The progress of research on the pathogenesis and treatment of multiple sclerosis (MS), the principal human demyelinating disease of the central nervous system (CNS), has intensified in the past 3 years. In part, this is due to the application of advances in molecular biology, like polymerase chain reaction (PCR), and to developments in cellular immunology, like technology for the growth of T-cell clones. Many lessons that have been learned in an animal model of CNS demyelinating disease, experimental allergic encephalomyelitis (EAE), have been verified in the human disease MS. Indeed, certain successful approaches for treatment of EAE are being attempted in MS at the present time.

This review describes the strong parallels that exist between T-cell receptor (TCR) usage in the pathogenesis of EAE, TCR usage in myelin basic protein (MBP)-specific T-cells in the peripheral blood of MS patients (Wucherpfennig et al. 1990; Ota et al. 1990; Martin et al. 1991) and in T-cells in demyelinating plaques in MS brain (Oksenberg et al. 1990). Based on these similarities, selective immunotherapy that targets either class II molecules of the major histocompatibility complex (MHC) or TCR variable regions will be described in EAE, with consideration given to application of these principles in MS. These new therapeutic approaches involve monoclonal antibodies (mAbs) directed to either HLA class II molecules or TCR V region molecules, or peptides that compete with HLA class II molecules or vaccinate against TCR V regions.

Relevance of EAE to Multiple Sclerosis

It has become increasingly clear that MS is a disease in which immunologic factors play a major role in the demyelinative lesion. This is supported by a large body of evidence of immune dysfunction in this disease (Reder and Arnason 1985). In EAE, we have considerable knowledge of the encephalitogenic antigen MBP and how T-cell recognition of that antigen is influenced by genetic susceptibility to the disease. In MS, on the other hand, the precise nature of the antigen remains unclear and the genetic elements that determine susceptibility are less completely understood. EAE continues to be the model
for MS, however, providing extensive information on the demyelinating process and allowing investigation into fundamental aspects of the autoimmune response, including providing a testing ground for new approaches to therapy which may potentially be extrapolated to demyelinating disease in man.

EAE is perhaps the best characterized model of an antigen-specific, T-cell-mediated autoimmune disease. It develops as a result of an immune response to the autoantigen MBP and can be induced in many species including rats and mice. It is characterized by the acute onset of paralysis subsequent to the inoculation of animals with either MBP or peptides of MBP in adjuvant, or by intravenous injection of T-cell clones. Perivascular infiltration by mononuclear cells in the central nervous system is seen with disease onset and demyelination can be clearly demonstrated. The disease is mediated by CD4+ T-lymphocytes and susceptibility to the resulting demyelination is linked to genes of the MHC class II region (Paterson 1960). The inbred mouse species we have utilized for EAE study include PL/J, (PLSJ)F1, and SJ/L, restricted by the MHC haplotypes H-2u, H-2u/s, and H-2s respectively. Within the H-2u/s haplotype H-2s appears to be differentially expressed and is thus non-functional. Many parallels exist in the etiopathogenesis of EAE and MS and it is based upon these similarities that successful immunotherapeutic strategies in EAE may have application to the human condition.

The T-Cell Response

We understand the lesion development in EAE and in MS to be a result of the abnormal activation of autoreactive class II-restricted CD4+ T-lymphocytes. The role for CD8+ T-cells is less clear. The trigger for T-cell activation in EAE is exposure to encephalitogenic antigen together with an adjuvant, while the trigger in MS has been proposed to be the result of either a viral or environmental influence (McFarland and Dhib-Jalbut 1989). Although the immune system of a given host has a wide repertoire of antigens it can recognize, response to each antigen is specific. To understand how T-lymphocytes participate in autoimmune disease it is necessary to be familiar with the fundamentals of antigen recognition.

T-cells recognize antigen only in association with a product of the MHC, the class I and class II antigens. The resulting ternary interaction of antigen, MHC, and the clonally distributed antigen-specific T-cell receptor is referred to as the trimolecular complex (McFarland and Dhib-Jalbut 1989; Hohlfeld 1989; Bjorkman et al. 1987a,b; Zamvil and Steinman 1990; Acha-Orbea et al. 1989) (Fig. 14.1). Major histocompatibility complex class I molecules are cell surface proteins expressed on all nucleated cells. In man these are the HLA-A, B, C antigens. In mice the homologous proteins are H-2K, D, L antigens. Class II molecules are cell surface glycoproteins expressed constitutively by macrophages, B cells and dendritic cells. In the CNS, class II molecule expression can be induced upon CNS endothelial cells and astrocytes (Hohlfeld 1989). In man these molecules are HLA-DP, DQ, and DR antigens. In mice they are I-A and I-E with the homologs being I-A to HLA-DQ and I-E to HLA-DR. Class II molecule cell-surface glycoproteins are heterodimers composed of an