Chapter 38

Diseases Involving Myelin

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The integrity of myelin sheaths is dependent upon the normal functioning of myelin-forming oligodendrocytes in the CNS and Schwann cells in the PNS as well as on the viability of the axons that they ensheathe. Neuronal death inevitably leads to subsequent degeneration of both axons and the myelin surrounding them. The title of this chapter was chosen to emphasize that myelin cannot be considered an isolated entity in the context of disease processes. Deficiencies of myelin can result from a multitude of causes, including autoimmunity, viral infections, genetic defects, toxic agents, malnutrition and mechanical trauma, that affect myelin, myelin-forming cells or myelinated neurons. More comprehensive clinical descriptions of most of the diseases described in this chapter are available in specialized books about myelin [1, 2].

General Classification

Myelin deficiency can result from failure of synthesis during development or from myelin breakdown after its formation. An impediment of normal myelin formation is referred to as hypomyelination or, in some cases, dysmyelination. According to the definition of Poser, dysmyelination is a genetically determined disorder of myelogenesis in which 'myelin initially formed was abnormally constituted, thus inherently unstable, vulnerable, and liable to degeneration' [1]. Diseases involving loss of normal myelin after it is formed, i.e. demyelination, can be subdivided into primary and secondary categories.
on the basis of morphological observations. Primary demyelination involves the early destruction of myelin with relative sparing of axons; subsequently, other structures may be affected. However, in recent years it has become increasingly apparent that some diseases that had been classified as primary demyelination may involve more injury to axons than originally thought. This axonal damage could be caused by inflammation in autoimmune and viral disorders or loss of the influence of myelin proteins on axonal structure. It is now known from transgenic knockout mice that the absence of some proteins localized in myelin sheaths, including proteolipid protein (PLP), 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase) and myelin-associated glycoprotein (MAG) results in pathological axonal changes in vivo (see Ch. 4). Secondary demyelination includes those disorders in which myelin is involved only after damage to neurons and axons. The classification for myelin disorders used in this chapter is based on etiology as well as on comparative neuropathology. Disorders causing hypomyelination and demyelination are both included in four categories: (1) acquired allergic and infectious diseases; (2) genetic disorders; (3) toxic and nutritional disorders; and (4) disorders primarily affecting neurons with secondary involvement of myelin.

Many of the biochemical changes associated with central nervous system demyelination are similar regardless of etiology. The most pronounced changes occur in white matter where there is a marked increase in water content, a decrease of myelin proteins and lipids and, in many demyelinating diseases, the appearance of cholesterol esters and/or glial fibrillary acidic protein (GFAP) [1]. Particularly noteworthy with regard to lipids are dramatic decreases in galactocerebroside, ethanolamine plasmalogens and cholesterol, all of which are enriched in myelin membranes (see Ch. 4). The major structural proteins of CNS myelin, myelin basic protein (MBP) and proteolipid protein (PLP), are also invariably decreased. These changes can be explained by the breakdown and gradual loss of myelin (which is relatively rich in solids) and its replacement by extracellular fluid, astrocytes and inflammatory cells (which are more hydrated, relatively lipid-poor and free of myelin-specific constituents). The frequent appearance of cholesterol esters in demyelinating diseases is related to the fact that cholesterol is not readily degraded and is esterified by phagocytes that often remain at the site of the lesion for some time. Since cholesterol esters are essentially absent from normal mature brain, their presence in myelin disorders is indicative of inflammation and recent demyelination. Such compounds are also responsible for the neutral fat staining, or sudanophilia, demonstrated histochemically in many demyelinating diseases. In the CNS, GFAP is specific to astrocytes, and an increase of this protein during demyelination is due to reactive astrocytes associated with the pathology (see Ch. 1). The magnitudes of the changes mentioned above vary considerably from disease to disease and from specimen to specimen in the same disease, depending on the severity, location, duration and activity of the pathological processes.

**ACQUIRED ALLERGIC AND/OR INFECTIOUS DISEASES OF MYELIN**

Nervous system damage in acquired demyelinating diseases is directed rather selectively against myelin or myelin-forming cells, but axons also are often affected. In most of these disorders (except where noted otherwise), the lesions are disseminated and characterized by perivascular demyelination and inflammation, macrophage activity, sudanophilic deposits consisting of myelin degradation products and relative sparing of axons. The extent to which these criteria are fulfilled depends on the particular type and phase of disease. Also, as mentioned above, axonal pathology may be more frequent than previously thought. Furthermore, it is not always clear whether the immunological activity is autoimmune in nature or whether it is related primarily to an antecedent viral infection, nor is the amount of damage directly caused by the virus always clear. The acquired diseases discussed here are reviewed in more detail elsewhere [1, 2].

Experimental allergic encephalomyelitis is an animal model of autoimmune demyelination. The animal model thought to most clearly resemble multiple sclerosis (MS) is experimental allergic encephalomyelitis (EAE). EAE is an acute or chronic demyelinating disease of the CNS; the disease is induced by immunization of susceptible animals with either myelin or various myelin components that are encephalitogenic. The EAE model was initially identified through efforts to understand the cause of encephalomyelitis developing after inoculation of patients with the Pasteur rabies vaccine, which was prepared from virus-infected nervous tissue. It was noted that even control experimental animals inoculated with uninfected neural tissue developed an encephalomyelitis, and EAE has been carefully studied since then as a model of human diseases such as MS. A detailed examination of the EAE model and the extensive immunological data that have been obtained are beyond the scope of this chapter, and readers are referred to recent reviews for more detail [3, 4].

In brief, EAE can be induced by immunization with several encephalitogenic proteins from myelin, most notably MBP, PLP and myelin-oligodendrocyte glycoprotein (MOG). MBP was the first protein shown to cause EAE, and this classical form of the disease is mediated primarily by CD4<sup>+</sup>, MHC class II restricted T cells, because it can be transferred from an immunized animal to a naive animal using these cells. These data document the importance of CD4<sup>+</sup> lymphocytes for EAE induction, but additional pathogenic roles for other T cell populations are possible, especially in later stages of the disease. Also, there is
considerable variation in susceptibility of various animals, and this variation is largely due to the genetic background, especially that of MHC genes. It is now understood that elements of the three components of antigen recognition, the T cell receptor (TCR), antigen and the MHC molecule that presents antigen, together known as the trimolecular complex, are central to disease induction. The encephalitogenic immunodominant part of MBP that causes the disease varies between different strains of mice and other species. The exquisite specificity seen for the trimolecular complex of encephalitogenic T cells has resulted in the development of numerous therapies that target the trimolecular complex and can modify disease. These include generating an immune response to the TCR or administration of a peptide that can bind to MHC but without activating T cells.

The most characteristic component of the EAE lesion is perivascular inflammation, and the extent of demyelination varies between species and the identity of the immunogen used to induce the disease. Evidence from studying EAE in the rat or mouse indicates that activated T cells, regardless of specificity, can cross the blood–brain barrier and enter the nervous system. If the T cell encounters its antigen, the cell will be further activated and begin production of proinflammatory cytokines such as gamma interferon (INFγ) and tumor necrosis factor (TNFα), which in turn activate the endothelial cells with upregulation of cell adhesion molecules (see Ch. 7) promoting an inflammatory response. The outcome of this process, at least in some animals, is myelin damage. The actual effector mechanisms for myelin damage include a direct toxic effect of TNFα or nitric oxide on oligodendrocytes or damage mediated by macrophages and microglial cells. The later possibility can be enhanced by the presence of antibodies, which bind to myelin and provide a ligand for activated monocytes. Indeed, demyelination associated with EAE in several animals including the rat, mouse and marmoset, a nonhuman primate, is increased by the presence of antibodies to surface components of myelin, such as galactocerebroside or MOG. In fact, immunization of rodents with MOG alone has been shown to induce a relapsing–remitting demyelinating disease with both cellular and humoral immunity to this glycoprotein [3].

Multiple sclerosis is the most common demyelinating disease of the central nervous system in humans. Multiple sclerosis is a chronic demyelinating disease affecting the CNS [1, 2, 7, 8]. The disease primarily affects young adults and is characterized by a highly variable course. Most often the disease begins in the third or fourth decade with neurological dysfunction, such as decreased vision, dysarthria, weakness in limbs, diplopia, nystagmus, sensory deficits and paresthesias. The initial course is characterized by acute episodes of one or more of these symptoms followed by subsequent recovery, and this course is known as relapsing–remitting MS. Over time, the improvement after attacks may be incomplete and the relapsing–remitting course may evolve into one of increasing progression of disability, termed secondary progressive MS. A small number of patients develop a form of disease that begins as a slowly progressive process, without acute episodes of worsening followed by improvement, which has been termed primary progressive MS. A few patients will have a very aggressive course, which can even lead to death over a short period.

The diagnosis of MS is dependent on clinical evidence of central nervous system involvement separated in both time and space. Thus, evidence that two areas of the CNS are involved and a history that this involvement occurred at two different times and without any other identifiable cause, is necessary to establish a diagnosis of clinically definite MS. While there is no diagnostic test that is specific for MS, the appearance of MBP, oligoclonal protein bands or elevated IgG/protein ratios in the CSF, as well as abnormalities in electrophysiological tests of visual, auditory and somatosensory evoked potentials and magnetic resonance imaging (MRI), can help to identify subclinical lesions and assist in establishing the diagnosis. Of all of these tests, the use of MRI has probably resulted in the greatest change in our understanding of MS. T2-weighted MRI images are extremely effective in identifying MS lesions.

A number of animal diseases caused by viruses involve primary demyelination and often are associated with inflammation. These diseases are studied as animal models, which may provide clues about how a viral infection could lead to immune-mediated demyelination in humans [1, 5, 6]. Canine distemper virus causes a demyelinating disease, and the lesions in dog brain show a strong inflammatory response with some similarities to acute disseminated encephalomyelitis in man [1]. Vira is a slowly progressive demyelinating disease of sheep caused by a retrovirus [1].

Two neurotropic viruses of mice are of particular interest with regard to the way in which immune-mediated demyelination of the CNS can be induced by a viral infection [5, 6]. JHM virus, which infects oligodendrocytes and produces acute and chronic inflammatory demyelination in rodents, is a neurotropic strain of mouse hepatitis virus in the coronavirus family. Theiler’s virus is a picornavirus that infects many neural cell types and induces a chronic CNS encephalomyelitis. Investigation of animal models such as these has revealed several mechanisms by which viral infections can cause demyelination including: (1) a direct infection of oligodendrocytes resulting in cell death; (2) a virus-specific inflammatory response in which cytokines or other immune mediators damage oligodendrocytes/myelin indirectly as a bystander effect; and (3) activation of an immune response directed at components of oligodendrocytes/myelin by molecular mimicry or epitope spreading. Molecular mimicry occurs when a viral antigen has structural homology to a myelin/oligodendrocyte component, resulting in cross-reactivity, and epitope spreading results from host immune cell processing of myelin/oligodendrocyte antigens released following tissue injury.
The areas of increased signal seen on T2-weighted MRI reflect increased water and therefore are neither specific for MS nor able to distinguish new from old lesions. This is because both inflammation and tissue loss associated with demyelination or gliosis after ischemic events will result in increased signal. Therefore, the interpretation must include the clinical context. A second technique, T1-weighted imaging after the administration of gadolinium-DTPA, which does not normally cross the blood–brain barrier, can identify new lesions in which the blood–brain barrier has been compromised. Serial studies of patients with early relapsing–remitting MS have shown that the first event in the development of a new MS lesion seen on a T2-weighted MRI is disruption of the blood–brain barrier seen on a gadolinium-enhanced MRI. Thus, postcontrast MRI provides a very sensitive technique for following at least one aspect of disease activity. Using this approach, several groups of investigators have shown that MS is an active and progressive disease even in the early relapsing–remitting phase and during periods of clinical stability in many patients. Newer imaging techniques now hold promise for providing greater specificity for the various stages of lesion development (see Ch. 38).

MS lesions or plaques can be identified grossly at autopsy (Fig. 38-1) and are sharply demarcated from the surrounding tissue. Plaques occur throughout the white matter, but areas of predilection such as the periventricular white matter are well known. Microscopic examination characteristically shows loss of myelin with preservation of axons (primary demyelination). However, although the most prominent pathology in MS is demyelination, there are recent indications also for axonal and cortical pathology. New techniques of confocal microscopy and immunocytochemistry have clearly demonstrated that transected axons are common in MS lesions [9]. It has become generally accepted that axonal loss is an important aspect of MS pathology and may account for much of the irreversible neurological impairment in this disease. Plaques commonly develop around venules, and ‘early lesions’ contain many lymphocytes, plasma cells and macrophages. The greatest cellularity is found at the margins of acute lesions, which are believed to be the locations at which some of the earliest changes associated with myelin loss are occurring.

For many years there has been discussion about whether the primary pathological effect in this disease is directed at myelin sheaths themselves or at the myelin-forming oligodendrocytes. Investigators utilizing sophisticated neuropathological and immunocytochemical methods for examining lesions have now reported that there are actually several subtypes of MS patients [10], and myelin sheaths are the primary target in some whereas oligodendrocytes are targeted in others. Most common were cases that resembled EAE in which myelin was the primary target. The pathology was characterized by macrophage/T-cell-mediated or antibody/complement-mediated demyelination. However, other MS patients had lesions characterized by oligodendrocyte dystrophy, which is reminiscent of viral or toxin-induced demyelination rather than autoimmunity. These patients were less frequent, and lesions of this type were generally observed in patients with a shorter disease course than those with EAE-like lesions. These findings indicate that the demyelinated plaque may be a common endpoint resulting from a variety of different immunological and pathological mechanisms. The pathogenic heterogeneity in different patients may have fundamental implications for the diagnosis and therapy of this disease. Generally, chronic lesions are sharply defined containing bare nonmyelinated axons and many fibrous astrocytes.

The biochemistry of demyelination in MS was reviewed in detail [11]. Affected areas of MS white matter exhibit the expected decrease of myelin constituents and a buildup of cholesterol esters. For example, polycrystalline gel electrophoresis of homogenates of macroscopically normal appearing white matter, outer periplate, inner periplate and plaque shows the expected decline of MBP and PLP in going from the normal appearing white matter to the center of the plaque in both chronic and acute lesions (Fig. 38-2). There is a virtual absence of these myelin proteins in the center of the chronic plaque and an accumulation of glial fibrillary acidic protein (GFAP) indicative of astrogliosis (Fig. 38-2B). A plaque from a more acute lesion is not completely demyelinated, as indicated by the presence of some MBP and PLP, and there is no accumulation of GFAP (Fig. 38-2C). The more acute plaque contains albumin as a result of breakdown of the blood–brain barrier. Immunocytochemical and quantitative biochemical analyses of myelin proteins have revealed that MAG is often decreased more than other myelin proteins at the periphery of plaques (reviewed in [12]), and this may be indicative of early pathological events in the

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**FIGURE 38-1** Coronal slice of brain from a patient who died with MS. Demyelinated plaques are clearly visible in white matter (large arrows). Small plaques are also observed at the boundaries between gray and white matter (small arrows). (Reproduced with permission from Raine, C. S. The neuropathology of myelin diseases. In P. Morell (ed.), Myelin. New York: Plenum Press, 1984, ch. 8.)
and based in part on evidence derived from animal models of autoimmune demyelinating disease such as EAE. In addition to providing insights into the natural history of the disease and a tool that can be used to monitor new treatments, MRI is also providing insights into the nature of the MS lesion. As indicated previously, blood–brain barrier disruption seems to be the initial event in lesions, and pathological studies suggest that enhancement is often characterized by acute inflammation. From findings derived from studies of EAE, it is likely that migration of activated T cells represents the initial step in lesion development.

What is not clear is the specificity of the T cells. There are numerous studies of T cell reactivity to myelin antigens such as MBP, PLP, and MOG, all of which are encephalitogenic in animals. However, the evidence taken as a whole has failed to demonstrate a substantially increased response to these antigens in most patients with MS compared to healthy controls. Nevertheless, at this time, MOG appears to be a leading candidate among myelin proteins to be an important target in the autoimmune aspects in many patients because of: (1) its accessibility to immune attack due to its surface localization on oligodendrocytes; (2) its capacity to produce a relapsing–remitting form of EAE resembling MS when used as an immunogen; and (3) the detection of immunoreactivity to MOG in a relatively high proportion of MS patients [3, 14]. It may be that several myelin antigens play a role in MS, and that the relative importance of different antigens varies among individuals depending on their immunogenetic background and environmental factors encountered during their life. Further, studies of TCR usage have generally failed to provide evidence for a restricted or limited TCR usage in myelin-antigen-specific T cells. What has emerged from studies of the T cell response to antigens such as MBP is that some portions of the molecule are immunodominant (e.g. MBP (83–99)), and these portions are regions that can be encephalitogenic in some animal models. Also, the HLA types that most readily present MBP to MBP-specific T cells, namely, the DR2 haplotype, are those that are over-represented in Caucasian patients with MS. Thus, it can be postulated that the T cell response to myelin antigens could represent one component of lesion development but one that, alone, is not sufficient for disease. Other factors could influence the integrity of the blood–brain barrier and regulation of cytokines.

Once a T cell enters the CNS and encounters antigen, it is postulated that a proinflammatory cytokine cascade is initiated that produces further compromise of the blood–brain barrier and amplifies the inflammatory response, which eventually results in demyelination. The cause of myelin damage is not known. Possibilities include direct toxic effects of some cytokines such as TNFα and NO on oligodendrocytes, or macrophage-mediated damage either through production of proteases or through ligand-mediated interaction with the myelin membrane. Electron microscopy of active MS lesions indicates that one
mechanism for myelin destruction is the direct removal, by macrophages, of myelin lamellae from the surface of intact sheaths. This involves the attachment of superficial lamellae to coated pits at the macrophage surface, implying the presence of receptors that bind to a ligand on the myelin. The Fc receptors on the macrophages may bind to immunoglobulins attached to the myelin and, as mentioned previously, studies of EAE have shown that antibodies to galactocerebroside, MOG or other surface molecules of myelin can augment demyelination.

There is much evidence indicating that proteases and other catabolic enzymes are involved in the myelin loss in MS [11]. MBP is highly susceptible to proteases even when present in myelin membranes. A neutral protease released by stimulated macrophages catalyzes the conversion of plasminogen to plasmin, which rapidly degrades MBP. Acid proteinase and other degradative enzymes, presumably lysosomal and of macrophage origin, are elevated in affected MS tissue and are likely to be involved in breakdown of myelin proteins and lipids. In addition, protease activities intrinsic to myelin sheaths (such as Ca\textsuperscript{2+}-activated neutral protease) may facilitate myelin destruction. Immunologically reactive, proteolytic fragments of MBP appear in the cerebrospinal fluid (CSF) and urine of MS patients during exacerbations of the disease, presumably reflecting myelin breakdown. However, the presence of this material is not specific for MS since it occurs in other conditions with myelin damage such as stroke and encephalitis. Matrix metalloproteases (MMPs) have attracted interest in recent years with regard to MS, because they participate in degradation of extracellular matrix, thereby allowing immune cells to move from the blood into the white matter.

In addition to immunological factors, it is likely that both genetic and environmental factors contribute to disease susceptibility [1, 2, 7, 8]. Two types of study have provided data that favor a genetic component in MS. First, the prevalence of MS varies substantially among ethnic groups, with Caucasian populations showing a higher frequency than some other groups. For example, MS occurs at low frequency both in Japan and in Japanese Americans living in high-prevalence regions of the United States. Secondly, there is increased risk among first-degree relatives of individuals with the disease, especially in monoygotic twins where the rate of concordance for the disease is 20–30% and even higher with careful examination by techniques such as MRI. Several possible genetic loci have been examined in MS and, as mentioned above, a fairly consistent association, although weak, with HLA makeup has been found in most studies. Investigators have attempted to examine the entire genome in patients with MS. While some areas of possible significance have been found, it is certain that the effect of any single genetic locus is relatively small. It is almost certain that multiple genes are involved, each with a small influence on susceptibility.

Several types of evidence point to an environmental influence in MS. These include unequal geographic distribution of the disease, effect of migration between low- and high-risk areas on susceptibility, and evidence for epidemics or clusters. Each of these sets of observations is open to variable interpretation and in many cases the genetic influence is difficult to separate from that of the environment. However, the bulk of evidence suggests that environment contributes to risk. The nature of an environmental influence is not known, but an infectious agent has long been suspected [1, 2]. There are a number of naturally occurring and experimental disorders in animals caused by viruses that have long incubation periods and involve primary demyelination with relative sparing of axons (see above). A possible viral etiology for MS has stimulated an extensive amount of research over the years, leading to many reports of viruses associated with MS. One way in which a viral infection could set off an autoimmune attack on myelin would be by molecular mimicry, in which a foreign peptide has sufficient sequence similarity to a neural antigen to set off an autoimmune attack. There is currently a substantial amount of interest in a possible involvement of human herpes virus 6 [15]. However, at this time a definite causative infectious agent has not been established. Nevertheless, a viral infection occurring before puberty and possibly modifying immune function, rather than resulting in a persistent infection, seems likely. Thus, although it is widely thought that MS is an autoimmune disease and associated with an infectious agent, the putative antigen(s) and virus(es) remain elusive. Furthermore, as stated above there is growing evidence that all cases of MS may not be associated with the same virus or antigen but rather the disease process may be set in motion by a variety of infectious agents leading to a spectrum of immune cascades varying from patient to patient depending on their genetic background, but leading to a similar final pathology as represented by demyelinated plaques.

Therapies that are thought to modify immunopathogenic aspects of the disease have been approved for use in treating patients with relapsing-remitting MS, including interferon beta and copolymer-1 (Cop-1, glatiramer acetate) [8, 16]. The mechanism of action of the beta interferons is not entirely clear, but appears to involve modulation of the expression of adhesion molecules and matrix metalloproteases, resulting in a decrease of blood-brain barrier breakdown, as well as suppressing T cell activation and inhibiting proinflammatory cytokine production. Cop-1 is a synthetic random polymer, composed of the amino acids L-alanine, L-glutamic acid, L-lysine and L-tyrosine, which is believed to selectively bind to HLA class II molecules and to block antigen presentation. It also induces a shift in cytokine production and the generation of Th2 cells, which cross-react with myelin components and mediate bystander suppression. Although these therapies are moderately effective, they only reduce disease exacerbations by about 30% or delay disease progression. Therefore, research aimed at interfering with the autoimmune process at different levels is under way.
in many laboratories [7, 8, 16], and MRI is providing a powerful tool for monitoring the initial testing of experimental therapies. One example is mitoxantrone, approved for treatment of secondary progressive and progressive-relapsing MS, a synthetic antineoplastic anthracyclene that inhibits proliferation of B and T cells and macrophages, impairs antigen presentation and secretion of INFγ, TNFα and interleukin (IL)-2 in vitro [17]. Another pharmacologic approach is to inhibit migration of T cells across the blood–brain barrier by antibody blocking of α4-integrin. An example is natalizumab, a humanized monoclonal antibody presently under clinical trials [18]. Other examples of therapeutic approaches under investigation are inhibitors of metallic proteinases, which also alter cell migration across blood–brain barrier; vaccination with pathogenic T cells specific for candidate autoantigens in myelin; and treatment with altered peptide ligands that block T cell activation or induce bystander suppression. Increasing use of powerful technologies such as gene microarray analysis of MS tissues and proteomics should help identify more disease markers and effectors that can be targeted and ultimately lead to therapies tailored to different stages of disease or subsets of MS patients. Alternative approaches to therapy involve repair both by stimulating remyelination and promoting the survival and regeneration of axons. The latter is likely to be a major emphasis in the future, now that it is known that much of the irreversible neurological damage in MS is caused by axonal loss. However, a serious problem to the use of methodologies to stimulate repair in MS is that the lesions of MS develop at different times and locations in optic nerve, cerebrum, cerebellum, brainstem and spinal cord, each of which may have its own unique requirements. The various approaches to repair tissue damage in myelin diseases is discussed in greater detail at the end of this chapter, because they also apply to other myelin disorders with differing etiologies. 

Some human peripheral neuropathies involving demyelination are immune-mediated. Guillain–Barré syndrome (GBS) is an acute inflammatory demyelinating polyneuropathy that is monophasic, self-limiting and frequently occurs following an antecedent bacterial or viral infection [1, 2, 19] (see also Ch. 36). It is generally characterized by primary demyelination, although variants with severe axonal involvement also exist. Chronic inflammatory demyelinating polyneuropathy (CIDP) is similar but is progressive or relapsing–remitting with a duration of many months or years [1, 2, 20]. With regard to potential target antigens for autoimmune diseases of the PNS, it should be kept in mind that, although PNS and CNS myelin are morphologically similar, they differ significantly in chemical composition, especially in protein constituents (see Ch. 4). Cumulative evidence suggests that nerve injury in GBS and CIDP is mediated by immunological mechanisms but, as in MS, the roles of the patients’ cell mediated and humoral responses in causing the demyelination have not been fully defined. An important role of humoral immunity in these diseases is strongly suggested by findings that sera from GBS patients cause demyelination in appropriate test systems and that plasmapheresis and intravenous administration of immunoglobulin are effective therapies in many of these patients. Neuropathies also occur in association with monoclonal gammopathy (also called paraproteinemia) in which there is expansion of a clone of plasma cells leading to large amounts of a monoclonal antibody in the patient’s serum. It is thought that the neuropathies in these patients are likely to be caused by binding of the monoclonal antibodies to neural antigens [21].

Although experimental allergic neuritis (EAN) is often considered to be a good animal model for GBS, and the P2 myelin protein is implicated as an important antigen in this model (see Ch. 36), neither cellular nor humoral immunity to P2 or other myelin proteins has been detected consistently in GBS. Similarly, although antibodies to galactocerebroside have been shown to cause peripheral demyelination in experimental animals, evidence for significant levels of antibodies to this glycolipid in GBS is lacking. However, a substantial body of research now indicates that antibodies to more complex glycolipids, such as gangliosides (see Ch. 3), are involved in the pathogenesis in many of the human immune-mediated neuropathies described above [21]. The first indications of this came from patients with demyelinating sensorimotor neuropathy in association with IgM gammopathy. The monoclonal antibodies in these patients were shown to react with a carbohydrate epitope in MAG that is shared with complex glycolipids and other glycoproteins, including P0 and peripheral myelin protein-22 (PMP-22) of compact PNS myelin. The principal antigenic glycolipid, which is present in much larger amounts in the mature PNS than the CNS, is sulfate-3-glucuronyl paragloboside (SGPG). The specificity of these human antibodies is very similar to that of the HNK-1 antibody, which reacts with a number of adhesion proteins in the nervous system (see Ch. 4). Several animal models involving administration of the human anti-MAG/SGPG antibodies or immunization with SGPG strongly suggest that this disease is caused by the antibodies, but the relative importance of the potential glycolipid and glycoprotein target antigens in contributing to the pathology remains to be established. About half of patients with neuropathy in association with IgM gammopathy have antibodies of this specificity. It is also noteworthy that monoclonal IgM antibodies in patients with neuropathy who are MAG/SGPG-negative frequently react with gangliosides, suggesting that complex glycolipids may be important target antigens in immune-mediated neuropathies.

Once the monoclonal antibodies reacting with complex glycolipids were shown to occur frequently in patients with neuropathy in association with gammopathy, antibodies were demonstrated in some patients with GBS and other forms of inflammatory demyelinating neuropathy [21].
For example, antibodies to GM1 ganglioside are strongly associated with a subset of GBS that is particularly severe, has a high degree of axonal degeneration and presents with predominantly motor symptoms. Antibodies to GM1 ganglioside are also found frequently in a distinct chronic progressive neuropathy defined by multifocal motor conduction blocks. This condition, known as multifocal motor neuropathy (MMN), is characterized by weakness, muscle atrophy and motor nerve demyelination, while sensory function is normal or only slightly affected. Generally, there appears to be a strong correlation between antibodies to GM1 ganglioside and motor nerve disorders, including GBS, MMN and the neuropathies in association with monoclonal gammopathy described below. Another correlation of clinical presentation with antibody specificity involves patients with ataxic neuropathies and antibodies to disialosyl epitopes in gangliosides such as GD1b, GT1b and GQ1b. This correlation is found both in patients with monoclonal gammopathy and those with the Miller–Fisher variant of GBS.

Research has resulted in major advances in animal modeling of anti-glycolipid antibody-associated neuropathies in vitro and in vivo, which make a strong case that the antibodies cause much of the neurological impairment in these patients [21]. Furthermore, molecular mimicry between immunogens expressed by antecedent infectious agents and neural gangliosides appears to account for the presence of the glycolipid antibodies in some cases. Thus, carbohydrate configurations very similar or identical to those of gangliosides occur in the lipopolysaccharide (LPS) of strains of *Campylobacter jejuni* that are associated with these subsets of GBS (Fig. 38-3). Although it is now well established that anti-glycolipid antibodies are important pathogenic agents in many patients, not all patients with acquired acute or chronic peripheral neuropathies express these antibodies. Therefore, much remains to be learned about the pathogenic roles of antibody and T cell responses to other neural antigens, the importance of cytotoxic immune mediators and other factors in the acquired immune-mediated neuropathies.

**Other acquired disorders affecting myelin in humans may be secondary to viral infections, neoplasias or immunosuppressive therapy.** Acute disseminated encephalomyelitis, also called postinfectious or postimmunization encephalitis, represents a group of disorders usually of mixed viral–immunological etiology. The condition is most commonly related to a spontaneous viral infection, of which major examples are measles, smallpox or chickenpox [1, 2].

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**FIGURE 38-3** Molecular mimicry in subsets of patients with Guillain–Barré syndrome. Carbohydrate configurations (dark orange triangles) in the lipopolysaccharide (LPS) on some strains of *Campylobacter jejuni* are the same as in GM1 ganglioside on neural membranes. The chemical structures of LPS and GM1 are shown in the inset with the shared terminal tetrasaccharide in dark orange. Antibodies produced in response to LPS during a *C. jejuni* infection are intended to fight the infection but may cross-react with GM1 on neural cells, causing pathogenic effects in Guillain–Barré syndrome by mechanisms such as those listed in the lower right of the figure. Similarly, the LPS in other strains of *C. jejuni* have carbohydrate structures similar to those in GQ1b ganglioside, and those strains are associated with the Miller–Fisher variant of Guillain–Barré syndrome with prominent cranial nerve involvement, ataxia and areflexia. Antibodies to GQ1b are found in essentially all patients with this variant.
The demyelination occurring in these conditions is likely to be mediated at least in part by immune mechanisms since T cells sensitized to MBP are detected in many of these patients.

The nervous system is affected in a high proportion of patients with acquired immunodeficiency syndrome (AIDS) [2, 22]. Abnormalities related to myelin include a generalized myelin pallor observed histologically, vascular myelopathy and focal demyelination. Although it was originally thought that the widespread myelin pallor could be indicative of substantial demyelination, it now appears that the reduced staining is related to accumulation of fluid resulting from breakdown of the blood–brain barrier and not to extensive myelin loss. It is generally accepted that HIV infection in the nervous system in vivo is largely restricted to macrophages and microglia, and that the myelin and oligodendrocyte damage associated with HIV may be mediated by cytokines released by infected macrophages (see section on toxins, below).

Progressive multifocal leukoencephalopathy (PML) is historically a rare demyelinating disease that is usually associated with disorders of the reticuloendothelial system, neoplasias and immunosuppressive therapy [1, 2]. However, it has become more important in clinical medicine because it is frequently seen as an opportunistic secondary infection in immunocompromised persons with AIDS. PML is characterized by focal lesions that are noninflammatory and caused by infection of oligodendrocytes with the JC papovavirus.

### Genetically Determined Disorders of Myelin

The human leukodystrophies are inherited disorders of central nervous system white matter. These disorders are characterized by a diffuse deficiency of myelin caused by a variety of genetic lesions and often manifest before 10 years of age (Table 38-1). Some are caused by mutations in the PLP gene and resemble the PLP animal mutants described in Chapter 4 [1, 23]. As with the animal models, depending on the nature of the mutation, they vary from a severe form in conntetal Pelizaeus–Merzbacher disease (PMD) through an intermediate phenotype in classical PMD to a mild phenotype in spastic paraplegia. It is noteworthy that some mutations of the PLP gene also cause a peripheral neuropathy [24], very probably related to the expression of low levels of PLP in peripheral nerve (see Ch. 4).

Other leukodystrophies are associated with the lysosomal and peroxisomal disorders in which specific lipids or other substances accumulate due to a deficiency in a catabolic enzyme – for example Krabbe’s disease, metachromatic leukodystrophy (MLD) and adrenoleukodystrophy (ALD) [1, 2]. (These are discussed in detail in Ch. 40.) Similarly, disorders of amino acid metabolism can lead to hypomyelination – for example phenylketonuria and Canavan’s disease (spongy degeneration) [1, 2, 25] (Ch. 40). The composition of myelin in the genetically

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Genetic lesion</th>
<th>Comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenoleukodystrophy</td>
<td>X-linked</td>
<td>Peroxinsomal membrane protein in the ABC transporter family</td>
<td>Decreased peroxidation of saturated, very-long-chain fatty acids, causing their accumulation in brain, adrenals and other tissues; variable phenotypes with regard to hypomyelination; see text</td>
<td>1, 26, Ch. 40</td>
</tr>
<tr>
<td>Canavan’s disease (spongy degeneration)</td>
<td>AR</td>
<td>Aspartoacylase</td>
<td>Widespread white matter edema with diminished myelin; N-acetylaspartic aciduria; see text</td>
<td>1, 25, Ch. 40</td>
</tr>
<tr>
<td>Charcot–Marie–Tooth disease and other inherited neuropathies</td>
<td>AD, AR or X-linked</td>
<td>PMP-2, P0, connexin-32 and other genes</td>
<td>Variable degrees of myelin deficiency specific for the PNS; see text</td>
<td>1, 28–30</td>
</tr>
<tr>
<td>Krabbe’s leukodystrophy</td>
<td>AR</td>
<td>Galactocerebrosidase–β-galactosidase</td>
<td>Globoid cells contain galactocerebrosidene; see text</td>
<td>1, 2, Ch. 40</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>AR</td>
<td>Aryl sulfatase A</td>
<td>Accumulation of sulfatide in brain; see text</td>
<td>1, 2, Ch. 40</td>
</tr>
<tr>
<td>Pelizaeus–Merzbacher disease (classical and conntatal forms) and spastic paraplegia</td>
<td>X-linked</td>
<td>PLP</td>
<td>Variable hypomyelination due to different mutations in the major structural protein of CNS myelin; similar to rodent mutants such as the jinny mouse</td>
<td>1, 23</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>AR</td>
<td>Phenylalanine hydroxylase</td>
<td>White matter is up to 40% deficient in myelin; hypomyelination may be caused by inhibition of amino acid transport and/or protein synthesis by the high level of phenylalanine that accumulates</td>
<td>1, Ch. 40</td>
</tr>
<tr>
<td>Refsum’s disease</td>
<td>AR</td>
<td>Oxidation of branched chain fatty acids; phytan-olyl CoA 2-hydroxylase in some cases</td>
<td>Increase of branched-chain phytanic acid, especially in PNS myelin</td>
<td>1, 38, Ch. 40</td>
</tr>
<tr>
<td>Vanishing white matter disease</td>
<td>AR</td>
<td>Eukaryotic initiation factor 2B (eIF2B)</td>
<td>Also referred to as childhood ataxia with central hypomyelination (CACH); see text</td>
<td>27</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive
determined disorders can be normal, have a specific alteration reflecting the genetic lesion or show a nonspecific pathological composition that is found in many myelin disorders. The composition of the small amount of myelin isolated from Krabbe’s disease is normal, and the hypomyelination is believed to be caused by the accumulation of galactosylsphingosine (psychosine) which has a cytotoxic effect on myelin-forming cells. By contrast, myelin isolated from postmortem metachromatic leukodystrophy (MLD) brain is highly enriched in sulfatide, but it is not known for certain if the myelin membrane contains more sulfatide or if the excess is due to sulfatide-enriched micelles that are co-isolated during the myelin purification. In some genetic disorders such as ALD and Canavan’s disease, as well as in a wide variety of disorders involving secondary demyelination, the myelin preparations have similar abnormal chemical compositions. In each case, the isolated pathological myelin has a generally normal ultrastructural appearance but has much more cholesterol, less cerebroside and less phosphatidyl ethanolamine than does normal myelin. Certain experimental disorders induced in animals by toxic agents show the same type of abnormal myelin. Myelin with this abnormal composition is referred to as the ‘nonspecific pathological type’ and probably represents a partially degraded form.

X-linked ALD has long been known to be a peroxisomal disease that involves a defect in the β-oxidation of very-long-chain fatty acids (VLCFAs), leading to their accumulation in complex lipids of myelin (Ch. 40) [1, 26] and it was thought that the genetic defect would turn out be in an enzyme such as VLCFA-CoA synthetase. However, the positional cloning approach showed that the defective gene is a 70 kDa peroxisomal membrane protein (ALD/ABCD1) in the ATP binding cassette transporter protein family (Ch. 5). An interesting aspect of ALD is that the phenotype can vary from a major neurological problem in the childhood form with a severe deficiency of myelin in the brain, through a milder form known as adrenomyeloneuropathy that occurs in young men and affects primarily spinal cord and peripheral nerve, to less common phenotypes without neurological involvement.

The function of the ALD protein is not fully understood, and knockout mice lacking it do not exhibit the severe CNS neurological deficits commonly associated with the human disease despite a similar accumulation of VLCFAs [26]. Furthermore, the clinical variability in human patients cannot be accounted for by the severity of the biochemical abnormality or the nature of the gene defect. These observations, plus other data from mice with defects in VLCFA metabolism, raise the issue of whether the accumulation of VLCFAs in myelin is crucial to the pathological mechanisms or is an epiphenomenon. Unlike most other lipid-storage diseases, active ALD brain lesions are characterized by perivascular accumulation of lymphocytes. For this reason, it has been hypothesized that the severity of CNS pathology may relate to an autoimmune reaction that varies from patient to patient and is minimal or missing in the ALD-deficient mice. Because of the inflammation, it is not surprising that substantial amounts of cholesterol ester accumulate in the ALD brain. Similar to other disorders in which myelin debris is phagocytosed, most of the cholesterol esters are in an abnormal floating fraction of lower density than the density of isolated myelin.

MRI has led to the frequent identification of inherited leukodystrophies of unknown cause, many of which exhibit a syndrome now called childhood ataxia with central nervous system hypomyelination (CACH) or vanishing white matter disease (VWMD) [27]. The syndrome is usually characterized by the onset of ataxia in early childhood followed by progressive neurological deterioration. Also, histological examination frequently reveals novel foamy appearing oligodendrocytes with numerous round inclusions in these patients. Most patients with this syndrome have mutations in the mRNA translation initiation factor eIF2B.

**Deficiencies of peripheral nerve myelin in common inherited human neuropathies are caused by mutations of genes for sheath proteins.** Remarkable progress in elucidating an expanding number of gene loci and pathogenic mechanisms for inherited neuropathies has been achieved, based on our increasing knowledge of the biology of Schwann cells, axons and their interactions [28–30]. From a historical perspective, the most common inherited neuropathies were divided into two forms of Charcot–Marie–Tooth (CMT) disease largely on the basis of electrophysiology – type 1 (CMT1), which primarily affects myelin, and type 2 (CMT2), which primarily affects axons. In addition, there are milder (hereditary neuropathy with liability to pressure palsies), more severe (Dejerine–Sottas syndrome), and congenital (congenital hypomyelinating neuropathy) inherited neuropathies. Mutations affecting the same gene can cause neuropathies falling into more than one of these clinical categories depending on the exact nature of the mutation, with gain-of-function phenotypes usually being more severe than those associated with loss of function. Common forms of CMT1 are caused by dominant mutations of genes for compact myelin proteins, PMP-22 in CMT1A and P0 protein in CMT1B. CMT1A is usually due to duplication of the PMP-22 gene with onset in the second or third decade of life and characterized by segmental demyelination, remyelination and onion bulb formation. Hereditary neuropathy with liability to pressure palsies is a milder neuropathy brought on by pressure or trauma to an affected nerve and is caused by a heterozygous deletion of the PMP-22 gene. These human disorders, caused by over and under expression of PMP-22, respectively, illustrate the importance of dosage of some myelin proteins for myelin stability (see Ch. 4). Some more severe forms of CMT1A and Dejerine–Sottas syndrome have missense mutations in transmembrane regions of PMP-22 similar to the murine trembler mutations (see Ch. 4). CMT1B and some forms of Dejerine–Sottas
syndrome are caused by a variety of mutations in the major P0 glycoprotein of compact myelin, presumably impairing its capacity to stabilize the intraperiod and/or major dense lines or interfering with a function in signal transduction (see Ch. 4).

There are other forms of inherited neuropathy affecting myelin that are caused by mutations of genes that alter Schwann cell proteins not localized in compact myelin [28–30]. Some examples include: (1) an X-linked form (CMTX) caused by mutations of the gap junction protein connexin 32 (CX32), which is localized in paranodal loops and incisures where it probably forms gap junctions between adjacent layers of myelin sheaths; (2) a recessive form (CMT4F) caused by mutations of periaxin, which is part of a protein complex linking the extracellular basal lamina to the actin cytoskeleton of Schwann cells; and (3) a dominant form of CMT1 caused by mutations of a zinc finger transcription factor (EGR2, also called Krox 20). It is clear that genetic defects in a variety of Schwann cell functions can cause myelin deficiencies, but discussion of the likely pathogenic mechanisms is beyond the scope of this chapter. Furthermore, as is the case for disorders of CNS myelin, it is becoming increasingly apparent that axonal pathology and degeneration are often responsible for much of the neurological impairment in these inherited disorders caused by mutations expressed in Schwann cell genes, possibly due to defects in Schwann cell–axon interactions.

TOXIC AND NUTRITIONAL DISORDERS OF MYELIN

A variety of biological and chemical toxins can impair myelin formation or cause its breakdown. Biological toxins affecting myelin-forming cells can be produced by exogenous infectious agents in diseases such as diphtheria or endogenously by lymphocytes and macrophages. For example, diphtheritic neuropathy [1] is a possible complication of Corynebacterium diphtheriae infection and is characterized by vacuolation and fragmentation of myelin sheaths in the PNS. Also, cytokines, such as tumor necrosis factor and lymphotoxins, released by lymphocytes and macrophages can be toxic to oligodendrocytes in vitro, but the nature of their involvement in the pathogenic mechanisms of autoimmune diseases in vivo may be quite complex [31]. Activated immune cells also release oxygen radicals and nitric oxide, which are harmful to oligodendrocytes. These toxins could lead to loss of myelin-forming cells and myelin independently of whether the immune reaction is directed against myelin or an exogenous infectious agent. Damage to myelin by an immune reaction directed to an unrelated antigen is referred to as a ‘bystander effect’.

Lead is a common environmental pollutant that is well known to cause hypomyelination and demyelination. Other chemical toxins affecting myelin-forming cells or myelin and that have been investigated experimentally include cuprizone, lyssolecithin, triethyltin, hexachlorophene and tellurium. The effects of these and other chemical toxins on the biochemistry of myelin is beyond the scope of this chapter but have been covered in more detail in earlier editions of this book or in other sources [1].

General undernourishment or dietary deficiencies of specific substances can lead to a preferential reduction in myelin formation. Much of the CNS myelin in mammals is formed during a relatively restricted time period of rapid development. During this period, a large portion of the brain's metabolic activity and synthetic capacity are involved in myelinationogenesis. Therefore, any metabolic insult during this 'vulnerable period' may lead to a preferential reduction in myelin formation [1]. The most vulnerable period appears to be the time of oligodendrogliogenesis, since animals deprived of food in this period have an irreversible deficit of myelin-forming cells and hypomyelination (see also Ch. 25). However, animals deprived at a later age can often demonstrate significant catch-up with regard to the amount of myelin when nutritional rehabilitation is instigated after a period of underfeeding. Failure to myelinate properly and demyelination are also associated with deficiencies of dietary protein, essential fatty acids, copper and several vitamins, including thiamine, B12 and B6 [1].

DISORDERS PRIMARILY AFFECTING NEURONS WITH SECONDARY INVOLVEMENT OF MYELIN

Many insults to the nervous system initially cause damage to neurons but eventually result in regions of demyelination as a consequence of neuronal degeneration. The archetypical model for secondary demyelination is Wallerian degeneration (see Ch. 30). When a nerve (in the PNS) or a myelinated tract (in the CNS) is cut or crushed, the proximal segment often survives and regenerates [1]. In the distal segment, Wallerian degeneration occurs with disappearance of both axons and myelin and phagocytosis of the debris. From such experiments, it is clear that the integrity of the myelin sheath depends on continued contact with a viable axon. Any disease that causes injury to neurons may result in axonal degeneration and lead to the onset of myelin breakdown secondary to the neuronal damage. During Wallerian degeneration in the PNS, there is a rapid loss of myelin-specific lipids and proteins within a week or two with a concomitant increase in lysosomal enzymes. Between the second and fourth week after nerve section most of the myelin debris has been removed by Schwann cells and macrophages, and remyelination of regenerating axons begins. Degeneration of CNS myelin is a much slower process than in the PNS and takes place primarily within macrophages/microglia (not within the myelin-synthesizing cells, as in the PNS).
Secondary demyelination occurs in a variety of acquired and genetic CNS disorders that initially affect neurons, including mechanical trauma, infarcts, tumors, motor neuron disease, viral diseases such as subacute sclerosing panencephalitis, and sphingolipidoses such as Tay–Sachs disease, generalized gangliosidosis and Niemann–Pick disease (see Ch. 40). The isolated myelin from these diseases is usually of the ‘nonspecific pathological type’ that was discussed earlier in the context of some inherited primary demyelinating disorders. No cholesterol esters are found in the myelin, although they are abundant in the white matter, indicative of phagocytosis by macrophages.

REPAIR IN DEMYELINATING DISEASES

The capacity for remyelination is generally greater in the peripheral than in the central nervous system. Much of this chapter has considered biochemical mechanisms of myelin loss, but the capacity of nervous tissue to repair the damage by remyelination is also an important factor in the eventual clinical outcome of disorders affecting myelin. Following transection of peripheral nerve, as described in the previous section, myelination of the regenerating axons occurs soon after the final clean-up of myelin debris by Schwann cells [1]. The Schwann cells that form the new myelin are probably not the same ones that phagocytose the debris but appear to arise by cell division. The smaller capacity for remyelination in the CNS in comparison to the PNS may be caused in part by the nature of the myelin-forming cells, i.e. in the requirement for oligodendrocytes to myelinate many axons in contrast to the single segments of myelin formed by Schwann cells. Under some circumstances, such as in EAE and MS, it has been demonstrated that Schwann cells will migrate into the spinal cord and remyelinate demyelinated CNS axons.

Remyelination in the CNS can be promoted by various treatments. Substantial remyelination can occur in the CNS depending on the nature of the pathogenic insult, and it is likely that therapeutic procedures that enhance remyelination are feasible [2, 32, 33] (discussed in detail in Ch. 30). For example, rapid remyelination by oligodendrocytes does occur following acute demyelination caused by toxins such as cuprizone or lyssolecithin, although the myelin sheaths are thinner than normal. The failure of significant remyelination in other circumstances may relate to the continuing effect of pathogenic processes. However, even in MS, careful observations of acute lesions have demonstrated the presence of healthy oligodendrocytes and regeneration of myelin in the presence of myelin breakdown. Although the remyelination attempt eventually fails and oligodendrocytes are lost from lesions that progress to advanced demyelinated plaques, such observations raise the possibility that management of patients with demyelinating diseases of the CNS may eventually involve treatments that take advantage of the capacity of oligodendrocytes for remyelination.

Research on experimental animals as well as human diseases indicates that remyelination can occur by proliferation and differentiation of host progenitor cells, which are quiescent in normal adult tissue (Ch. 29). Several approaches are being used to attempt to enhance the natural capacity of oligodendrocytes or their progenitors to remyelinate. Because a large number of growth factors (Ch. 27), such as epidermal growth factor, basic fibroblast growth factor, platelet derived growth factor, ciliary neurotrophic factor and insulin-like growth factor, are known to affect the survival, proliferation, migration and differentiation of oligodendrocyte progenitors, it is feasible that remyelination might be promoted in patients by treatment with one or more of these factors. An interesting finding in MS is that transforming factor-β produced by inflammatory cells induces expression in hypertrophic astrocytes of jagged, which activates the Notch signaling pathway in oligodendroglial precursors [34]. This appears to inhibit their capacity for remyelination and may provide a specific site for therapeutic intervention. Another observation that has relevance for enhancing remyelination is that various immunoglobulin preparations containing antibodies reacting with surface antigens of oligodendrocytes have the capacity to promote remyelination in experimental animals by activating a calcium ion signaling system [35]. An approach actively being pursued at this time in many laboratories involves the capacity of transplants of myelin-forming glial cells to repair demyelinated lesions [2, 35]. Much of this research involves the transplantation of Schwann cells, oligodendrocytes, oligodendrocyte progenitors, glial cell lines or stem cells into hypomyelinated mutants or focally demyelinated lesions and has clearly demonstrated that transplanted cells have the capacity to remyelinate. A promising report shows that xenografting isolated fetal or adult human oligodendroglial progenitors into dysmyelinated shiverer mouse brain results in widespread and robust myelination [36].

A serious problem in MS is that, if there is a window of time after an insult during which a particular stimulus is effective for regeneration, in MS there are multiple windows of time for multiple locations. Finally, it is worth noting that a combination of these different therapies may provide the best results, and the optimal treatment may vary from one myelin disorder to another. Further research is needed to evaluate the success of these approaches in the presence of astrocytic gliosis and inflammation (Ch. 30).

Measures to enhance axonal survival and regeneration also are critical in demyelinating conditions. With the increasing awareness that substantial axonal degeneration occurs in many diseases that had previously been thought to affect primarily myelin and that this may account for much of the permanent neurological deficit, increasing attention is being given to therapies that promote axonal
survival and regeneration. Various growth factors are likely to be beneficial in this regard. However, a complicating factor is that white matter is well known to contain a number of inhibitors of axonal regeneration, including Nogo, MAG and OMgp [37] (see Ch. 30). Nevertheless, it is promising that each of these inhibitory proteins appears to act through the same Nogo receptor signaling system, so that it may be feasible to block the effects of all three simultaneously. In conclusion, therapy for myelin disorders in the future may involve a combination of approaches aimed at preventing myelin loss, while at the same time promoting the survival, regeneration and remyelination of axons.

REFERENCES

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