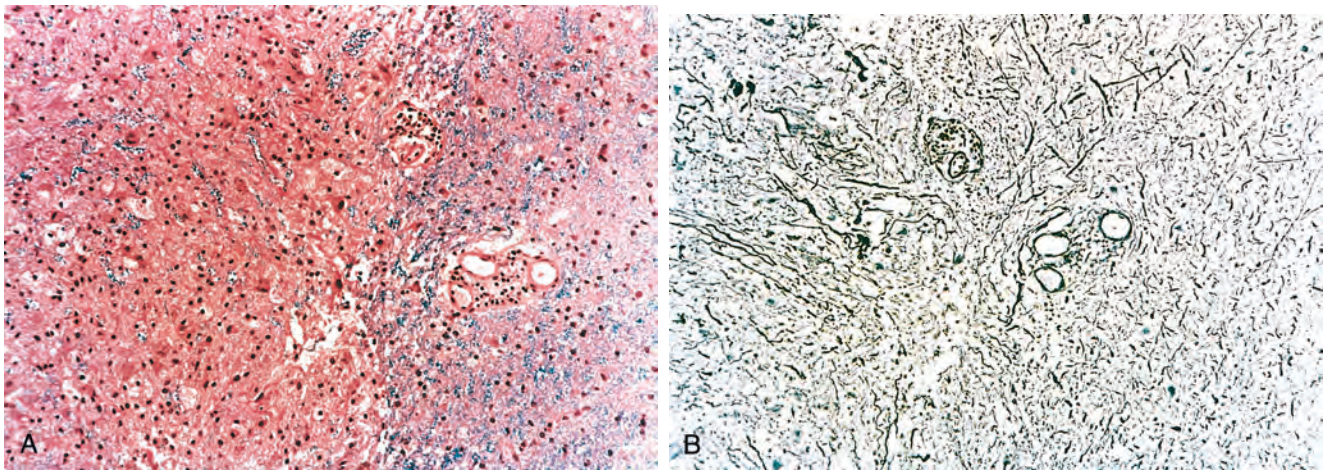

Figure 28-35 Multiple sclerosis. **A,** Myelin-stained section shows the sharp edge of a demyelinated plaque and perivascular lymphocytic cuffs. **B,** The same lesion stained for axons shows relative preservation.

microscopically to confluent plaques that involve large portions of the deep white matter. Plaques commonly occur adjacent to the lateral ventricles, and are also frequent in the optic nerves and chiasm, brainstem, ascending and descending fiber tracts, cerebellum, and spinal cord. Plaques can also extend into gray matter, since myelinated fibers are present there as well.

Microscopically, in an **active plaque** there is ongoing myelin breakdown associated with abundant macrophages containing lipid-rich, PAS-positive debris. Lymphocytes and monocytes are also present, mostly as perivascular cuffs, especially at the outer edge of the lesion (Fig. 28-35*A*). Active lesions are often centered on small veins. Within a plaque there is relative preservation of axons (Fig. 28-35*B*) and depletion of oligodendrocytes. In time, astrocytes undergo reactive changes. As lesions become quiescent, the inflammatory cells slowly disappear. Within **inactive plaques**, little to no myelin is found, and there is a reduction in the number of oligodendrocyte nuclei; instead, astrocytic proliferation and gliosis are prominent. Axons in old gliotic plaques show severe demyelination and are also greatly diminished in number.

In some MS plaques **(shadow plaques)**, the border between normal and affected white matter is not sharply circumscribed. In this type of lesion some abnormally thinned-out myelin sheaths can be demonstrated, especially at the outer edges. This phenomenon is most commonly interpreted as evidence of partial and incomplete remyelination by surviving oligodendrocytes. Abnormally myelinated fibers have also been observed at the edges of typical plaques. Although these histologic findings suggest a limited potential for remyelination in the CNS, the remaining axons within most MS plaques remain unmyelinated; studies aimed at promoting remyelination are an important focus of research.

Clinical Features. Although MS lesions can occur anywhere in the CNS and consequently may induce a wide range of clinical manifestations, certain patterns of neurologic symptoms and signs are more common. Unilateral visual impairment due to involvement of the optic nerve *(optic neuritis, retrobulbar neuritis)* is a frequent initial manifestation of MS. However, only a minority of individuals (10% to 50%, depending on the population studied) with an episode of optic neuritis go on to develop MS (which requires multiple episodes to support the diagnosis). Involvement of the brainstem produces cranial nerve signs, ataxia, nystagmus, and internuclear ophthalmoplegia from interruption of the fibers of the medial longitudinal fasciculus. Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function.

Examination of the CSF in individuals with MS shows a mildly elevated protein level and in one third of cases a moderate pleocytosis. IgG levels in the CSF are increased and oligoclonal IgG bands are usually observed on immunoelectrophoresis; these are indicative of the presence of a small number of activated B cell clones, postulated to be self-reactive, in the CNS. Radiologic studies using magnetic resonance imaging have taken on a prominent role in assessing disease progression; these studies, when correlated with autopsy studies as well as clinical findings, indicate that some plaques may be clinically silent even in otherwise symptomatic patients.

Neuromyelitis Optica

Neuromyelitis optica (NMO) is a syndrome with synchronous (or near synchronous) bilateral optic neuritis and spinal cord demyelination. Once considered a variant of MS, it is now clear that it has distinct epidemiology and pathophysiology. NMO has an even greater skewing toward affecting women than MS, is more commonly associated with poor recovery from the first attack, and is characterized by the presence of antibodies against aquaporin-4. This protein is the major water channel of astrocytes, and areas of demyelination in NMO show loss of aquaporin-4. These antibodies injure astrocytes through complement-dependent mechanisms; they are not, however, capable of transferring disease in animal models. In NMO, white cells are common in the CSF, often including neutrophils. Within the damaged areas of white matter, there is typically necrosis, an inflammatory infiltrate including neutrophils, and vascular deposition of immunoglobulin and