Diseases of myelin comprise a variety of illnesses with varied etiology. They range from clearly infectious diseases such as progressive multifocal leukoencephalopathy to hereditary metabolic disorders such as adrenoleucodystrophy and metachromatic leucodystrophy to a group of disorders of unknown etiology (Table 14.1). Whether multiple sclerosis (MS) and its variants comprise a single disease with a highly varied course or a group of syndromes of diverse etiology remains controversial, although recent evidence suggests that it actually involves at least four different pathologic variants (1). Numerous clinical demyelinating disorders may be part of the MS spectrum or may represent different diseases with similar clinical and pathologic features. For years, many clinicians have felt that primary progressive MS and Devic syndrome (neuromyelitis optica) were distinct from relapsing remitting and secondary progressive MS. Balo concentric sclerosis was felt to be a different disease, but recent evidence has suggested that it is a variant of relapsing remitting MS. Whether the Marburg variant and acute disseminated encephalomyelitis (ADEM) are part of the MS spectrum or represent different disease entities remains a matter of debate. Recent immunopathologic studies are beginning to clarify these issues, but, ultimately, clarification of the relationship of the variants to each other will have to await determination of the etiology of these conditions.

Recent developments in immunopathology have suggested that MS is several different diseases with a common clinical presentation (1). These immunopathologically different disorders are likely to have different etiologies. Guillain-Barre syndrome has been shown to have several variants caused by different agents including *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumonia*, swine flu vaccine, and probably several others (2–4). Typical relapsing remitting MS now appears to have several variants, and these are likely to have different etiologies. The inflammatory demyelination in different cases has immunologic features that are sufficiently different from each other to suggest that this is really a group of diseases (1).

These demyelinating disorders appear to have central myelin and the cells that form central myelin, the oligodendrocytes, as the target of attack. MS usually does not affect peripheral myelin, although there are cases of a disease clinically and pathologically indistinguishable from MS in which there is also peripheral demyelination in a pattern indistinguishable from chronic inflammatory demyelinating polyneuropathy (5–7). Because there is good evidence that molecular mimicry is involved in Guillain-Barre syndrome (3), molecular mimicry of a shared epitope could cause this rare combination of cen-
The etiology of MS remains unknown. The most widely accepted hypothesis is that it is an autoimmune disease. The increased risk of MS in first-order relatives of MS patients, the higher concordance rate in identical versus fraternal twins, and the overrepresentation of certain HLA types (8) point to significant genetic risk factors, although it is clear that no single gene is responsible for genetic susceptibility.

**ETILOGY**

The etiology of MS remains unknown. The most widely accepted hypothesis is that it is an autoimmune disease induced by a virus or other infectious agent. The possibility of it being a primary infectious process with or without an associated autoimmunee reaction has not been entirely ruled out despite repeated failure to identify a causative agent. Over the past four decades, there have been a number of reports of viruslike particles in brain tissue from MS patients (9). At least 14 different viruses have been isolated from the brains of MS patients, yet none has been shown to be etiologically related (10). Cook listed 22 agents suspected of being related to MS for which substantial evidence of a causative role has not thus far appeared (11). The demonstration of viral nucleic acid by polymerase chain reaction in MS brain and cerebrospinal fluid (CSF) (12,13) has created some interest, but it has never been possible to clearly demonstrate a connection between any of these agents and the disease process. No agent has been found in 100 percent of active plaques. The demonstration of herpes viruses, in particular herpes I, II, and VI, in a significant proportion of MS plaques over the past decade (12,13), evidence that the anti-herpes drug acyclovir will reduce the number of attacks of MS (14), and, more recently, evidence for chlamydial infection (15) have renewed interest in infectious hypotheses. Because herpes viruses are activated by other infections and viral infections are known to precipitate some MS attacks, reactivation of herpes viruses may be related to some attacks or may be significant aggravating factor even if not causative. Only time will tell if any of these agents plays a role in disease causation. The report of a patient with MS developing acute optic neuritis two months after an allogenic bone marrow transplant for chronic myelogenous leukemia suggests that it is not purely an autoimmune disease (16). The possible role of infectious agents in MS is discussed in more detail in Chapters 7 and 8. Part of the problem in determining the role of infectious agents in MS may be multiple causation, as occurs in Guillian-Barre syndrome, in which several different agents can induce acute autoimmune neuropathies that are difficult to differentiate clinically (2).

Extensive efforts have gone into the attempt to understand the role of the immune system in MS. Much of this effort has been directed toward understanding the immunology of experimental autoimmune encephalomyelitis (EAE), which is the most extensively studied animal model of the disease (see Chapter 6). This work has taught us an enormous amount regarding immunology in general and immunology as it applies to the human nervous system. Unfortunately, attempts to apply to MS what has been learned about EAE have rarely been successful. Numerous treatments that work well in EAE have failed completely when tried in MS, making it clear that MS is not simply EAE. However, there is good evidence that autoimmunity is involved in the disease, and immunomodulating agents such as the interferons and glatiramer acetate and immunosuppressant drugs such as cyclophosphamide, methotrexate, and mitoxantrone can slow the disease process. With the development of a more detailed understanding of immunology and the ability to directly assess various immunologic components in situ, it is possible to begin to define the immune reaction in the acute plaque of MS and to begin to understand the nature of the immune reaction in MS, as discussed below.
CLINICAL SPECTRUM OF HUMAN INFLAMMATORY DEMYELINATING DISEASES

The entities described here have at different times been considered distinct diseases and, largely because of overlap syndromes, been considered part of the MS spectrum. Recent advances in pathology are clarifying the relationships, but definitive answers to the relationship of these diseases remain to be established.

Relapsing Remitting Multiple Sclerosis
This is the classic MS clinical pattern marked by exacerbations, with a variable amount of improvement between attacks.

Secondary Progressive Multiple Sclerosis
About 80 percent of relapsing remitting MS cases go on to develop a secondary progressive disease pattern, with a slowly progressive ascending paralysis from a few to 20 or so years after onset. This represents a later stage of relapsing remitting disease rather than a separate variant, although not all relapsing remitting MS goes on to develop secondary progression.

Primary Progressive Multiple Sclerosis
This disease pattern has a later onset, usually after age 40 years, and begins with an insidious progression of disability affecting primarily the spinal cord without exacerbations or remissions. Unlike exacerbating remitting disease, in which two-thirds of the cases are female, primary progressive MS is only slightly more common in females with a ratio of about 1.3:1 (17). Magnetic resonance imaging (MRI) of the brain is sometimes normal in these cases, and MRI of the spinal cord may show only cord atrophy.

Devic Syndrome (Neuromyelitis Optica)
Devic syndrome is an acute disorder in which optic neuritis and transverse myelitis occur within a short time of each other, with little or no involvement of other parts of the central nervous system (CNS) (18). It has generally been considered a monophasic disease without relapses after the initial episodes; however, numerous cases that begin with optic neuritis and transverse myelitis proceed to develop a relapsing remitting course similar to typical relapsing remitting MS, but with more severe residua from attacks and a more necrotic pathology. MRI in these cases shows no lesions within the brain itself but generally shows evidence of cord inflammation usually extending over three or more segments. Whether this is a variant of MS or a distinct disease remains controversial. It may be a distinct disease entity, or the course and intensity differences may relate more to the genetic makeup of the host than to the etiology.

Marburg Disease (Acute Multiple Sclerosis)
This acute, fulminant demyelinating disorder was first described by Otto Marburg in 1906 (19). It is a severe, unrelentingly progressive demyelinating disease that typically leads to death within a few months to a year.

Balo Concentric Sclerosis
This has been thought to be an aggressive variant usually leading to death in weeks to months. It is marked by large plaques of demyelination with concentric bands of preserved or regenerated myelin. These bands can sometimes be seen on MRI. There is now good evidence that some cases with Balo-like lesions on MRI improve and have a course typical of relapsing remitting MS. It may be that the Balo type lesion is a feature of some early MS with very active remyelination, features that disappear as the disease progresses so that the concentric lesions are observed only pathologically in individuals who die soon after the onset of the disease.

Acute Disseminated Encephalomyelitis
This is usually a monophasic demyelinating disorder that typically follows a viral infection. It appears to be closely analogous to EAE. The most severe cases are seen after measles infection, smallpox vaccination, or rabies vaccine. It is marked by the rapid, sometime sudden, onset of confusion, fever, and depressed consciousness, often with seizures and multiple focal neurologic signs such as ataxia, paraplegia, or cranial nerve signs. It can be fatal within days to weeks, although survivors often recover remarkably well over a period of many months.

PATHOLOGY OF RELAPSING REMITTING MULTIPLE SCLEROSIS

The pathology of typical relapsing remitting MS consists of lesions (plaques) disseminated in location and varying in age, as would be expected from the clinical features. In addition, there is a second demyelinating process consisting of the demyelination of individual fibers or small groups of fibers that is best seen in the spinal cord. Plaques can be found wherever there is central myelin. They are present in white and gray matter, but the gray matter lesions are much less obvious and generally do not appear on MRI, possibly because of the relatively small amount of myelin present and a less intense inflammatory reaction. The lesions occur in different parts of the nervous system.
and are in different stages of activity or maturity. Lesions range from acute plaques with active inflammatory infiltrates and macrophages loaded with lipid and myelin degeneration products, through various degrees of lesser activity to plaques that are active only at their margin, to chronic, inactive demyelinated shrunken glial scars. Although plaques can appear anywhere there is central myelin, there is a predilection for the periventricular white matter, optic nerves, spinal cord, and juxtacortical areas. Areas of white matter outside the plaques are not normal. They show biochemical abnormalities that some feel can be explained on the basis of Wallerian degeneration (18) and gliosis, whereas others believe that they represent an important aspect of the pathology, particularly in secondary progressive MS. (20). This appears to occur concurrently with plaque formation and consists of patchy demyelination in one or a few fibers with minimal inflammation. This is best seen in the spinal cord.

Recent reports by Lucchinetti et al. (1) and Lassman et al. (21) have dramatically altered our view of the pathology of MS. They described four different patterns of demyelination in active MS lesions based on a variety of modern staining and labeling techniques, suggesting that MS is a group of diseases with similar clinical and pathologic features rather than a single entity. Three of these patterns are seen in exacerbating remitting MS, and the fourth has been seen only in primary progressive MS. These recent observations already have had a major impact on our thinking regarding etiology and pathogenesis. It seems likely that the different patterns relate, at least in part, to different etiologies and may provide the basis for associating particular agents with particular disease patterns. They also explain some of the discrepancies found in the description of various investigators. The first two patterns appear to be autoimmune reactions against myelin, whereas the third and fourth patterns more closely resemble a disease primarily of oligodendrocytes. Pattern four appears to be associated exclusively with primary progressive MS, although it is likely that some cases that appear clinically to be primary progressive will have one of the other pathologies, because many cases of relapsing remitting MS are essentially silent clinically, and some apparently primary progressive cases are likely actually secondary progressive (22). The pathology of the fourth group is discussed below. The patterns can be summarized as follows.

**Pattern 1: Active Demyelination Associated with T-Lymphocyte and Macrophage-Dominated Inflammation without Significant Amounts of Antibody or Complement Deposition**

Plaques were perivenular in location, and loss of all types of myelin protein appeared to occur simultaneously. There was some diffuse immunoglobulin G (IgG) staining throughout the lesion. Staining for complement components was negative. This pattern comprised about 12 percent of the reported cases.

**Pattern 2: Active Perivenular Demyelination Associated with T-Lymphocyte and Macrophage-Dominated Inflammation with Extensive Antibody Deposition in the Tissue and in Astrocyte Cytoplasm**

Complement C9 neoantigen was deposited at sites of active demyelination, indicating that the antibody plays a role in the demyelinating process. Plaque borders were well defined, and lymphocytic perivascular cuffs were frequent. Loss of all types of myelin protein appeared to occur simultaneously. There was heavy staining of myelin degradation products in the macrophages. In older, inactive plaques, there was variable loss of oligodendrocytes at the plaque borders, with reappearance of oligodendrocytes in the plaque centers. A high incidence of shadow plaques was seen in these cases, indicating that some remyelination is common. This was the most common pattern, comprising 53 percent of the reported cases. The formation of clathrin coated pits (caveolae) seen on electron microscopy reported by Prineas and Connell is consistent with a role for antibody in the demyelination; thus, these two cases were most likely type II (Figure 14.1) (23).

**Pattern 3: Active Demyelination with an Infiltrate of T Lymphocytes and Activated Macrophages and Microglia**

No IgG deposition, possible preservation of a rim of myelin around venules, and the plaque borders were ill defined. With this lesion pattern, there was preferential loss of myelin-associated glycoprotein (MAG) relative to other myelin proteins such as MBP and proteolipid protein (PLP) as originally described by Itoyama et al. (24). A concentric (Balo type) pattern was seen in some of these cases. This pattern comprised about 30 percent of the cases.

Forty-three of the lesions examined by Lucchini and others were biopsies of initial clinical lesions. Thirty-three of these patients developed clinically definite MS in the follow-up period, including individuals with each of the first three disease patterns. Multiple lesions were examined from most of the cases, and the pattern was the same in all of the lesions from a given patient (1). Conversion of one pattern to another would seem possible, but, except for conversion of pattern 1 to pattern 2 with the development of an antibody reaction, conversion between types seemed a priori unlikely.
THE ACUTE PLAQUE

According to Prineas (25), most MS plaques appear to begin with margination and diapedesis of lymphocytes and macrophages forming perivascular cuffs about capillaries and venules. This is followed by diffuse parenchymal infiltration by inflammatory cells, edema, macrophage activity with stripping of myelin from axons, astrocytic hyperplasia, and the appearance of increased numbers of lipid-laden macrophages and demyelinated axons. Prineas also described plaques in which myelin fragmentation preceded the appearance of macrophages. This would seem to correspond to a type 4 case of Lucchinetti et al. In type 2 cases, as plaques enlarge and coalesce, the initial perivenular distribution of the lesions becomes less apparent. The inflammatory reaction in the plaques usually is less pronounced in gray matter, probably because of the smaller amount of myelin in these areas and the correspondingly fewer macrophages needed to remove cellular debris.

Acute plaques begin in a perivenular location (25, 26), and are marked by perivascular cuffs (Figure 14.2 and 14.3) of inflammatory cells including lymphocytes.
Polymorphonuclear leukocytes, activated macrophages, microglia, and occasionally plasma cells. Polymorphonuclear leukocytes and eosinophils are rare except in Devic syndrome, in which they are much more common. Myelin breakdown occurs with stripping of myelin from the axons by macrophages, and many of the macrophages are filled with myelin debris and neutral lipid. Extracellular myelin debris is rarely, if ever, seen, but some of the myelin breakdown is extracellular, because recognizable myelin fragments are frequently seen on electron microscopy of CSF sediment taken at the time of an acute attack (27,28).

**CHRONIC ACTIVE AND INACTIVE PLAQUES**

As plaques mature, the lipid-laden macrophages and microglia exit the central plaque area, which becomes hypocellular (Figure 14.4). Gliosis gradually increases, followed by gradual shrinkage of the plaque. The plaque margin may remain active with continuing or recurring activity, or the plaque margin may gradually lose inflammatory cells and become inactive. Plaque reactivation can commonly be seen on MRI during acute attacks, in which a known plaque shows ring enhancement thus indicating active inflammation with breakdown of the blood-brain barrier. The pathologic correlate of this recurring activity is a plaque with a gliotic, sparsely cellular center and a band of lipid-filled macrophages and lymphocytes at the plaque margin.

Considerable axonal interruption even in new acute plaques. Axonal interruption is marked by axonal ovoids that are easily demonstrated with special stains and confocal microscopy. Over time, these interrupted axons undergo retrograde degeneration and the ovoids disappear. Axonal damage is demonstrated on MR spectroscopy by loss of N-acetyl aspartate (NAA), an axonal marker (29). Trapp and colleagues reported an average of about 11,000 axonal ovoids/mm³ in acute plaques, indicating that significant axonal loss begins early in the disease process (30,31). How much of the NAA loss is due to axonal interruption and how much is due to loss in axonal diameter and impairment of axonal transport remains to be determined. Demyelinated axons initially become irregular in diameter but in later stages appear to have a uniformly reduced diameter (Figure 14.4). They may lose as much as 50 percent or more of their diameter, which would reduce the axoplasmic volume by 75 percent, so that, even if the concentration in the axons remained the same, the amount would be markedly decreased. At the same time, axon transport is seriously impaired, which also could reduce the amount of NAA out of proportion to the actual axonal loss and might well decrease the concentration distal to the site of demyelination (see Chapter 16).

Wallerian degeneration due to axonal destruction in acute plaques can be extensive enough to be detected by MRI (32) (see Chapter 15). Additional axonal destruction occurs when older plaques are reactivated with demyelination at the plaque margins. The fact that sparing of axons is relative and not absolute has been known since the time of Charcot, but the extent of the damage to the axons has been only recently quantified. Cerebral atrophy and atrophy of the corpus callosum, which is commonly seen in advanced disease, is probably due to a combination of myelin and axonal loss and shrinkage due to scarring.

Most investigators now believe that axonal loss accounts for most of the chronic, irreversible disability in MS. Cumulative axonal loss in long pathways such as the pyramidal tracts and the dorsal columns of the spinal cord, where there may be several plaques along their course, is often very substantial. This in part accounts for the pallor that is frequently seen in these tracts at autopsy. It is important to recognize that axonal loss is an important factor in MS and that experimental efforts to improve conduction in surviving fibers will not affect those symptoms due to axonal loss, even though they may produce dramatic improvement in symptoms that are due to conduction failure in surviving axons.

Immunocytochemical studies of inflammatory cytokines indicate that most of the lymphocytes at the plaque margins are T-cells. CD4⁺ T-cells (helper/inducer) are seen in the plaque margin and extend beyond the margin into periplaque white matter. CD8⁺ T-cells (suppressor/cytotoxic) are fewer in number and more confined to the plaque margin. Occasional B cells and a few plasma cells may be seen. Macrophages may be seen.

---

**FIGURE 14.4**

Inactive plaque center, with the axon stain showing numerous demyelinated axons and very little inflammation. The axons have a relatively uniform diameter, unlike newly demyelinated axons, which are irregularly dilated.
throughout the plaque but are rarely seen beyond the plaque margin (33).

**GRAY MATTER PLAQUES**

Although juxtacortical plaques extending into the adjacent gray matter have long been recognized, isolated cortical plaques are rarely mentioned in the literature. Nevertheless, they are an important part of the pathology of MS. The failure to detect these plaques arises from two factors: they are much less inflammatory than white matter plaques and cannot be detected with myelin staining techniques. The instructions after staining with luxol fast blue, the most commonly used current myelin stain, is to destain until the gray matter no longer shows any staining. Thus gray matter plaques do not stain for myelin and are difficult to see with myelin stains. Gray matter involvement is frequently reported when plaques at the gray–white junction extend into the cortex, but isolated gray matter plaques were rarely discussed or commented on until the recent report of Peterson et al. (34). They reported a careful analysis of gray matter plaques and classified them into three types: type 1 were contiguous with subcortical lesions and accounted for 34 percent of the cortical lesions; type 2 were small, usually perivascular lesions confined to the cortex, and constituting 16 percent of the lesions; and type 3 extended from the cortical surface to layer 3 or 4 of the cortex, constituting 50 percent of the lesions (34). These plaques are much less inflammatory than those in the white matter, with only one-thirteenth as many CD3+ lymphocytes and one-sixth as many microglia and macrophages (34). They found isolated microglia apposed to and ensheathing neuronal perikarya and apical dendrites. Apoptotic neurons were increased in the cortical plaques. Transected neurites were found with an average density of 4119/mm^2, which is about one-third the number found in white matter plaques. They were about one-fourth as frequent in chronic gray matter plaques and much less common in inactive lesions. These cortical lesions may account for many of the cognitive changes seen in MS.

In chronic active lesions, astrocytes in and about the plaque express class I and class II histocompatibility antigens, although expression of class II antigens was both more common, intense, and consistent than expression of class I antigens (33,35). Class I and class II positive astrocytes extended into the periplaque area, but astrocytes outside the plaque and peri-plaque areas are negative for both antigens. Astrocytes in the plaque margin and peri-plaque area often stain for interferon-γ and a bit less frequently for interferon-β (33). Astrocytes in the plaque center and in normal-appearing tissue away from the plaques were consistently negative except in patients dying with intercurrent infections in whom staining was more generalized.

Staining for the intercellular adhesion molecule 1 (ICAM-1) revealed diffuse staining of the plaque periphery, most intense at the plaque margin but extending well beyond the zone of inflammation. Staining also was seen in perivascular cuffs, which included diffuse and cellular staining. LFA-1 is a ligand for ICAM-1 and is present on essentially all of the hematogenous cells in the plaque and peri-plaque areas. LFA-3, with its ligand CD2, is more selective for T-cells than ICAM-1, but it has a very similar distribution to that of ICAM-1 in the plaque and peri-plaque areas (33).

Old inactive plaques generally have sharp margins without hypercellularity, a few widely scattered T-cells, and do not stain for adhesion molecules or interferon. They are marked by gliosis and stain heavily for glial fibrillary acidic protein. Inflammatory cells are scarce, and most cells in the plaque are astrocytes. A few nonmyelinating oligodendroglia may be seen near the plaque margins.

Immunocytochemical studies have shown the inflammatory cells in the actively demyelinating central area of acute plaques to be mainly Ia-positive cells. These are mostly activated microglia and macrophages with a few T-cells and antibody-producing plasma cells. The T cells in the acute plaque are a mixture of T4^+ (helper-inducer) and T8^+ (suppressor/cytotoxic) lymphocytes and are more numerous near the center of the plaque, diminishing in numbers peripherally. As the lesion enlarges, T cells become relatively more numerous peripherally, whereas macrophages take their place centrally. T4^+ (helper) cells invade the normal appearing white matter about the lesion, whereas T8^+ (suppressor) cells are confined largely to the plaque margins and perivascular cuffs. The plaque margins contain increased numbers of oligodendrocytes, astrocytes, and inflammatory cells (33–35). As the lesions become more mature, myelin remnants and macrophages progressively disappear from the central part of the plaque (Figure 14.4), which eventually becomes a gliotic scar. At the plaque margin, a hypercellular “glial wall” contains lymphocytes, oligodendrocytes, and a few macrophages and astrocytes. In many instances, the disease process appears to continue, with low-grade activity at the plaque margins, manifested by lipid-laden macrophages and lymphocytes, often accompanied by a few thin perivascular cuffs. In chronic-active MS, inflammatory cells are scattered in small numbers through much of the normal-appearing white matter. These include T4^+, T8^+, and Ia^+ cells (35,36).

Chronic inactive MS plaques usually have a sharply demarcated border with little, if any, hypercellularity. Occasional T4^+ and Ia^+ cells are scattered throughout the lesions. At the edges, a few T4^+, T8^+, and Ia^+ cells, including macrophages and B lymphocytes, may be seen, and these also occur in small numbers throughout the otherwise normal-appearing white matter.
REMYELINATION

Plaquelike areas of very pale myelin staining are a frequent occurrence in many cases of MS. On examination, these areas have increased cellularity and abnormally thin myelin sheaths of relatively uniform thickness (Figure 14.1 and 14.5). Numerous studies in experimental animals have demonstrated the characteristics of regenerated myelin with thin sheaths (Figure 14.6) and short internodes (Figure 14.7). The thickness of the myelin about individual axons in these shadow plaques bears no relationship to fiber diameter as it does in normally myelinated areas. Some have regarded these shadow plaques as evidence of partial demyelination; however, it is now clear that most, if not all, represent areas of remyelination (37).

Until the late 1950s, it was accepted dogma that remyelination did not occur and that oligodendroglia, like neurons, were endstage cells incapable of regeneration. Since Bunge et al. (38) first unequivocally demonstrated central remyelination in the cat in 1958, remyelination has been shown to occur in the CNS in essentially every species tested, including tadpole, mouse, rat, guinea pig, rabbit, cat, and dog (39). The characteristics of the shadow plaque are essentially identical to those of remyelinated areas in experimental animals: an increased number of oligodendrocytes that, contrary to traditional views, have been demonstrated to be capable of proliferation (40–42), thin myelin sheaths of relatively uniform thickness, and short internodes. The alternative possibility that shadow plaques arise from partial demyelination seems unlikely because partial demyelination has been convincingly demonstrated only during the acute phase of the demyelinating process or where the myelin is under mechanical pressure. In addition, these thin myelin sheaths, particularly those at plaque margins, have been shown to have short internodes (37). There is abundant evidence for remyelination in experimental animals and humans, and the appearance of shadow plaques and short internodes indicates that these are indeed remylinated fibers.

Regeneration of central myelin in some cases is accompanied by Schwann cell invasion of the CNS; consequently, the peripheral myelin can be seen within a demyelinated or remyelinated area (43). Schwann cells occur in small numbers in normal spinal cord, but it is uncertain whether they come from peripheral nerves innervating CNS blood vessels or occur independent of blood vessels. In pathologic conditions, most of the Schwann cell remyelination within CNS occurs near root

![FIGURE 14.5](image1)

Luxol fast blue stain of a shadow plaque in optic nerve. Note the myelin pallor at lower left compared with the deeper staining of the undemyelinated area at upper right.

![FIGURE 14.6](image2)

Electron micrograph of remyelination 28 days after mouse hepatitis virus inoculation. The newly regenerated myelin sheaths are very thin, and the myelin thickness bears no relationship to axon diameter. An oligodendrocyte can be seen at upper left. Original magnification, 5800X. Herndon RM and Weiner LP, unpublished observations.
Breaches in the glial limitans caused by the demyelinating process allow Schwann cells in the nerve roots or autonomic nerves accompanying cerebral blood vessels to migrate into the central white matter, where they retain their capability to form myelin. With progression of the pathologic process, recurrent demyelination at the plaque margins causes slow enlargement of the plaques. Although remyelination appears to be a regular event in early MS, it clearly becomes less common and less effective as the disease progresses, so that, at autopsy in patients with long standing disease, evidence of remyelination may be quite limited. Over time, demyelination of newly remyelinated areas may result in scarring, so that further remyelination cannot occur and the plaque becomes a hypopcellular glial scar. Shadow plaques are thus more likely to be seen in autopsies of younger patients with continued active remitting disease (37), and much less common in older patients with inactive disease or chronically active, indolent disease progression. In most cases, the end result is a nervous system riddled with chronically scarred, inactive plaques and a considerable amount of Wallerian degeneration resulting in the pallor of long tracts in myelin-stained preparations.

SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS

Secondary progressive MS is usually marked by a slowly ascending paralysis or, much more rarely, progressive ataxia. It commonly occurs in patients in their 40s or early 50s who have had MS for a number of years. The pathologic substrate for this appears to be a progressive loss of axons in the spinal cord with cord atrophy. Examination of the cord, in addition to chronic inactive or occasionally active plaques, shows demyelination and/or degeneration of multiple individual fibers. Careful examination of the cord shows widely scattered individual fiber demyelination with a few scattered macrophages along the sheaths (20). This could result from an inadequate supply of transported materials with a resulting inability of the axon to adequately signal the myelin-forming oligodendrocytes. Certainly such scattered fiber demyelination could be a part of a dying axonopathy and thus the substrate for the slowly progressive ascending paralysis of secondary progressive MS (44) (Chapter 16).

What mechanisms could be invoked for such a process? It might be a problem in axonal transport, with retrograde degeneration, or axonal interruption secondary to scarring with Wallerian degeneration. The former seems more likely. Extensive studies in animals have shown that fast and slow axonal transport are markedly slowed by demyelination. Such axonal damage upstream would lead to an inadequate supply of the structural materials needed to maintain energy metabolism and axonal structure. These conditions, particularly if the axons metabolic resources are stretched due to induced sprouting of the distal axon to take over synapses vacated by death of other axons, could lead to a dying back axonopathy. Clinically this would result initially in death of the longest axons with gradual progression to shorter and shorter axons. The second major possibility is that they are undergoing Wallerian degeneration secondary to...
Primary Progressive Multiple Sclerosis

In the studies of Lucchinetti et al., all of the cases of primary progressive MS had pattern 4 (1). Inflammation was dominated by T lymphocytes, and macrophages, IgG, and complement deposition were absent. Death of oligodendrocytes occurred in peri-plaque white matter adjacent to areas of demyelination. The dying oligodendrocytes demonstrated DNA fragmentation without features of apoptosis. Staining for the various myelin proteins showed an essentially simultaneous loss in staining for each of the proteins. Thus, it appears to be an oligodendrogliopathy.

Primary progressive MS constitutes about 10 percent of MS cases and is equally common in men and women. This pattern was the least common in the series of Lucchinetti et al., comprising 4 percent of the cases studied, and was the only one associated with a particular clinical disease pattern. Its association with primary progressive MS strongly supports the frequently expressed view that true primary progressive MS is a disease distinct from relapsing remitting and secondary progressive MS. Some cases that clinically appear as primary progressive disease undoubtedly will have the pathology of secondary progressive disease because relapsing remitting cases can be asymptomatic or nearly so (22) and thus may present clinically only when they move into the secondary progressive phase. Such cases show the pathology of secondary progressive disease even though clinical attacks were never observed. This will tend to confuse the clinical distinction between the disease types but is explained by the fact that a person can have multiple demyelinating events without symptoms in relapsing remitting MS, so that secondary progressive disease can masquerade clinically as primary progressive disease.

Acute Multiple Sclerosis (Marburg Disease)

Acute MS is fortunately rather rare. It is marked by the rapid onset and almost continual progression of demyelination. It can begin in the hemispheres or the brainstem, and typical cases display on MRI multiple high signal areas that increase in size and become confluent. Many patients die within a few weeks to several months. Many of those who survive go on to have a typical relapsing remitting course.

Pathologically, it is marked by intense and widespread inflammation with T lymphocytes, large numbers of lipid-laden macrophages, and a scattering of B lymphocytes (18,19). The lipid-laden macrophages stain intensely for neutral lipid with oil red-O but show little staining with most myelin stains. Essentially, total demyelination occurs within the lesions, although beginning remyelination can be seen. Extensive IgG and complement product is deposited in the lesions, which pathologically resemble type 2 lesions of Lucchinetti et al. There is no evidence of death of oligodendroglia in the area surrounding the plaques. In semithin sections, partly digested bits of myelin are seen in macrophages. The demyelinated axons are irregularly constricted and dilated, unlike those in more chronic plaques, which have a more uniform diameter. Perivascular lymphocytic cuffs may be present but often are sparse.

Oligodendrocytes are usually considerably reduced in the acute lesions, although larger numbers may appear in somewhat older lesions (19), indicating that oligodendrocyte regeneration occurs in humans as it does in experimental animals.

Acute Disseminated Encephalomyelitis

ADEM has a host of names, including perivenous encephalomyelitis, encephalitis periaxialis diffusa, acute hemorrhagic encephalomyelitis, postinfectious encephalomyelitis, and postvaccinal encephalomyelitis. Of the demyelinating diseases, this appears to correspond most closely to EAE. It is an acute diffuse inflammatory demyelinating disorder that often occurs 1 to 3 weeks after a viral infection or immunization. Its severity and intensity vary, but it usually runs a monophasic course, with a very small percentage later developing into a relapsing remitting disease. In those who survive the acute episode, slow improvement usually occurs over many months, often with remarkably good recovery and little residua. Most fatal cases follow smallpox vaccination or measles infection. The hemorrhagic form has been considered to represent a different entity by some (18), although some have considered it to be a more severe form of ADEM (45) because, in addition to the perivenous hemorrhages, perivenous inflammation and demyelination are regularly observed.

The gross pathology is marked by swelling and congestion, often with evidence of uncal and foraminal herniation. The fresh brain may show numerous petechia or simply appear swollen. Microscopically, it is marked by extensive perivenous inflammation and demyelination. The venules are surrounded by prominent cuffs of lymphocytes and macrophages. Often, long strips of perive-
nous demyelination occur, giving the tissue a reticulate appearance. In some cases, there is spread of macrophages and lymphocytes into the parenchyma. The macrophages may be laden with neutral lipid even rather early in the disease process.

In the hemorrhagic cases, in addition to the perivascular cuffs, there is edema and necrosis of blood vessels with fibrin deposition and numerous ring or ball hemorrhages. In these cases, there are usually numerous neutrophils in the infiltrate, and there may be areas of frank necrosis of tissue. Attempts to recover virus in these cases or to demonstrate by antibody staining or in situ hybridization have usually failed. Overall, the pathologic picture is essentially identical to EAE as seen in experimental animals (45).

**NEUROMYELITIS OPTICA (DEVIC DISEASE)**

The place of neuromyelitis optica in the MS spectrum has long been in dispute. It has been said to be a monophasic disease, with optic neuritis and transverse myelitis occurring within a few weeks to a month or two of each other, without recurrences. However, it is clear that over half the cases that fit these criteria initially go on to develop relapses and remissions. Wingerchuk and coworkers reviewed 71 patients with neuromyelitis optica (46). Of these, 23 had a monophasic course and the other 48 had a relapsing remitting course. In the cases of monophasic illness, they noted that the initial optic neuritis and transverse myelitis occur quite close together, with a median of 5 days between the two events, whereas the median was 166 days for the relapsing cases. The relapsing cases had a poor prognosis with poor recovery between attacks. They frequently developed respiratory failure secondary to cervical cord disease.

Clinically Devic syndrome differs from typical MS in its clinical pattern and in the relatively poor recovery usually seen after the attacks. It also differs in its distribution in the population, being more common in Asians and Africans than in Caucasians. In Japan, the Devic pattern makes up about 7 percent of reported cases (47).

In the acute stages there is necrosis of the cord, usually extending over three or more segments. The cord is usually swollen and soft in the affected area. There may be additional demyelinating lesions in other cord segments but the brain itself is not involved. The CSF has a variable pleocytosis, often with 50 to 100 or more cells. These are predominantly lymphocytes with a variable number of monocytes and neutrophil leucocytes and occasionally a few eosinophil leucocytes. There may be extensive perivascular cuffs containing macrophages and granulocytes, including eosinophils and CD3⁺ lymphocytes (48). The inflammation and necrosis are marked by extensive macrophage infiltration with lymphocytes and often polymorphonuclear leucocytes. Extensive deposition of IgG and C9 neoantigen is a marker for complement deposition in areas of myelin necrosis. Extensive oligodendrocyte destruction occurs, and all the myelin proteins disappear at about the same time. Thus the pathology resembles a more severe, necrotic pattern similar to the type 2 of Lucchinetti et al. It differs in that much of the IgG and complement deposition is on and around blood vessels in the Devic’s cases (48).

In the late stages, cavitation and necrosis of gray and white matter occurs in the cord, and most of the length of the cord is affected. There is extensive scarring with marked hyalinization and thickening of blood vessels and perivascular fibrosis (49). Numerous macrophages are present in necrotic areas. In the optic nerves, similar necrosis and thickening and hyalinization of blood vessels is not seen, but demyelination typically includes the entire optic chiasm.

Axonal destruction in the lesions is much greater than that usually seen in MS. The destructiveness of the lesions is emphasized by the clinical findings, with relatively poor recovery from the lesions. For example, complete blindness is extremely rare in exacerbating remitting MS but common in neuromyelitis optica. Similarly, permanent paraplegia or quadriplegia is rare after a single attack of relapsing remitting MS but fairly common in Devic disease.

**STRUCTURES RESEMBLING INFECTIOUS AGENTS IN MS TISSUES**

Despite a number of reports of “viruslike particles” seen by electron microscopy of MS biopsy and postmortem material (9,50,51), credible morphologic evidence for the presence of true virions has not been reported. Dense bodies surrounded by a membrane have been seen intracellularly, mainly in macrophages, in proximity to actively demyelinating areas. These are of variable size, do not closely resemble any particular virus or class of viruses, and are generally regarded as myelin breakdown products. Many other investigators, beginning with Prineas in 1972 (9), have reported “paramyxoviruslike” tubules in the nuclei of inflammatory cells in MS plaques. These consist of strands of 18- to 20-nm intranuclear filaments or tubules. In size and appearance, they resemble the nucleocapsid of paramyxoviruses. They have been seen in a variety of conditions including normal tissues fixed under acidic conditions (R.M. Herndon, unpublished observations) and appear to be chromatin strands, which have an altered appearance due to the metabolic state of the cell or conditions of tissue fixation (52).

With newer techniques of polymerase chain reaction, representational difference analysis, in situ hybridization, and immunocytochemical techniques,
viruses are frequently found in MS plaques. The effort to tie viruses found in brain to the disease process has failed thus far. The viruses of greatest interest are the herpes viruses. These viruses are found latent in nervous tissue, are activated by other viral infections, just as new attacks of MS frequently follow viral infection, and might activate an inflammatory process in the nervous system resulting in a new attack of MS. Challoner et al. (12) reported the detection of herpes type 6 in MS brain using polymerase chain reaction and representational difference analysis followed by localization in plaques using immunocytochemistry. Subsequently, Sanders et al. (13) detected several herpes viruses in brain tissue (Table 14.2). Although several were more common in MS brains and more common in MS plaques, the differences did not reach statistical significance. Many of these viruses are carried in macrophages, so they would be more likely to appear in sites with large numbers of macrophages, such as MS plaques. Nothing in this work indicated an etiologic relationship to MS, but the presence of latent viruses, which are easily activated in plaques, suggests that they could contribute to the pathology.

CHLAMYDIA PNEUMONIAE

The presence of Chlamydia pneumonia in the CSF of individuals with MS has been demonstrated by polymerase chain reaction and culture (15,53) and is discussed in detail in Chapter 10. Chlamydia has not been reported pathologically in MS tissue thus far, but structures resembling microorganisms compatible with C. pneumonia have been seen in the CSF sediment in MS cases (R.M. Herndon, unpublished observations). Whether this will prove to be related to the disease or yet another incidental occurrence remains to be determined.

<table>
<thead>
<tr>
<th>Virus plaque</th>
<th>MS BRAIN PLAQUE</th>
<th>ACTIVE BRAIN</th>
<th>INACTIVE</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex</td>
<td>37%</td>
<td>41%</td>
<td>20%</td>
<td>28%</td>
</tr>
<tr>
<td>Herpes 6</td>
<td>57%</td>
<td>32%</td>
<td>17%</td>
<td>43%</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>43%</td>
<td>14%</td>
<td>10%</td>
<td>32%</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>27%</td>
<td>5%</td>
<td>10%</td>
<td>38%</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>16%</td>
<td>9%</td>
<td>10%</td>
<td>22%</td>
</tr>
</tbody>
</table>


CONCLUSION

MS is an inflammatory demyelinating disorder or, more likely, a group of disorders of unknown but most likely autoimmune or infectious origin. Current pathologic evidence suggests that MS may have more than one etiology and that primary progressive MS is a separate disease. Much of the permanent disability in MS results from axonal destruction, which falls most heavily on very long pathways such as the pyramidal tract supplying the legs and the dorsal columns carrying sensory information from the legs. These long pathways take multiple hits over the years, with increasing axonal destruction leading to the loss of lower extremity function so common in advanced MS. Other aspects of the disease, such as incoordination and imbalance are caused by delayed and degraded information resulting from slowed conduction of proprioceptive information and the inability to monitor, on line, motor processes due to conduction delays and signal dispersion occurring as the signals pass through demyelinated areas, as discussed further in the chapter on pathophysiology. Every attack, even subclinical ones, causes some permanent damage, and it is the accumulation of damage from repeated demyelinating episodes that accounts for most of the long-term disability. It is this progressive accumulation of damage that provides the best rationale for early use of disease-altering therapies.

References


