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CHAPTER 48

Demyelinating Disorders of the Central Nervous System

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HISTORY
ROLE OF MYELIN
MULTIPLE SCLEROSIS
NEUROMYELITIS OPTICA
ACUTE DISSEMINATED ENCEPHALOMYELITIS

HISTORY

Multiple sclerosis (MS) is now known to be a common malady even though it was first recognized as a distinct clinicopathological entity less than 150 years ago.[1] The lack of clear medical reports before the early 1800s is sometimes interpreted as evidence that MS is a relatively new disease. However, it is more likely that the evolution of medicine into science led to more precise observation and description of human diseases, including MS. Saint Lidwina of Schiedam (1380–1433) developed a relapsing neurological disorder at the age of 18 and may be the first case of clinically described MS.[2] Ollivier was the first to report a clinical case in the medical literature in 1824.[1] Shortly thereafter, Carswell illustrated a case of what is now clearly recognizable as MS in his atlas of anatomical pathology. Cruveilhier published gross pathological and clinical descriptions of MS. Vulpian first suggested the rubric of "sclerose en plaque" in 1866. Charcot was primarily responsible for establishing MS as a unique and recognizable syndrome.[3] He also described the clinical spectrum and the histological appearance. Pierre Marie was the first to suggest an infectious cause of MS in 1884, a hypothesis that is still debated. Toxins were also considered to be responsible in the early 1900s. A major advance toward the understanding of demyelinating diseases was the discovery of experimental allergic encephalomyelitis (EAE) by Rivers in 1935.[4] A variety of different demyelinating diseases have subsequently been described (Table 48-1).

ROLE OF MYELIN

Myelin provides insulation for axons and is necessary for saltatory conduction. It is composed of tightly wrapped lipid bilayers with specialized protein constituents. Peripheral nervous system (PNS) myelin is formed by the extension of Schwann cells, and central nervous system (CNS) myelin is produced by oligodendrocytes. The myelin coating is interrupted at regular intervals (nodes of Ranvier) where the axon membrane with its concentration of voltage-gated sodium channels is exposed to the extracellular environment (Fig. 48-1).[5] The presence of myelin is essential to maintain conduction velocity; its loss or damage can lead to significantly slower conduction or conduction block. Other factors affect conduction velocity including certain antibodies and chemicals like nitric oxide. In certain cases, blockade may be the initial event in the cascade of events leading to demyelination.

CNS and PNS myelin differ in a number of important ways. Schwann cells myelinate only one internodal segment from a single PNS axon, whereas oligodendrocytes myelinate multiple CNS axons. The proteins also differ. Proteolipid protein (PLP) accounts for approximately 50% of the CNS myelin proteins. Mutations in this highly conserved protein cause Pelizaeus-Merzbacher disease. Protein zero is the major PNS myelin protein and performs a function similar to PLP in compacting the intraperiod line. Myelin basic protein (MBP) makes up 30% of CNS and 10% of PNS myelin proteins. MBP is not an integral protein but binds to the cytoplasmic surface and is responsible for compaction at the major dense line. Myelin associate glycoprotein accounts for about 1% of both peripheral and central myelin. Myelin oligodendrocyte glycoprotein and cyclic nucleotide phosphodiesterase are minor constituents of CNS myelin and are not found in the PNS. Peripheral myelin protein 22 is a minor component of PNS myelin.

MULTIPLE SCLEROSIS

MS is an inflammatory relapsing or progressive disorder of CNS white matter and is a major cause of disability in young adults. Pathologically, it is characterized by multifocal areas of demyelination, loss of oligodendrocytes, and astrogliosis but with relative preservation of axons. While demyelination is the classic hallmark of MS, axonal and neuronal injury are important aspects of the disease and are gaining more recognition. Although certain clinical features are characteristic of MS, investigative studies are often needed to confirm the clinical suspicion and exclude other possibilities. Recently, there have been advances in understanding the etiology, mechanisms of myelin injury, and potential for repair, and several partially effective agents are now approved for use in relapsing-remitting and secondary progressive MS.

TABLE 48-1

Primary (Idiopathic) Inflammatory Demyelinating Disorders of the Central Nervous System

Acute disseminated encephalomyelitis
Monophasic
Multiphasic
Relapsing (controversial)
Monosymptomatic syndromes
Optic neuritis
Acute transverse myelitis (partial and complete)
Brain stem demyelination
Multiple sclerosis
Neuromyelitis optica
Marburg's disease
Schilder's myeloclastic diffuse sclerosis (controversial)
Balo's concentric sclerosis

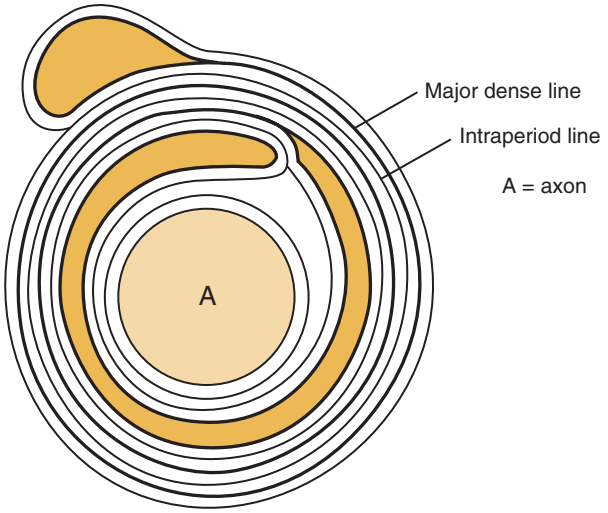

Figure 48-1. Major constituent components of CNS myelin. (Modified from Raine CS: Morphological aspects of myelin and myelination. In Morrell P [ed]: Myelin. New York, Plenum Press, 1984, p 26.)

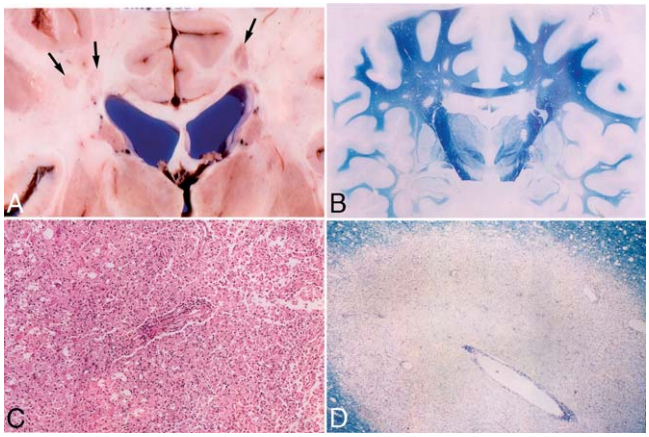

Figure 48-2. Pathology of MS. **A,** Coronal brain slice showing several focal areas of sclerosis (*arrows*). **B,** Luxol fast blue stain of a coronal brain section showing numerous discrete areas of myelin loss. **C,** Hematoxylin and eosin stain of a chronic lesion showing perivascular mononuclear cells and prominent gliosis. **D,** Luxol fast blue/periodic acid–Schiff stain showing perivascular inflammation and loss of myelin.

PATHOGENESIS AND PATHOPHYSIOLOGY (Fig. 48-2). The pathogenesis and pathophysiology of MS remains incompletely understood. Several mechanisms may be important to MS plaque formation: autoimmunity, infection, bystander demyelination, and heredity. Although convincing proof is lacking, dietary factors and toxin exposure have been hypothesized to contribute as well. These mechanisms are not mutually exclusive, and the true pathophysiology is likely to depend on more than one of them.

Autoimmunity. During ontogenesis, autoreactive lymphocytes normally undergo clonal depletion, but some escape and are merely suppressed, becoming tolerant to their antigens. Low levels of autoreactive T and B cells persist even in normal individuals. Autoimmune disorders occur when the tolerance of these cells toward their antigen is broken. The decreased suppressor activity of circulating lymphocytes from patients with MS and other presumed autoimmune diseases may reflect loss of tolerance.[6] One potential mechanism that may break tolerance is molecular mimicry between self and foreign antigens. Autoreactive T4 lymphocytes may become activated on exposure to structurally similar foreign antigens. Some evidence suggests that molecular mimicry is relevant in MS. Not only do several viral and bacterial peptides share structural similarities with MBP, but it has also been demonstrated that these antigens may activate MBP-specific T-cell clones derived from MS patients.[7] Blood-brain barrier leakage alone may break tolerance because it gives CNS-reactive lymphocytes easy access to otherwise inaccessible antigens. Alternatively, a primary event such as an infection or injury may release CNS antigens into the periphery, where they may activate corresponding autoreactive cells.[8] The major support for autoimmunity in the pathogenesis and pathophysiology of MS is by analogy to EAE, the major animal model for MS. EAE is, however, an artificial situation and there is no spontaneous autoimmune animal model of MS. While EAE is the most commonly studied model of MS, several features of human MS can not be adequately captured by this model.[9,10] Over a hundred different effective treatments have been described for EAE; however, almost all of them are ineffective and some are harmful in human MS. A recent editorial discusses the merits and important limitations of EAE as a model for MS.[10] In EAE, just like in classic human autoimmune diseases such as systemic lupus erythematosus (SLE) or rheumatoid arthritis, the main target antigens are known. However, despite the discovery of several "weak" antigens in human MS, no dominant antigens have been identified to date. The only human demyelinating disease with an identified specific antigen is Devic's disease (neuromyelitis optica), which appears to be a novel autoimmune chanellopathy with an antigen that is neither neuronal nor myelin related (see later discussion of Devic's syndrome under Neuromyelitis Optica).[11]

Infection. The role of viral infections in the initiation and maintenance of MS has been debated for some time. Several viral infections are known to cause demyelination in animals, including visna virus of goats and sheep, canine distemper virus, and Theiler's murine encephalomyelitis virus. Viral infections in humans can also cause demyelination (progressive multifocal leukoencephalopathy [JC papillomavirus], subacute sclerosing panencephalitis

[measles virus], and human T-cell lymphotropic or leukemia virus type 1 [HTLV-1]-associated myelopathy). The epidemiology of MS suggests that environmental factors may promote the disease state, possibly due to one or more viruses. A virus may be involved in the pathogenesis of MS in several ways:

1. Transient or persistent infection outside the CNS may activate autoreactive T cells by means of molecular mimicry or by other nonspecific means (as superantigens do).
2. Transient CNS infection may initiate a cascade of events that fosters autoimmunity (breach the blood-brain barrier, release CNS antigens).
3. Recurrent CNS infections may precipitate repeated inflammation and demyelination.
4. Persistent CNS viral infection could either incite inflammatory reactions detrimental to oligodendrocytes or directly injure them.

Beyond speculation and epidemiological observations, there is insufficient evidence for a viral infection playing a causative role in MS. Early serological studies are difficult to interpret because of nonspecific immune activation and resulting elevation of titers to many different viruses. Many MS patients have elevated cerebrospinal fluid (CSF) titers to measles and herpes simplex (HSV) viruses, but this finding appears nonspecific. Virus has rarely been cultured from CSF of MS patients, but a new strain of HSV (the MS strain) and a new virus (Inoue-Melnick virus) were first isolated from the CSF of MS patients.[12,13] Newer molecular techniques to search for a viral genome in CSF and brain have rejected the claim that HTLV-1 is associated with MS. The finding that human herpesvirus 6 (HHV6), although present in 70% of brains from both control subjects and MS patients, is localized to the oligodendrocyte nuclei near plaques of MS patients and to oligodendrocyte cytoplasm in control subjects indicates that persistent CNS viral infection is common.[14] This raises the possibility that MS may depend on an aberrant host response to this normal condition or that a defective virus that lacks the ability to evade immune detection may be to blame.

More recently, measles and canine distemper virus antibodies were found elevated in blood and CSF samples of MS patients, although their relationship is not clear to the disease process. In a study from Denmark, patients with serological markers for late-stage Epstein-Barr virus (EBV) infection had a threefold increase in the likelihood of developing MS. A follow-up study from Sweden failed to reach this conclusion. In general, serum samples of MS patients may contain higher titers of antibodies to the following infectious organisms: adenovirus, canine distemper virus, HSV, HHV6, and influenza, measles, mumps, parainfluenza, rubella, vaccinia, and varicella zoster virus (VZV). Similarly, CSF samples from MS patients may show higher titers of adenovirus; *Chlamydia pneumoniae*; cytomegalovirus (CMV); EBV; HHV6; coronavirus; influenza viruses A and B; measles or mumps virus; *Mycoplasma pneumoniae*; parainfluenza viruses 1, 2, and 3; respiratory syncytial virus; rubella virus; vaccinia; and VZV. There has been an interest recently in a potential link between *C. pneumoniae* infection and the development of MS. No direct cause-and-effect relationship has been observed between any of these infections and MS.

"Bystander" Demyelination. Immune actions may mediate myelin injury in a nonspecific manner. Many soluble products of the immune response other than immunoglobulins are known or suspected to be toxic to myelin and oligodendrocytes. Activated complement is capable of lysing oligodendrocytes in an antibody-independent fashion.[15] The proinflammatory cytokine tumor necrosis factor-α causes myelin disruption and oligodendrocyte apoptosis in vitro.[16] Arachidonic acid metabolites may also participate in myelinolysis, and reactive oxygen species released by macrophages cause lipid peroxidation that can damage myelin. Other soluble substances that are potentially toxic to myelin include nitric oxide and vasoactive amines.

Histological Subtypes of MS Lesion Development. Through the groundbreaking work of Lucchinetti and associates in the MS lesion project, it is postulated that the formation of MS lesions follows one of four patterns.[17] Patterns I and II are related to immune-mediated damage to myelin sheaths. In pattern I, cellular mechanisms of injury seem to prevail (macrophages and T-lymphocytes) whereas in pattern II humoral mechanisms of injury predominate (e.g., antibody and complement-mediated mechanisms). Patterns III and IV are related to oligondendrocye pathology: in pattern III, a distal oligdendrogliopathy and apoptosis have been reported, whereas in pattern IV, primary oligodendrogliopathy and degeneration of oligodendrocytes have been described. Currently these subtypes can be diagnosed only by biopsy; serum and magnetic resonance imaging (MRI) markers are not yet known, although lesional T2 hypointense rims and response to plasma exchange may correlate well with pattern II pathology. It is important to note that the patterns do not correlate with clinical subtypes of MS, with the exception of pattern IV, which has been identified only in primary progressive (PPMS) patients. Evidence to date suggests that the pattern of lesion formation remains the same within an individual patient; patients do not "switch" from one pattern to the other. Also, the patterns do not seem to represent different chronological stages of lesion formation.

Gray Matter Involvement. It has been known since the late 19th century that MS affects both gray and white matter structures. The importance of gray matter involvement has received little attention until recently, largely due to the development of advanced MRI techniques (see later) that indicate neuronal and axonal involvement even in the earliest stages of this disease. A classification system of gray matter plaques was proposed by Peterson and associates[18] They described three patterns of cortical demyelination: type I lesions are contiguous with subcortical white matter lesions; type II lesions are confined to the cortex, and are often perivascular; type III lesions extend from the pial surface to cortical layer 3 or 4. Besides cortical gray matter involvement, there is also evidence for prominent basal ganglia involvement, which can be seen in the early stages of MS, and may correlate better with motor outcome and cognitive measures than measures of white matter involvement.

Lucchinetti and associates demonstrated that biopsy samples from newly diagnosed demyelinating cases contain numerous infiltrating immune cells, and can be destructive. The pathological classification of cortical lesions as described by Petersen can also be found in these early

MS biopsy samples. Approximately 20% of biopsy cases in which gray matter was also sampled had evidence of clear cortical demyelination.

In 2005, an extensive histological study by Kutzelnigg and associates investigated the role of cortical demyelination in all clinical subtypes of MS.[19] In this study, 52 brains of MS patients (relapsing-remitting [RR], secondary progressive [SP], and PPMS) and 30 control subjects were studied using advanced quantitative morphological techniques. Cortical demyelination and diffuse axonal injury in the normal appearing white matter (NAWM) were reported as hallmarks of progressive forms of MS. Cortical demyelination was mainly seen in the subpial layer of cortex, and was associated with significant inflammatory infiltrates in the surrounding meninges. Diffuse inflammation was also found throughout the white matter of the progressive cases, associated with activation of microglia. No significant correlation was shown between focal white matter lesion load and cortical demyelination. This study defines three crucially important pathological hallmarks of MS—focal demyelinated white matter lesions, diffuse injury in the white matter, and cortical plaque formation—and concludes that white matter lesion formation predominates in active forms of MS, while cortical pathology and diffuse white matter injury characterizes the progressive forms. The authors of this landmark paper also established that these three processes are potentially independent of each other.

Heredity. Epidemiological findings support a polygenic hereditary predisposition to MS. A number of candidate genes have been investigated, often with conflicting results. The only definitive genetic association in MS is with the serologically defined human leukocyte antigen (HLA) DR15, DQ6. This is one of the DR2 haplotypes, also known as Dw2 in cellular terminology and DRB1*1501, DQA1*0102, DQB1*0602 in molecular nomenclature. Though its link to MS is well established, the risk conferred by this haplotype is small (relative risk of 3 to 4), and it is neither necessary nor sufficient for the development of MS. Linkage to this locus has not been proved, indicating that it plays only a minor role in familial susceptibility. Other susceptibility genes likely contribute, possibly the T-cell receptor variable β region and the IgG heavy-chain variable region (especially the VH2–5 gene). But their specific roles have not been established. Other genes under study have been the MBP coding gene, the CTLA-4 gene on chromosome 2q33, and the interleukin-1ra associated gene, in concurrence with the HLA-DR15 haplotype. Mitochondrial mutations are also under investigation, and an LHON-associated mtDNA mutation may be an important cofactor in developing MS in some patients. The ApoE4 gene, as in Alzheimer's disease, has been associated with a higher incidence of MS. On the other hand, ApoE3 is considered to have neurotropic, immunomodulatory, and antioxidant properties. These findings are yet to be confirmed by larger studies.

Twenty percent of MS patients have at least one affected relative. Only about 4% of first-degree relatives of patients develop MS, but this represents a 20- to 40-fold increase in risk compared with the general population. Unaffected family members sometimes have abnormal findings on cranial MRI, implying that this risk is even higher. One study of MS rates in adopted relatives of MS patients verified that the familial distribution is due to genetic factors rather than shared environment.[20] Twin studies lend support to both genetic and environmental influences on MS development. Genetically identical monozygotic twins are more often concordant for MS than dizygotic twins (26% and 2.4%, respectively), indicating a genetic component;[21] however, even after following monozygotic twins past age 50 or using MRI data, less than 50% are concordant, suggesting a role for environmental factors.

EPIDEMIOLOGY AND RISK FACTORS. MS is not a rare disease. It affects millions worldwide and approximately 400,000 in the United States alone. Symptoms usually begin during young adulthood, with the peak onset at age 24. Approximately 0.3% of MS cases are diagnosed before age 15. Women are affected nearly twice as often as men. MS has a predilection for whites, especially those of northern European heritage. Other races and ethnic populations are resistant to a variable extent. MS is virtually unknown among black Africans but occurs in African-Americans at half the rate of whites, possibly due to racial admixture or environmental factors. MS is rare in tropical areas, and the prevalence increases proportionally to the distance from the equator, excluding polar regions. The prevalence is less than 5 cases per 100,000 in tropical areas; in high prevalence areas it can be higher than 30 per 100,000,[22] reaching up to 100 per 100,000 in selected areas. Although usually interpreted as the effect of environmental factors, the prevalence gradient is at least partially due to racial susceptibility.[23]

Perhaps the most incriminating evidence for the role of environmental factors in the development of MS is the changing risk with migration and the occurrence of MS clusters and epidemics. Immigrant populations tend to acquire the MS risk inherent to their new place of residence. Migration from high to low prevalence before the age of 15 lowers the MS risk, whereas migration after this age does not affect risk.[18] Migration from low to high prevalence areas increases the risk of MS, but the effect of age is less clear. Many clusters of MS have been reported.[24,25] The occurrences of MS epidemics in Iceland and the Faroe Islands have been proposed to be the result of exposure to a pathogen brought by British troops during their occupation in World War II. Other environmental factors associated with the development of MS include cigarette smoking (odds ratio of 1.81, CI: 1.1–2.9), animal fat intake, and deficiency of vitamin D.[26,27]

Epidemiological data support the view that MS is caused or triggered by an environmental factor in persons who are genetically susceptible. The familial frequency and distribution implies that several genes contribute to susceptibility, and this is consistent with the low relative risk conferred by the genetic loci studied so far. Data from clusters, migration studies, and family studies reveal that there is a latent period of some 20 years between exposure to the environmental factor and the development of clinical symptoms and that the age at exposure is around 15, the putative age at acquisition.

The precise environmental events that lead to CNS demyelination are uncertain. Viral infection is the most plausible, but because of the nonspecific elevation of viral titers and long latent period, there is little direct evidence.

Minor respiratory infections precede 27% of relapses in patients with established MS. Measles infection was found to have occurred at a later age in MS patients than control subjects, although the incidence of MS has not been reduced by immunization against measles. Head injury and trauma have received attention as putative triggering events, but cohort studies have not verified any link. Pregnancy does not alter the risk of developing MS, but it does seem to influence disease activity. The annualized relapse rate drops from approximately 0.56 to 0.12 by the third trimester, but this is offset by an increase to 1.2 in the first 3 postpartum months. Most studies have found no long-term effects of pregnancy on the prognosis for progression or disability, although one did report a favorable effect.[28] A multitude of other environmental factors have been suspected to alter the risk for MS (cold climate, precipitation, amount of peat in the soil, exposure to dogs, and consumption of meat, processed meat, and dairy products), but none has been verified to be an independent risk factor.

CLINICAL FEATURES AND ASSOCIATED FINDINGS. MS can cause a wide variety of clinical features. Many signs and symptoms are characteristic, and a few are virtually pathognomonic for the disorder. Conversely, some symptoms are atypical and some are so rare as to suggest a different diagnosis (Table 48-2). The course of the illness is also variable, but it remains a critical consideration in the diagnosis of MS.

Sensory symptoms are the most common presenting manifestation in MS (21% to 55%) and ultimately develop in nearly all patients.[29] Loss of sensation (numbness), paresthesias (tingling), dysesthesias (burning), and hyperesthesias are common. These symptoms may occur in practically any distribution: one or more limbs, part of a limb, trunk, face, or combinations. The more distinctive sensory relapses of MS consist of the sensory cord syndrome and the sensory useless hand syndrome. A common scenario is that of numbness or tingling beginning in one foot, ascending first ipsilaterally and then contralaterally. The sensory symptoms may ascend to the trunk, producing a sensory level, or may involve the upper extremities. Associated symptoms commonly include poor balance, weakness, urinary urgency, constipation, and Lhermitte's sign (see later). Brown-Séquard syndrome may occur with sensory disassociation and hemiparesis. The sensory cord syndrome reflects an evolving demyelinating lesion that begins in the medial posterior column ipsilateral to the first symptoms. Sensory cord syndromes are common in MS and suggest the diagnosis when they occur in young persons and remit spontaneously or in response to corticosteroids. Patients with the sensory useless hand may note subjective numbness and lose discriminatory and proprioceptive function, resulting in difficulty writing, typing, buttoning clothes, and holding onto objects, especially when not looking at the hand. This problem can occur bilaterally even without lower extremity symptoms. The responsible lesion is in the lemniscal pathways either in the cervical spinal cord or in the brain stem. This syndrome usually remits over several months. The useless hand syndrome is a very specific symptom and is only rarely caused by other disorders.

A large portion of MS patients have persistent sensory loss, usually consisting of diminished vibratory and position sensation in distal extremities (Video 5, Sensory Ataxia). Itching may occur in a dermatomal distribution with relapse or in paroxysms. Pain is not a major manifestation of MS, but distressing lower extremity dysesthetic pain associated with spinal cord involvement, radicular pain from lesions at the root entry zone, paroxysms, and an uncomfortable sensation of pressure or tightness surrounding a leg or the trunk may be present.

Pyramidal tract dysfunction is common in MS and causes weakness, spasticity, loss of dexterity, and hyperreflexia (Video 80, Hyper-reflexia). Motor deficits can occur acutely or in a chronic progression with weakness of one or more limbs and facial weakness, leg stiffness that impairs gait and balance, or extensor and flexor spasms (Video 3, Spastic Gait). Exercise or heat frequently worsens subtle deficits. Muscle atrophy is usually due to disuse, but lesions of lower motor neuron fibers or of the anterior horn itself can cause a pseudoradiculopathy with segmental weakness, atrophy, and diminished reflexes. Motor symptoms are presenting manifestations of MS in 32% to 41% of all cases; their prevalence is higher than 60% in long-standing MS.

The initial symptom of MS is optic neuritis (ON) in 14% to 23% of patients, and more than 50% experience a clinical episode of ON during their lifetime. The most common manifestation is visual loss in one eye that evolves over a few days. Periocular pain, especially with eye movement, usually accompanies and may precede the visual symptoms. Bilateral simultaneous ON is uncommon in adults, but formal visual field testing reveals unexpected defects in the clinically normal eye in a substantial number of patients. Children and Asian patients are more likely to have bilateral simultaneous ON; it may also be seen in neuromyelitis optica (NMO) patients. Examination shows an afferent pupillary defect, diminished visual acuity, subdued color perception, and often a central scotoma (Video 200, Afferent Pupillary Defect). Funduscopic examination is usually normal but occasionally will reveal papillitis (more common in children) or venous sheathing. Most patients begin to recover within 2 weeks, and significant visual

TABLE 48-2

Diagnosis of Multiple Sclerosis

CLINICAL FEATURES SUGGESTIVE OF MS	CLINICAL FEATURES NOT SUGGESTIVE OF MS*
Onset between ages 15 and 50	Onset before age 10 or after 55
Relapsing-remitting course	Continued progression from onset without relapses
Optic neuritis	Early dementia
Lhermitte's sign	Seizures
Partial transverse myelitis	Aphasia
Internuclear ophthalmoplegia	Agnosia
Sensory useless hand	Apraxia
Acute urinary retention (especially in young men)	Homonymous or bitemporal hemianopia
Paroxysmal symptoms	Encephalopathy
Diurnal fatigue pattern	Extrapyramidal symptoms
Worsening symptoms with heat or exercise	Uveitis
	Peripheral neuropathy

*Whereas features listed in the right column may be seen in MS, they are atypical and should prompt consideration of alternate explanations.

recovery is common. There may be persistent visual blurring, altered color perception, or Uhtoff's sign. MS patients without a clinical history of ON often have evidence of optic nerve involvement on funduscopic examination or visual evoked potentials. Recurrent optic neuritis can occasionally be seen without evidence for dissemination to other areas of the CNS. A retrospective study of 72 cases with recurrent ON concluded that the 5-year conversion rate to neuromyelitis optica was 12.5%; conversion rate to MS was 14.4%; while 73% did not convert to either condition. Patients with frequent and severe ON events in the first 2 years were more likely to convert to NMO; they also had a higher likelihood for significant persistent vision loss.[30]

Cerebellar pathways are frequently involved during the course of MS, but a predominately cerebellar syndrome is uncommon at onset. The manifestations include dysmetria, dysdiadochokinesia (Video 12, Dysdiadochokinesis), action tremor with terminal accentuation, dysrhythmia, breakdown of complex motor movements, and loss of balance (Video 14, Tremor with Ataxia). Patients with long-standing MS may develop a "jiggling" gait and an ataxic dysarthria with imprecise articulation, scanning speech, or varying inflection, giving it an explosive character.

Urinary urgency, frequency, and urge incontinence (due to detrusor hyper-reflexia or detrusor-sphincter dyssynergia) result from spinal cord lesions and are frequently encountered in MS patients. The combined incidence of bowel and bladder dysfunction in MS is thought to be higher than 70%. Symptoms of bladder dysfunction may be transient and occur with an exacerbation but are commonly persistent. Impaired vesicular sensation causes a high capacity bladder and may lead to bladder atonia with thinning and disruption of the detrusor muscle. Incontinence results in constant dribbling of urine in this irreversible condition. Interruption of brain stem micturition center input sometimes leads to cocontracture of the urinary sphincter and detrusor muscles (detrusor-sphincter dyssynergia). The resulting high pressure may lead to hydronephrosis and chronic renal failure if untreated.

Constipation is a common problem, occurring in 39% to 53% of MS patients, especially with limited activity and spinal cord involvement. Fecal incontinence is a socially devastating symptom that is often associated with perineal sensory loss in MS patients.

Sexual dysfunction is seldom mentioned, even though it is a frequent problem in MS. Nearly two thirds of patients report diminished libido. One third of men have some degree of erectile dysfunction, and a similar percentage of women have deficient vaginal lubrication. Besides direct neurological impairment, sensory loss, physical limitations, depression, and fatigue additionally contribute to sexual difficulties in MS patients. In addition, the partner's attitude and psychological factors dealing with self-image, self-esteem, and fear of rejection may also lead to impotence or loss of libido.

Intense vertigo associated with nausea and emesis is an occasional manifestation of MS relapse. In the absence of a clear diagnosis of MS, these symptoms are often attributed to vestibular neuronitis. Patients may also develop a persistent but mild vertigo that is precipitated by movement, or this may be a residual finding after an acute relapse. Internuclear ophthalmoplegia, caused by a lesion in the medial longitudinal fasciculus, is the most common cause of diplopia in MS patients (Video 200, Afferent Pupillary Defect). When symptomatic, it produces horizontal diplopia on lateral gaze that usually remits. Examination discloses incomplete or slow adduction of the eye ipsilateral to the lesion and nystagmus of the contralateral eye during abduction (see Chapter 9). Dissociated nystagmus may be the only finding of an old or subtle internuclear ophthalmoplegia (Video 19, Internuclear Ophthalmoplegia). Bilateral internuclear ophthalmoplegia is strongly suggestive of MS, although this rarely may occur with tumor, infarct, mitochondrial cytopathy, Wernicke's encephalitis, and Chiari malformation (Video 229, Wernicke's Encephalopathy). Vertical and diagonal diplopia usually results from skew deviation. Nystagmus, slow saccadic movements, broken ocular pursuits, and ocular dysmetria are other eye findings produced by lesions of cerebellar and vestibular pathways (see Chapters 9 and 12; Video 228, Saccadic Dysmetria). Abducens paresis occurs on occasion, but oculomotor and trochlear nerve impairment is rare.

Corticospinal, spinothalamic, lemniscal, vestibular, and cerebellar pathways can all be affected. Cranial nerve impairment may be seen with lesions that affect brain stem nuclei or exiting and entering fibers. Usually this occurs in association with other symptoms. Because of the long spinal tract and nucleus, the trigeminal nerve is frequently involved (Video 106, Trigeminal Neuralgia). Facial nerve paresis does occasionally occur, but MS is an extremely rare cause of Bell's palsy in patients without previous symptoms. Acute unilateral hearing loss is an uncommon manifestation. Dysphagia is often due to impairment of cranial nerves IX, X, and XII and generally appears late in the course of some patients.

Once thought uncommon, cognitive disorders are now known to be present in 40% to 70% of MS patients.[31] Age, duration of MS, and physical disability do not completely predict the presence of cognitive dysfunction, but classic MRI measures like the total T2-weighted lesion load does not seem to correlate well with the degree of cognitive decline. Measures of cortical atrophy, venticular enlargement, and neuronal integrity seem to correlate better with the cognitive aspects of MS. The problems are often subtle and may not be detected on standard mental status evaluation. The pattern of cognitive decline is typified by decrease of episodic memory, processing speed, verbal fluency, and difficulty with abstract concepts and complex reasoning. To a lesser extent, executive functioning and visual perception, semantic memory, and attention span may also be also decreased. General intelligence is not typically affected. As expected, cortical symptoms such as aphasia, apraxia, and agnosia are unusual. Homonymous hemianopia, which can be caused by cortical or subcortical lesions, is also uncommon. Despite prominent cerebral white matter involvement, many of the disconnection syndromes such as alexia without agraphia, conduction aphasia, and pure word deafness have not been reported in MS patients.

Affective disorders are more frequent in MS patients than in the general population. These include both anxiety and depression. In long-term studies, the incidence of depression in MS patients is close to 75%. Neither depression nor anxiety is related to physical or cognitive disability or

MRI lesion load. Patients sometimes experience uncontrollable weeping or less commonly laughter incongruent with their mood. Interruption of inhibitory corticobulbar fibers is responsible for these symptoms (pseudobulbar affect).

Fatigue is a pervasive symptom among MS patients that is not related to disability or depression. Over 75% of MS patients experience fatigue during their disease course. A diurnal pattern is characteristic and follows the normal circadian pattern of body temperature fluctuations, with the worse symptoms occurring in afternoon hours (peak core body temperature) often giving way to improvement in the late evening.

MS symptoms may fluctuate in a predictable fashion. Transient worsening of symptoms frequently follows exercise or elevation of body temperature. One example is Uhtoff's phenomenon, in which visual blurring occurs during strenuous activity or with passive exposure to heat. These episodes resolve when the body temperature cools to normal or after a period of rest. An intercurrent infection with fever can induce worsening of symptoms and may be confused with a relapse. Heat sensitivity is presumably related to conduction block, as demyelinated axons are more prone to failed conduction than normal, myelinated fibers.[32]

Paroxysmal symptoms are characteristic of MS and are believed to be due to the lateral spread of excitation (ephaptic transmission) between denuded axons in areas of demyelination. Symptoms are typically brief (seconds to 2 minutes) and recur frequently, occasionally dozens of times per day. They may be precipitated by hyperventilation, certain sensory input, or particular postures. Tonic spasms (paroxysmal dystonia) most often affect the arm and leg on one side, but the face, one limb, or bilateral limbs are sometimes involved (Video 20, Tonic Spasms). These spasms may result from lesions anywhere along the corticospinal tract. They often begin during the recovery phase after an acute relapse and remit after a few months. Intense pain and ipsilateral or crossed sensory symptoms may accompany them. Paroxysmal weakness occurs, but it is uncommon. A wide variety of paroxysmal sensory symptoms may occur with MS, including tingling, prickling, burning, or itching, and sharp neuralgic pain is common. Trigeminal neuralgia may appear in patients with MS (Video 106, Trigeminal Neuralgia). The occurrence of trigeminal neuralgia in a person younger than age 40 is suggestive of MS. Lhermitte's sign (transient sensory symptoms usually precipitated by neck flexion) is usually described as an electrical or tingling sensation that travels down the spine or into the extremities. Although quite common in MS, Lhermitte's sign can also occur with a wide variety of other disorders, such as vitamin B_{12} deficiency, spondylosis, Chiari malformation, and tumors, and after cisplatin chemotherapy. Several other paroxysmal symptoms are occasionally encountered, including paroxysmal dysarthria and ataxia, paroxysmal diplopia, and combinations of these symptoms. Facial myokymia and hemifacial spasm are additional transient (lasting months) phenomena sometimes due to brain stem demyelination (Video 110, Facial Myokymia; Video 224, Hemifacial Spasm). Trismus, kinesigenic dystonia, paroxysmal kinesigenic choreoathetosis, and segmental myoclonus have also been described in case reports of MS patients as rare and unusual examination findings.

Seizures occur in a larger proportion of MS cases compared to normal control subjects. A recently published review of 29 case series of MS patients with epileptic seizures yielded a prevalence of 2.3%.[33] This represents an approximately three- to sixfold increase compared to the general adult population. Cortical and juxtacortical lesions may be responsible for the increased incidence of seizures in MS patients. However, such plaques are common and seizures in MS are not, which suggests that other factors may also contribute to the relationship between epilepsy and MS. Focal motor seizures, possibly with secondary generalization, are the most frequent. The occurrence of seizures usually follows one of two patterns. On occasion, focal onset seizures begin early in the course of MS and later remit. The start of seizures late in the course of MS more often poses a chronic problem and may be difficult to control.

The eye is the only organ outside the nervous system that is sometimes involved in MS. Uveitis and retinal periphlebitis each occur in at least 10% of MS patients. In a recent study, most patients with MS-associated uveitis were white females between 20 and 50 years of age.[34] The diagnosis of MS preceded the onset of uveitis in 56%, followed it in 25%. In over 90% of the cases, the uveitis was bilateral. Pars planitis was found to be the most frequent form of uveitis (over 80%), and concomitant anterior chamber inflammation was also common. Usually MS-associated uveitis is benign from the standpoint of visual acuity. Uveitis can involve the posterior, intermediate (pars planitis), or rarely anterior portion and resembles that seen in other inflammatory (e.g., sarcoid, Reiter's syndrome, Behçet's syndrome, inflammatory bowel disease, systemic lupus erythematosus) and infectious (e.g., syphilis, tuberculosis, Lyme disease) conditions. Periphlebitis is seen as venous sheathing on funduscopic examination and is histologically identical to the perivascular inflammation present in brain white matter. It is interesting that inflammation commonly occurs in the retina, which has a peripheral type of myelin produced by Schwann cells.

There are occasional reports of peripheral nerve or nerve root demyelination in MS patients as well as central demyelination in acute inflammatory demyelinating polyradiculoneuropathy and chronic inflammatory demyelinating polyradiculoneuropathy (see Chapter 49). Some of these cases may be due to the incidental occurrence of two unrelated disease processes. However, because the PNS and CNS share many antigens, including MBP, it is possible that an autoimmune reaction or a viral infection could involve both the CNS and PNS.

Persons with one autoimmune disorder generally have an increased risk of others. Even though there are several reports of systemic and organ-specific autoimmune diseases in MS patients, population-based studies have not confirmed any increase in prevalence of these disorders among MS patients.[35] In fact, there appears to be a negative association between MS and rheumatoid arthritis.

Multifocal CNS involvement and acute relapses, remissions, and slow progression of neurological deficits typify MS. A single episode of neurological dysfunction can be suggestive of MS if it follows the typical time course of a relapse: progression over less than 2 weeks (usually days), with or without a period of stabilization, and

improvement or resolution (often over months). Insidious progression of deficits localized to a single site in the CNS can also be due to MS, but other causes must be excluded. The temporal course of MS can be described by one of four categories: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR).[32] Many physicians use the term *relapsing progressive,* which encompassed patients with SPMS, PRMS, and even those with RRMS who have stepwise relapse-related worsening disability. This term has recently been abandoned. Other terms that relate to the course of MS but have no consensus regarding their definition are sometimes encountered. *Benign MS* generally refers to patients who have had MS for a long time but have little or no disability. *Malignant MS* is sometimes used to describe patients with frequent relapses and incomplete recovery but is also used in reference to patients with acute fulminant demyelinating syndromes (see later). The term *clinically isolated syndrome* (CIS) refers to patients presenting with their first episode of region-restricted episodes of CNS inflammatory demyelination. This may remain an isolated syndrome (no recurrence), it may remain a forme fruste of acute disseminated encephalomyelitis (ADEM), or it may be the harbinger for one of the relapsing forms of MS. The probability of recurrent demyelinating episodes (e.g., clinically definite MS) has been the subject of several important investigations, and several clinical features and test results are of predictive value. Optic nerve, spinal cord, and brain stem are the most common sites of these recurrent monosymptomatic events, and the time profile follows that of MS relapses. The pathogenesis, pathophysiology, epidemiology, clinical features, associated disorders, differential diagnosis, evaluation, and management are the same as in MS.

The prognosis for visual recovery after each episode of ON is good, and most patients regain normal visual acuity. Profound visual loss, recurrent ON, and age older than 35 are associated with a higher risk for poor recovery. Investigators have concluded that recurrent multifocal demyelinating episodes, fulfilling the diagnostic requirements of clinically definite MS, develop in 50% or more of patients after isolated ON when follow-up is extended beyond 20 years.[36] Most of this risk is incurred within the first few years, although significant risk may continue into the fourth decade after the event. Children much more often develop simultaneous bilateral ON and have a lower risk for subsequent MS than adults. Factors that are associated with an increased risk of *developing* MS as a disseminated illness are the presence of venous sheathing, recurrent ON, family history of MS, white race, previous vague or nonspecific neurological symptoms, and the presence of oligoclonal bands (OCBs), elevated IgG index, or IgG synthesis rate in CSF. The severity of acute transverse myelitis is inversely related to the risk of acquiring further symptomatic demyelinating lesions. Complete transverse myelitis with profound loss of motor, sensory, and sphincter function imparts a relatively low risk of 3 to 14 for the later diagnosis of MS. Partial transverse myelitis with preservation of significant motor function at peak is associated with a much higher incidence of MS. Although monosymptomatic brain stem demyelination is not as common as either ON or acute transverse myelitis, similar conclusions have been reached. In the only study available, two thirds of these patients with cerebral white matter lesions detected on MRI developed MS within 5 years, compared with none of 5 patients with normal head MRI.[37,38]

A recently published 10-year follow-up of the original Queen Square series continues to demonstrate the value of the baseline cranial MRI study in determining risk of recurrence (MS risk). In this cohort study of 81 CIS patients, approximately two thirds had at least one asymptomatic lesion (54 of 81, 67%) at baseline. After 5 years of follow-up, slightly more than half with one to three asymptomatic baseline cerebral lesions had developed MS (13 of 24) compared with the majority of cases presenting with at least four baseline lesions (28 of 33, 85%). After 10 years of follow-up, the majority of patients with any asymptomatic cerebral lesions had developed definite MS (45 of 54, 83%).[39] The recently published 14-year follow-up data on this group of patients reveals that 88% of the initially MRI positive patients developed MS versus 19% of the MRI negative subgroup.[40] This information is helpful for treating patients in the setting of CIS.

DIFFERENTIAL DIAGNOSIS. Only a few diseases cause neurological deficits that regress spontaneously and relapse in different areas of the CNS over the course of many years. However, because of the remarkable heterogeneity of MS, many disorders may resemble MS (Table 48-3), especially in the first years of active disease.

TABLE 48-3

Differential Diagnosis of Multiple Sclerosis

- Other inflammatory demyelinating CNS conditions
  - Acute disseminated encephalomyelitis
  - Neuromyelitis optica
- Systemic or organ-specific inflammatory diseases
  - Systemic lupus erythematosus
  - Sjögren's syndrome
  - Behçet's disease
  - Inflammatory bowel disease
  - Vasculitis
    - Periarteritis nodosa
    - Primary CNS angiitis
    - Susac's syndrome
    - Eales' disease
  - Granulomatous diseases
    - Sarcoidosis
    - Wegener's granulomatosis
- Infectious disorders
  - Lyme neuroborreliosis
  - Syphilis
  - HTLV-1 associated myelopathy
  - Viral myelitis (HSV, VZV)
  - Progressive multifocal leukoencephalitis
  - Subacute sclerosing panencephalitis
- Cerebrovascular disorders
  - Multiple emboli
  - Hypercoagulable states
  - Sneddon's syndrome
- Neoplasms
  - Metastasis
  - Lymphoma
  - Paraneoplastic syndromes
- Metabolic disorders
  - Vitamin B_{12} deficiency
  - Vitamin E deficiency
  - Central (or extra) pontine myelinolysis
  - Leukodystrophies (especially adrenomyeloneuropathy)
  - Leber's hereditary optic neuropathy
- Structural lesions
  - Spinal cord compression
  - Chiari malformation
  - Syringomyelia/syringobulbia
  - Foramen magnum lesions
  - Spinal arteriovenous malformation/dural fistula
- Degenerative diseases
  - Hereditary spastic paraparesis
  - Spinocerebellar degeneration
  - Olivopontocerebellar atrophy
- Psychiatric disorders
  - Conversion reactions
  - Malingering

CNS, central nervous system; HSV, herpes simplex virus; HTLV-1, human T-cell lymphotropic virus type 1; VZV, varicella-zoster virus.

Other primary idiopathic inflammatory demyelinating CNS disorders may be mistaken for MS. ADEM usually causes monophasic CNS demyelination. Although it frequently involves multifocal areas of white matter simultaneously, ADEM cannot be reliably differentiated from the initial clinical episode of MS. Fulminant brain demyelination in persons without previous symptoms of MS is more likely due to ADEM or other conditions (Schilder's myelinoclastic diffuse sclerosis, Balo's concentric sclerosis, Marburg's variant of MS). Neuromyelitis optica differs from MS primarily in the topography and intensity of the lesions.

Several systemic or organ-specific inflammatory conditions can involve the CNS white matter. ON, myelitis, and other syndromes sometimes occur with systemic lupus erythematosus. Whether this autoimmune disease increases the risk of developing MS or causes similar syndromes by a different pathological process is unknown. Sarcoidosis can affect the nervous system in several ways, including multifocal, corticosteroid-responsive white matter lesions. Sjögren's syndrome sometimes occurs with MS, but this may only represent a chance association. Neuro-Behçet's disease has a predilection for the brain stem. Occasionally, isolated demyelinating syndromes are associated with inflammatory bowel disease.

A wide variety of vasculitic syndromes (e.g., primary angiitis of the CNS, periarteritis nodosa, Wegener's granulomatous angiitis, vasculitis associated with rheumatoid arthritis, Susac's syndrome, Eales' disease) may mimic MS. However, these syndromes can usually be distinguished by involvement of the cortex, seizures, early dementia, personality changes, psychosis, infarcts involving large vessel territories on MRI, and lack of improvement. Findings characteristic to the particular vasculitis (uveitis and vitreal hemorrhage in Eales' disease, retinal and cochlear involvement in Susac's syndrome, upper and lower respiratory tract involvement in Wegener's granulomatosis) also aid in the correct diagnosis.

A few infections must also be considered in the differential diagnosis of MS. Both Lyme disease and syphilis may cause multifocal white matter lesions. HTLV-1 causes a chronic progressive myelopathy (HTLV-1-associated myelopathy/tropical spastic paraparesis). Acute or recurrent myelitis can be caused by VZV. Progressive multifocal leukoencephalopathy and *Toxoplasma* abscesses should be considered in immunocompromised patients with progressive neurological decline. Bacterial endocarditis with brain abscess formation, subacute sclerosing panencephalitis, or chronic rubella encephalomyelitis may need to be considered in the appropriate circumstances.

Cerebrovascular disease is only rarely mistaken for MS. Occasionally, an MS relapse has an abrupt onset that may mimic an infarct, especially in those not previously diagnosed with MS. The usual circumstance is that of a hemisensory or hemimotor deficit imitating a lacunar infarct. Disorders with multiple cerebral infarcts (emboli, hypercoagulable states, Sneddon's syndrome, CADASIL, vasculitis) may produce an MRI appearance and course resembling MS. Vascular malformations may also produce symptoms similar to MS.

Additional neurological illnesses capable of producing multifocal lesions rarely mimic MS. Metastatic tumors and multifocal gliomas are often cited examples, but rarely is this distinction difficult for an experienced clinician. Lymphoma more commonly masquerades as MS because the lesions may involve the white matter, may be multifocal, and are corticosteroid responsive. In addition, demyelination sometimes presents as one (or a few) mass lesion(s). In this situation, biopsy may be needed for diagnosis. Neoplasms can cause paraneoplastic syndromes that may be confused with MS. A high index of suspicion must be kept for older age at presentation, subacute ataxia, early dementia, and personality changes. A few metabolic disorders may resemble MS, such as vitamin B_{12} deficiency, vitamin E deficiency (seen in Bassen-Kornzweig syndrome, hypobetalipoproteinemia, and Refsum's disease), and central pontine or extrapontine myelinolysis (Video 113, Pontine Myelinolysis). Leukodystrophies are usually not difficult to distinguish from MS. Krabbe's disease (galactocerebroside-β-galactosidase deficiency), metachromatic leukodystrophy (MLD; arylsulfatase A deficiency), and the usual adult form of adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) exhibit both central and peripheral dysmyelination. Blood leukocyte or fibroblast culture enzyme activity levels will confirm the diagnosis of Krabbe's disease and MLD, and elevated levels of very long chain fatty acids occur in ALD/AMN. Mitochondrial disorders should also be given consideration because symptoms and MRI appearance may be similar to MS. A relapsing remitting disorder identical to MS is sometimes seen in patients with the mutations responsible for Leber's hereditary optic neuritis (LHON).[41] This usually occurs in female patients, and there may not be a family history of visual loss. A number of rare biochemically defined illnesses and other genetic disorders may occasionally merit consideration (including cobalamin and folate dysmetabolism, adult polyglucosan body disease, hereditary spastic paraparesis, spinocerebellar degeneration, and hereditary cerebroretinal vasculopathy).[42]

Several additional disorders must be excluded before diagnosing primary progressive MS (PPMS). Spinal cord compression from spondylosis or tumor may produce chronic progressive myelopathy. Chiari malformations, syringomyelia, syringobulbia, other foramen magnum lesions, spinal arteriovenous malformations, and dural fistulas may also need consideration. Careful imaging readily identifies these structural abnormalities. Degenerative diseases such as olivopontocerebellar atrophy may mimic PPMS. MRI and CSF examination will help distinguish between the two.

Conversion reactions and somatization disorders are commonly encountered in a busy referral practice and must be accurately diagnosed to afford optimal patient management.

EVALUATION. The diagnosis of MS is based on the demonstration of white matter lesions disseminated in time and space in the absence of another identifiable explanation. MS remains a clinical diagnosis, although MRI, evoked potentials, and CSF examination can help clarify less certain cases. For research purposes, various categories of MS have been defined based on the certainty of the diagnosis.[43] At least two attacks and evidence of two separate CNS lesions (clinical or paraclinical) are required for the designation of *clinically definite MS* (CDMS). Two

attacks and evidence of one CNS lesion or one attack and evidence of two CNS lesions (clinical or paraclinical) is considered *clinically probable MS*. Cases that fulfill the criteria for clinically probable MS and have supportive CSF findings are labeled as *laboratory-supported definite MS*. Patients with a clear history of at least two attacks and supportive CSF but a normal neurological examination and no paraclinical evidence of CNS lesions are categorized as having *laboratory-supported probable MS*. Suspected cases that do not fit any of these criteria may be regarded as *possible MS*. Paraclinical evidence generally refers to abnormalities on evoked potential studies or imaging procedures.

As a result of increasing availability of refined paraclinical diagnostic modalities (especially MRI) and an overall better understanding of the disease process, new diagnostic criteria for MS were proposed by an international expert panel in 2001.[44] Three out of four of the following findings should be present on MRI: (1) one gadolinium enhancing lesion, or nine T2 hyperintense lesions; (2) at least one infratentorial lesion; (3) at least one juxtacortical lesion; and (4) at least three periventricular lesions.

According to the clinical diagnostic criteria, if a patient had two or more attacks with objective evidence on examination of two or more anatomical areas involved, no additional data is required to make the definite diagnosis. However, if such diagnostic studies were done and are not supportive of a diagnosis of MS, then the diagnosis should be reconsidered.

If a patient presents with a history of two or more attacks, but objective clinical evidence only suggests one lesion, the following additional data is needed to confirm the diagnosis: the disease process has to be disseminated in space as demonstrated by MRI; alternatively, two or more MRI-detected lesions consistent with MS plus positive CSF would suffice to meet the newly defined criteria. The clinician also may elect to await a further attack implicating a different anatomical site.

In case a patient had one attack, with objective clinical evidence of two or more lesions, dissemination in time as demonstrated by serial MRIs separated by at least 3 months or a second clinical attack would clarify the diagnosis. If a patient has a clinically isolated syndrome, or "monosymptomatic" presentation, the following criteria should be met: dissemination in space as demonstrated by MRI (again separated by at least 3 months), or two or more MRI-detected lesions consistent with MS plus positive CSF and dissemination in time on serial MRI scans, or a second clinical attack.

In case the patient presents with a progressive course, the presence of positive CSF is required, and dissemination in space should be present, as suggested by nine or more T2-weighted brain lesions, or two or more cord lesions, or four to eight brain lesions plus one cord lesion on MRI. Alternatively, abnormal visual evoked potentials (VEPs) with four to eight brain lesions, or fewer than four brain lesions plus one cord lesion, and dissemination in time on serial MRI scans, or continued progression for a year would meet the diagnostic criteria.

"Positive CSF" according to this set of criteria is defined by either the presence of oligoclonal bands detected by established methods (preferably isoelectric focusing on agarose gel followed by immunoblotting) different from any such bands in serum, or by a raised IgG index. The presence of both enhancing and nonenhancing white matter lesions on a single MR image must not be used as evidence of dissemination in time as well as space, because these can also be seen in ADEM. Oligoclonal bands (OCBs) and an elevated IgG index provide supportive CSF findings.

Ancillary tests are frequently required to confirm the diagnosis of MS and to exclude other possibilities in uncertain cases. Laboratory tests on peripheral blood can help to exclude many of the infectious and other inflammatory disorders. A chest x-ray is generally needed to assess for sarcoid or paraneoplastic disorders if these are under consideration. An ophthalmological examination may be needed to search for alternative causes of visual loss. Imaging studies, CSF examination, and evoked potentials are often helpful because characteristic abnormalities are frequently present.

MRI of the head is the most sensitive imaging study for MS (Fig. 48-3). Focal areas of increased T2-weighted and decreased T1-weighted signal reflect the increased water content associated with demyelinated plaques. The MRI appearance of MS lesions, however, is not specific and similar abnormalities may be seen in normal aging, small penetrating vessel infarcts, Lyme disease, tropical spastic paraparesis/HTLV-1-associated myelopathy, sarcoid, systemic lupus erythematosus, Sjögren's syndrome, mitochondrial cytopathies, vasculitis, and ADEM. The specificity for MS can be increased by consideration of lesion number, size, location, and shape.[45] This is especially important in persons older than age 50. MRI characteristics, other than the ones suggested by the international criteria outlined previously, are size larger than 6 mm, oval shape (often with the long axis directed perpendicular to lateral ventricles), and locations in the periventricular area, corpus callosum, and posterior fossa.

Longitudinal MRI studies have shown the evolution of MS lesions.[46] Gadolinium enhancement, indicating blood-brain barrier disruption, sometimes precedes the development of T2-weighted lesions and typically lasts for 4 weeks in the brain (occasionally longer, especially in larger hemispheric lesions), and perhaps somewhat longer in the spinal cord. FLAIR imaging is especially helpful for evaluating periventricular lesions that may go unnoticed on regular T2-weighted scans. The disadvantage of the technique is its relative insensitivity to posterior fossa lesions. Proton density weighted images are also part of the usual sets of images used in the MR diagnostics of MS. These images can be evaluated similarly to T2-weighted images. Technically, they are usually acquired together with the T2-weighted datasets, as a first echo in conventional fast spin echo sequences, where the subsequent echoes can be used for generating the T2-weighted images. New T2-weighted lesions have a fuzzy border and enlarge over a few weeks. After a period of stabilization, the T2-weighted lesion regresses and becomes more sharply delineated from the surrounding white matter as edema resolves. Most of the time, a residual abnormality with increased T2 weighting and decreased T1-weighted signal remains, reflecting demyelination and gliosis. The low attenuation T1 signal, or "T1 black hole," is more often seen in secondary progressive MS and is thought to represent actual tissue loss.

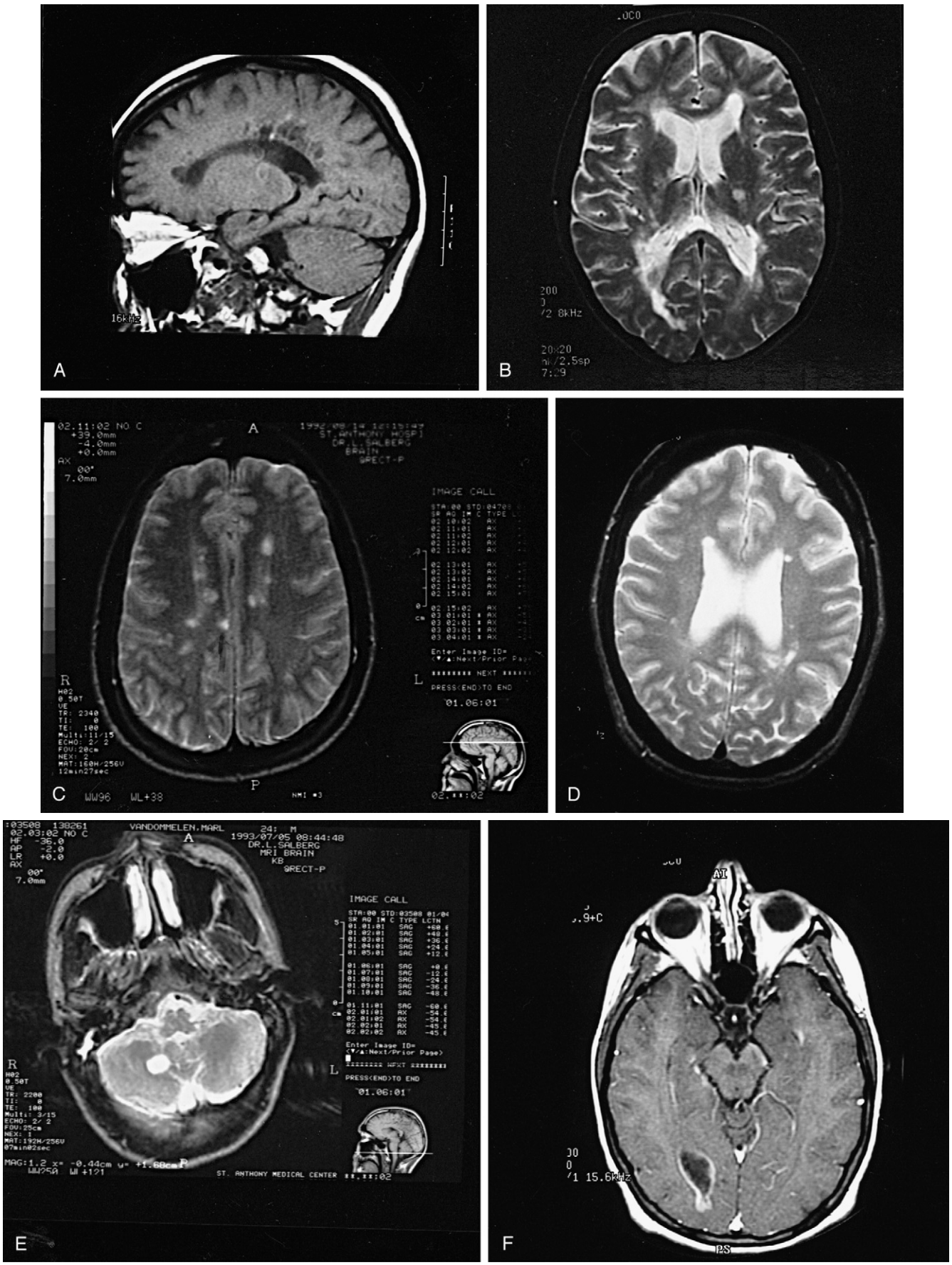

Figure 48-3. Head MRI of patients with MS. **A,** T1-weighted sagittal image showing multiple hypointense periventricular lesions. **B,** Axial T2-weighted image showing confluent periventricular high-intensity lesions most prominent at the frontal and occipital horns. A focal lesion is also present in the posterior limb of the left internal capsule. **C** and **D,** Periventricular lesions suggestive of MS. **E,** A single large right cerebellar hemisphere lesion seen on T2-weighted MRI. **F,** Peripherally gadolinium-enhanced large right occipital white matter lesion. Enhancement can also be seen along the temporal horn of the lateral ventricles.

In several well-documented cases, hypointense lesions on T2-weighted scans were described in subcortical gray matter structures in MS patients. On a molecular level these areas are thought to represent iron deposition; their significance in MS is not fully understood. The MRI activity of disease, defined as either the number of new, recurrent, and enlarging lesions or the number of gadolinium-enhancing lesions, is usually higher than the clinical activity. This may be either because of the involvement of asymptomatic areas of the CNS or because of a pathophysiological difference between symptomatic and nonsymptomatic lesions based on the presence or absence of axonal dysfunction.

There is only poor correlation between disability and lesion load (volume of white matter abnormalities) determined by head MRI. Sometimes individuals have severe impairment and few MRI abnormalities, and the converse may occur. This disparity is partially explained by variable spinal cord involvement, but a pathophysiological difference may account for some of the discrepancy. Several MRI markers of gray matter involvement correlate better than measures of white matter pathology with clinical functional outcome measures in MS. In a recent study[47] EDSS showed the strongest correlation with gray matter volume loss and with T1 black hole volume increase ($p < 0.01$); both are considered to reflect neuronal and axonal pathology. Ambulatory function, assessed as the 25-feet timed walk, also correlated well with gray matter volume loss and T1 black hole volume. On normal appearing gray matter magnetization transfer ratio (MTR) histograms, normalized peak heights inversely correlated with EDSS in 18 RRMS patients ($r = -0.65$, $p = .01$).[48] In a study evaluating a number of MRI parameters (including brain T1-hypointense and FLAIR-hyperintense lesion volume, third ventricle width, brain parenchymal fraction and T2 hypointensities in the dentate nucleus), the best correlation with EDSS (and the only correlating parameter with 25-feet timed walk) was T2 hypointensity in the dentate nucleus.[49] In 41 MS patients, an MRI study concluded that gray matter atrophy correlated with clinical status (EDSS, 25-feet timed walking and disease duration).[47] A study of patients with PPMS and RRMS showed that neocortical volume as determined by MRI correlated with EDSS scores across all the patients, but the strength of the correlation was stronger ($p < 0.05$) in the PPMS ($r = -0.64$, $p < 0.0001$) than in the RRMS group ($r = -0.27$, $p = 0.04$).[50]

MR spectroscopy is increasingly becoming an accepted diagnostic modality, where information can be obtained about the biochemical constituents of selected voxels of interest. With this technique, a cubic volume of interest is defined based on a regular MR image set. Simultaneous acquisition of multiple volume units is possible. With long echo time (TE) studies, NAA (*N*-acetylaspartate), choline, creatinine, and lactate peaks can be identified on the MR spectrum. With short TE studies, myoinositol, lipids, and some neurotransmitters may be identified. The resolution of the MR spectrum (the "number of lines" in the spectrum) is proportionate to the magnetic field strength used. NAA is the second most abundant amino acid constituent in the brain after glutamate. It is localized almost exclusively in neurons and axons. Creatinine is used as the "constant" peak in a MR spectrum, since it is the least likely to be altered by CNS-specific processes. Therefore, numeric MRS data are usually presented as ratios related to creatinine. The NAA/creatinine ratio is decreased in areas of axonal or neuronal loss. It correlates well with disability. It can be decreased in normal appearing white matter, also in early stages of lesion formation, thus representing a challenge to the usual dogma of axonal loss being secondary to myelin damage. The decrease of the NAA/creatinine ratio may return to normal following the resolution of the acute phase. This process may be related either to reversibility of neuronal injury or to disappearance of edema in the involved areas. In general, more reduced NAA peaks are seen in progressive forms of MS with more profound tissue loss. If a relatively large hemispheric lesion shows decreased NAA content, similar findings may be seen in the other hemisphere in a "mirror" location. The lactate peak can be elevated in a variety of acute processes, and as such, carries relatively low specificity. The short TE spectrum is used less frequently; the "mobile lipid" peak (which is thought to represent macromolecular protein fragments) is increased in areas of acute demyelination.

Another newer MRI technique used in MS research is magnetization transfer imaging. The principle behind this imaging modality is relatively simple. In complex macromolecular systems, there is a baseline magnetization exchange in equilibrium between macromolecular protons and mobile protons. If the macromolecular protons are saturated before each excitation (and subsequent data acquisition) with a prolonged off-resonance broadband pulse, then the signal intensity of the image will be reduced owing to magnetization transfer exchange between the saturated ("bound") and free ("mobile") protons. By obtaining duplicate sets of images (with and without magnetization transfer pulse), a magnetization transfer ratio can be calculated. The ratio reflects the integrity of the macromolecular environment. It is reduced by approximately 3% to 5% in areas of edema, but it is more significantly reduced in areas of demyelination or axonal loss. If the ratio "normalizes" in a lesion, no subsequent tissue loss is usually seen on other imaging modalities. Despite these advantages, the magnetization transfer imaging is technically difficult because it produces variable findings depending on the technical environment and is not universally available. It has not become an accepted and standard technique for evaluation of MS patients. It may be very useful as a marker for remyelination and tissue repair in future neuroprotective or tissue restorative trials.

Diffusion-weighted imaging is well known from its widespread use in the diagnosis of ischemic stroke. This technique can show early stages of MS plaque formation. The increase in apparent diffusion coefficient correlates with acute plaques, and seems to best correspond with T1-enhancing lesions; this technique may show the lesions at an even earlier stage.

MRI has become an important component of clinical trials in MS. Because of the high sensitivity of MRI for disease activity, it is reasoned that periodic MRI may determine treatment efficacy more quickly than monitoring relapse rate or disability level. Many studies have used MRI as a secondary outcome, but clinical outcomes are still used as the primary outcome for definitive trials. Additional MRI techniques have also proved useful in the diagnosis of MS. MRI of the spinal cord shows discrete lesions in about

80% of CDMS patients. Several semiautomatic methods exist to determine lesion volume, ventricle volume, or hemispheric volume. These are generally applied for research purposes only, and are not part of the usual workup or diagnostic follow-up of MS.

CSF evaluation remains a valuable diagnostic tool for MS. A lymphocytic pleocytosis occurs during acute exacerbations in about one third of patients, but this seldom exceeds 50 cells. Eighty percent of the lymphocytes are CD3 positive. The ratio of CD4 to CD8 cells is 2:1. Less than 20% of the cells are B cells. CSF protein is normal in up to 60%; levels above 100 mg/dL are unusual and may suggest a different disorder. The proportion of γ globulin is high owing to the synthesis of immunoglobulins within the blood-brain barrier. The majority of CSF immunoglobulin is IgG, although IgM and IgA may also be elevated. Measures of intrathecal IgG production have been devised that are more useful than simple γ-globulin levels. The IgG index and synthesis rate are elevated in 70% to 90% of CDMS patients and occasionally in other disorders. Agarose gel electrophoresis, or the more sensitive isoelectric focusing of CSF proteins, often reveals discrete bands of immunoglobulin, each a monoclonal antibody. It is pertinent to compare serum and CSF banding patterns because peripheral monoclonal gammopathies may produce CSF bands. To reduce false-positive results, only unique CSF OCBs should be reported. Between 85% and 95% of clinically definite MS patients have OCBs; however, early in the course they are not as prevalent. Once present, OCBs persist and the pattern does not vary, although new bands occasionally appear. Unlike subacute sclerosing panencephalitis, in which the majority of OCBs are antibodies specific for measles virus, the antigenic specificity of OCBs in MS is unknown; they are unlikely to be pathogen specific or autoantigen directed; there is some evidence that they may be genetically determined germline antibodies. Five percent to 10% of noninflammatory CNS samples and 30% of inflammatory samples are also positive for OCBs.[51] More detailed recommendations about the inclusion of CSF parameters to the diagnosis of MS were recently published[52] suggesting that the cell count and differential should be completed within 2 hours. The new and recommended method for the detection of OCBs includes immunoelectophorsesis on agarose gel followed by immunoblotting. The reported sensitivity of this technique is above 95%, with a specificity of 86% to 87%. In other inflammatory or infectious illnesses, OCBs are often transient features. Their persistence is more suggestive of MS. The presence of myelin components, antimyelin antibodies, and kappa light chains in CSF has also been used in the diagnosis of MS. However, the sensitivity and specificity of these products is less than that of OCBs.

In late 2005, a new set of recommendations were published based on the first 5 years of using McDonald's criteria in diagnosing MS.[53] The original McDonald Criteria have been incorrectly interpreted by some as mainly relying on MRI for making a diagnosis of MS. In reality, the McDonald Criteria *cannot even be applied without careful clinical evaluation* of the patient. Neurological deficits must be evident to the examiner, and must be suggestive of MS. Scans that "look like" MS (and meet the criteria of Barkhof and Tintore) but have never been accompanied by an obvious and documented neurological examination finding do not fulfill the McDonald Criteria. There was some sympathy among the International Panel members revising the McDonald Criteria to allow selected symptoms that are clearly and specifically enunciated by the patient (e.g., Lhermitte's symptom, trigeminal neuralgia, numbness ascending to the waist or higher) coupled with objective paraclinical (such as imaging and CSF) findings to be sufficient as an indicator of a prior or current attack needed for an MS diagnosis. However, the panel was *reluctant to endorse the diagnosis of MS in the absence of any objective clinical findings*, even if objective paraclinical findings are in place, at least until such a scheme is tested in prospective settings. Patients with imaging and CSF findings suggestive of MS but not showing any objective evidence for neurological deficits commonly seen in MS require careful clinical and radiological monitoring. Until objective evidence for neurological deficits are found, MS can not be diagnosed.

MS may be the correct diagnosis with less stringent imaging criteria than originally proposed; however, the panel was uncomfortable making changes that would allow MRI confirmation of dissemination in space based on lower stringency imaging criteria without appropriate prospective data. Most studies performed to date have been inadequately designed to address this issue. Advanced imaging technologies are constantly evolving and will likely one day be shown to aid in making the diagnosis of MS. Visualization of intracortical lesions, use of higher field strength magnets, and analysis of "normal appearing brain tissue," may be conrnerstones of a future MRI criteria for MS. Preliminary evidence suggests that "occult" damage in normal-appearing white and gray matter seen with magnetization transfer, diffusion tensor imaging, or spectroscopy is an early feature of MS, whereas it likely does not occur in other demyelinating conditions such as acute disseminated encephalomyelitis and NMO.

Important changes have been made to the original definition of "dissemination in time" by MRI. In keeping with the definition that clinical relapses must be separated by at least 1 month, it was agreed that new T2 lesions on MRI should occur at least 30 days after disease onset. This means that any new T2 lesion occurring at any time point after a so-called reference scan performed at least 30 days after the onset of the initial clinical event is useful in meeting imaging diagnostic criteria for dissemination in time. It should be noted though that a new T2 lesion must be of sufficient size and location to exclude lesions that could have been missed previously for technical reasons of slice orientation, thickness or spacing, tissue contrast, patient motion, or other artifacts. This requires standardized scanning procedures with emphasis on careful repositioning, as well as input from *qualified evaluators experienced in MS imaging*. With the new revision, *there are two ways to show dissemination in time using imaging*: (1) detection of gadolinium enhancement at least 3 months after the onset of initial clinical event, if not at the site corresponding to the initial event; or (2) detection of a new T2 lesion if this appears at any time compared with a reference scan done at least 30 days after onset of the initial clinical event.

Spinal cord lesions can be important in differentiating MS from other white matter diseases; however, the original

McDonald Criteria did not provide sufficient guidelines for the use of cord imaging in MS. Spinal cord imaging that detects typical MS cord lesions (minimal or no swelling of the cord; clearly hyperintense on T2-weighted imaging; at least 3 mm in size, but less than two vertebral segments long; and occupying only part of the cord cross section) is particularly helpful if brain imaging does not detect dissemination in space in a patient suspected to have MS. For dissemination in space, a spinal cord lesion *is equivalent to, and can substitute for, a brain infratentorial lesion*, but not for a periventricular or juxtacortical lesion. An enhancing spinal cord lesion is equivalent to an enhancing brain lesion, and an enhancing spinal cord lesion *can "count" doubly in fulfilling the criteria* (e.g., a single enhancing spinal cord lesion can "count" for an enhancing lesion and an infratentorial lesion). Individual cord lesions can contribute together with individual brain lesions to reach the required nine T2 lesions to satisfy the Barkhof-Tintore criteria (the MRI criteria incorporated in the original McDonald's criteria). The panel recognized that diffuse cord changes may occur in MS, especially in the progressive forms; however, these changes are not sufficiently reliable to allow for their incorporation into the diagnostic criteria at this time. Repeat spinal cord imaging in patients without new symptoms of myelitis has a low yield in efforts to demonstrate dissemination of lesions in time. In other words, while it is common to see asymptomatic new brain lesions on repeated scans, new cord lesions generally do result in new neurological symptoms. Therefore, repeat cord imaging is recommended only to support an MS diagnosis *when there is a clinical reason to suspect a new cord lesion*.

Important changes have been proposed in diagnosing primary progressive MS. These Revised Criteria stress clinical and imaging (brain or spinal cord) evidence for diagnosis and place less emphasis on CSF findings. The new criteria for PPMS is as follows: (1) at least 1 year of disease progression (retrospectively or prospectively determined) (2) plus two of the following: (a) positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP), (b) positive spinal cord MRI (two focal T2 lesions), (c) positive CSF (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both).

Evoked potentials are summed cortical electrical responses to peripheral sensory stimulation that can be used to localize sites of disease and measure conduction velocity along sensory pathways. VEP and somatosensory evoked potentials (SSEPs) may detect subclinical sites of demyelination, thus providing evidence of multifocality. Brain stem auditory evoked potentials (BAEPs) are occasionally informative. More than 90% of persons with a history of ON have an abnormal VEP, and 85% of CDMS patients have abnormalities on VEPs even when the history of ON is absent. Slowed conduction is present on SSEP in nearly three fourths of patients with CDMS. BAEs are the least sensitive, with abnormalities in less than 50%. MRI has largely supplanted the use of evoked potentials in MS because of the greater sensitivity in the diagnosis and the detailed anatomical information it provides. In 2001, the American Academy of Neurology released practice parameters regarding the usefulness of evoked potential studies in MS. According to these recommendations, VEPs are considered probably useful (class II evidence) to identify patients at increased risk for developing clinically definite MS. SSEPs are possibly useful, whereas the evidence for BAEPs supporting the diagnosis of CDMS is insufficient.

MANAGEMENT. There is no available prevention or cure for MS. Treatments focus on three areas: treating acute exacerbations and hastening their recovery; altering the natural history of MS; and providing symptomatic relief of current symptoms by enhancing physical abilities and preventing or treating complications. A fourth management topic concerns special treatment issues related to pregnancy.

Acute Exacerbations. Corticosteroids are the most commonly used treatment for MS, although there have been few studies to address their efficacy. Adrenocorticotropic hormone (ACTH) was shown to speed recovery from an exacerbation but had no effect on the ultimate degree of recovery. Because of the unpredictable cortisone response to ACTH, oral prednisone and later intravenous methylprednisolone became the preferred treatments. The Optic Neuritis Treatment Trial verified that intravenous methylprednisolone but not prednisone increased the recovery rate and unexpectedly increased the time to the next relapse, thus delaying the diagnosis of CDMS.[54] Moreover, the prednisone-treated group had twice as many recurrences. The finding was not replicated in a second study, but it has affected the practice of treating acute MS exacerbations. The current recommendation is to treat disabling attacks with 500 to 1000 mg of intravenous methylprednisolone per day for 3 to 5 days with or without a short tapering dose of oral corticosteroids. According to the practice parameters for steroid treatment of acute ON attacks released by the American Academy of Neurology in 2001, oral prednisone in doses of 1 mg/kg/day has no proven value. Higher dose of oral or parenteral methylprednisolone may result in quicker and more thorough recovery of visual function. There is no evidence of long-term benefit for visual function.

A study suggested that intravenous steroids may also have long-term effects on disease progression when given regularly.[55] In this study, RRMS patients randomized to receive regularly scheduled pulses of IV methylprednisolone (every 4 months for 3 years, then every 6 months for 2 years) demonstrated stability or improvement in disability measures, fewer "T1 black holes," and less brain atrophy than did control patients randomized to receive steroids only with relapses. These findings suggest a possible long-term benefit of pulsed IV methylprednisolone therapy on brain atrophy and disability. This as yet unconfirmed approach to long-term therapy might be considered a reasonable "control arm" in future phase III trials of experimental therapies.

Up to one third of patients do not have an adequate recovery after a relapse despite the use of corticosteroids. Plasma exchange (PLEX) alone was found beneficial in a substantial proportion of patients with severe inflammatory demyelinating episodes who had failed to improve following treatment with high-dose IV methylprednisolone.[56,57] A randomized, sham-controlled, double-blind trial in 22 patients (seven exchanges over 14 days) without concomitant use of immunosuppressants in acute demyelinating events confirmed these findings.[58] Moderate or greater

clinical improvement was observed in over 42% of participants. A trial of seven PLEX treatments (alternate days) is a reasonable option for patients who fail to respond to conventional IV methylprednisolone therapy in acute, severe episodes of demyelinating diseases. The response to PLEX is stongly associated with the histological MS subtype.[59] Antibody and complement plays a crucial role in pattern II lesion formation. In a study of 19 biopsy-proven MS cases by Keegan and associates, 10 pattern II cases showed good response to PLEX, whereas 9 cases of pattern I or III did not respond at all to PLEX. Neuromyelitis optica, which is now considered an antibody-mediated condition with a known serological marker, also shows good response to PLEX: in a study by the Mayo group, 60% of NMO patients showed moderate or marked improvement to PLEX, and an additional 10% showed mild improvement.[60]

Alteration of the Natural Course. The primary goal of drug treatment is to alter the natural course of the disease (e.g., reducing the frequency and severity of relapses, preventing the chronic progressive phase, and slowing the progression of disability). The disease activity seen on MRI is often used as a secondary outcome, although MRI measures currently correlate imperfectly with clinical outcome. Knowledge on altering the course of MS is largely restricted to three patient groups, those with clinically isolated syndromes, those with RRMS, and those with secondary progressive MS.

Before we discuss the known data in each of these demyelinating disease categories, it may be worth while to review the use of the most important evidence-based medicine (EBM) statistics that are applied to measure the magnitude of treatment effect. Relative risk reduction (RRR) is the metric most commonly cited in publications and promotional materials about clinical trials. The RRR is the degree that the treatment reduced the frequency of the outcome measure (experimental event rate, e.g., relapse, progression) compared with the control treatment (control event rate). The RRR is a ratio, not an absolute number, and is calculated as follows:

$$\text{RRR} = (\text{Control event rate} - \text{experimental event rate})/\text{control event rate}$$

If the control event rate is low (making the denominator smaller), it will obviously inflate the RRR. An "impressive" 50% RRR may have a low biological significance if the outcome occurs infrequently. Therefore, the absolute risk reduction (ARR) should be calculated as this corrects for the frequency of the outcome.

$$\text{ARR} = \text{Control event rate} - \text{experimental event rate}$$

For most of the approved MS agents, the calculated ARR is considerably less than RRR. This metric is usually not cited in reports of clinical trials of disease-modifying agents. To calculate risk reduction, one must have access to the data citing comparisons of proportions (ratios), and this is not always immediately available in publications.

Another useful measure of treatment effect is the "number needed to treat" (NNT). It is calculated as the inverse of the ARR:

$$\text{NNT} = 1/\text{ARR}$$

Overall, the NNTs for the disease-modifying agents in MS are in the 7 to 14 range for treatment periods of 2 to 3 years. However, these NNTs are for outcomes that have limited predictive value for long-term outcomes (e.g., relapse behavior does not precisely predict long-term disability) and the agents are expensive, inconvenient to use, and not without risk. We must also remember that clinical trials typically enroll patients with very restricted eligibility criteria (often a history of considerable recent disease activity or progression), and considerable efforts are in place in trials to optimize compliance with the treatment plan. As such, the NNT experienced in a practice setting (effectiveness) may considerably exceed what was reported in the trial setting.

Altering the Course of a Clinically Isolated Syndrome. When should treatment be initiated in patients with very early demyelinating disease? Two recently published multicenter studies have addressed this issue in persons at high risk of developing MS. In the CHAMPS study,[61] 383 patients with their first episode of presumed demyelinating disease ("clinically isolated syndrome") in the setting of an abnormal, asymptomatic baseline cranial MRI scan, were randomized to receive either weekly interferon-β 1a 30 μg IM or placebo after an initial course of steroid therapy. This study was terminated early when the primary outcome measure of conversion to "clinically definite MS" (CDMS) status was reached in a greater number of placebo-treated patients. These findings were not unexpected given the known effect of interferons on reducing relapse rate but do provide some support for early treatment. The duration of follow-up in this study (71% 1 year, 34% 2 years, 16% 3 years) is insufficient to determine long-term benefit from early intervention, however. It is also clear that the treatment is only partially effective, as 50% of interferon (IFN)-treated patients in the CHAMPS trial had clinical or MRI evidence of recurrent disease within 18 months of starting treatment.[62] The analysis of treatment effect related to the CHAMPS trial reveal a RRR of 38%, an ARR of 14.6%, and an NNT of 7 patients over 2 years to prevent one conversion to "clinically definite MS."

In a second placebo-controlled study of 309 patients with either monosymptomatic (61%) or multifocal onset (39%) early demyelinating disease, early treatment with interferon-β 1a in an unusually low dose (22 μg subcutaneously once weekly), reduced conversion to CDMS (34% versus 45%) at 2 years.[63] Again, there is no data on whether these treatments offer long-term benefit. The EBM calculations regarding this trial show an RRR of 24%, and ARR of 11%, and an NNT of 9 patients over 2 years in order to prevent one conversion to "clinically definite MS." These two studies provide support for considering early treatment in patients presenting with first attack, in the presence of multiple asymptomatic MRI lesions, but further studies are needed to determine whether this approach will provide a prolonged benefit on disease course. It is important to note that these studies do not provide guidance about clinically isolated syndromes that present with a brain MRI that is not suggestive of MS (i.e., only one optic nerve lesion, or one brain stem or cord lesion explaining the CIS symptoms). We do not recommend that CIS patients with fewer than two asymptomatic MRI lesions receive treatment with interferons. Please see the discussions under "Summary of Recommendations for the Treatment of RRMS Patients" for further advice on patient counseling and decision making about the use of the disease-modifying medications.

Altering the Course of Relapsing-Remitting Multiple Sclerosis

β-Interferons. Interferons are a class of peptides that have antiviral and immunoregulatory functions. Both interferon-α and interferon-β are part of the anti-inflammatory T_H2 response. Interferon-β 1b (Betaseron) was the first drug approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of MS. A large clinical study in RRMS patients demonstrated a reduction in the frequency of relapses by about one third with subcutaneous injection every other day.[64] The severity of relapses was also lessened. Interferon-β 1b had a striking effect on MRI measures of disease activity. The placebo-control group continued to accumulate white matter lesions, whereas patients in the high-dose arm (8 million IU) had stabilization of their MRI lesion load. No difference was found in the disability levels, however. Side effects include injection site reactions, flu-like symptoms (low-grade fever, myalgias, headache; these lessen in frequency after treatment for a few months), mild liver enzyme elevation, and lymphopenia. Depression and attempted suicide were more common in the treated groups.

To illustrate the magnitude of treatment effect of the pivotal interferon-β 1b trial, the RRR was 18%, the ARR was 15%, and the NNT analysis showed that 7 patients are needed to be treated over 3 years to increase the number of those who were relapse free by one. One particularly disturbing result was the production of neutralizing autoantibodies (NAbs) in 38% of patients after 3 years of treatment. Not only do patients with these antibodies thereafter fail to respond to this drug, but there is also a concern that NAbs may cross-react with natural interferon-β and interfere with its function. All positive sera for NAbs seem to cross-react with both interferon-β 1a and 1b. Switching from one preparation to the other does not change the pattern of antibody response.[65] The long-term effects of NAbs are unknown. Recent studies seem to support that NAb formation reduces clinical and MRI effects although often NAb formation subsides with time. There are no firm guidelines for monitoring NAb formation. Most physicians do not measure NAbs but rather change therapies empirically when patients appear to be failing treatment. Low titer Nabs may be just transient phenomenon related to IFN treatment; persistent high titer NAbs on two consecutive tests at least 6 months apart is likely associated with poor treatment response to INF.

Interferon-β 1a (Avonex) has the same amino acid sequence as natural interferon-β and differs from interferon-β 1b by one amino acid as well as by the presence of carbohydrate moieties. Once-weekly intramuscular interferon-β 1a has been found to have effects similar to that of interferon-β 1b in reducing the frequency of MS relapses. In addition, a favorable effect on disability was also demonstrated and side effects were less common. In the original interferon-β 1-a intramuscular trial, the primary outcome measure was time to EDSS progression. The RRR was 37%, the ARR was 13%, and the NNT was 8 for 2 years to prevent one patient from developing EDSS progression. The calculations for "proportion relapse free" show an RRR of 16%, and ARR of 12%, and an NNT of 8 over 2 years (8 patients need to be treated for 2 years to increase the number of patients who were relapse free by one). NAbs occurred half as often as with interferon-β 1b. Interferon-β 1a has been approved by the FDA for treatment of "relapsing MS."[66]

The "correct" dose of interferon continues to be debated. In a recent placebo-controlled trial, patients randomized to a high dose of interferon-β 1a (44 μg three times per week) did better than those receiving half this weekly dose. Both groups outperformed placebo and the high dose seemed to have more effect on relapse severity, hospitalizations, MRI activity, and lesion volume accumulation, and possibly on delaying disability in the most severely disabled patients. At the end of the 2 years of follow-up, placebo-treated patients were randomized to 22 or 44 μg subcutaneously three times weekly; patients on active treatment were continued on their original dose.[67] The authors reported a benefit for the higher dose and for those treated for the full 4 years, again suggesting that early treatment and perhaps higher doses of interferons may be beneficial. The primary outcome, however, was relapse count per patient per 4 years and, as such, patients treated early had a significant advantage using this outcome measure. There were trends favoring the higher dose (relapse rate, MRI volumes; not for time to first confirmed progression, however). The authors did not make statistical adjustments for multiple comparisons and there were many dropouts in the high-dose groups, making it difficult to draw firm conclusions. Again, the answer to the question about the benefit of early treatment can best come from long-term (perhaps 8 to 10 years) studies using "hard outcomes" (e.g., time to progression, major milestones in disability). The EBM calculations based on the "proportion relapse free" data for the original interferon-β 1a (Rebif) study show an RRR of 19%, and ARR of 16%, and an NNT of 6 over 2 years to increase the number of relapse free by one. Relative treatment advantages of interferon-β 1a and 1b have not been clearly established but are under study.[68,69] A pilot study in RRMS patients suggests that interferon-α may also have a therapeutic effect.[70] A study of interferon responders showed that younger patients with frequent relapses, and higher EDSS scores upon entry may be associated better response.[71]

Laboratory Monitoring of Interferon Products. It is important to note that even though the interferon products are generally safe to use, they can be associated with potentially harmful adverse reactions. We recommend that every newly starting patient should have a baseline complete blood count, liver function tests, and thyroid-stimulating hormone (TSH) test. The liver function tests and blood count studies should be repeated in 1 week, 1 month, and every 3 months thereafter; the TSH should be repeated every 6 to 12 months.

Glatiramer Acetate. Glatiramer acetate (GA) is a synthetic mixture of polypeptides produced by the random combinations of four amino acids that are frequent in MBP. After a preliminary study suggested efficacy,[72] a phase III randomized, double-blind, placebo-controlled, multicenter trial showed a 29% reduction in relapse rate.[73] The FDA has approved this medication for use in RRMS. Even though this disease-modifying therapy requires daily subcutaneous administration, the side effects are relatively minor compared to the interferons, and patients do not need regular laboratory monitoring (Table 48-4). Glatiramer acetate reduces new lesion formation, the number of T2-enhancing

TABLE 48-4

Therapeutic Options in MS

MS TYPE	AGENT	DOSAGE	PROVEN BENEFITS	ADVERSE EFFECTS	MONITORING
Acute episodes	Methylprednisolone (Solu-Medrol)	500–1000 mg IV for 3–7 days	Hastens recovery Effects on blood-brain barrier (transient restoration) Long-term effects (as of yet uncertain)	Usual steroid-related side effects	As usually with short-term steroid therapy
	Plasma exchange	7 exchanges every other day	Promotes recovery in patients not responding to high-dose IV steroids	Problems with venous access site (hematoma, bleeding, pneumothorax); Anemia (usually asymptomatic); Risk of infection and sepsis Fatigue, thrombosis, hypotension Citrate toxicity (perioral numbness) Heparin-associated thrombocytopenia	CBC before therapy and at regular intervals
Relapsing-remitting	Interferon-β 1b (Betaseron, Betaferon)	8 million IU subcutaneously every other day	Relapse rate reduction MRI benefits: reduces development of new lesions, delays increase in volume of lesions	Flulike symptoms Hepatotoxicity Leukopenia, anemia, thrombocytopenia Myalgias, depression, anorexia Menstrual disorders Hypocalcemia, injection site reaction, necrosis, neutralizing antibodies, pregnancy category C	CBC and LFT before therapy, every week in the first month, every month in the first 3 months, then every 3 months
	Interferon-β 1a (Avonex)	30 μg IM once weekly	Relapse rate reduction May delay progression of disability MRI benefits: reduces development of new lesions, delays increase in volume of lesions	Flulike symptoms Hepatotoxicity Anemia, eosinophilia Syncope Depression Nausea, dyspepsia, anorexia Neutralizing antibodies Injection site reaction, necrosis Pregnancy category C	CBC and LFT before therapy, every week in the first month, every month in the first 3 months, then every 3 months
	Glatiramer acetate (Copaxone)	20 μg SC daily	Relapse rate reduction Moderate, delayed MRI effects	Pain/edema at injection site Flushing Transient chest pain Transient dyspnea Transient eosinophilia Facial edema Palpitations Nausea, anorexia Anxiety Vasodilation Lymphadenopathy Pregnancy category B	None
	Interferon-β 1a (Rebif)	22 μg or 44 μg SC every other day	Relapse rate reduction MRI benefits: reduces development of new lesions, delays increase in volume of lesions Possible dose-related benefit in patients with more severe disease	Flulike symptoms Hepatotoxicity Anemia, granulocytopenia, lymphopenia Blocking antibodies Injection site reaction Pregnancy category C	CBC and LFT before therapy, every week in the first month, every month in the first 3 months, then every 3 months

Continued

TABLE 48-4

Therapeutic Options in MS—cont'd

MS TYPE	AGENT	DOSAGE	PROVEN BENEFITS	ADVERSE EFFECTS	MONITORING
Relapsing-remitting—cont'd	Intravenous immunoglobulin (IVIG)	0.15–0.2 g/kg IV every 2 months for 2 years	Relapse rate reduction One phase III trial to date	Hyperviscosity syndrome Aseptic meningitis Headaches Neutropenia Anemia Pseudohyponatremia Renal failure	IgA level before therapy Renal function tests before therapy and at regular intervals
Secondary progressive	Interferon-β 1b (Betaseron, Betaferon)	8 million IU subcutaneously every other day	Reduces disability regardless of relapse rate Relapse rate reduction MRI benefits	See above	See above
	Mitoxantrone (Novantrone)	5 or 12 mg/m^2 every 3 months Not to exceed 100–140 mg/m^2 cumulative lifetime dose (cardiac toxicity)	Relapse rate reduction Delays progression of disability MRI benefits	Cardiomyopathy Menstrual disorders Leukopenia Nausea, vomiting Urticaria, skin rash Acute leukemia Pregnancy category D	Echocardiogram to determine EF before initiating therapy and every 6 months, more frequently if cumulative dose to exceed 100 mg/m^2 ECG LFTs before each infusion CBC before each infusion

CBC, complete blood count; ECG, electrocardiogram; LFT, linear function tests; MRI, magnetic resonance imaging.

lesions, lesion volumes, and the percentage of new lesions that will evolve into T1 "black holes," although the MRI effect may be less pronounced compared to the interferon products, and is not apparent until the agent has been used for at least 6 months.[74–76] The EBM calculations for GA using the "proportion relapse free" data show an RRR of 10%, ARR of 7%, and an NNT of 14 over 2 years to increase the number of relapse free by one.

Combined Azathioprine and Interferon-β 1b. A small trial at NIH showed significant reduction in the number of contrast-enhancing lesions when azathioprine in an average maintenance dose of 2 mg/kg/day was added to interferon-β 1b in a study of six RRMS patients followed for a median period of 15 months. The addition of azathioprine may be considered in "treatment failure" cases, but this study was hampered by the small number of patients, no control subjects, and no blinding.[77]

Intravenous Immunoglobulin. Monthly treatment with low-dose (0.15 to 0.2 g/kg) intravenous immunoglobulin (IVIG) in RRMS patients resulted in fewer and less severe relapses in addition to slowing the accumulation of disability in a single randomized trial. The outcome was similar to that of injectable interferons.[78] This therapy is less accepted in the United States. More studies with larger number of patients and extended follow-up are needed to confirm these limited observations. Recent studies have failed to demonstrate that IVIG administration reverses long-standing deficits from MS and ON.[79–81] IVIG was also recently studied in acute ON and failed to demonstrate benefit on any of the outcome measures.[82]

Natalizumab. In late 2004, natalizumab was approved for the treatment of RRMS.[83] Natalizumab is a humanized α-4 integrin antibody that inhibits the migration of all leukocytes (except for neutrophils) to target organs. A phase 2 study established[84] that a 300-mg monthly dose reduced the number of gadolinium-enhancing lesions by 90% and the clinical relapse rate by over 50% compared to placebo. This study was followed by the AFFIRM and SENTINEL phase III studies. The AFFIRM study enrolled over 900 patients with RRMS; none of them had been on other approved immunomodulators for longer than 6 months. The annualized relapse rate at 1 year was reduced from 0.74 in the placebo group to 0.25 in the treated group (66% relative reduction, $p < 0.0001$). The proportion of relapse-free patients was 76% in the treated group, 53% in the placebo group. The number of enhancing lesions was reduced by 92%, and the number of new or newly enlarging T2 lesions was reduced by 80%. The proportion of patients without clinical and MRI activity was 46% in the natalizumab group, and 14% in the placebo group. In the SENTINEL trial, the combination of intramuscular interferon-β 1a and natalizumab was studied against IM interferon-β 1a and placebo in patients who had demonstrated an incomplete response (relapse suppression) to interferon therapy. The EBM calculations of the AFFIRM data based on proportion with relapses suggests an RRR of 49%, an ARR of 23%, and an NNT of 4 over 1 year to increase the proportion of relapse free by one. The SENTINEL data shows an RRR of 31%, an ARR of 17%, and an NNT of 6 over 1 year to increase the proportion relapse free. The original pilot trial data shows a RRR of 50% and an ARR of 19%, with an NNT of 5 over 6 months to increase the proportion relapse free. Based on these data, the FDA granted expedited approval of natalizumab on November 23, 2004.

On February 28, 2005, the medication was voluntarily withdrawn from the market by the sponsor (Biogen-Elan) after two cases of progressive multifocal leukoencephalopathy (PML) were reported in the SENTINEL study cohort.[85] Both patients were in the combined interferon and natalizumab arm. A third PML case was later identified from one of the phase III inflammatory bowel trials of this agent. At the time of writing this manuscript, natalizumab is still off the market. The natalizumab story has received significant media attention. Several consequences can be drawn from this failure. First, highly potent immunomodulators like natalizumab are best used by specialists in selected cases. A large number of prescriptions were written for natalizumab during its short 3 months on the market, including prescriptions by general practitioners. Widespread use of such medication in relatively stable cases of MS is not indicated. Second, the combination of potent immunomodulators may result in unpredictable adverse outcomes. Many MS experts anticipate that in the future MS therapies will need to be administered in combination to optimize therapeutic benefit. However, the exact effect of such combinations on the highly complex immune system is difficult if not impossible to predict. Furthermore, our inability to treat MS more effectively does not stem from the fact that we can not provide powerful immunosuppression, as evidenced by the autologous bone marrow transplantation studies. MS is a complex disease with a prominent inflammatory component; however, increasing evidence suggests that the neurodegenerative component of this illness may be independent of the inflammatory component, and is just as important, if not more important, from the standpoint of long-term disability. Third, in chronic diseases such as MS, a short 1-year trial, no matter how convincing the outcome may be, should not be considered sufficient to approve a medication, which will then be used in tens of thousands of patients on a "lifelong" basis. There clearly is a need for new and more effective medications for treating MS; however, clinical trials in chronic conditions are very difficult to sustain. To overcome this, many MS trials use primary MRI outcome measures, since inflammation and new lesion formation-related MRI markers respond more immediately to treatment; however, these markers do not correlate well with long term disability, as discussed earlier.

Summary of Recommendations for the Treatment of RRMS Patients. When making decisions about starting an MS patients on immunomodulators, several factors must be considered. One must realize that even though there are medications available for relapsing forms of MS, all the currently available therapies are only partially effective, the most reliable data is about short-term relapse rate reduction, and a relapse rate reduction does not necessarily translate into reduction of future disabilities. Natural history data clearly suggest that a subset of MS patients will do very well without treatment (see discussion about the Olmsted County cohort later); this information can be very useful when deciding about treatment in patients with a 5- or 10-year disease history and minimal disability (EDSS $\leq$ 2.0). In this patient group, a careful wait and see approach with appropriate monitoring is acceptable. Counseling of

newly diagnosed MS patients is of crucial importance, and it should usually include family members. Most patients have easy access to an abundance of frequently misleading information on the Internet, or from relatives and friends with MS. It is important to realize that every case is different; however, through the rational use of natural history data, clinical and MRI features of the specific case, and the clear understanding of the available clinical trial data, the clinician should be able to provide customized and relevant advice to patients and families. Considering that the treatments are only partially effective, the wishes of an educated patient constitute an important part in the decision-making process. Ultimately, the treatment decisions should remain individualized between the patients and their treating physicians, and the physician's role as an information clearinghouse and educator cannot be overemphasized in this process.

The three interferon products and GA represent the most commonly used MS immunomodulators in the United States; therefore, it is important to draw some practical conclusions about these agents. By now, several class I studies demonstrate that these agents are effective in reducing the relapse rate in RRMS over a 2- to 3-year period; the reduction is roughly 30% with the high-dose interferons and GA. The above-mentioned NNT data are also very useful for the clinician and the well-informed patient when making treatment decisions. There is evidence for a dose-response relationship among the interferon products, mostly from the EVIDENCE and INCOMIN studies. The double dose IM interferon-β 1a study did not show a dose-response relationship; this may be related to the fact that the increased dose was given with the same frequency as the standard dose. The injectable immunomodulators have incomplete evidence for efficacy in disability-based outcome measures. Many of the long-term extension studies suffer from several drawbacks, including open label unblinded design, significant dropout rate, and lack of control subjects; this is especially true for the GA extension data. The currently available few head-to-head comparison studies are also hampered with methodological issues; new comparative studies are under way. Overall, these agents remain partially effective in relapsing forms of MS; their long-term effects on reducing the clinically most important feature of MS—disability—still remains unclear.

Altering the Course of Secondary Progressive MS. Within 15 years of onset, almost 60% of RRMS patients will enter the secondary progressive phase of the disease. Treatment approaches aimed to affect the natural course of disease are available for these patients.

Interferons. Interferon-β 1b may have a beneficial effect on the overall outcome of SPMS and may also alter MR lesions,[86,87] but this question remains incompletely answered. In the placebo-controlled European study[88] of inteferon-β 1b in SPMS, the time to worsening was extended for treated patients. Treated patients were less likely to be wheelchair-bound and had fewer hospitalizations. Another analysis[89] of this study confirmed the benefits, though the dropout rate in this study was relatively high. The patients who responded best to interferon therapy were those who experienced relapses during their disease course. MRI monitoring suggested that the benefit on T2 lesion activity was seen early and persisted into the second half of the second year of treatment. T2 lesion load increased in placebo- but not interferon-treated patients in the first 2 years of treatment.[90]

Contrasting with these results, in another trial involving patients with SPMS,[91] both high dose (44 μg) and lower dose (22 μg) interferon-β 1a failed to change the primary outcome of time to disability worsening. Positive effects were seen on relapse rate and reduction of MRI activity, but the effect on disability did not replicate the European interferon-β 1b report. A combined analysis of the American and European trials concluded that continued relapse activity and more rapid progression over the preceding year (by >1 on the EDSS scale) are the best predictors of response.[92]

IVIG in Secondary Progressive MS. A recent European trial reported that IVIG did not have a significant impact on clinical and disability related outcome measures. IVIG did reduce the accumulation of brain atrophy in SPMS, but did not reduce the incidence of blood-brain barrier abnormalities. There was no statistically significant change on magnetization transfer MRI measurements; however, a trend for conservation of normal-appearing brain tissue was found.[93]

Overall Recommendations for SPMS. In general, as the evidence that interferons alter long-term disability is limited and controversial, we generally do not newly start SPMS patients on interferon products. In a subset of patients still having disabling relapses, interferon therapy may be offered to specifically reduce relapse rate. The data by Confavreux and associates, however, suggest that the EDSS in populations of SPMS patients continues to progress independent of relapses[94] once a "fixed" baseline level of moderate disability has been reached. Therefore, while interferons may reduce the relapse rate in SPMS, the rate of progression of disability may not be reduced by these treatments. More usually, SPMS patients are already on an injectable immunomodulator, and the question of whether it is worth continuing the therapy may come up, especially in patients who have a hard time tolerating these medications and feel that the side effects of the medications have a clear negative impact on their overall health. In these cases, we usually allow the patients to stop their medications. Just like in the RRMS cases, however, patient education about SPMS trials and realistic expectations about the treatment is a crucial element in the decision-making process. Understanding the patient's needs and fears and clarifying potential misconceptions constitute a very important role of the treating neurologist. In those patients who continue their interferon therapy, we must continue to follow them for toxicity and disease activity. Please also see the following discussion under mitoxantrone for recommendations on the potential use of that specific agent in SPMS.

Mitoxantrone. Mitoxantrone (Novantrone) is an anthracenedione chemotherapeutic agent licensed

. . .for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis (i.e. patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated in treatment of patients with primary progressive multiple sclerosis.

Significant benefits were observed in a group of SPMS patients as in a European phase III study of mitoxantrone.[95] It has also been used in combination with methylprednisolone.[96] Several clinical and functional outcome measures

were reported to stabilize or improve with every 3-month administration of this intravenous medication. Secondary MRI outcome measures, including enhancing lesion formation and overall T2 lesion load, were also better in the treated patients. The greatest concern regarding this medication is its cardiac toxicity: the cumulative lifetime maximum dose was established at 140 mg/m^2. Mitoxantrone can induce a seemingly dose-dependent cardiomyopathy, leading to potentially fatal congestive heart failure. We generally avoid exceeding a total lifetime dose of 96 mg/m^2 (8 doses of 12 mg/m^2). Patients receiving mitoxantrone should also be monitored every 3 months with echocardiograms or MUGA (multiple gated acquisition) scans to determine the ejection fraction. Reduction in the ejection fraction should prompt discontinuation of this therapy.

Besides the cardiac side effects, mitoxantrone may cause menstrual irregularities or overall ablation of the menstrual cycle, which may be permanent. In a review of the literature, Ghalie[97] estimated the risk of mitoxantrone therapy-related acute leukemia in MS patients at 0.05% to 0.1%; in an international registry of MS patients taking mitoxantrone, the risk of leukemia seems somewhat higher. This therapy has been approved by the FDA for treatment of SPMS, but no peer-reviewed full report of the MIMS study had been published until 4 years after the initial report in an abstracts form. The study[98] showed a treatment effect in RRMS and SPMS patients with "recent rapid worsening." The study had a high dropout rate and a small sample size. Most patients (74%) had relapses in the preceding 2 years, suggesting this cohort mostly includes worsening RRMS or PRMS patients, in whom a positive treatment effect is expected; however, it does not mean that for classic SPMS patients who no longer have relapses the study outcome is applicable, and it is especially not applicable to PPMS cases. The primary outcome measure was a composite score comprised of five clinical measures: change in EDSS at 2 years; change in Ambulation Index at 2 years; change in the baseline standardized neurological status at 2 years; number of relapses requiring corticosteroid treatment; and time to first relapse. Seventy-seven percent completed 24 months of follow-up. At 24 months, benefit was reported in all five components of the composite measure for both active treatment arms, with the overall greatest benefit noted between placebo and the group receiving mitoxantrone at a dose of 12 mg/m^2. The magnitude of the effect on EDSS was rather modest (mean EDSS change for high-dose mitoxantrone, –0.13 [SD 0.90] versus +0.23 [SD 1.01] in the placebo group). The MRI results of the MIMS trial were published in 2005 and are frankly disappointing.[99] In a subset of 110 patients (out of 194 in the trial overall), the 12 mg/m^2 dose failed to reach a significant difference from placebo as measured by the primary MRI outcome (total number of scans with gadolinium-enhancing lesions). The 12 mg/m^2 dose reduced the number of T2-weighted lesions at month 24 ($p = 0.027$) and showed a trend at month 12 ($p = 0.069$). The number of active MR lesions showed a trend toward reduction in the 12 mg/m^2 group only at month 24 ($p = 0.054$).

Overall, the limited evidence to date supports the conclusion that mitoxantrone reduces relapse frequency and MRI evidence for blood-brain barrier disruption in patients with *very active* MS. *The benefit for patients with relapse-independent progression is uncertain at best.* From the MIMS results, one would need to treat 11 patients with secondary progressive multiple sclerosis for 2 years to prevent one person from worsening by 1.0 EDSS point. This modest benefit must be carefully examined in light of the significant risk for toxicity.

Therapy of PPMS. Unfortunately, for classical PPMS cases that present with insidious progression of usually myelopathy symptoms, none of the currently available treatments offer any clear benefit. The PROMISE trial, in which over 900 PPMS patients were treated with GA, was terminated early owing to lack of effectiveness. The results of this trial have not yet been published. A small study with intramuscular interferon-β 1a was also negative.[100] Currently a large trial is under way with rituximab in CSF OCB-positive PPMS patients. Until we clearly understand the pathophysiology of slow progression in MS, it is unlikely that we will find a treatment that has an important impact on this form of MS. Symptomatic treatment modalities, including physical and occupational therapy, are very important, yet frequently overlooked in this patient population.

Other Immunomodulator Therapies. Cyclophosphamide is an alkylating agent that has indiscriminate cytotoxic effects on rapidly dividing cells, including lymphocytes, making it a potent immunosuppressant. Several studies have claimed a beneficial effect in both relapsing and progressive patients. Because one of the major studies included ACTH, IV methylprednisolone is sometimes given with the cyclophosphamide. Other trials have not found a favorable effect. Because of the inconsistent results, high potential for serious side effects, and adverse reactions, including hemorrhagic cystitis and malignancy, cyclophosphamide is not widely used. Some centers, however, use cyclophosphamide in patients with aggressive disease in whom more conventional treatments have failed.

Azathioprine, a purine analog antimetabolite, has marginal efficacy in the treatment of MS. A meta-analysis of all blinded, placebo-controlled studies confirmed a slight benefit of slowed progression and less frequent relapses.[101] The toxicity of azathioprine and its slow onset of action have prevented its widespread use. Besides the liver toxicity and hematological effects, the induction of malignancies has been a concern. One retrospective study did not find an increased incidence of cancer in MS patients treated with azathioprine, but this remains a potential risk.

Methotrexate is a folate antagonist that is effective in rheumatoid arthritis. Weekly low-dose oral methotrexate was found to delay upper extremity dysfunction in SPMS patients, although it had no effect on the more traditional measures of disability, including the Expanded Disability Status Scale (EDSS).[102]

The use of cyclosporine in the treatment of MS has been evaluated in three clinical trials, none of which have demonstrated a convincing benefit. In addition, side effects such as hypertension and elevation of creatinine were common.

Numerous additional therapies have been tested, and many others are undergoing evaluation. The antiherpesvirus drug acyclovir has been shown to reduce relapse frequency in a small prospective trial. Total lymphoid irradiation was found to slow the chronic progression of MS,

but because this approach precludes the later initiation of immunosuppressant drugs and may be associated with a higher mortality rate, it is not widely used. Cladribine is a nucleoside derivative that was found to decrease relapse rate and slow the progression in patients with SPMS in an initial investigation.[103] The drug is better tolerated than other parenteral immunosuppressants, although bone marrow suppression is a risk. In a more extensive clinical trial,[104] cladribine therapy did not change disability scores, but significant reduction in enhancing lesions and overall T2 lesion burden was observed with higher dose treatment. A study of a small number of patients treated with autologous stem cell transplantation[105] suggested possible clinical stabilization or minor improvement over a 15-month period of follow-up in both secondary and primary progressive MS. The induction chemotherapy (BEAM regimen) resulted in one fatality in this trial; similar incidences are known in patients undergoing this procedure. The small number of patients and the different methods used (some patients received $CD34^+$ selected graft) makes the interpretation of this data very difficult. Trials with higher number of patients under standardized circumstances are needed to verify the validity of these observations.

Symptomatic Treatment of Existing Disabilities

Spasticity. Spasticity is common even in patients with only minimal weakness (Video 3, Spastic Gait). It is usually prudent to begin treatment of mild spasticity with a stretching program. A randomized controlled crossover trial[106] of physical therapy (8-week blocks of therapy twice a week, for 45 minutes per session) showed significant benefit on several outcome measures related to improved mobility. No apparent differences were observed between home-based or hospital-based therapy. The addition of an evening dose of benzodiazepine may help relieve extensor spasms and clonus that may interfere with sleep. As spasticity worsens, it becomes necessary to use baclofen. Doses should be escalated slowly to prevent the occurrence of overt side effects, and up to 120 mg/day may be required. Although baclofen is well tolerated in most patients, limiting side effects such as sedation and increased muscle weakness may occur, and rarely a paradoxical increase in spasticity is noted. Liver enzyme elevation and nonconvulsive status epilepticus presenting as encephalopathy have also been reported in association with baclofen. Abrupt withdrawal of baclofen may result in hallucinations or seizures, making it necessary to taper doses. Despite symptomatic improvement, antispasticity measures may not increase function or independence. In paraplegic patients with severe spasticity and intolerance to the required oral dose, intrathecal baclofen delivered by a subcutaneously implanted pump allows a much smaller dose and is often effective in alleviating intractable spasticity and may lessen urinary urgency. Tizanidine seems to be as effective as baclofen, although it may be associated with more fatigue. Dantrolene has been used for spasticity, although the therapeutic window is small.

Fatigue. For treating fatigue, medications are only partially effective. Amantadine at 100 mg twice a day is the standard initial treatment, although pemoline 37.5 mg daily is also superior to placebo. A recent, small pilot study by the Mayo group suggested that high-dose aspirin (1300 mg/day) may sometimes be effective in the treatment of MS-related fatigue.[107] This finding needs to be confirmed by a second, larger trial, however. The stimulating effects of the selective serotonin reuptake inhibitors may also be somewhat effective in combating MS-related fatigue. Modafinil, a medication approved for the treatment of narcolepsy, has also been used with good success. Often, however, patients need to limit activities and schedule rest periods.

Paroxysmal Symptoms of MS. Paroxysmal symptoms are highly responsive to medical treatment. A small dose of carbamazepine is often very effective. If not tolerated, several alternative medications may be tried, including phenytoin, acetazolamide, baclofen, and gabapentin. In addition, misoprostol has been claimed to be effective in MS-related trigeminal neuralgia. After about 1 month of treatment, a periodic attempt at tapering off these medications is a reasonable approach because these symptoms usually remit.

Seizures in MS are treated no differently than in non-MS conditions.

Heat Sensitivity. Heat sensitivity may require avoidance of precipitating activities, but this depends on the nature of symptoms and the situation in which they occur. If the precipitating activity cannot be avoided, a cooling jacket may be an option. A potassium channel blocker, 4-aminopyridine, improves temperature sensitivity in some patients but occasionally causes seizures or disturbing paresthesias.

Action Tremor. Action tremor is a common disabling symptom (Video 14, Tremor with Ataxia). Unfortunately, it is often only marginally amenable to medical therapy. Clonazepam may offer some relief, but tolerance frequently develops, necessitating increasing doses. Isoniazid and carbamazepine have also been found marginally beneficial. One clinical trial showed ondansetron to reduce tremor-related disability. Anecdotal reports suggest that gabapentin may be partially effective. Improvements in stereotactic neurosurgery have made thalamotomy a legitimate option in those whose disability is mainly due to tremor and not ataxia.

Cognitive and Memory Problems. Cognitive problems can also be seen in MS patients. These symptoms are generally not very severe; however, in some patients these may be one of their subjectively most bothersome complaints. It is important to make sure that such complaints are not depression related, as mood disorders are otherwise rather common in MS, and may explain the subjective cognitive impairment. While it is not FDA approved for the treatment of MS related cognitive dysfunction, in a placebo controlled, randomized, 24-week long study of donepezil in 69 patients, significant improvement was found on the Selective Reminding Test (SRT).[108] This improvement was independent of MS subtype, gender, age, reading ability, and baseline SRT results. The patients did not improve on other cognitive scales, but they were twice as likely to report cognitive improvement.

Dysesthetic Pain. Dysesthetic pains are difficult to control but sometimes respond to tricyclic antidepressants, carbamazepine, or baclofen. Gabapentin, tramadol, and duloxetine may also be effective. Standard analgesics are not often useful in MS-associated pain, and narcotics should be avoided in the treatment of chronic pain.

Emotional incontinence may be amenable to a low dose of a tricyclic antidepressant (Video 10, Dysarthria).

Symptoms of Bladder Dysfunction. Symptoms of a hyper-reflexic bladder (urgency, frequency, and urge incontinence) are often manageable with anticholinergics such as oxybutynin, propantheline, or imipramine. A flaccid bladder can sometimes be aided by bethanechol, although intermittent self-catheterization is more often needed. Symptoms that suggest urinary retention (a feeling of incomplete emptying, frequency, hesitancy, or a need to apply pressure to the lower abdomen to urinate) should prompt evaluation with urinalysis and a post-void residual urine measurement. Residuals in excess of 15 mL are abnormal; and if they are above 50 mL, consideration should be given to urological consultation for more thorough investigation and to blood chemistries to determine urea and creatinine levels. Detrusor-sphincter dyssynergia, diagnosed by cystometrography, is treated with anticholinergics, sometimes with the addition of an α-1 blocking agent (terazosin) or intermittent catheterization. It is important to reassess bladder function periodically, and residual urine volumes should be monitored if there are any persistent changes in function or symptoms. Intermittent catheterization should be considered when post-void residuals reach 100 mL. A chronic indwelling urinary catheter should be avoided if reasonably possible. It is usually not necessary to use antibiotics prophylactically in the prevention of urinary tract infections. Urinary calculi may be prevented by acidification of the urine with cranberry juice.

Bowel Dysfunction in MS. Constipation can usually be managed with bulk laxatives and stool softeners. More severe cases may require osmotic agents, bowel stimulants, anal stimulation, suppositories, or enemas. Bedridden patients may develop fecal impaction unresponsive to these measures and require manual disimpaction. Fecal incontinence can be minimized by adherence to a schedule for bowel movements. Fiber supplementation may be of some benefit even in these cases.

Sexual Dysfunction in MS. The clinician should determine the precise nature of any sexual dysfunction in patients with MS. Physical difficulty from spasticity may be alleviated by premedication with baclofen, and a fast-acting anticholinergic such as oxybutynin may calm urinary urgency. Sexual dysfunction should not be automatically attributed to MS. It may be necessary to investigate hormonal levels and to obtain urological or gynecological consultation. Manual lubrication with gel is a ready solution to vaginal dryness. Erectile dysfunction responds very well to sildenafil. Less frequently, vacuum devices, intracavernous injections of papaverine (or combinations of papaverine, prostaglandins, and epinephrine; triple agent), or penile implant are also used in the treatment of erectile dysfunction. Thalamotomy or thalamic stimulation may provide some short-term clinical benefit to patients disabled by appendicular cerebellar tremor and ataxia. The benefits on disability and quality of life are much less clear, however, and the early benefits may wain within 1 to 3 years.[109,110] Further studies are needed to clarify how best to select patients for these ablative and stimulation treatment interventions.

General Recommendations for MS Patients. It is advisable for MS patients to attain good health habits, including proper diet and fitness. Smoking, excess alcohol intake, and obesity should be avoided. Exercise can help maximize function by increasing and maintaining joint mobility, strength, and stamina; may promote improved sleep hygiene; and may reduce the severity of fatigue. Physical and occupational therapy can play an important role in regaining independence. Canes, walkers, and wheelchairs or scooters may be needed to maintain safe mobility. Hand controls can be installed in automobiles for patients with lower extremity dysfunction. In debilitated, immobilized patients, periodic shifts in posture to change weight-bearing regions and air or water mattresses prevent bedsores. Passive range of motion exercises prevent contractures. When ventilatory dysfunction occurs, it should be evaluated and activity schedules should be appropriately modified.[111]

Special Considerations during Pregnancy. Before initiation of any drug in a woman of reproductive age, the potential for teratogenicity must be discussed. In general, immunomodulator therapy should be avoided if one is planning a pregnancy. The treatment of acute exacerbations is unchanged during pregnancy, although one might have a higher threshold for treatment. Both corticosteroids and plasma exchange are relatively safe during pregnancy. None of the drugs used to alter the disease course, however, should be used during pregnancy. Interferon-β drugs should be stopped 2 to 3 months before planning pregnancy. Interferons are associated with an approximately 39% likelihood of abortions. This is close to eight times higher than the usually quoted approximately 5% spontaneous abortion rate in women. Interferon-β use is also associated with lower birth weight.[112] The cytotoxic immunosuppressants have teratogenic effects. The effects of many of the other drugs are unknown. It is best if these drugs are stopped several months before a planned pregnancy.

PROGNOSIS AND FUTURE PERSPECTIVES. Because most information on the prognosis of MS is reported in terms of the EDSS, it is important to have some understanding of this scale. The EDSS is a 10-point scale, with each increase representing worsening symptoms of function. The score is derived from severity scores in each of six systems as well as ambulation and work ability. A score of 0 means no signs or symptoms; 1 to 3 represent mild disability with no or minimal impairment of ambulation; 3.5 to 5.5 refer to moderate disability and impairment of gait; the need for a cane to walk one-half block (100 m) receives a score of 6; an EDSS of 8 refers to the need for a wheelchair and effective upper extremity function; an EDSS of 10 refers to death related to MS.

MS has a highly variable outcome, ranging from asymptomatic to fulminant with death ensuing in a matter of months. Autopsy series have estimated that unsuspected MS may occur in as many as 0.2% of the population. Even when symptomatic, MS may cause only nuisance symptoms. Benign MS, when defined as unrestricted ambulation or EDSS of 3 or less 10 years after onset, accounts for about one third of cases. However, many of these patients acquire more disability later. When considering all patients with MS, Weinshenker found that 15 years after onset, 80% had EDSS worse than 3, 50% had reached EDSS of 6 or more, 10% were at EDSS 8, and 2% had died. The percentage of patients with initially RRMS who develop SPMS increases steadily with disease duration.[113] At 10 years, 40% to 50% have continual deterioration;

after 25 years, approximately 80% have slow progression. In the most recent study published about the Olmsted County MS prevalence cohort consisting of 161 patients, the mean change in EDSS over 10 years was 1 point, and only 20% of patients had a change larger than 2.0 points.[114] Eighty-three percent of the patients with mild symptoms (EDSS < 3.0) were still ambulatory without cane 10 years later. Among the patients with an EDSS of 3 to 5, 51% were using a cane; in the 6 to 7 EDDS range, 51% were wheelchair bound. Strong predictors for the outcome were not identified in this study. Population-based studies with complete ascertainment can effectively remove the bias of a referral practice, which is inherently biased towards the more active and more serious cases. These studies also provide some much needed balance to the "heavily skewed for recent disease activity" clinical trial experience.

From the most recent extensions to the Olmsted County MS cohort studies conducted by the Mayo group, several conclusions can be drawn. The number of relapses in the first year of the disease do not predict long term outcome. The time to disability is not influenced by ongoing relapses once patients achieve an apparently permanent degree of moderate disability (EDSS 3.5). Overall, 80% patients who are still classified as RRMS into their second decade of disease continue to do well for 15 to 20 years with limited permanent disability. Patients doing extremely well (EDSS $\leq$ 2.0) after 10 years of MS generally do well in the next decade. However, very rarely patients doing well even for 2 to 3 decades may develop severe late disability. We advise that neurologists share these findings with patients who are in periods of prolonged remission during the discussions about the merits of beginning disease-modifying agents.

Natural history studies have identified several prognostic indicators that predict outcome to a limited extent. Factors associated with a better prognosis (slower accumulation of disability, longer time before chronic progression) include young age at onset, female gender, RR course (as opposed to PPMS), initial symptoms of sensory impairment or ON, first manifestations affecting only one CNS region, high degree of recovery from initial bout, longer interval between first and second relapses, low number of relapses in the first 2 years, and less disability at 5 years after onset (both EDSS and number of systems affected—sensory, motor, sphincter, brain stem, vision, cerebral). Despite the indolent nature, a PP course is the worst prognostic factor, with the median time to reach EDSS 6 of only 6 years, compared with approximately 20 years in RR patients. Men and patients with an older age at onset are more likely to have PPMS.

The survival of MS patients is only slightly below expected. Seventy-six percent of patients are alive 25 years after onset, which is 85% of that seen in age- and sex-matched control subjects.[35] MS is rarely the direct cause of death. Complications of MS such as pneumonia, pulmonary emboli, aspiration, urosepsis, and decubiti are responsible for 50% of deaths. Most of the other deaths are from heart disease, cancer, cerebrovascular disease, and trauma. Suicide is the only cause of death that is overrepresented among these cases. The suicide rate among MS patients may be as high as two to seven times that of non-MS persons.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO) is an uncommon neurological illness characterized by the occurrence of optic neuritis and myelitis. The names Devic's syndrome, Devic's disease, and NMO are often used interchangeably, although the first name encompasses all patients who fit the preceding definition and the second and third should only be used to refer to those patients presumed to have a distinct disorder. The term *opticospinal MS* is often used in the Far East to denote patients with exclusive or predominant involvement of optic nerves and spinal cord, encompassing most patients with Devic's syndrome. Devic's disease (NMO) may be a monophasic illness, or may show a relapsing-remitting course.[115] It is the first inflammatory demyelinating disease with a known serum marker, the NMO-IgG antibody.

PATHOGENESIS AND PATHOPHYSIOLOGY. Devic's syndrome may occur with ADEM, autoimmune disorders (e.g., systemic lupus erythematosus), MS, and possibly viral infections. Also, patients with Devic's disease may have other coexisting autoimmune conditions. Classically, acute spinal cord lesions demonstrate diffuse swelling that extend over several levels or involve nearly the entire cross section of the cord. Acutely, there is destruction with dense macrophage infiltration involving white and gray matter, loss of myelin and axons, and lymphocytic cuffing of vessels. In chronic lesions, the cord is atrophic and necrotic, occasionally with cystic degeneration and gliosis. In the absence of perivascular cuffing, these extensive lesions resemble infarctions. The prominent spinal cord swelling in the confines of the restrictive pia presumably may raise intramedullary pressure, leading to the collapse of small parenchymal vessels, further propagating tissue injury. Proliferation of vessels with thickened and hyalinized walls similar to that seen after infarction or other extensive injury may occur.[116] Less fulminant lesions may coexist and are much more typical of inflammatory demyelination. The optic nerve lesions often involve the chiasm. Even though NMO is usually restricted to the optic nerves and spinal cord, one may see classic MS like lesions in up to 10% of cases, and hypothalamic lesions have also been described in approximately 10%. The newly discovered serum marker, NMO-IgG has a sensitivity of 73% and specificity of 91%.[117] The discovery of this novel immune marker also clarified that most if not all cases of "opticospinal MS" reported in the Japanese literature are also cases of NMO. To the surprise of the MS research community, the antigen is neither myelin nor neuron related: it is the aquaporin-4 water channel, a component of the dystroglycan protein complex located in astrocytic foot processes at the blood-brain barrier.[11] NMO thus may represent the first example of a novel class of autoimmune channelopathies.

EPIDEMIOLOGY AND RISK FACTORS. Devic's syndrome occurs in patients of varied ages (range, 1 to 73 years). The mean age at onset of monophasic Devic's syndrome is 27, whereas relapsing NMO (see later) tends to occur in an older age group (mean age at onset of 43). Monophasic Devic's syndrome affects males and females equally, whereas relapsing NMO affects females predominantly (F:M, 3.8:1). One third of patients have a preceding

infection within a few weeks of neurological symptom onset. Most commonly this is a nonspecific upper respiratory tract infection, flu, or gastroenteritis. The most common specific infections preceding the development of Devic's syndrome are chickenpox and pulmonary tuberculosis. Devic's syndrome has also followed vaccination for swine flu and mumps. Only a few instances of a possible familial occurrence of Devic's syndrome have been reported, and in one of these families, a unique mitochondrial mutation was found. Devic's syndrome is said to be more common in Japan and East Asia, although even there it is uncommon (less than 5 per 100,000). Three cases have been described in the literature with familial occurrence of Devic's disease in the Far East. In a genetic study, HLA-DPB1*0501 was more frequently associated with "opticospinal MS," whereas HLA-DPB1*0301 is the most strongly associated allele with conventional MS in the Japanese.

CLINICAL FEATURES AND ASSOCIATED FINDINGS. Symptoms of ON and myelitis develop over hours to days and are often preceded or accompanied by headache, nausea, somnolence, fever, or myalgias. Continued progression of symptoms over weeks or months occasionally occurs. Most patients (greater than 80%) develop bilateral optic neuritis. Bitemporal or junctional field deficits, indicating chiasm involvement, are sometimes present early in the course of the ON. Visual loss is often accompanied by periocular pain, and myelitis onset is sometimes heralded by localized back or radicular pain. Lhermitte's sign is common. Severe degrees of neurological deficits are usual, and the degree of recovery is variable.

Approximately 35% of NMO patients have a monophasic illness, 55% develop relapses usually limited to the optic nerves and spinal cord (relapsing NMO or opticospinal MS), and rarely patients have a fulminantly progressive course without relapses or a course typical of MS.[115] According to a study conducted at the Mayo Clinic,[115] patients with a monophasic course usually presented with rapidly sequential events (median, 5 days) with only moderate recovery. Patients showing characteristics of the relapsing form of Devic's had a median interval of 166 days between index events, followed within 3 years by clusters of severe relapses isolated to the optic nerves and spinal cord. Most relapsing patients developed severe disability in a stepwise manner. Approximately one third died from respiratory failure. Predictors of a relapsing course in NMO[118] include longer inter-attack intervals (relative risk [RR]: 2.16 per month increase), older age at onset (RR = 1.08 per year increase), female sex (RR = 10.0), and less severe motor impairment with sentinel myelitis event (RR = 0.48 per severity scale point increase). Autoimmune disease history (RR = 4.15), higher attack frequency in first 2 years (RR = 1.21 per attack), and better recovery following index myelitis (RR = 1.84 per point) are associated with increased mortality rate. Features of NMO distinct from "typical" MS included normal initial brain MRI, more than 50 cells/μL in CSF with polymorphonuclear predominance, and lesions extending over three or more vertebral segments on spinal cord MRI. Relapsing NMO is often associated with autoimmune disorders, most commonly systemic lupus erythematosus. These patients also frequently have an elevated erythrocyte sedimentation rate and nonspecific elevation of autoantibodies, including antinuclear antibodies, anti-ds-DNA, and antiphospholipid antibodies. Tonic spasms and neuropathic lower extremity pain are common sequelae to the spinal cord damage. Symptoms referable to brain stem lesions (nystagmus, ophthalmoparesis, and vertigo) can occur in these patients as well.

DIFFERENTIAL DIAGNOSIS. The differential diagnoses for Devic's syndrome includes MS, ADEM, pulmonary tuberculosis, and viral infection (especially in the immunocompromised patient). In patients with an apparent affected family member, consideration should be given to mitochondrial disease. Relapsing NMO should raise the suspicion for associated autoimmune disorders. Because Devic's syndrome can occur in persons older than age 60, when an unrelated ischemic optic neuropathy could occur, and because isolated or recurrent myelopathy may precede the ON, additional consideration must be given to spinal cord compression, spinal cord tumor, and spinal arteriovenous malformation (AVM) or dural fistula.

EVALUATION. Imaging is needed to exclude structural lesions and provide information on the pathological process. Optic nerve or chiasm enlargement, T2-weighted signal changes, and enhancement may be seen on head MRI during the acute phase. Increased T2-weighted signal in the medulla is not uncommon and usually represents extension of high cervical lesions. Spine MRI characteristically shows cord swelling, signal changes, and enhancement extending over at least three levels (Fig. 48-4). This appearance may resemble a spinal cord tumor, prompting consideration for biopsy.

On magnetization transfer (MT) MRI, no significant difference was found on normal-appearing white matter of Devic's patients and control subjects, whereas MS patients had a significantly lower MT ratio peak and histogram average.[119] T1 hypointense lesions in the cord and linear lesions that cross over more than two segments are more suggestive of Devic's disease.

An occasional patient may need prone and supine myelography to exclude a spinal dural-based AVM. Laboratory investigations reveal an elevated erythrocyte sedimentation rate in one third, positive antinuclear antibodies in nearly one half, and occasionally other autoantibodies (e.g., thyroperoxidase antibodies).[39] It is reasonable to exclude syphilis, Lyme disease, and human immunodeficiency virus by laboratory testing. In a few patients with the Far East variety of Devic's disease, hyperprolactinemia was described predominantly with optic nerve involvement. A chest x-ray helps to exclude pulmonary tuberculosis and sarcoidosis. CSF examination is an essential part of the evaluation for Devic's syndrome, and repeated studies are sometimes necessary to ensure that there is no infection in that the CSF findings are sometimes atypical for inflammatory demyelination.

A marked pleocytosis is often present, sometimes exceeding 100 cells. Moreover, neutrophils are commonly seen in CSF and may predominate, a situation virtually unknown in MS.[120] The protein concentration is often very high and in 41% exceeds 100 mg/dL. Anti-MOG antibodies are the predominant autoantibody detected in CSF; anti-MBP or anti-S100β antibodies are less frequently

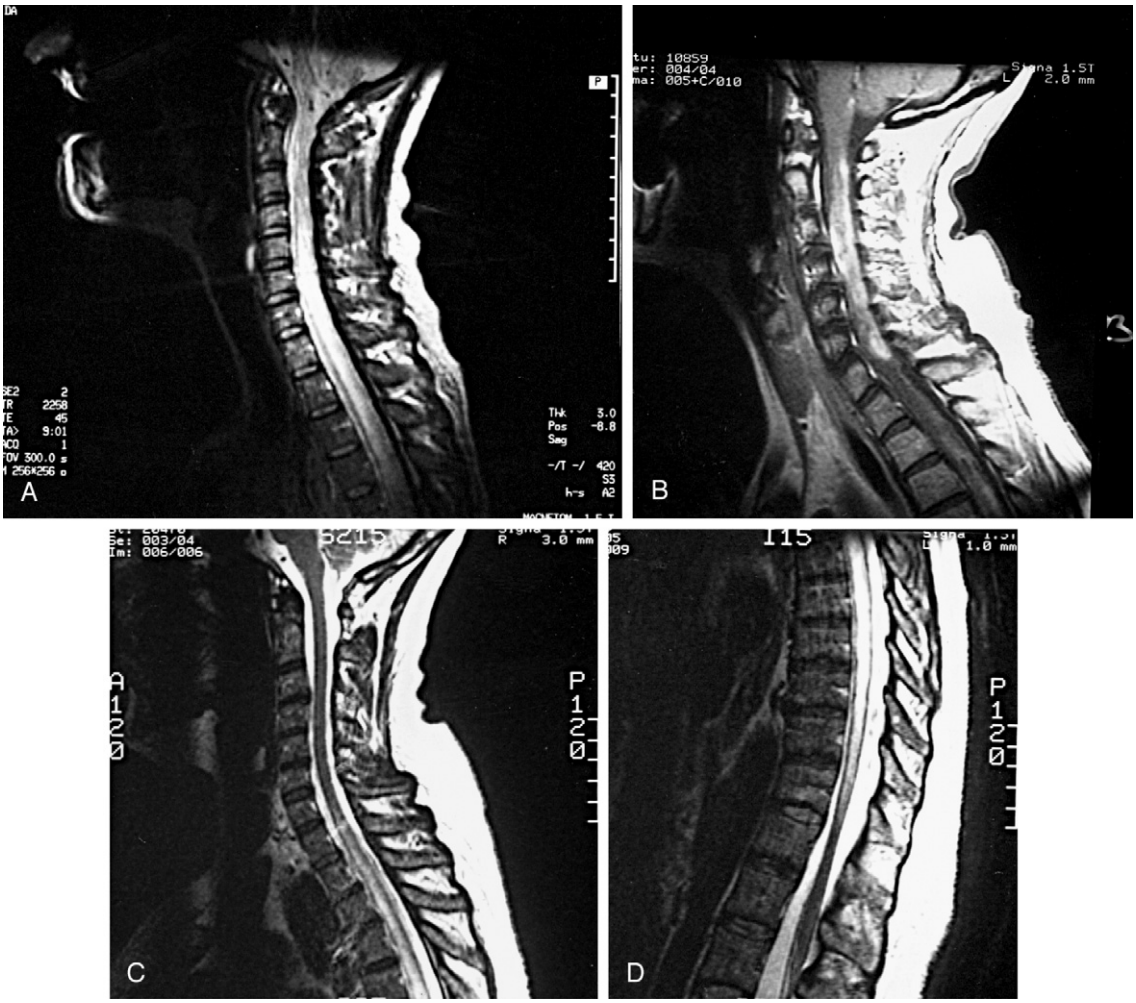

Figure 48-4. Spine MRI of patients with relapsing NMO. **A,** Sagittal T2-weighted image of the cervical spine showing cord expansion and signal abnormalities extending through the cervical and upper thoracic cord. **B,** T1-weighted sagittal MRI showing cord swelling and extensive gadolinium enhancement from C1 to C7. Further enhancement is seen in the upper thoracic area. **C** and **D,** Sagittal T2-weighted spine MRI showing a diffuse hyperintense lesion extending from T1 to the conus.

seen. Despite the intense inflammatory response, OCBs are conspicuously absent in the majority, being present in fewer than 20% of patients. CSF serology for the herpesvirus family (HSV types 1 and 2, VZV, EBV, and CMV) is important, and polymerase chain reaction testing should be done in cases suggestive of viral infection (immunocompromised patients).

MANAGEMENT. Patients with acute or subacute Devic's syndrome may respond to corticosteroids (e.g., intravenous methylprednisolone). They may respond to plasma exchange even when intravenous methylprednisolone does not produce significant improvement. Attempts at preventing relapses and the subsequent disability are often disappointing even with the use of immunosuppressive agents. The classic injectable immunomodulators used in MS are insufficient to reduce the relapse rate in relapsing NMO. Most commonly, a combination of azathioprine and prednisone is used for secondary prevention. Other agents including mycophenolate mofetil, IVIG, and mitoxantrone have been described to be effective in some cases. A small study of rituximab, a humanized anti-CD20 antibody showed a siginifcant reduction in the relapse rate of 8 patients, making 6 of 8 relapse free.[121] A large multicenter study of rituximab in NMO is in the planning stages.

Supportive care is important in the management of NMO. These patients are prone to many complications and require measures to prevent deep venous thrombosis and pulmonary embolism, urinary tract infection, decubiti, and contractures. Mechanical ventilation may be needed either temporarily or permanently. Patients with monophasic Devic's syndrome generally have simultaneous or rapid onset of the ON and myelitis (interval usually less than 1 month). Although some have significant residual disability, many recover remarkably and have little or no permanent deficits. A history of previous vague neurological symptoms or definite demyelinating events is predictive of future relapses, either typical of MS or relapsing NMO. Those patients destined for recurrent myelitis and ON have a longer interval between the onsets of myelitis and ON. The vast majority of patients with relapsing NMO have very aggressive disease with frequent and severe exacerbations and a poor prognosis.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

ADEM is a monophasic inflammatory demyelinating disorder that characteristically begins within 6 weeks of an antigenic challenge such as infection or immunization. It occurs more often in the young and causes the rapid development of multifocal or focal neurological deficits. Perivenous inflammation, edema, and demyelination are the pathological hallmarks of ADEM, although these lesions commonly enlarge and coalesce, forming lesions pathologically indistinguishable from MS. Moreover, perivascular changes typical of ADEM are common in patients with MS. There is considerable overlap in the epidemiological, clinical, CSF, imaging, and pathological features between ADEM and MS, often making it difficult to distinguish between the two with reasonable confidence when encountering patients with a single demyelinating event.

PATHOGENESIS AND PATHOPHYSIOLOGY. ADEM closely resembles the experimental allergic encephalomyelitis animal model of MS (EAE) both clinically and pathologically, and is most likely due to a transient autoimmune response toward myelin. The occurrence of ADEM after vaccination with the rabbit spinal cord preparation of rabies virus led to the discovery of EAE. Infections and non-CNS-containing vaccinations may induce ADEM by molecular mimicry or by activating autoreactive T-cell clones in a nonspecific manner. Lymphocyte reactivity toward MBP has been identified in blood and CSF from patients with ADEM, but its absence in others indicates a role for other antigens. Increased peripheral blood γ interferon-producing T cells have been described in ADEM.

EPIDEMIOLOGY AND RISK FACTORS. ADEM can occur at any age but perhaps because of the higher frequency of immunization and exposure to new antigens; it is most common during childhood. Unlike MS, both sexes are affected with equal frequency. No association has been noted with pregnancy.

ADEM has been reported to follow a number of different immunizations, usually within 6 weeks, including those for pertussis, diphtheria, measles, mumps, rubella, influenza (postvaccination ADEM), tetanus, and yellow fever. In addition, there are case reports of ADEM following hepatitis B vaccination. However, the only epidemiologically and pathologically proved association is with rabies vaccination, which also causes demyelinating peripheral neuropathies. The original Pasteur rabies vaccine, prepared in rabbit spinal cord, was associated with an incidence of ADEM of approximately 1 per 3000 to 1 per 35,000 vaccinations and is no longer in use. A later vaccine, made in duck embryo, which contains little neural tissue, carries a risk for ADEM of 1 per 25,000 vaccines. The use of human diploid cell lines, which contain no nervous system tissue, for the production of rabies vaccine has virtually eliminated the risk of ADEM. The association of bee stings with ADEM has also been reported.

Parainfectious ADEM usually follows onset of the infectious illness, often during the recovery phase, but because of the latency between pathogen exposure and illness it may precede clinical symptoms of infection or the two may occur simultaneously. The most commonly reported associated illness is a nonspecific upper respiratory tract infection. There have been a vast number of specific infections associated with ADEM, such as virus infections (including rubella, mumps, VZV, EBV, CMV, influenza, coxsackievirus, and hepatitis C) and infection with *Mycoplasma, Borrelia burgdorferi,* and *Leptospira.* Measles carries the highest risk for ADEM of any infection, occurring in 1 per 400 to 1 per 1000 cases. Although ADEM has been reported in association with measles immunization, the risk is far lower than the risk of acquiring measles and its neurological complications.

CLINICAL FEATURES AND ASSOCIATED DISORDERS. A prodrome of headache, low-grade fever, myalgias, and malaise often precedes the onset of ADEM by a few days. In a German study of 40 cases,[122] the most frequent clinical signs were motor deficit (80%), followed by sensory deficits, brain stem signs, and cerebellar signs. CSF findings were variable; normal results were present in up to 20% of patients. Oligoclonal bands were positive in over 60%. Almost all patients improved during the acute phase of the disease. Of the 26 patients with the final diagnosis of ADEM, 21 had minor or no symptoms, 2 died, the rest had moderate symptoms. Compared to MS patients, the ADEM patients were older, and more often had a preceding infection, clinical signs of brain stem involvement, a higher CSF albumin fraction, and infratentorial lesions. Neurological symptoms develop rapidly in the acute phase and are commonly associated with encephalopathy, stupor, coma, meningismus, and seizures. Peak severity occurs within several days, and recovery may begin soon afterward. Occasionally, ADEM may evolve over a few months and there may be a second clinical deterioration or subacute progression for a time. In these unusual cases, the distinction from MS is difficult. Three recent large retrospective series and an accompanying editorial have highlighted that there remain no clinical or laboratory features that accurately allow one to predict which adult or pediatric ADEM patients will develop.[122–125]

DIFFERENTIAL DIAGNOSIS. One of the primary concerns after a single demyelinating episode is whether other bouts can be expected (e.g., MS). Several features may tip the balance toward one or the other, but the proper diagnosis becomes apparent only with time. Classically, ADEM is characterized by the multifocal involvement at onset whereas MS often presents with monosymptomatic deficits such as ON. However, ADEM may cause unifocal symptoms and MS may present with multifocal CNS involvement, especially in children. The monosymptomatic deficits caused by ADEM are more commonly severe, such as bilateral ON and complete transverse myelitis. Although OCBs occur transiently in about one third of ADEM cases, their persistence implies a diagnosis of MS. The subsequent disappearance of OCBs, when performed by consistent techniques, is evidence against MS. The MRI appearance of these two disorders is often identical,[125] but the presence of basal ganglia or cortical lesions, or large globular white matter lesions, is more frequent in ADEM.

The fulminant development of ADEM is distinctive but not pathognomonic, because a rare form of MS known as Marburg's MS is also rapid in onset and often deadly. The appearance of brain stem, periventricular, and multiple, large cerebral white matter lesions and the presence of OCBs may distinguish Marburg's variant from ADEM.

On rare occasions, inflammatory demyelinating lesions may reach a large size and resemble tumors (especially lymphoma) on MRI, necessitating biopsy for clarification. There is usually one dominant lesion, but smaller separate lesions may be identifiable. These have been referred to as both ADEM and MS in the literature. The prognosis for recovery is often quite good, although approximately one third suffer subsequent attacks. Some develop typical MS, whereas others have recurring tumor-like lesions. The term *multiphasic ADEM* has been used when patients have large recurrences in the same location, and *relapsing ADEM* refers to recurrences at different sites. The relationship of these entities with MS is unclear.

Balo's concentric sclerosis refers to the pathological finding of alternating bands of demyelination and remyelination. These patients typically have large lesions and subacute deficits similar to those described earlier. Typical demyelinating lesions commonly coexist, and rarely CDMS patients are noted to have similar-appearing lesions. The reason for this peculiar alternating pattern is unknown.

Schilder's myelinoclastic diffuse sclerosis is another rare condition that may be confused with ADEM or other demyelinating conditions. This progressive demyelinating disorder usually begins in childhood. The features are often atypical and include dementia, aphasia, homonymous hemianopia, seizures, psychosis, elevated intracranial pressure, and the absence of OCBs. The most characteristic finding is the presence of two large, roughly symmetrical lesions on MRI, one in each hemisphere. The diagnosis is made by excluding the known inherited leukodystrophies, especially adrenoleukodystrophy.

MANAGEMENT. Treatment with intravenous methylprednisolone seems to halt progression and allow recovery to begin sooner, just as with MS. Plasma exchange can be tried in those with severe deficits and little response to corticosteroids. IVIG has also been used successfully according to case reports in the literature. One fulminant case responded to hypothermia only.

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