF can be valuable for two reasons. First, the pattern of CSF findings can help confirm the presence of demyelinating disease. The protein level is often slightly elevated but is rarely greater than 0.1 g/L unless the patient is experiencing a severe exacerbation, particularly optic neuritis or transverse myelitis. A modest elevation in cell count, generally less than 50/mm³, is seen in some patients. The cell pattern usually consists mostly of mononuclear cells. If more sophisticated testing is conducted, most cells can be identified as T lymphocytes.

Qualitative analysis of proteins can be helpful in suggesting the diagnosis of MS. At electrophoresis oligoclonal immunoglobulin bands can be identified in the CSF but not in the serum of many patients with MS³⁴,⁶⁷ (Fig. 4). The IgG index, a comparison between IgG levels in the CSF and IgG levels in the serum, is elevated in many patients with MS.⁶⁸,⁶⁹ Although these findings suggest MS, they also are found in other diseases, most commonly other inflammatory diseases of the CNS. These diseases include Lyme disease, systemic lupus erythematosus, progressive multifocal leukoencephalopathy, encephalitis, and subacute sclerosing panencephalitis.³⁵,³⁶ Oligoclonal bands or an elevated IgG index will be seen in about 92% of patients with clinically definite MS.⁶⁹

ELECTRODIAGNOSTIC STUDIES

Evoked potentials can be useful in the identification of electrical evidence of separation of lesions in space. This separation is made evident by a slowing of electrical impulses in the central regions of
FIG. 5. Visual evoked potential shows a delay of the P100 (P1) in a patient with multiple sclerosis. Normal value is less than 112 msec. The patient had no history of optic neuritis or other visual symptoms, and visual acuity was normal. Many patients with MS and normal vision have a prolonged visual evoked potential, suggesting subclinical demyelination.

The CNS. The evoked potentials used for identifying lesions in MS are visual evoked responses (VER), brainstem auditory evoked responses (BAER), and somatosensory evoked responses (SSER), which include the median nerve-evoked response (MNER), and the posterior tibial nerve-evoked responses (PTNER).

The VER is abnormal in approximately 70% of patients with MS, regardless of whether there is a history of optic neuritis. A slowed P100 in a patient without a history of optic neuritis can be paraclinical evidence of a second lesion and can be used to confirm a diagnosis of MS (Fig. 5).

The BAER is more difficult to interpret than the VER and is abnormal in approximately 30% of patients with MS. In the BAER, five
consecutive waves are identified; these are numbered I–V. The wave interval I–III is considered the peripheral system. Abnormalities in this wave suggest a lesion in the peripheral auditory nerve. The wave interval III–V is generated from the central hearing areas in the brainstem. Slowing in this area suggests a brainstem lesion. Abnormalities in waves III–V are seen in approximately 30% of patients with MS.\textsuperscript{70}

The SSER is a technically more difficult study than the other responses, but it is useful for identification of slowed central conduction in the sensory pathway in the spinal cord and brain. The SSER is abnormal in approximately 80% of patients with definite MS.\textsuperscript{70} The SSER also is useful in the identification of peripheral lesions, suggesting that peripheral neuropathy rather than a central lesion is the cause of numbness.

**MAGNETIC RESONANCE IMAGING**

The development of MRI has been extremely important in both making the diagnosis of MS and helping researchers understand the dynamics of MS in patients with the disease. MRI findings should be interpreted with caution, however. Abnormal MRI findings alone are not sufficient to confirm a diagnosis of MS without clinical evidence.\textsuperscript{71,72}

In patients with MS, patchy areas of abnormal white matter are seen on T2-weighted and spin-echo images. These are most commonly found in the cerebral hemispheres in the periventricular areas. In some patients, however, lesions also are identified in the brainstem and cerebellum. MRI also helps identify lesions in the cervical and thoracic spinal cord. Gadolinium enhancement can be seen around some lesions, particularly if a patient is having an exacerbation or fairly rapid chronic progression. Gadolinium enhancement is considered a sign of an active lesion. Patients with MS may have enhancing lesions on MR images without clinical evidence of increased disease activity.

MR images are abnormal in more than 90% of patients with a definite diagnosis of MS. However, they are abnormal in only about 70% of patients with probable MS and about 30% to 50% of patients with possible MS.\textsuperscript{70,73} It is important to realize that patients may have MS and still have normal MR findings.\textsuperscript{72}

MR images may show abnormalities in white matter in many persons who do not have MS. Minor abnormalities are identified in 10% to 15% of the healthy population.\textsuperscript{74} Many healthy persons older than 50 years have abnormalities on MR images.\textsuperscript{74-76} Patients with other diseases, such as systemic lupus erythematosus, diabetes mellitus, hypertension, Behcet’s disease, Sjögren’s syndrome, Lyme disease, progressive multifocal leukoencephalopathy, and multi-
TABLE 4. MRI features of lesions in the white matter in diseases or conditions that may resemble MS

| Disease or condition                      | MRI features                                                                 |
|------------------------------------------|-----------------------------------------------------------------------------|
| Aging                                    | Lesions tend to be smaller and less extensive than those of MS               |
|                                          | Less involvement of posterior fossa                                         |
| Cerebrovascular disease                  | Lesions often involve cortex                                                |
|                                          | Smooth periventricular lesions                                              |
| HIV encephalitis                         | Punctate or patchy lesions in the white matter, often involving basal ganglia|
| HTLV-I associated myelopathy             | Small number of supratentorial lesions                                      |
| Progressive multifocal leukoencephalopathy| Extensive symmetric abnormalities in the white matter with atrophy          |
| Systemic lupus erythematosus             | Subcortical lesions, often involving arterial territories                   |
| Neurosarcoidosis                         | Lesion may be identical to those of MS, but meningeal enhancement and prominent brainstem involvement may be seen |
| Migraine                                 | Small number of lesions                                                    |
| Spinocerebellar degeneration             | Normal findings or cerebellar and brainstem atrophy                        |
| Behçet syndrome                          | Lesion may look like MS lesion but often has prominent brainstem involvement|

Infarct dementia, may have abnormalities in the white matter that are indistinguishable from those of MS (Table 4).76-78 MR images should be interpreted with caution, particularly in patients with chronic illness of any kind or in patients older than 50 years.

Fazekas et al.79 attempted to differentiate the MR images of healthy persons older than 50 years from those of patients with MS. They identified the following three criteria for the diagnosis of MS: lesions abutting the lateral ventricles, lesion diameter greater than 0.6 cm, and lesions present in the posterior fossa. If two of the three criteria were met, the specificity for MS was 88% and the sensitivity was 100%. A follow-up study in which 1500 consecutive MRIs were examined yielded a sensitivity of 81% and a specificity of 96%.80 These criteria may be useful in the interpretation of MRI findings in some patients, but they should be used with caution for patients with other diseases that can affect MRI, such as hypertension and diabetes mellitus. Patients with those diseases were excluded from the study by Fazekas et al.

The size and area of the lesions present on MR images correlate poorly with the patient’s disability.4,81 Many patients with large lesions on MR images have minor clinical findings, whereas some patients with small lesions have severe disability. One area in which
MRI may indicate the severity of the problem is in the cognitive status of the patient. An increase in the area of the lesions in the cerebral hemispheres or thinning of the corpus callosum may correlate with poor cognitive function.

The presence of lesions in the spinal cord does not correlate with disease severity. A recent study in which body coil imaging was used showed that 74% of patients with MS had lesions in the spinal cord that were identified by this technique. Although the presence of lesions and the area and number of lesions did not correlate with a patient's level of disability, the presence of spinal cord atrophy did correlate with greater disability. Patients with partial or complete transverse myelitis who subsequently are found to have MS often have lesions on MR images that correspond to the level indicated by symptoms and the level of neurologic findings (Simnad V, Rose JW, Manuscript in preparation).

The use of MRI for the follow-up evaluation of MS has become an integral part of research into the course of the disease. However, because MRI findings do not correlate with a patient's clinical condition, new abnormalities on MR images in the absence of clinical worsening should not be treated as an exacerbation of the disease. New abnormalities can, however, indicate that the disease remains active. MRI should be repeated in patients in whom the diagnosis has not been confirmed or in patients who have new symptoms that suggest a second disease. As the choice of treatments of MS increases, monitoring of disease activity may become useful in determining the course of treatment.

**RELATION BETWEEN MS AND OPTIC NEURITIS AND TRANSVERSE MYELITIS**

Optic neuritis is often seen as a first demyelinating episode in patients with MS. The diagnosis of MS should be considered in patients with optic neuritis, and a careful history and examination should be performed to exclude other neurologic abnormalities. However, many patients who have a single episode of optic neuritis never have other demyelinating episodes. One study of 60 patients found that MS developed in 74% of women and 34% of men within 15 years of an attack of optic neuritis.

Transverse myelitis, inflammation of an area of the spinal cord causing ascending weakness and numbness up to the level of the lesion, can also be seen as the initial demyelinating event in MS. Other causes include infectious, postinfectious, and postvaccinal demyelination. Sometimes the cause is never determined. When transverse myelitis occurs, an inflammatory lesion can be identified on MRI images of the cervical or thoracic spinal cord. Estimates of the risk of MS after an isolated episode of transverse myelitis range from 50% to 80%.91-93
The use of the cranial MR images in patients with optic neuritis or transverse myelitis may be helpful in predicting which patients are more likely to have additional problems. One prospective study identified patients with a single demyelinating episode such as optic neuritis or transverse myelitis. Patients with abnormal MRI findings at the time of the first episode had a 65% risk of a second episode within 5 years. Patients with normal MRI findings at the time of the first episode had a 5% risk of development of a second lesion in 5 years.4

A syndrome in which optic neuritis and transverse myelitis develop with no other demyelinating events is called Devic's neuromyelitis optica. In this disorder, cranial MRI findings remain normal. This is considered a monophasic illness—both abnormalities occur within a year of each other, and patients may never have another demyelinating event. This is a rare syndrome.5

PROGNOSTIC FACTORS

The following characteristics are associated with a favorable prognosis: (1) female sex, (2) early age at onset, (3) onset of symptoms referable to a single neurologic system, (4) substantial recovery from relapses, (5) early symptoms of numbness rather than corticospinal or cerebellar symptoms. Unfavorable prognosis is associated with chronic progressive disease (either primary or secondary), older age at onset, and male sex.6-8

DIAGNOSTIC CRITERIA

Because of the difficulties involved in the diagnosis of MS, several criteria have been published to standardize the terms used to describe the certainty of the diagnosis. The two primary sets of criteria are those of Poser et al.6 and Shumacher et al.8 The Poser criteria are more recent and are summarized in Table 5. It is important to remember that no abnormality should be used as a criterion if it can be explained by another medical problem.

DIFFERENTIAL DIAGNOSIS

Other conditions may commonly be confused with MS and should be considered in the differential diagnosis. The differential diagnosis depends in part on the clinical and laboratory findings in an individual patient.

Postinfectious encephalomyelitis is a subacute syndrome, possibly caused by an autoimmune response to a viral infection. Patients with this illness experience the acute or subacute onset of confusion, disorientation, gait abnormalities, loss of bowel or bladder control, weakness, or other symptoms. Abnormalities in the white mat-
TABLE 5. Poser criteria for the diagnosis of MS

| Diagnosis                        | Criteria                                                                 |
|----------------------------------|--------------------------------------------------------------------------|
| Clinically definite MS           | History of at least two attacks                                          |
|                                  | Clinical evidence of at least one lesion                                  |
|                                  | Clinical or paraclinical* evidence of a second lesion                    |
| Laboratory-supported definite MS | 1. History of two attacks and clinical or paraclinical* evidence of one lesion with CSF evidence of oligoclonal bands or increased IgG |
|                                  | 2. History of one attack, clinical evidence of one lesion, and clinical or paraclinical* evidence of a second lesion, with CSF oligoclonal bands or increased IgG |
| Clinically probable MS           | Meets clinical criteria for laboratory-supported definite MS without CSF evidence |
| Laboratory-supported probable MS | History of two attacks, with no clinical or paraclinical* evidence of a lesion but CSF oligoclonal bands or increased IgG |

*Paraclinical evidence consists of abnormal evoked potentials, urodynamics, MR images, or computed tomographic scans. These studies should implicate a lesion not present at clinical examination. No other explanation for the findings must be evident (eg, previous history of surgical lesion that would account for the findings).

ter can be seen with MRI, and evidence of inflammation frequently is seen in the CSF. The patient's condition may or may not return to normal; recovery may take months or even years.84

Lyme disease is a prominent concern and appears to be a cause of intermittent neurologic events,85 the most common of which is Bell's palsy. Encephalomyelitis may develop, with vague symptoms of numbness, fatigue, and memory deficit. Abnormalities in the white matter may be seen with MRI, and CSF findings may resemble those in MS, including mild leukocytosis and oligoclonal bands. Patients may have a history of a tick bite, a rash, or recent arthralgia. Lyme titers or a Lyme PCR in the blood or CSF may be helpful to these patients.85

Systemic lupus erythematosus is a well-known syndrome that may cause transverse myelitis, strokes, encephalopathy, and optic abnormalities. Clues to the differential diagnosis are systemic abnormalities such as hematuria or leukopenia, arthritis, or an elevated antinuclear antibody titer, erythrocyte sedimentation rate, or other blood measurement. Sometimes both systemic lupus erythematosus and MS occur in the same patient.85

Primary CNS vasculitis can cause a syndrome similar to MS. Differentiating features include prominent headaches, confusion, and sudden strokelike episodes. An elevated erythrocyte sedimentation rate may be present in some patients, as may an elevated CSF protein level. Patients may have an abnormal cerebral angiogram. Bi-
opsy of the temporal lobe or meninges may be helpful in the diagnosis of this syndrome.77

The HTLV-I, a retrovirus, causes a syndrome known as tropical spastic paraparesis or HTLV-I-associated myelopathy. It may cause progressive spastic paraparesis or generalized white matter disease. HTLV-I is relatively rare in the United States but is present in some patients who have resided around the Caribbean Sea.86

Behçet’s syndrome can cause MRI findings identical to those in MS. Cardinal features of Behçet’s syndrome include oral ulcers, genital ulcers, and uveitis. Variable features include involvement of the skin, eyes, joints, lungs, intestines, and heart and venous thrombosis. Neuropsychiatric symptoms, including quadriparesis, pseudobulbar palsy, cranial neuropathy, cerebellar ataxia, peripheral neuropathic lesions, or cerebral venous thrombosis may be present.79,87

Sarcoidosis and Sjögren’s syndrome are autoimmune diseases that may show lesions on MR images that resemble those of MS. Meningeal enhancement is a clue to CNS sarcoidosis. A chest radiograph may show granulomatous lesions suggestive of systemic sarcoidosis. Although IgG levels are raised in the CSF of patients with CNS sarcoidosis, oligoclonal bands are found in some patients. CSF angiotensin-converting enzyme determination may be used to further differentiate CNS sarcoidosis from MS.78 Vitamin B12 deficiency and syphilis can cause posterior column abnormalities and dementia. Tests for these problems should be performed when a patient with these symptoms is seen.

Certain leukodystrophies may appear in adulthood. These include adrenal leukodystrophy, Krabbe’s disease, and metachromatic leukodystrophy. MRI findings in these diseases show large areas in which no normal white matter is present. Female carriers of the adrenal leukodystrophy gene may have an MS-like syndrome.86,89

Hereditary degenerative syndromes, such as familial spastic paraparesis, olivopontocerebellar degeneration, and spinocerebellar degeneration, may be confused with MS, particularly with primary progressive MS. In these diseases, MR images may be normal or may show atrophy of the brainstem, spinal cord, or cerebellum. The CSF is normal in these patients.

TREATMENT
GENERAL HEALTH MEASURES
Exercise

Studies support the concept that exercise is beneficial for the patients with MS.96,100 Simple measures such as walking, using an exercise bicycle, and swimming may be of considerable value. Exercise should be performed in a cool environment whenever possible to prevent heat-associated transient declines in neurologic function.
Swimming and water aerobics in pools that are not overly heated are particularly valuable, because the patient is cooled while exercising.

**Physical and Occupational Therapy**

Physical and occupational therapy are often invaluable for maintenance or improvement of neurologic function. Bracing disabled portions of limbs, particularly the ankle, provides considerable benefit. Exercise regimens tailored to the patient may help to maintain or improve strength, range of motion, and mobility. Devices that provide assistance with walking can be important in reducing the risk of falls, allowing for greater independence and increased activity. Other assistive devices can be helpful in reducing fatigue and increasing independent activity. Careful consultation with a specialist in rehabilitative medicine can assist the patient with management of work and daily activities.100

**Nutrition**

It is advisable for persons with MS to maintain a balanced diet. Weight control is a prominent concern. Overweight patients with motor, sensory, or coordination deficits that impair ambulation are at particular risk of falls, which may result in serious injuries, including fractures. Patients who are overweight and whose strength is decreased lose any reserve strength they may have because of their weight. Some patients with MS lose weight and require dietary supplementation. Patients with dysphagia may require feeding tubes to help prevent aspiration pneumonia.

Although various diets have been advocated for MS, there are no substantial data from controlled trials to support the assertions. As a general health measure, it is commonly suggested that patients with MS restrict cholesterol and fat in the diet. Diets that meet the requirements of the American Heart Association are likely to be useful, because most patients with MS live into middle age and beyond.

**Precautions Related to Pregnancy and Motherhood**

Pregnancy is a concern among young women with MS. Many studies of the effect of pregnancy on MS have been undertaken. An increased risk of exacerbations in the first 3 months postpartum has been reported.101-104 However, the risk of exacerbations during pregnancy appears to be unchanged or slightly reduced.105 Overall long-term disability does not appear to be altered by pregnancy.104,105

The increased relapse rate seen during the postpartum period has been postulated to be caused by an increase in immune tolerance during pregnancy, followed by a return to normal in the postpartum
period. It has also been postulated that the relapses are secondary to the decrease in the level of female hormones after parturition.\textsuperscript{101-103}

In addition to the physical effects of pregnancy, another major concern is the care of an infant or child by a person with physical problems. Persons with MS need to consider carefully whether they can handle the additional work of caring for a child. Persons with chronic physical problems may need special provisions, such as extra assistance in the home or special equipment. The physician should discuss pregnancy, delivery, and child care with women of childbearing age.

**TREATMENT OF ELEVATED BODY TEMPERATURE AND INFECTION**

Increased core temperature, whether due to heat exposure or to a febrile response, may lead to a transient increase in neurologic symptoms.\textsuperscript{106} If the event is due to heat exposure, the patient simply needs to rest in a cool environment and await recovery. If an infection is responsible, the source of the infection should be determined and treated. An antipyretic medication such as acetaminophen can then be administered. Many patients with MS are susceptible to urinary tract infections and may not have clinical manifestations of the infection. In some patients this is due to impaired sensory capabilities, and some patients have chronic urinary symptoms that may not change substantially with an infection. One study of MS exacerbations pointed to an association with antecedent infection.\textsuperscript{107} If a patient has persistent worsening after an infection that has been appropriately treated and resolved, steroid therapy should be considered in the event the infection recurs.

**TREATMENT OF RELAPSES**

A relapse is considered to be the onset of new neurologic symptoms or marked worsening of old symptoms lasting longer than 24 hours. Certain conditions may mimic an exacerbation and should be ruled out or treated before steroid therapy is considered. These include fever, infection (commonly urinary tract infection or viral illness), overheating, fatigue, severe emotional stress, or the effects of medications such as baclofen, which can increase weakness. If these problems are appropriately treated, the patient's condition usually improves.

Mild relapses may be best treated without steroid therapy. The symptoms include a mild numbness, mild changes in bladder function, mild optic neuritis (visual acuity better than \(20/40\)), slight increase in spasticity, or a dysesthetic pain syndrome. Any new abnormality that does not change a person’s ability to perform his or her usual daily activities may not require steroid therapy. In these patients, rest is sometimes helpful. Patients with more severe worsen-
ing may benefit from steroid therapy. The symptoms include gait disturbances, severe numbness or paresthesia, moderate to severe paresis, moderate or severe optic neuritis, severe vertigo, or marked impairment of eye movement. It is often appropriate for the physician to observe the patient for a few days before making a decision about the use of steroids.

**Standard Therapy**

For many years, immunosuppression with corticotropin (ACTH) or steroids has been used in the treatment of the exacerbations of MS. The primary effect of these agents is to shorten the duration of an attack, and no benefit has been proven in the overall outcome from an attack. Steroids should not be given until an abnormality resolves because this may never occur.

ACTH was the first immunosuppressant to be widely used in MS. Although it is still given to some patients who respond well to the medication, ACTH has been largely supplanted by other steroids, most commonly prednisone and methylprednisolone. Many different regimens have been used. A typical regimen is 80 units by intravenous or intramuscular injection once a day for 10 days.

Prednisone is commonly used for mild or moderate exacerbations of MS. Although low doses do not appear to have any effect on an exacerbation, larger doses do appear to shorten the duration of an MS attack. There is no standard treatment regimen; a dose of at least 1 mg/kg per day is commonly recommended and should be continued for 7 to 10 days. Our regimen is 80 mg once a day by mouth for 10 days, then tapered by 20 mg every 3 days. Other regimens range from 10 days to 6 weeks or longer.

Methylprednisolone with sodium succinate (Solu-Medrol) is often used in the treatment of severe relapses, or when the patient’s condition continues to worsen after several days of high-dose prednisone. Typical dosages range from 500 to 1000 mg/day and last from 3 to 14 days. A typical dose is 250 mg in 250 ml of 5% dextrose in water over 45 minutes every 6 hours to a total of 16 doses. Another is 500 mg in 250 ml of 5% dextrose in water over 45 minutes every 12 hours for 10 doses. An oral prednisone taper over about 10 days to 2 weeks may be used afterward.

One study of optic neuritis suggested that high-dose methylprednisolone produces more favorable results than oral prednisolone for patients with poor visual acuity. This study showed only a faster recovery time; follow-up examinations at 1 year did not show any difference in final outcome. The study involved patients who did not necessarily have a diagnosis of MS. However, a follow-up evaluation with patients in whom MS subsequently developed did suggest that the methylprednisolone-treated group had a longer time interval to the development of a second demyelinating event than
those who received prednisone or placebo.\textsuperscript{112} For this reason, some neurologists believe that all attacks of MS should be treated with intravenous methylprednisolone.

**Problems With Steroid Therapy**

The side effects of steroids are well known. These include non-specific immunosuppression leading to opportunistic infections, induction of hyperglycemia, fluid retention, hypertension, emotional abnormalities, hypokalemia, peptic ulcers, occasional aseptic necrosis of the femoral head or other bones, and demineralization of bone. Chronic use may lead to cataracts, osteoporosis, muscle wasting, hypertension, diabetes, increased susceptibility to infections, and a cushingoid appearance. Steroids should be used with caution.

We have found the following precautions helpful: administration of calcium and possibly vitamin D during the administration of steroids and restriction of foods with a high sugar or sodium content. We encourage our patients to eat foods rich in potassium, such as bananas, orange juice, and tomatoes. Patients who experience indigestion may benefit from the use of histamine blockers such as ranitidine. Some patients may need sedation with diazepam or other agents because of severe mood swings, anxiety, or sleeplessness. Patients who receive high doses of methylprednisolone should be observed for hypertension, electrolyte imbalance, and hyperglycemia. These problems should be treated appropriately. Occasional psychiatric symptoms, including depression, psychosis, and severe anxiety, may necessitate cessation of steroid therapy.

**PREVENTION OF RELAPSES**

Betaseron, a recombinant interferon-\(\beta\), has been approved by the U.S. Food and Drug Administration (FDA) for use in ambulatory patients with relapsing-remitting MS. This approval followed a 2-year, controlled, double-blind study that showed in patients treated with 8 million units of Betaseron administered subcutaneously every other day the relapse rate was reduced to 0.84 relapse per year compared with 1.27 relapses per year in patients given placebo.\textsuperscript{113} An MRI study performed with the same population revealed fewer new lesions in the treatment group than in the control group.\textsuperscript{10} The drug did not improve ongoing symptoms. The study was limited to patients with relapsing-remitting disease, and the findings should not be extrapolated to patients with chronic progressive disease. A study of the use of Betaseron by patients with chronic progressive MS is planned. Patients whose condition is stable would not benefit from the use of Betaseron.

There are problems with the use of Betaseron. Although the drug may be helpful in patients with frequent relapses, it does have seri-
ous side effects. Almost all patients experience local reactions at the site of injection, and some patients have had tissue necrosis at injection sites. The injection site must be changed regularly to reduce the likelihood of ulceration. Many patients have a flulike reaction, which may include fever, chills, malaise, and myalgia. This reaction resolves with time and commonly lasts only a few months; however, it may last as long as a year. These symptoms can be partially controlled with acetaminophen or ibuprofen. Liver function studies may show abnormalities, and leukopenia may be present. Fatigue and emotional disturbances have been reported. Our patients have experienced episodes of acute depression and anxiety, and one patient had an episode of uncontrollable rage. Depression may necessitate temporary or permanent cessation of Betaseron treatment. However, antidepressants, such as fluoxetine, sertraline, and paroxetine hydrochloride, may help counteract the depression. In a few cases, MS appears to worsen when the patient is taking Betaseron. Acute weakness develops in some patients with the first few injections. This is not always associated with fever and may resolve with time. Menstrual irregularities have been reported, and Betaseron cannot be used during pregnancy. Some patients tolerate the medication better if the full dose is titrated up over approximately 1 month. Periodic blood tests to check for leukopenia and abnormal liver function are suggested.

Clinical trials of other preparations of interferon-α and interferon-β are nearing completion. One clinical trial involved administration of a weekly intramuscular injection of interferon-β1a. The results suggested that this drug reduces the likelihood of progression in patients with early disease.¹¹¹ A phase III clinical trial of another investigational agent, copolymer 1, has been completed. This drug appears promising in reducing relapses and has a good safety profile.¹¹⁵,¹¹⁶ These agents will likely be available in the near future, pending FDA approval.

**TREATMENT OF CHRONIC PROGRESSION**

Although most treatment aimed at chronic progression remains experimental, the use of intermittent intravenous methylprednisolone has become a common practice. Most commonly, patients who experience subacute worsening may respond to a course of high-dose Solu-Medrol similar to that given for a severe relapse. The condition of some patients appears to stabilize, at least temporarily, with this course of therapy. Some patients with progressive disease may respond to a single dose of 1000 mg of Solu-Medrol in 250 ml of 5% dextrose in water given over 1 hour once a month for 6 to 12 months. Subsequent treatments may be given every 6 to 8 weeks.

Azathioprine has been used for the treatment of chronic progres-
sion with some success. Studies have shown a modest benefit of azathioprine, primarily in stabilizing the condition of some patients. Patients who take this drug should be examined for leukopenia or hepatotoxicity. About 15% of patients are unable to tolerate azathioprine because of fever, rash, or nausea. Patients with continued progression during therapy with azathioprine or Solu-Medrol may benefit from combined therapy.

Cyclosporine was evaluated in a multicenter clinical trial and was found to have modest clinical benefit. The prolonged use of cyclosporine in patients with chronic progressive MS was complicated by side effects, principally nephrotoxicity and hypertension.

The use of cyclophosphamide in the treatment of chronic progressive MS is controversial. The results of clinical trials of this agent in chronic progressive MS are contradictory. The drug may have use in rapidly progressive MS that does not respond to steroid therapy. Further investigation with MRI and neuropsychological testing and careful clinical assessment should resolve the controversy.

**INVESTIGATIONAL TREATMENTS**

A number of promising phase III clinical trials of therapeutic agents for relapsing-remitting MS are being conducted. For two of these agents, the 2-year placebo-controlled phase has been completed. These are an interferon-β, given once a week by intramuscular injection, and copolymer 1. Both drugs reduce the frequency of relapses and favorably influence disability. The interferon-β is identical to human interferon-β and differs from Betaseron in that it has the sequence of amino acids and glycosylation of human interferon. The results of a review of the safety profile of this drug compared with that of Betaseron will be of considerable interest.

Copolymer 1 appears to have activity similar to that of Betaseron with regard to reduction of relapses in MS. The side-effect profile appears to be favorable compared with that of Betaseron. Laboratory investigations demonstrate additive effects of copolymer 1 and interferon-β in vitro. Because the drugs theoretically act through different mechanisms, combined therapy might be possible.

Because of the results of a pilot study, oral myelin is being tested in a phase III clinical trial. In the pilot trial, the efficacy of the drug was observed in only a subgroup of patients (DR2-negative men).

Two pilot studies of the use of methotrexate for MS have been performed. Methotrexate in low doses is used for the treatment of rheumatoid arthritis, psoriasis, and Crohn's disease. Similar therapy may be of benefit to patients with advanced MS. A phase III controlled trial and dose response testing will be of considerable interest. Methotrexate should be used in clinical settings that allow careful neurologic and laboratory follow-up evaluation.
Cladribine by intravenous administration appears to alter the progression of MS.\textsuperscript{126} The drug has relatively selective toxicity for lymphocytes; however, the side effects can be substantial. Additional studies to evaluate dose and route of administration are being initiated. The clinical effects of repeated dosage with this medication also require study.

Immunoglobulin therapy may be useful in MS; however, controlled trials of intravenous immunoglobulin (IVIG) must be completed.\textsuperscript{127} This therapy may be useful in relapsing disease and can be considered for patients with both MS and diabetes. IVIG therapy is not necessarily benign and can be responsible for the transmission of viral hepatitis.

Several clinical trials of monoclonal antibodies are in progress. A number of monoclonal antibodies with specificities for either lymphocytes or adhesion molecules are being subjected to initial trials in human beings. A monoclonal antibody that appears to lower lymphocytes and have an appreciable effect on the lesions of patients with MS as seen on MR images is being studied.\textsuperscript{128}

\textbf{SYMPTOMATIC THERAPY}

One of the most important aspects of the treatment of MS is helping patients manage their ongoing symptoms. Because of the chronic nature of the problems associated with MS, medication and adjustments in lifestyle are used to help patients cope with their disabilities. Table 6 gives a summary of possible symptomatic treatments.

\textbf{Fatigue}

Fatigue can be disabling in patients with MS. It is described in different ways by different patients. The classic description of fatigue is increased weakness with exercise or as the day progresses. The patient may walk fairly well in the morning but need a cane or walker by afternoon. Other descriptions include sudden attacks of sleepiness or excessive chronic sleepiness, even though the patient has had enough sleep at night.\textsuperscript{129}

Patients who describe fatigue should be questioned closely about their sleep habits and other symptoms of depression. Many patients with fatigue may have poor sleep habits or insomnia, which lead to daytime fatigue. Depression is a common problem in patients with MS.\textsuperscript{130} If the fatigue is a product of depression, treatment of the depression should be helpful.

Fatigue is sometimes managed without medication. Patients may respond to one or two brief (15 to 30 minutes) naps during the day. If this is not helpful or not possible, amantadine may be given to help control the problem. The mechanism of action of amantadine is not known, but it is helpful in approximately 40% of patients.\textsuperscript{129}
**TABLE 6. Treatment of symptoms of MS**

| Symptom                  | Treatment                                                                 |
|--------------------------|---------------------------------------------------------------------------|
| Fatigue                  | Short naps                                                                |
|                          | Moderate exercise                                                          |
|                          | Amantadine, 100 mg twice a day                                             |
|                          | Pemoline, 18.75–37.5 mg twice a day                                         |
|                          | Fluoxetine, 20–40 mg/d                                                     |
| Depression               | Antidepressants                                                            |
|                          | Psychotherapy                                                              |
| Dysesthetic pain         | Tricyclic antidepressants                                                  |
|                          | Carbamazepine                                                              |
|                          | Phenytoin                                                                  |
|                          | Valproic acid                                                              |
| Spasticity and muscle spasms | Physical therapy                                                        |
|                          | Baclofen, titrate up to 100 mg/d as needed                                 |
|                          | Diazepam (works best in conjunction with baclofen)                        |
|                          | Clonidine patch                                                           |
|                          | Quinine sulfate (sometimes relieves muscle spasms)                        |
|                          | Baclofen pump (may work in severe spasticity)                             |
| Mood swings              | Amitriptyline and other tricyclic antidepressants                          |
| Sexual dysfunction       | Psychological counseling                                                   |
|                          | Urologic evaluation                                                        |
|                          | Yohimbine                                                                  |
|                          | Papaverine injections                                                      |
|                          | Prosthetic devices                                                         |
| Urinary problems         | See Table 7                                                                |
| Constipation             | High fiber diet                                                            |
|                          | Bulking agents                                                             |
|                          | Stool softeners                                                            |
| Tremor                   | Clonazepam                                                                 |
|                          | Propranolol                                                                |
|                          | Isoniazid                                                                  |
| Vertigo                  | Meclizine, 25 mg up to 4 times a day                                        |
|                          | Diazepam, 2 mg two to 4 times a day                                         |

Side effects, such as dizziness, headaches, nervousness, or edema, may limit the usefulness of the drug.

Pemoline is a CNS stimulant that may be helpful in some patients.\(^{131}\) It should be used in low doses and should generally be given early in the day because it may cause insomnia. Anxiety and anorexia are other problems that may occur with this drug. Liver function studies should be performed periodically to monitor for hepatotoxicity.

Fluoxetine (Prozac) may be helpful both to increase energy and to treat depression.\(^{132}\)
**Vertigo**

Vertigo can be an intractable and disabling problem. Vertigo can occur in sudden spells that last a few minutes, or it can be chronic and last for hours. Some physical therapy techniques involve habituation exercises to help with vertigo. Medications that may be helpful include meclizine, promethazine hydrochloride, and low-dose diazepam. Oscillopsia may occasionally respond to clonazepam or baclofen. Vertigo with nausea and vomiting may respond to metoclopramide.

**Spasticity and Muscle Spasms**

Spasticity can appear in many different ways. It may be seen at direct examination as a “catch” in the muscles with passive rapid movement of the limbs, or it may cause severe stiffness or rigidity. Some patients may have severe spasms of the affected limb, which may be precipitated by movement or occur at night. These are most common in the lower limbs and may be either flexor or extensor spasms. The spasms can be quite painful.

Primary treatment of spasticity includes physical therapy with stretching exercises, combined with medication. Baclofen is the most commonly used drug for spasticity, although its mechanism of action is not known. The dose of baclofen should be low when treatment begins and should be titrated slowly and carefully. Patients who take an overdose of baclofen experience weakness. The dose of baclofen is extremely variable—some patients with only moderate spasticity tolerate high doses, whereas others with severe spasticity tolerate only low doses. Other limiting side effects include drowsiness, confusion, and nausea. Use of baclofen should not be discontinued abruptly but should be tapered over a few weeks.\textsuperscript{132,133}

Diazepam in combination with baclofen may be helpful for patients with severe spasticity or those who cannot tolerate high doses of baclofen but need to control spasticity. Diazepam can be used alone for spasticity, but it is not as effective as baclofen.\textsuperscript{133} Diazepam can be particularly helpful for flexor or extensor spasms at night.

Dantrolene has limited value because of its hepatotoxicity and the weakness that accompanies the muscle-relaxant effect. It may be helpful in intractable cases of spasticity.

The baclofen pump was developed for use in patients with intractable spasticity.\textsuperscript{134} This device is an intrathecal pump with a subcutaneous reservoir of baclofen that administers continuous doses of baclofen directly into the spinal canal. This method of administration can be effective. With the lower dose delivered directly to the spinal cord, patients seem to have fewer side effects than with other routes of administration. Dose levels can be programmed to change throughout the day, so patients with problems that are worse during the night or another part of the day can take increased doses of the drug during those times.
Tizanidine is an agent used outside the United States for spasticity. It is being studied in the United States and may become available in the near future.

Other agents that may be useful in the treatment of spasticity include carbamazepine, phenytoin sodium, methocarbamol, and cyclobenzaprine hydrochloride. Clonidine patches may be used for adjunctive therapy in patients with persisting spasms who are taking other drugs.

Spastic dysarthria is an uncommon symptom in MS. Speech is hesitant and stuttering, and breath control is difficult. Baclofen sometimes is helpful in this condition.

**Urinary Dysfunction**

Bladder dysfunction is an extremely common problem in MS. Examination of postvoid residual urine volume and urodynamic testing are extremely important in delineating the causes of bladder dysfunction. Other urologic examinations, such as cystoscopy, may help eliminate mechanical problems as the cause of urinary dysfunction. Consultation with a urologist skilled in the evaluation of neurologic dysfunction of the bladder is essential to the best therapeutic outcome.

The most common problem is a spastic bladder. This is a small, hyperactive bladder. Symptoms of this type of bladder dysfunction are urgency, increased frequency, and incontinence in which the bladder empties completely with brief warning. This condition can be treated with anticholinergic agents such as oxybutynin or propantheline. Sometimes baclofen or amitriptyline can be of use in the control of this problem (Table 7).

Detrusor-external sphincter dyssynergia is a common problem. In this syndrome, the bladder attempts to empty, but the urethra remains closed. Symptoms may be urgency and hesitancy, double voiding, and increased frequency with a feeling of incomplete emptying. Anticholinergic or tricyclic agents alone may be of help with this syndrome, but more commonly a combination of anticholinergic drugs and intermittent catheterization is needed to control the problem. The patient performs self-catheterization two to four times a day.

A flaccid bladder is less common than the other types of bladder dysfunction. This is an enlarged bladder that empties poorly. Symptoms include hesitancy, double voiding, a feeling of incomplete emptying, and dribbling incontinence. Untreated urinary retention can result in hydronephrosis. Urecholine can be of use in a few patients. Frequently, however, a schedule of intermittent self-catheterization may be needed (Table 7).

Patients with flaccid bladder or sphincter dyssynergia may have frequent urinary tract infections. Acidifying agents such as hippuric acid or vitamin C may be useful in the prevention of infections. Long-term administration of antibiotics should be avoided to reduce the risk.
**TABLE 7. Treatment of urinary problems in MS**

| Problem                                      | Common symptoms                                                                 | Mechanical methods                   | Medications                                                                 |
|----------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------------|
| Hyperreflexic bladder without outlet obstruction | Urinary frequency with urgency and incontinence  
Loss of entire contents of bladder | Behavior modification: timed voiding, perineal muscle exercises  
Biofeedback | **Anticholinergic**  
Oxybutynin, 5 mg 2–4 times a day  
Propantheline bromide (Pro-Banthine), 15 mg 2–4 times a day  
Hyoscyamine sulfate (Levsin), 0.125 mg 1–2 to 4–6 times a day  
**Antispasmodic**  
Flavoxate, 100 mg 2–4 times a day  
**Miscellaneous**  
Desmopressin (DDAVP)  
Imipramine 25–100 mg/d  
Phenylpropanolamine/chlorpheniramine 75 mg/12 mg (Ornade), 1 capsule twice a day  
Anticholinergic agents listed above |
| Hyperreflexic bladder with outlet obstruction  | Urinary frequency with urgency and hesitancy  
Feeling of incomplete voiding  
Urge to urinate again within a few minutes of voiding | Credé maneuver  
Strain to void  
Double voiding  
Intermittent catheterization with anticholinergics | Medications rarely work  
Bethanechol 10–50 mg 3 times a day  
Phenoxybenzamine 10 mg 3 times a day  
Clonidine 0.1–0.4 mg/d  
Terazosin (Hytrin) 1–10 mg/d |
| Hyporeflexic bladder                         | Urinary hesitancy with dribbling  
Sometimes overflow frequency and incontinence | Credé maneuver  
Intermittent catheterization  
Indwelling catheter  
Urinary diversion | **Anticholinergic**  
Oxybutynin, 5 mg 2–4 times a day  
Propantheline bromide (Pro-Banthine), 15 mg 2–4 times a day  
Hyoscyamine sulfate (Levsin), 0.125 mg 1–2 to 4–6 times a day  
**Antispasmodic**  
Flavoxate, 100 mg 2–4 times a day  
**Miscellaneous**  
Desmopressin (DDAVP)  
Imipramine 25–100 mg/d  
Phenylpropanolamine/chlorpheniramine 75 mg/12 mg (Ornade), 1 capsule twice a day  
Anticholinergic agents listed above |
of infections with resistant organisms. Patients with frequent urinary
tract infections undergo a renal scan or ultrasonography once a year.

Patients with severe bladder problems that are unresponsive to
noninvasive therapy may require a chronic indwelling catheter or
urinary diversion. These techniques may be required by patients
who cannot perform intermittent self-catheterization.

**Sexual Problems**

Sexual dysfunction is common in both men and women with MS.
Women often report decreased sensation, lack of vaginal lubrica-
tion, difficulty achieving orgasm, or painful muscle spasms in the
legs or pelvis during intercourse. Men report diminished sensation
and difficulty in achieving or maintaining an erection or experienc-
ing orgasm. There is no simple answer to the sexual problems that
occur with MS. A multidisciplinary approach is needed in which
the physical and psychological aspects of sexual problems are con-
sidered.

For women, treatment of muscle spasms with medications for spastic-
tity may allow intercourse with less pain. Techniques to increase
vaginal and clitoral stimulation may help women experience orgasm.
Other methods of increasing arousal may be helpful.

Men are interviewed to determine whether there are other causes
of erectile dysfunction. Medications that may affect erectile func-
tion should be eliminated if possible. Yohimbine, an α-2-adrenergic
receptor antagonist, can sometimes help restore function in a pa-
tient with borderline function.¹³⁸ Other methods, including papav-
erine or phentolamine injections, a vacuum erectile device, or a pe-
nile prosthesis, may be considered.¹³⁷

**Psychological Problems**

Inappropriate affect can be a problem in patients with MS. Many
patients have severe mood swings that can affect both their work
and their social relationships. Low-dose amitriptyline or another tri-
cyclic antidepressant is frequently helpful in controlling mood
swings.¹³⁹ Depression is a common problem in MS.¹³⁰,¹³²,¹⁴⁰ The sui-
cide rate among persons with MS is estimated to be 7.5 times that of
the healthy population.¹³⁹ Whether the depression is a primary symp-
tom of MS or a situational problem is not known. Physicians should
be alert to the possibility of depression in their patients. Full-dose
antidepressant medications and psychological counseling may be
beneficial.

**Tremor and Incoordination**

Tremor can be a limiting factor in many patients with MS. Treat-
ment with medications is frequently unsuccessful. Agents that may
be useful include clonazepam, acetazolamide, propranolol, primidone, and diazepam. Isoniazid has been reported to be helpful in some patients. We have found clonazepam to be the most helpful of these agents in our patients, but treatment may be limited by drowsiness.

**Pain**

A common misconception is that pain is not a symptom in patients with MS. The truth is that pain is often a problem and may be a prominent concern for patients with MS. This can be a primary factor in the disease, or it can be a consequence of disability associated with the disease. Much of the pain reported with MS is musculoskeletal and is related to abnormal use of muscles and joints. For example, patients who use a wheelchair may experience wrist, shoulder, or elbow pain from manipulating the wheelchair. Patients with paraparesis or ataxia may experience back or leg pain from poor posture and balance when walking. These problems should be treated with antiinflammatory medications and physical therapy.

Primary MS pain is often dysesthetic. The patient describes a burning sensation or perhaps even electric shock–like pain. This pain can be in any location, but it is most commonly in the lower extremities. Some patients experience tic douloureux or atypical facial pain. This primary pain may be controlled with tricyclic antidepressants, phenytoin, or carbamazepine. In patients with refractory pain, valproic acid can be tried.

Headaches can become a problem in patients with MS. It is not known whether these headaches are caused by MS or are a separate problem. Both tension and migraine headaches are common, and treatment is similar to the treatment of headaches in patients who do not have MS. Retro-orbital pain is frequently observed in patients with optic neuritis. These patients may require steroid therapy. Spasticity and muscle spasms can cause severe pain. Treatment of the spasticity helps the pain.

**Cognitive Dysfunction**

Many patients with MS experience cognitive abnormalities. Unlike the dementia of Alzheimer's disease, the cognitive deficits seem to be more scattered and tend to be retrieval deficits rather than memory loss. Patients can have substantial cognitive difficulties but still have normal mini–mental state examination findings. Neuropsychological studies have shown that as many as 40% of patients may have some cognitive difficulties. These difficulties can be important in terms of disability and ability to cope with illness. Only a minority of patients have severe cognitive abnormalities.

MR images in patients with cognitive problems tend to show a larger number and size of lesions in the white matter of the cerebral
hemispheres. Frontal lesions are more common in patients with cognitive difficulties. The corpus callosum may be thinner than normal, as seen on sagittal images.

Patients with cognitive problems should undergo careful neuropsychiatric testing. Sometimes depression or anxiety can be contributing factors in these symptoms. The Minnesota Multiphasic Personality Index or the Beck Depression Scale in conjunction with cognitive testing may be helpful in differentiating emotional problems from structural cognitive deficits. Proper treatment of the anxiety or depression may lead to improved cognitive function.

Recognition of the areas and degree of cognitive difficulty in patients with MS may be helpful in the care of the patients. Patients may be able to learn ways of working around a problem. Problems with a job may be related to cognitive problems, and ways of altering the job may be found. Patients may become disabled from working because of these problems. This testing also may help the family understand the need for helping the patient deal with problems that have become too difficult to handle alone.

Cognitive rehabilitation techniques are being tested for patients with MS in some centers. Further investigation is needed to evaluate the efficacy of these techniques.

SUMMARY

Careful assessment of the patient's abilities and disabilities is crucial for proper management. In many patients, chronic symptoms cannot be prevented. Symptomatic therapies are often effective for alleviating the afflictions produced by MS and for allowing the patients to live a productive and comfortable life.

CURRENT PERSPECTIVE AND FUTURE PROSPECTS

The cause of MS is unknown. Theories revolve around the idea that the disease is either autoimmune or virus-mediated. It is still reasonable to question which pathologic feature is the inciting event. Much research is focused on the T cell and potential mechanisms by which these cells could initiate MS. HLA associations are found in many populations; however, HLA markers are neither necessary nor sufficient to confer disease susceptibility, and other factors that confer disease susceptibility are being sought.

At this time there is no confirmed evidence of a viral cause of MS. Investigations with in situ hybridization and PCR technology are being conducted in an attempt to identify viral nucleic acids in the CNS. Perhaps these techniques will assist in unraveling the pathogenesis of MS.

An intriguing possibility is that molecular mimicry may be re-
sponsible for the initial generation of autoreactive lymphocytes. This mechanism involves exposure to viral or bacterial antigens, which generates an immunologic response that consists of reactive T-cell populations. Because T cells cross-react with myelin peptides, a potential for demyelination exists. This theoretic mechanism is known to cause demyelination in rabbits.\textsuperscript{144}

An interesting investigation of human MBP-reactive T cells demonstrates that MBP-specific T-cell clones can recognize multiple viral polypeptides presented by DR2 or DQ1 MHC antigens.\textsuperscript{145} This would imply that MS could be generated by exposure to any one of a number of antigenic stimuli, such as influenza viruses or herpes-viruses or even bacterial antigens. Selected activated T-cell populations that enter the CNS could then recognize a myelin epitope and initiate the autoimmune response, which would persist long after the inciting infection was cleared.

Recent investigation with MR spectroscopy demonstrates that white matter outside MS plaques may be abnormal.\textsuperscript{146} These findings may signify that there is a fundamental abnormality in the white matter. Whether these findings are secondary to genetic, biochemical, autoimmune, or viral factors remains to be determined.

Despite the deficiencies in our understanding of disease pathogenesis, therapy for MS has advanced. Phase III clinical trials with interferon-\textsuperscript{\textbeta} and copolymer 1 have demonstrated modest but definite benefit. The mechanisms by which these drugs favorably influence the clinical course of MS remain to be elucidated. Recent studies of chemotherapeutic agents suggest that control of chronic progressive disease may be a real possibility. Future clinical trials will attempt to define the efficacy of and parameters for these therapies. Another question that remains unanswered is whether the use of multiple-drug therapy might be beneficial in the treatment of MS. For example, combined therapy with interferon-\textsuperscript{\textbeta1b} and copolymer 1 may produce more benefit than either drug alone. In chronic progressive disease, the use of Solu-Medrol in combination with another immunosuppressant such as azathioprine or methotrexate also should be explored.

Remyelination is another topic of interest for future research. Research is being conducted into the use of IVIG as a remyelinating agent. In addition, oligodendrocyte transplant experiments are being conducted in canine modes and may eventually be used for human patients.

Research involving medications to improve the symptoms that limit the lives of many patients with MS is ongoing and should continue. 4-Amino-pyridine and 2,3-diamino-pyridine are being studied as agents that may improve conduction through poorly myelinated areas. These agents may reduce double vision, improve strength, and possibly reduce tremor. More research is needed to evaluate these
and other compounds that may improve the quality of life of many patients with MS.

Although the cause of MS remains a mystery, important advances have been made in the understanding and treatment of MS in the past few years. As this trend continues, we may have more diverse and effective therapies to offer patients with MS in the years to come.

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