Chapter 5

Pathogenesis of Multiple Sclerosis: Relationship to Therapeutic Strategies

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Introduction

Ten chapters of this book are devoted to specific therapeutic strategies for multiple sclerosis (MS). It will be immediately noted that all of these strategies involve manipulation of the patient's immune system. These immune-modulatory strategies comprise a broad spectrum. At one end are the global immunosuppressives, both anti-inflammatory (corticosteroids), cytotoxic (azathioprine, cyclophosphamide), and total lymphoid irradiation and plasmapheresis. Slightly more specific immune modulators include cyclosporine A and anti-T cell antibodies. The rationale for using interferons to treat MS relies primarily on their immunoregulatory potential although antiviral effects may also be desirable. Finally, several elegant strategies for specific immunotherapy directed against small numbers of presumed pathogenic immunocompetent cells are also described. If the majority of effort in studying experimental therapies for MS is directed at manipulating the immune system, then the task of explaining the rationale for this approach reduces to explaining why MS is thought to be an immune-mediated disorder. In this chapter, the concept of MS immunopathogenesis will be reviewed, with concentration primarily on the epidemiologic data and derivative clinical investigations. Where possible, references are to reviews, to facilitate further reading.

Historical Background

The gross pathology of MS was described approximately 150 years ago, and 30 years later Charcot described the histopathology and clinical characteristics of MS (Adams 1983). Until the early 1950s, despite intensive investigation, there was very little agreement about the pathogenesis of the demyelinating disorders (Wolf 1952). Investigations carried out since then have served to focus attention progressively on immune-mediated tissue injury. It is important, however, to remember that a variety of other possibilities have been considered and extensively pursued. The essential characteristics of the MS pathologic lesion are not in doubt. They include: perivascular inflammation,

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segmental demyelination and reactive gliosis (Adams 1983; Lampert 1983; Lassmann 1983). Interpretation of the preferential destruction of myelin in these lesions has been difficult in that myelin is the most sensitive component of the CNS to injurious influences of all sorts. Therefore, the selective destruction of myelin in MS invited two possible explanations: either the pathologic process was directed specifically at myelin, or a low-intensity pathologic process could damage myelin while leaving other elements of the CNS unharmed. A variety of exogenous toxins, all capable of producing demyelinating lesions, have been considered as potential causes of MS. These include carbon monoxide, lead and arsenic poisoning, and a variety of biologically-derived exotoxins (Merritt 1970; Scheinberg and Korey 1962; Wolf 1952). There has never been evidence implicating these toxic substances or processes related to them (such as anoxia) in the human demyelinating disorders. A recent observation of an occupational cluster of MS may in the future provide some further insight into this issue (Stein et al. 1987).

As an alternative to exogenous toxins, it was proposed that endogenous toxins might activate myelinolytic enzymes within CNS white matter. A suggestion that subclinical hepatic insufficiency might lead to accumulation of endogenous toxins which could activate myelinotoxic processes was extensively investigated in both human and animal material in the 1930s and 1940s (Wolf 1952). No circulating substances specific to MS and capable of inducing demyelination could be demonstrated. It remains possible that inflammatory cells produce or induce myelinolysis, as part of the final common pathway of immune-mediated demyelination (Lampert 1983).

The occurrence of demyelination in association with pernicious anemia led to the suggestion that other demyelinations might similarly be a consequence of nutritional deficiency. However, dietary manipulation in MS patients has been generally unrewarding. Furthermore, it has not been possible to produce experimental animal models of nutritional deficiency which closely mimic the spontaneous human demyelinating disorders.

Early pathologic descriptions of MS lesions remarked on the similarity of their distribution to the consequences of embolic showers. Indeed, in the late 1930s vascular thrombosis was advocated as a prominent component of MS pathogenesis. However, multiple negative investigations for occlusive vascular phenomena cast doubt on this hypothesis, and disappointing results were obtained in clinical studies of anticoagulation as an MS treatment (Wolf 1952).

The occurrence of a clinico-pathologically distinct demyelination in association with metabolic disturbance (central pontine myelinolysis (CPM)) provoked interest in altered homeostasis as a causative factor for spontaneous inflammatory demyelination. However, CPM was subsequently attributed to rapid correction of hyponatremia, without any evidence that similar metabolic aberrancy underlies MS.

Epidemiology

The genetic and environmental components of MS pathogenesis appear to underlie the complex epidemiology of the disease (Acheson 1985; Kurtzke

1983). MS epidemiology has provided highly suggestive data despite extraordinary difficulties imposed by the absence of a sensitive and specific laboratory diagnostic test (Acheson 1985). MS is accordingly a clinical diagnosis. Further, because the prevalence of MS is low, the diagnostic data for epidemiologic studies are generated by local practitioners. The effect of this circumstance is to bias prevalence data to distribute an excess of MS diagnoses to regions of more accessible medical care and cases are included and excluded with variable accuracy. Therefore, prevalence data are reliable only insofar as they are obtained from regions with comparable levels of access and quality of neurologic care. Bearing these limitations in mind, the following observations have consistently emerged in carefully-performed epidemiologic studies:

1. MS occurs in women more frequently than in men with a relative risk of approximately 1.8
2. Onset of MS symptoms shows a world-wide unimodal peak beginning in mid-adolescence, with maximal rates in the late twenties or early thirties and a drastic decline after age 60
3. In both northern and southern hemispheres, the occurrence of MS increases with increasing distance from the equator. This MS risk gradient has been carefully documented in the USA, Australia, and in comparisons of genetically-similar populations in South Africa and the British Isles
4. Migration from a high-risk to a low-risk area in early life confers a significant reduction in risk. The most convincing evidence in support of this notion comes from the US Veterans study; compatible data have been derived in studies of Israeli immigrants, South African immigrants, and others
5. Different racial groups are differentially susceptible to MS. For groups of low susceptibility, prevalence rates are low regardless of geographical location. For groups of high susceptibility, rates are significantly affected by geography
6. MS clusters in families. Sibs of patients with MS carry a greater-than-tenfold excess of MS relative to the population at large
7. Other clusters of MS occur. The best-documented of these occurred in the Faroe Islands after World War II (Acheson 1985; Kurtzke 1983).

These observations may be considered useful insofar as they provide testable hypotheses about the etiology of MS. The universal excess in women and globally-uniform age of onset provide some reassurance that MS in differing locales is a single disease, but have not otherwise been informative. The predilection for MS to occur in some racial backgrounds while sparing others suggests that MS, as practically every disease of humans, expresses itself differentially according to innate differences in susceptibility. The distinctive geographic distribution of MS cases has been a focus of intense speculation and study. The relationship to latitude implies a relationship to climate and thus to two major factors affected by climate: diet and social conditions affecting transmission of infection. As is noted above, the world-wide relationship to latitude in the face of variable geology, soil and water supply makes it extremely unlikely that a single trace constituent of diet is causally related to MS. Similar comments may be made about the influence upon diet of climate, namely that

diets in high-risk and low-risk zones for MS are so extraordinarily variable that a single protective or deleterious component is unlikely to be identified.

Efforts to understand further the clues provided by these epidemiologic studies have focused, therefore, on the attempt to understand the virology and genetics of MS.

Virology

For many years, speculation has centered upon the role of infectious agents in MS (Johnson 1982, 1983; ter Meulen and Stephenson 1983). Several hypotheses have been considered: that MS could be associated with a slow virus infection; that MS could be a rare sequela of a common human infection or family of infections; that MS could be a common sequela of exposure to a pathogen for which humans are an accidental host. With the accumulation of epidemiologic data about geographical case distribution these speculations have been extended to postulate either that early exposure to a common enteric pathogen in regions of low prevalence is protective against MS or that late-childhood exposure to a respiratory pathogen in high prevalence areas is an inciting event, followed after a latent period by emergence of neurologic disease. The enterovirus hypothesis is made somewhat less likely by the failure of late-childhood migration from high-risk zones to low-risk zones to confer increased risk of MS for those migrants.

The notion that a unique virus infection could be causally implicated in MS is supported by the occurrence of viral demyelinating disorders of several mammalian species including humans (Johnson 1983; Johnson and McArthur 1987). Both progressive multifocal leukoencephalopathy (PML) and subacute sclerosing panencephalitis (SSPE) were investigated in parallel with MS as cryptogenic demyelinating disorders for many years. PML has been attributed to papovavirus infection of immunocompromised individuals, while SSPE is caused by a persistent measles virus infection (Johnson 1982).

Very recently, a demyelinating leukoencephalomyelitis variously described as HTLV-I-associated myelopathy (HAM) or tropical spastic paraparesis (TSP) has been firmly linked to infection with the lymphotropic retrovirus HTLV-I (Brew and Price 1988; Jacobsen et al. 1988; Johnson and McArthur 1987).

Demyelination is also associated with post-infectious sequelae of human viral infections, most prominently observed with measles (Johnson 1982). Several viral demyelinating diseases also occur in other mammalian species. These include visna virus infection of sheep, canine distemper virus of dogs, Theiler's virus infection of mice, and rodent infection with variant strains of mouse hepatitis virus (Johnson 1983; Knobler and Oldstone 1983; Narayan et al. 1983).

Two major hypotheses about the pathogenesis of virus-induced demyelination have been entertained. In one case direct viral impairment of oligodendrocyte function is proposed, while in the second case virus-induced immune-mediated tissue injury is proposed. Of the mammalian viral demyelinations, Theiler's virus murine encephalomyelitis (TME) and mouse hepatitis virus (MHV) infection of rats have been studied most intensively. In the case of TME,

persistent virus infection of oligodendroglia appears likely, and demyelination may be mediated by immune mechanisms directed against viral determinants expressed on infected cells (Rodriguez et al. 1987). In the case of MHV-induced demyelination in rats, it has been demonstrated that T-cell recognition of myelin antigens occurs during the course of disease, which can be passaged to syngeneic uninfected rats with lymphocyte transfer (Knobler and Oldstone 1983). Therefore, virus-induced demyelination in these model systems utilizes a variety of mechanisms including direct viral tissue injury and immunologic attack upon viral and host antigens.

Virologic studies of MS patients have focused on evaluation of viral antibodies, attempts to isolate viruses, and morphologic studies. Both intrathecal and circulating antiviral antibodies are significantly elevated in MS material. The most significant elevations, both in terms of absolute titres and frequency, are against measles virus, but intrathecal antibodies directed against numerous paramyxoviruses, poxviruses, herpes viruses, orthomyxoviruses and others can be detected. It is not clear whether the elevated viral antibodies are of pathogenic significance or reflect non-specific polyclonal B cell recall responses, in the context of intrathecal immune dysregulation (Salmi et al. 1983).

Viral (and spirochetal) isolates from MS tissue have a venerable and uniformly disappointing history. More than 20 viruses have been "isolated" from MS tissue, using a variety of methods including coculture with tissue culture cells; intrathecal or intravenous inoculation of pathogenic tissue in recipient animals which are screened for viral antibodies or pathology; and molecular cloning experiments. To date, none of these isolates has been reproducibly obtained by a majority of investigators (Johnson 1982). Recently, molecular cloning experiments which initially suggested the presence of an HTLV-I-like retrovirus in MS lymphocytes could not be reproduced, and the potential involvement of a pathogenic retrovirus in MS remains indeterminate (Bangham et al. 1989; Reddy 1989; Richardson et al. 1989; Waksman 1989). These studies are important, since lymphotropic retroviruses have a distinct capacity to cause peripheral immune dysregulation (as in HIV infection) and inflammatory demyelination (as in HAM). The failure to isolate a virus from MS tissues is consistent with the possiblity that the virus–host interaction results in virus clearance, but elicits pathogenic autoimmunity. According to this notion, virus infection could induce autoreactivity to myelin antigens in the appropriate susceptible host (Waksman 1983). The feasibility of this concept was demonstrated by Johnson and co-workers who documented lymphocyte proliferative responses to myelin basic protein in post-measles encephalomyelitis patients (Johnson 1982).

Genetics

Evidence favoring a genetic component to MS susceptibility came early in assessment of the epidemiology of the disease. Racial groups exhibiting distinct disparity in MS prevalence were described by numerous epidemiologic studies in the 1950s, 1960s and 1970s. The disparate occurrence of MS cases in different racial groups appeared particularly striking in high-risk geographic

locales, as noted above (Acheson 1985; Johnson and McArthur 1987). Familial clustering of MS cases has also been a focus of epidemiologic study and is consistent with the postulate of genetic susceptibility to MS (Batchelor 1985). More recently, population-based studies of MS concordance in monozygotic and dizygotic twins were reported (Ebers et al. 1986; Kinnunen et al. 1987). Significantly, MS concordance in dizygotic twins approached expected rates for siblings, while monozygotic concordance rates were at least ten-fold higher (Ebers 1986). Such studies strongly support the hypothesis of a genetic component to MS susceptibility, since both monozygotic and dizygotic twins tend to share a common environment. These studies also imply a contribution of environment to occurrence of MS since monozygotic concordance rates were far short of 100%.

Over 20 years ago, Fog and co-workers reported an association of MS with certain HLA antigens (Jersild et al. 1972). Numerous studies have subsequently confirmed these associations and it has been clarified that allelic variation in the D/DR locus accounts for the increased susceptibility (Stewart and Kirk 1983). In Caucasian populations, HLA-DR2/Dw2 is very significantly over-represented in MS patients compared with relevant control populations. It is most important to note that different racial groups possess different MS-susceptible HLA-D haplotypes (McFarlin and Lachman 1989). Recent studies on the function of the gene products of the HLA-D locus (in the human major histocompatibility complex class II region) in determining specificity of immune responses (see R.B. Bell and L. Steinman in this volume) have excited great interest in these associations. The finding that different HLA haplotypes confer increased MS risk in different genetic backgrounds has several potential explanations. One possibility is that the different HLA-DR alleles are in linkage disequilibrium with another polymorphic susceptibility gene. In this regard, suggestive evidence was provided by Vartdal and colleagues that HLA-DQβ-chain alleles common to a number of susceptible HLA-DR haplotypes shared structural features in the predicted antigen binding cleft (Vartdal 1989). This intriguing report requires wider confirmation. An alternative explanation for different HLA-linked susceptibility genes in different racial groups could be that a number of different pathogens can each elicit autoimmunity to myelin in the appropriate susceptible host, determined in part by HLA haplotype. Reports of myelin basic protein (MBP) peptides which are differentially encephalitogenic in mice, as determined in part by Class II MHC haplotype, are consistent with this concept (Weller 1985).

To date, investigations of various polymorphic MHC loci have failed to disclose MS associations tighter than those with HLA-DR. Indeed associations tend to become less significant as one evaluates markers either centromeric or telomeric of HLA-D/DR suggesting that HLA-D antigen genes may indeed encode susceptibility factors.

Epidemiologic studies of populations using HLA antigens as genetic markers can establish association, but cannot address linkage to disease. Two studies of HLA haplotype-sharing in affected sibling pairs from multiplex MS families have demonstrated linkage between inheritance of the HLA-bearing chromosome and susceptibility to MS (Batchelor 1985).

With advancing suspicion that MS could be a reflection of cell-mediated immunopathology, attention has turned to genetic analysis of T-cell receptor (TCR)-associated MS susceptibility. As indicated by Bell and Steinman, the

TCR is a critical component of antigen-specific immune recognition. Molecular characterization of the T-cell receptor germ-line repertoire has allowed both association and linkage studies to be performed. Unrelated patients were screened for biased inheritance of TCR variable region genes by Beall and co-workers (Beall et al. 1989). Significant biases were demonstrated in MS patients' germ-line TCR β-chain repertoire. Hauser and co-workers performed elegant TCR β-chain polymorphism linkage analysis in affected sibling pairs of MS multiplex families, analogous to earlier studies of HLA haplotype-sharing. A highly-significant increase in haplotype-sharing among affected sibs was demonstrated, linking inheritance of chromosomes containing the TCR β-chain with MS susceptibility (Seboun et al. 1989). In the aggregate, results described in this section are consistent with the linkage of inheritance of immune-recognition molecules with MS susceptibility. As described by Bell and Steinman, analogous observations have been made in regard to murine and rat susceptibility to autoimmune demyelination.

The third component of immune recognition of myelin, in addition to the HLA antigens and T-cell receptors, is the antigenic myelin peptide. To date, polymorphisms in the coding sequence of the important myelin antigens (myelin basic protein, myelin proteolipid protein, myelin-associated glycoprotein) have not been described. Therefore, genetic susceptibility in MS appears to be determined in part by the genes encoding immune-recognition molecules. It should be noted that the best estimate of the contribution of these genes to genetic susceptibility of MS is approximately 30% indicating that other inherited traits must also be implicated in MS susceptibility (Seboun et al. 1989).

Immunology and Immunopathology

Immunologic abnormalities have been described in a wide variety of studies of MS peripheral blood, cerebrospinal fluid (CSF), and brain tissue. None of the individual observations is uniquely observed in MS and it has not been possible to define the detailed mechanism of immune-mediated tissue injury through such studies. Furthermore, immune activation clearly could be secondary to the host response to a pathogenic orgainsm. Thus immunologic aberrations observed in MS are important only in that they indicate the presence of potential targets of therapeutic intervention, monitoring or etiologic insight. In this regard, the bulk of evidence strongly suggests the presence of an activated T-lymphocyte-directed immune response in patients with MS.

The immune aberration most characteristic of MS is elevated immunoglobulin protein of restricted heterogeneity within the CSF (Walsh and Tourtellotte 1983). This elevated immunoglobulin is directed in part against multiple viral antigens, although antibody reactivity to myelin antigens has also been described. The majority of intrathecal immunoglobulin is of unknown specificity. While it has not been directly proven, there is strong evidence to support the assertion that this oligoclonal immunoglobulin is synthesized within the central nervous system.

An "immunologic profile" of circulating components in MS patients consists of: normal serum immunoglobulin levels; detectable circulating immune complexes; normal T-lymphocyte numbers with normal reactivity to mitogen and recall antigens; intermittent moderate distortion of T-lymphocyte subsets with decreased numbers of CD8+ and CD45R+ T-cells; decreased functional in vitro T-cell suppressor activity (Leibowitz 1983; Batchelor 1985). These studies have provided an impression of disturbed immune regulation and are in many respects consistent with studies of patients with other proposed immunopathologic conditions such as rheumatoid arthritis and systemic lupus erythematosus.

Studies of CSF T-lymphocytes have been difficult due to limited availability of cells. Recent advances in techniques for T-cell culture and analysis have permitted studies of T-cells in CSF. In regard to subset representation, these T-cells reflect the composition of peripheral blood. Activated T-lymphocytes in CSF from patients with MS have been described by several techniques including flow cytometric quantitation of DNA content and expression of activation antigens. Recently, analysis by Hafler and co-workers of TCR gene rearrangements in T-cell clones derived from CSF provided evidence in favor of the "oligoclonality" of the intrathecal T-cell population (Hafler et al. 1988). This observation would be consistent with the postulate of an antigen-specific immune response occurring within the CNS compartment.

Clearly, the demonstration of T-cell recognition of myelin antigens in MS patients would be of tremendous importance in supporting an immunopathologic mechanism of disease. Several elegant and powerful studies have recently addressed this issue. Allegretta and co-workers documented the presence of increased numbers of MBP-reactive activated T-cells in MS patients (Allegretta et al. 1990). More recently, Hafler and co-workers described responses to an immunodominant epitope of MBP in MS patients. The further evaluation of the human response to the important myelin encephalitogens MBP and PLP is a very active focus of on-going research. The implications of such work for specific immunotherapy are described in the chapters by Bell and Steinman and by Hafler, Brod, and Weiner.

The pathologic characteristics of the MS lesion have suggested the presence of pathogenic inflammation to observers since Dawson's seminal work of 85 years ago. With the advent of specific reagents for defining components of the immune system within these inflammatory lesions has come delineation of the composition of the cellular infiltrate, demonstration of the presence of immunologically functional secretory products and definition of cell membrane expression of the molecules of immune recognition. The cellular infiltrate in MS is mononuclear and is composed primarily of T-cells and macrophages (Traugott et al. 1983; Hayashi et al. 1988). The T-cells may express either CD8 or CD4 phenotypes, without a clear-cut predilection for either. The CD45R+ T-cell subset appears to be depleted in MS brain, in comparison with control inflammatory lesions (Sobel et al. 1988). Unambiguous delineation of the cellular composition of the MS inflammatory infiltrate has been hampered by variable tissue preservation in autopsy material available to different investigators (Sobel 1989).

Several studies have addressed the presence of secretory immune mediators within MS tissue. Hofman and co-workers documented the presence of interleukins and tumor necrosis factor in easily-detectable amounts in the MS lesion (Hofman et al. 1986; Hofman et al. 1989). Traugott and co-workers have

carefully delineated the presence and distribution of interferons in MS lesions (Traugott and Lebon 1988a). These investigators have also underscored the elevated expression of MHC Class I and II antigens on parenchymal brain cells, endothelial cells and infiltrating leukocytes within MS lesions; the expression of intercellular adhesion molecule (ICAM-1), a significant accessory molecule for immune recognition events, was also demonstrated (Traugott 1987; Traugott and Lebon 1988a,b). In summary, the requisite components for a cell-mediated immune response have been demonstrated in MS plaques.

Conclusion

Convergent lines of evidence suggest that tissue injury in MS results from aberrant immune reactivity to one or more myelin antigens. These suggestive data are summarized above, and include the fruits of epidemiologic, genetic, pathologic and immunologic investigations. The effects of intervention with immunomodulatory agents are also consistent with this concept, since treatments which augment immune function (from intrathecal tuberculin to interferon-gamma) have tended to exacerbate disease activity, while immunosuppressive treatments have produced neutral or beneficial consequences.

Lately, the great bulk of attention has focused on T-lymphocyte-directed immunopathologic mechanisms. This development has been hastened by rapid progress in understanding the role of T-cells in EAE, a highly-informative animal model of myelin-specific autoimmunity. Studies in MS patients have produced suggestive data about the potential parallels between EAE and MS. Virtually every element in the intricate and complex cascade of the immune response can now be considered a potential target for therapeutic intervention. Candidates include: the T-cell antigen recognition event, as described by Hafler and Steinman and their colleagues; a different approach is represented by copolymer 1, described by Bornstein. T-lymphocyte activation, proliferation and effector functions can be affected by corticosteroids, azathioprine, cyclophosphamide, total lymphoid irradiation or cyclosporine A, as described by Myers, Hughes, Weiner, Cook and Wolinsky. In some cases these agents affect laboratory indices of disturbed immunoregulation, such as antigen-nonspecific T-cell suppressor function or intrathecal immunoglobulin synthesis. Our current level of knowledge about the pathophysiology of MS does not allow any firm conclusion about whether these latter effects are relevant for clinical response. Following T-cell antigen recognition, a multitude of secreted polypeptides, collectively termed cytokines, serves locally to amplify the number and activation state of immunocompetent cells within tissue sites of inflammation. The first attempt to manipulate the cytokine environment in MS is represented by clinical trials of interferons, as described by Jacobs. It is possible that plasmapheresis, described by Noseworthy, may also have the effect of modifying cytokine levels. The explosive growth in understanding immunobiology should promote the detection of progressively more effective means of downregulating pathogenic autoimmunity in the near future. With these techniques will come the critical test of the immunopathogenesis hypothesis for MS: ability to temper the course of the disease by modulating function of the immune system.

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