approximately 1 per 1000 persons in most of the United States and Europe. The disease may become clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare. Women are affected twice as often as are men. In most individuals with MS, the clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual, partial recovery of neurologic function. The frequency of relapses tends to decrease during the course of time, but there is a steady neurologic deterioration in most affected individuals.

Pathogenesis. **The lesions of MS are caused by an autoimmune response directed against components of the myelin sheath**. As in other autoimmune disorders, the pathogenesis of this disease involves both genetic and environmental factors (Chapter 6). The incidence of MS is 15-fold higher when the disease is present in a first-degree relative and roughly 150-fold higher with an affected monozygotic twin. Despite a series of well-powered studies, only a portion of the genetic basis of the disease has been explained. There is a strong effect from the DR2 extended haplotype of the major histocompatibility complex; each copy of the DRB1*1501 allele an individual inherits brings with it a roughly 3-fold increase in the risk of MS. Genome-wide association studies first identified additional associations with the IL-2 and IL-7 receptor genes, and subsequently with a number of other genes encoding proteins involved in the immune response, including cytokines and their receptors, co-stimulatory molecules, and cytoplasmic signaling molecules. Many of these loci have been found to be associated with other autoimmune diseases. These genetic studies have not explained variations in clinical course for individuals with MS.

Immune mechanisms that underlie the destruction of myelin are the focus of much investigation. The available evidence indicates that the disease is initiated by T_H1 and T_H17 T cells that react against myelin antigens and secrete cytokines. T_H1 cells secrete IFN-γ, which activates macrophages, and T_H17 cells promote the recruitment of leukocytes (Chapter 6). The demyelination is caused by these activated leukocytes and their injurious products. The infiltrate in plaques and surrounding regions of the brain consists of T cells (mainly CD4+, some CD8+) and macrophages. How the autoimmune reaction is initiated is not understood; a role of viral infection (e.g., EBV) in activating self-reactive T cells has been proposed but remains controversial.

Experimental autoimmune encephalomyelitis is an animal model of MS in which demyelination and inflammation occur after immunization of animals with myelin proteins. Many of our concepts of MS pathogenesis have been derived from studies in this model. The experimental disorder can be passively transferred to unimmunized animals with T_H1 and T_H17 cells that recognize myelin antigens.

Based on the growing understanding of the pathogenesis of MS, therapies are being developed that modulate or inhibit T-cell responses and block the recruitment of T cells into the brain. A potential contribution of humoral immunity has also been suspected for a long time, based on the early observation of oligoclonal bands of immunoglobulin in CSF. The demonstration that treatment with agents that deplete B-cells decreases the incidence of demyelinating lesions in patients with MS lends support to this idea.

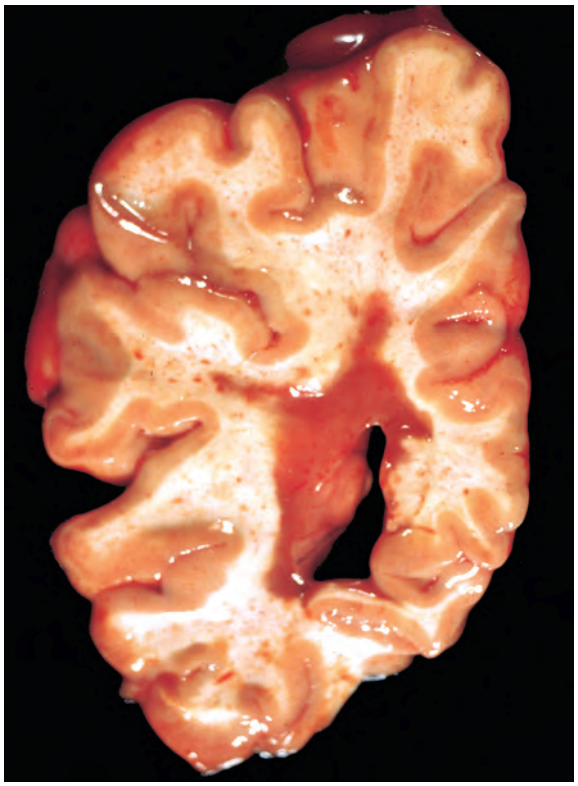

Figure 28-33 Multiple sclerosis. Section of fresh brain showing brown plaque around occipital horn of the lateral ventricle.

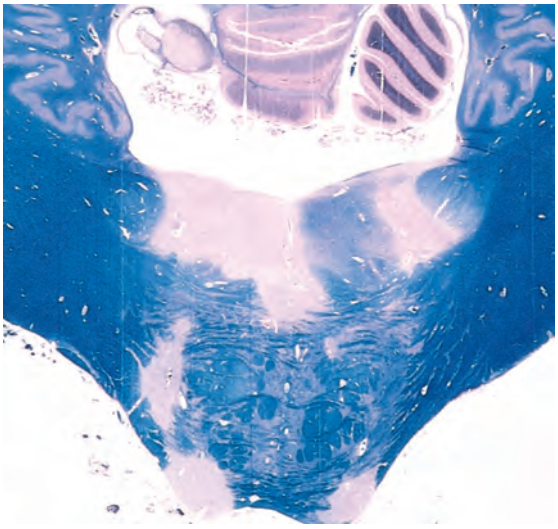

Figure 28-34 Multiple sclerosis (MS). Unstained regions of demyelination (MS plaques) around the fourth ventricle (Luxol fast blue periodic acid-Schiff stain for myelin).

MORPHOLOGY

MS is a white matter disease that is best appreciated in sections of the brain and spinal cord. In the fresh state, the lesions are firmer than the surrounding white matter **(sclerosis)** and appear as well circumscribed, somewhat depressed, glassy, gray-tan, irregularly shaped **plaques** (Fig. 28-33). The area of demyelination often has sharply defined borders, a feature best appreciated with stains for myelin (Fig. 28-34). The size of lesions varies considerably, from small foci that are only recognizable