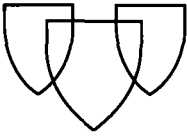




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SYMPOSIUM ON MULTIPLE SCLEROSIS—PART I

Multiple Sclerosis: Basic Concepts and Hypothesis

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Multiple sclerosis, an inflammatory disease of the central nervous system, is characterized by primary destruction of myelin. This review covers recent advances in neuropathology, immunogenetics, neuroimmunology, and neurovirology that have provided insights regarding its pathogenesis. Three hypotheses are discussed: (1) autoimmunity, (2) “bystander” demyelination, and (3) immune destruction of persistently infected oligodendrocytes. A paradigm for induction of primary demyelination is proposed in which immune cells recognize “foreign” antigens on the surface of oligodendrocytes in the context of major histocompatibility complex gene products. The final result of this scheme may be “dying-back gliopathy,” the alteration being noted first in the most distal extension of the oligodendrocyte—that is, the myelin sheaths.

PATHOLOGY

Multiple sclerosis (MS) affects scattered areas of the central nervous system with a predilection for periventricular white matter, brainstem, spinal cord, and optic nerves.¹ The plaques are characterized by primary demyelination (destruction of myelin sheaths with preservation of axons) and death of oligodendrocytes (myelin-producing cells) within the center of the lesion. During the early evolution of the plaque, perivascular inflammatory cells (lymphocytes, plasma cells, macrophages) invade the substance of the white matter and are thought to play a critical role in myelin destruction.² This process is followed by extensive

gliosis by astrocytes and aberrant attempts at remyelination with oligodendrocytes proliferating at the edges of the plaque.¹ In addition, immunoglobulins are deposited within each plaque.³

Whether the principal effector cells that mediate demyelination are T cells or macrophages is unknown. Attempts to type the cells that infiltrate the brain in MS have yielded conflicting results.⁴⁻⁷ Both CD8⁺ (cytotoxic/suppressor) T lymphocytes and CD4⁺ (helper/inducer) T lymphocytes surround the MS plaque. The relative proportions of T-cell subsets are controversial. Some investigators have found an excess of CD8⁺ cells in the perivascular cuffs at the edge of the lesion.⁷ Others have found an excess of CD4⁺ cells.⁴ These discrepancies probably result from examination of the plaques at different stages of their evolution.

Recent experiments have analyzed antigens of the major histocompatibility complex (MHC) in the brains of patients with MS.⁸ The MHC is a set of closely linked genes that play a central role in the control of immune responses to self and foreign antigens. This

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function is of particular importance because CD4⁺ and CD8⁺ T cells recognize foreign antigen in the context of class II (HLA-DR, Ia) or class I (HLA-ABC) MHC gene products, respectively. The class II gene products, found primarily on macrophages and B cells, are important in presentation of antigen to T cells. Class I gene products are on the majority of cells in the body and are important in the generation of the cytotoxic response against viruses.

The central nervous system is unique because MHC antigens normally are not present on neurons and glial cells.⁸ In MS, however, class I and class II MHC-positive astrocytes are found with high frequency in active lesions. The class I-reactive glia are primarily associated with T-cell infiltrates, whereas class II-reactive astrocytes are found in many lesions, independently of the composition of inflammatory cells. Thus, class I and II MHC-positive astrocytes might play a role in local antigen presentation to T cells. In addition, the simultaneous presence of high numbers of class I MHC-positive astrocytes and CD8⁺ cells in acute lesions suggests the possibility that CD8⁺ cells play a role as cytotoxic T cells during early development of the lesion.

The final consequence—that is, demyelination—in chronic active plaques may be attributable to several immunologic mechanisms, including receptor-mediated endocytosis by macrophages, cytotoxicity by T cells, or lymphokine release.

IMMUNOGENETICS AND IMMUNOLOGY

One piece of evidence that provides an important clue to the pathogenesis of MS is the association between susceptibility and specific MHC haplotypes.⁹ Northern Caucasians with MS have an overrepresentation of the A3, B7, DR2, and Dw2 histocompatibility alleles with relative risks of 2 to 3 for the class I MHC alleles (A3, B7) and 4 to 5 for class II MHC alleles (DR2, Dw2). Because linkage disequilibria exist between these class I alleles and DR2, the possible increased representation of one group of alleles may merely reflect this phenomenon.

The indefinite association between susceptibility and MHC haplotypes suggests that either more than one gene is involved or a strong environmental agent “breaks through” to disease in the absence of the MS susceptibility allele. The frequency of occurrence of A2, B12, DR7, and Dw7 is decreased in patients with MS.⁹ The data that pertain to this occurrence are in much better agreement, suggesting that some MHC alleles may protect against MS. Investigators have also reported that some MHC alleles (DR2) are asso-

ciated with more progressive disease whereas others (DR3) are associated with more benign disease.¹⁰ Studies in various populations (American blacks, Japanese, Arabs, Israeli Jews) have also shown an association with MHC but with different alleles in each case.

The risk of MS developing among first-degree relatives of patients with MS is increased 15- to 20-fold over the risk in the general population.⁹ This finding may reflect either genetic factors or shared environmental agents. Attempts to analyze linkage between disease and HLA haplotypes in siblings affected by MS have substantiated a loose link between MS and MHC but do not permit conclusions about the mode of inheritance.¹¹ For more distant relatives, concordance for MS is lower but exceeds chance expectation. In contrast, for non-blood-relatives living together (for example, husband and wife), the concordance for MS is not increased above chance. Studies in twins have shown greater concordance between monozygotic twins than between dizygotic twins.¹²⁻¹⁵ Many monozygotic pairs, however, are discordant for MS, a strong argument that genetic influence is insufficient for the development of MS. Also, the severity and expression of the disease vary greatly between members of concordant pairs.

Diseases that have been linked to the HLA complex have numerous similar features, including chronic course, inflammatory component, and weak genetic predisposition that does not obey mendelian genetics. One theory is that these disorders may have an autoimmune basis. The development of experimental autoimmune encephalomyelitis (EAE) as an animal model of MS has prompted investigation of the autoimmune basis of human demyelinating diseases.¹⁶ EAE can be induced by injection of central nervous system myelin or its components along with adjuvants. From the EAE model has evolved the concept that the primary target in MS may be myelin and not the oligodendrocyte.¹⁷ In addition, the disease can be transferred to naive animals with cells enriched for T lymphocytes reactive to the basic protein component of myelin.¹⁷⁻¹⁹ Therefore, attempts have been made to determine whether an immune response to normal myelin develops in patients with MS. To date, efforts to measure such a response in patients with MS have failed even though these responses can be detected in patients with postinfectious encephalomyelitis.²⁰

Although certain immunologic abnormalities have been reported in MS, many of the findings are still controversial.²¹ CD8⁺ lymphocytes apparently are decreased in the blood of patients with active MS and

in those with a progressive course,²²⁻²⁵ a situation that leads to a relative increase in the CD4/CD8 ratio. Disease activity is not always associated with these T-cell changes, however. The data on T-cell subsets in the cerebrospinal fluid are more discordant.²⁶⁻²⁸ Some investigators have reported a corresponding decrease in CD8⁺ cells in the cerebrospinal fluid,²⁸ whereas others have found no change.^{26,27} Some investigators have argued that the loss of CD8⁺ cells from the blood represents a disorder of immunoregulation.²² Others have suggested that the imbalance is the result of preferential sequestration of CD8⁺ cells in the central nervous system or lymphoid organs.²⁵

Recent experiments suggest a decrease in the suppressor/inducer subset (CD4⁺, 2H4⁺) in serum of patients with progressive MS.²⁹ These suppressor/inducer cells are not found in the cerebrospinal fluid, an indication that the loss of such cells is not due to migration into the central nervous system. Suppressor T-cell function is also defective during active disease, as measured by concanavalin A-induced T-cell suppression^{30,31} or by polyclonal IgG stimulation of peripheral blood mononuclear cells by pokeweed mitogen.³² Natural killer cell activity against tumor or virally infected targets may be decreased in MS,³³ but these results have not been confirmed.^{34,35}

VIRUSES

Attempts to identify a single infectious agent as the cause of MS have been unsuccessful thus far.³⁶ Many infectious agents have been isolated in cultures of specimens from patients with MS, but the majority represent contaminants or noncausal agents. In addition, direct inoculation of brain material into primates, so successful in identifying a transferable agent in Creutzfeldt-Jakob disease, has been negative or inconclusive. The more sensitive technique of looking for "footprints" of virus infection in brain tissue by nucleic acid hybridization with radiolabeled DNA probes or RNA probes (riboprobes) complementary to viral genomes has suggested that some brains of subjects with MS harbor measles virus.³⁷ The finding of measles virus genome in several control subjects without MS, however, suggested that viruses may reside in the nervous system without causing disease.³⁷

Analysis of the cerebrospinal fluid of patients with MS shows increased IgG levels along with oligoclonal Ig bands.³⁸⁻⁴⁰ Attempts to identify the antigen to which the IgG is directed have been unsuccessful.⁴⁰ In serum samples from patients with MS, titers of antibody to measles virus are increased.^{40,41} In many

patients with MS, however, antibody titers to two or more viruses are increased in the cerebrospinal fluid. In diseases that are known to be caused by a virus (subacute sclerosing panencephalitis [measles] and mumps meningitis), IgG and oligoclonal bands in the cerebrospinal fluid are directed almost exclusively against the infectious agent.^{42,43} Because this is not the case with MS, some investigators have suggested that, in MS, the IgG in the central nervous system is "nonsense antibody" that represents a dysfunction in immune regulation. The alternative hypothesis is that the humoral immune response is to an unrecognized infectious agent that is the cause of MS.

Two approaches to distinguish whether antibody is "nonsense" or "sense" have been used: analysis of banding patterns of IgG eluted from different MS plaques in the same patient⁴⁴ and study of idiotypes (combining sites of antibody molecules) of the oligoclonal IgG in cerebrospinal fluid from multiple patients.^{45,46} The first approach showed that each MS plaque may have unique IgG banding patterns. The second approach showed that anti-idiotypic antisera raised against cerebrospinal fluid IgG fail to cross-react with cerebrospinal fluid from other patients with MS. These results are consistent with the possibility that the antibody is, indeed, a "nonsense antibody."

An important impetus to continuation of the search for a viral cause for MS has come from study of several naturally occurring model diseases in animals in which viruses cause demyelination.⁴⁷ These diseases include canine distemper virus (paramyxovirus) in dogs,⁴⁸ visna virus (nononcogenic retrovirus) in sheep,⁴⁹ JHM virus (coronavirus) in mice⁵⁰ and rats,⁵¹ Semliki Forest virus (togavirus) in mice,⁵² and Theiler's virus (picornavirus) in mice.⁵³ The mechanisms of the demyelination in these viral models are beginning to be understood. For example, in JHM virus infection in mice the demyelination seems to be the result of direct cytopathic injury of oligodendrocytes, the myelin-producing cells.⁵⁰ In contrast, in rats the demyelination by JHM may be a consequence of autoimmune mechanisms by which sensitized T cells recognize myelin antigens.⁵¹ In visna virus, macrophages that are persistently infected are actively involved in the demyelinating process.⁵³ With infection by Theiler's virus, viral antigens have been detected on the inner and outer glial loops of oligodendrocytes such that an immune response seems to be directed against viral or "novel" antigens on the surface of these glial cells.⁵⁴⁻⁵⁶ These experiments emphasize that viruses from different "families" may induce

primary demyelination, probably by unique mechanisms.⁴⁴

The recent discovery, in Japan⁵⁷ and in the Caribbean,⁵⁸ that chronic progressive myelopathy may be the result of persistent infection with human T-lymphotropic virus type I (HTLV-I) has stimulated speculation that viruses may be implicated in MS. Koprowski and associates⁵⁹ reported that serum and spinal fluid samples from patients with MS in Sweden and in Key West, Florida, contained antibodies reactive with viral protein (p24) of HTLV-I. Others have failed to detect any antibody to HTLV-I, II, or III in patients with MS.^{60,61} In Japan, however, investigators⁶² found that 11 of 46 patients with MS reacted to purified HTLV-I proteins by Western blot analysis. The discrepancies in the results may be due to differences in sensitivity of various methods. Recently, Reddy and associates⁶³ amplified and molecularly cloned HTLV-I sequences from DNA of lymphocytes from patients with MS. Confirmation of these results by other investigators will be necessary before a firm statement can be made about its role in pathogenesis.

IMMUNE HYPOTHESES FOR THE CAUSE OF MS

Several hypotheses have been proposed to explain the clinical and experimental features of this demyelinating disorder, three of which will be discussed. They are relevant to the possibility of an immune-mediated demyelination triggered by viral infection.

Autoimmunity.—The most widely considered hypothesis is that MS is the result of an immune reaction directed against self myelin antigens.⁶⁴ T cells are thought to enter the central nervous system through endothelial cells and to react with normal white matter. The myelin antigens may be presented to helper T cells (CD4⁺) by endothelial cells⁶⁵ or astrocytes,⁶⁶ which are known to carry class II MHC antigens in MS lesions. As a result of T-cell activation, lymphokines and macrophages could mediate myelin destruction.³

This hypothesis is supported by elegant experiments, using EAE, that demonstrated that T-cell clones (CD4⁺) sensitized to myelin proteins can mediate demyelination in the central nervous system.^{18,19} In addition, the linkage of the disease with class II MHC gene products (DR2) is further evidence that this mechanism may be important. A series of crucial experiments by Hafler and associates²⁰ on T-cell clones isolated from the cerebrospinal fluid of patients with MS, however, failed to identify a single clone that was reactive for myelin antigens despite the ongoing

demyelination. In contrast, myelin-reactive clones were demonstrated in patients with postinfectious encephalomyelitis.

"Bystander" Hypothesis.—One important hypothesis being considered is that in MS the myelin is an "innocent bystander" that is destroyed as a consequence of an immune response occurring within the nervous system.⁴⁷ This hypothesis may help explain why different viruses can induce demyelination in the nervous system of rodents and why different "etiologic" agents have been isolated from MS-involved brains. The scenario would be that viruses or other infectious agents frequently invade the central nervous system. During the defense against this infection, T lymphocytes and macrophages are recruited to the lesion. Subsequently, in the process of clearance of virus by T cells, myelin is destroyed nonspecifically by lymphokines or neutral proteases released by activated macrophages.

Experiments by Wisniewski and Bloom⁶⁷ support this hypothesis by demonstrating that animals previously sensitized to purified protein derivative (PPD) of tuberculin will undergo demyelination if challenged by this antigen in the nervous system. In addition, myelin basic protein can be degraded by neutral proteases *in vitro*.⁶⁸ The concept of bystander demyelination, however, is not supported by the observation that demyelination is a rare consequence of an immune response to viral or fungal encephalitis. If bystander demyelination were more prominent, then demyelination would occur each time the immune system interacts with viruses that infect the central nervous system (that is, measles, mumps, and herpes). It may be argued, however, that genetic factors control whether specific lymphokines that could induce demyelination are released.

Immune Destruction of Persistently Infected Oligodendrocytes.—On the basis of the paradigm of demyelination in mice induced by Theiler's virus, Rodriguez and colleagues⁵⁶ proposed that the demyelination in MS may be the result of immune-mediated destruction of virus-infected oligodendrocytes. This hypothesis would incorporate epidemiologic data (exogenous agent) and a contribution of immunogenetics to pathogenesis. Immunogenetic data in MS implicate that specific genes within the MHC protect against the development of MS. Genes may play a role in host resistance against the exogenous agent that is acquired early in life.

In resistant hosts, viral antigens would be recognized in the context of class I or class II MHC gene products, and viral replication would be limited as a

consequence of a protective immune response. Virus would be cleared from the central nervous system without long-term sequelae.

In susceptible hosts, absence of specific MHC gene products may result in failure of clearance of the virus; thus, the virus persists in glial cells. During the course of infection, the virus could infect oligodendrocytes in a manner such that novel antigens are present on the surface of these cells (Fig. 1). These novel antigens may be virus antigens or "up-regulated" normal host antigens that are seen as foreign in the context of specific MHC alleles. The virus itself may be capable of inducing demyelination by interfering with the function of the myelin-producing cell. The current evidence suggests, however, that immune cells must also play a role in demyelination because immunosuppression seems to have a favorable effect on the course of MS. The presence of a novel antigen on an oligodendrocyte or on myelin could result in immunoglobulin-directed killing (injury by complement, antibody-dependent cell-mediated cytotoxicity, or activation of macrophages). Processed viral antigens may be recognized by CD8⁺ cells (class I-restricted cytotoxic T cells) or CD4⁺ cells (class II-restricted cytotoxic T cells), which could be effectors in demyelination.

The final result would be injury to the myelin-producing cell or to the myelin sheath. This result may occur as a dying-back gliopathy,^{69,70} the alteration being noted first in the most distal extension of the oligodendrocytes (that is, the glial loops and myelin sheaths) and interfering with the differential function of the oligodendrocyte (that is, the maintenance of myelin).

CONCLUSION

The evidence suggests that an exogenous agent (that is, a virus) may be important in triggering demyelination in MS. If multiple exogenous agents are able to induce this pathologic process, however, then identifying the offending agent may prove to be difficult. If common pathogens can produce demyelination, then distinguishing these etiologic agents from the viruses that "normally" reside in the central nervous system may be impossible. Alternatively, attempts to interfere specifically with various arms of the immune response by use of monoclonal antibody therapy may be beneficial without the requirement of knowing the causative agent. The scheme proposed in Figure 1 may provide the basis for designing specific immunotherapy to interfere with demyelination.

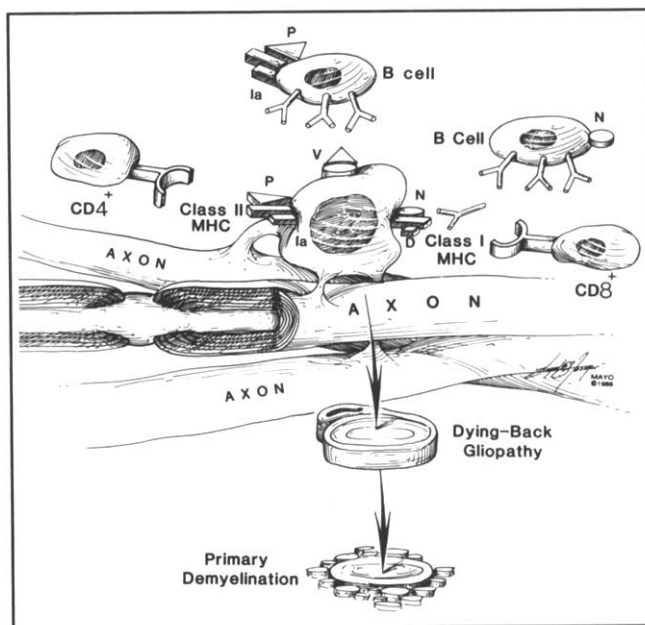


Fig. 1. Hypothesis by which immune cells injure persistently infected oligodendrocytes and produce primary demyelination. During the course of viral infections of the central nervous system, specific viruses in "susceptible" patients may not be cleared by the immune system. Viruses may then persist in oligodendrocytes (myelin-producing cells) and injure these cells either by direct effects or by becoming targets of immune-mediated destruction. Oligodendrocytes infected by virus may express viral antigen (V), processed viral antigen (P), or novel antigens (N) on their surfaces. Immunoglobulins secreted by B cells may be directed at viral or novel antigens and thus result in injury to oligodendrocytes by complement, antibody-dependent cell-mediated cytotoxicity, or receptor-mediated phagocytosis by macrophages. Processed viral antigens (peptides) may be expressed on surface of oligodendrocytes and be presented to CD4⁺ cells in context of class II major histocompatibility complex (MHC) antigens (Ia antigens). These CD4⁺ cells (class II-restricted cytotoxic T cells or "helper" T cells) could directly injure oligodendrocytes or help B cells. Novel virus-induced antigens may be expressed on surface of oligodendrocytes and be seen in context of class I MHC antigens by CD8⁺ cells (cytotoxic T cells). These CD8⁺ cells may injure oligodendrocytes in an effort to clear viral infection or by interacting with normal host proteins. The final consequence of these mechanisms would be injury to the oligodendrocyte. The initial pathologic process could be in the inner and outer glial loops of myelin-producing cells such that destruction of myelin would occur before visible structural damage to the oligodendrocyte ("dying-back gliopathy"). This process would result in primary demyelination. Therapeutic strategies to deplete B cells, CD4⁺ cells, or CD8⁺ cells and to "down-regulate" expression of class I or class II MHC gene products may prove beneficial.

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