MINIREVIEW

Multiple Sclerosis as a Disease of Immune Regulation (41798)

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The possibility that certain neurological diseases, of which multiple sclerosis (MS) is the leading example, might be of an immunological nature was suggested in the 1930s by Pette, Schaltenbrand, and others, primarily on morphological grounds. The combined presence of inflammation and parenchymal damage, in the absence of a known toxic, or infectious agent, was considered to demonstrate an underlying immunological process. At that time immunological events were poorly understood, and what we now recognize as distinct immunopathological mechanisms had not yet been sorted out.

The production in 1932 by Rivers and his colleagues of an experimental autoimmune encephalomyelitis (EAE) in rabbits immunized with myelin provided the first solid experimental verification of this point of view. With the demonstration, a half century later, that MS can be arrested, in the majority of patients tested, for a year or more by the powerful immunosuppressive agent cyclophosphamide (1), the likelihood that MS is immunologically based has become a virtual certainty.

Nevertheless, most of our still evolving insights into the possible mechanisms of MS have been derived from the study of EAE (2–4). This animal model has been the subject of literally hundreds of research reports in the years since its discovery. It is of interest that a chronic relapsing form of the disease, with many similarities to MS was well known to the first investigators. However, when myelin basic protein (MBP) was found in the mid-fifties to be an effective encephalitogen, scientists seeking greater precision and reproducibility in their experiments turned to the use of purified homogenous preparations of this protein which, however, tends to produce only an acute monophasic disseminated encephalitis. Thus relapsing disease was lost sight of, only to be rediscovered in the last few years (5–8).

The disease MS affects young adults (9, 10). It occurs as a series of attacks separated by periods of partial or complete remission and quently followed by a phase of chronic progression. Alternatively the disease may progress inexorably from the start. The initial lesions consist of perivenular inflammation in myelin-containing regions of the central nervous system (CNS, white matter) (11, 12). These coalesce to form larger "plaques," which may then grow by activity at the margins. Perivascular cuffs contain lymphocytes, blasts, plasma cells, and monocytes. The monocytes invade the parenchyma and are transformed into macrophages, which actively phagocytize the damaged myelin. Whether these cells are the actual agents of myelin damage is unclear. Early lesions also show massive edema, presumably due to vascular damage. Myelin breakdown, and preservation of axis cylinders, is the hallmark of MS and of other "demyelinating diseases." Oligodendrocytes also disappear in the MS plaque, and it is possible that the target of the disease process is these cells, which produce and maintain myelin, rather than the myelin itself.

In disease of long duration, one sees lesions of different ages and the extension of old plaques by activity at their margins. Astrocytes proliferate early in the lesions (gliosis) and lay down glial fibers, which ultimately form a dense scar. A characteristic finding is the presence of elevated concentrations of all the immunoglobulin isotypes and, in particular, oligoclonal bands of IgG_1 in the cerebrospinal fluid (CSF). Such bands, however, are also seen in neurosyphilis and transiently in mumps meningoencephalitis.

The study of MS and the closely similar study of EAE have taken a "great leap forward" with the conceptual and technological revolutions in immunology, genetics, and molecular virology of the last decade (13–20). A parallel advance has occurred in our understanding of other immunologically based

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disorders of the nervous system. Pertinent examples are polyneuritis of the Guillain-Barré type and chronic relapsing inflammatory polyneuropathy and the corresponding animal model, experimental autoimmune neuritis, induced by immunization with peripheral myelin antigens such as P2 (G. Zito et al., in (19)); also myasthenia gravis and its experimental counterpart, induced by autoimmunization against purified acetylcholine receptor (J. Newsom-Davis, in (19)).

The following appear to be the principal questions about MS which require an answer today (20, 21):

1. The nature and specificity of the neural antigens which may be involved;

2. The role of viral and/or bacterial infection in triggering an immune response, and the contribution of viral antigens to its specificity;

3. The role of genetically determined abnormalities in immune regulation in permitting the evolution of a chronic (or intermittent) process;

4. The relative roles of T-cell-mediated immunity and various antibody isotypes in producing the essential lesion.

1. Neural Antigens. Of all the proteins and glycolipids known to be present in CNS myelin (22), MBP has received the major attention as a cause of EAE and possible cause of MS (23). MBP, as noted above, is found by most investigators to produce a monophasic experimental disease in animals resembling acute disseminated encephalomyelitis in man. Even in genetically susceptible animals, such as Strain 13 guinea pigs and SJL mice, only whole myelin rather than MBP alone appeared effective in inducing a chronic relapsing form of EAE (R-EAE) (5–8).

The trivial explanation that myelin in adjuvant differs from MBP merely by providing a persistent antigenic stimulus was suggested by the observation that early excision of the depot of injected material prevented relapses or chronic progression (24). It seemed that MBP might simply diffuse rapidly out of the depot and lose its ability to stimulate. However, in a favorable experimental situation, MBP alone induces multiple successive attacks of disease (25). In recent cell transfer studies

in mice (26), lymphocytes primed and boosted with MBP alone have been found to induce clinically and histologically typical R-EAE when transferred to normal syngeneic recipients.

A second myelin antigen, more difficult to work with because of its physical properties, is proteolipid protein (PLP). It was reported some years ago that whole bovine proteolipid was active in producing EAE in rabbits (27), but this work could not be accepted in the absence of controls to show that there was no MBP in the preparations used. In recent guinea pig studies with whole white matter, a variety of indirect evidence suggested that the active encephalitogen was in fact PLP (28). Preparations containing both MBP and PLP appeared more effective than those containing PLP alone. Finally, EAE has been produced in both guinea pigs and rabbits with purified PLP apparently free of MBP contamination (29–31). This was manifested, in rabbits, as a chronic relapsing disease. In Hashim's guinea pig study skin testing suggested the occurrence of cross reactivity between MBP and PLP in the induction of skin reactivity of the delayed type.

Other myelin antigens, which have been tested by several investigators and appear to be unable alone to produce CNS disease, include myelin-associated glycoprotein (MAG), galactocerebroside, and gangliosides GM1 and GM4. The combination of MBP and galactocerebroside produces an intense but monophasic EAE (32). As noted, P2, especially in combination with various glycolipids induces demyelinative disease, localized, however, in the peripheral nervous system (PNS) (33). Purified preparations of oligodendrocytes have been injected, in the hope of inducing a unique type of EAE, but without success.

Viral infections followed by demyelinative disease have been thought to induce autoimmunization to myelin antigens. In mice developing chronic demyelinative disease after infection with Theiler's virus, sensitization to whole myelin is seen but not sensitization to MBP (34). In human subjects with postinfectious encephalomyelitis after measles, rubella, and varicella, lymphocytic sensitization to MBP appears and seems to parallel the disease process (35).

Attempts to identify a clearcut immune response to one or more neural antigens in patients with MS have, on the whole, been unrewarding, though there are many claims in the literature (35a). Low levels of antibody to MBP have been found in cerebrospinal fluid IgG (2, 36, 37) (K. P. Johnson *et al.*, in (19)). Myelinotoxic factors, identified in tissue-culture assays, are undoubtedly present in MS sera, but appear not to be immunoglobulin (M. B. Bornstein, I. Grundke-Iqbal, in (19)). In contrast, sera from animals with EAE frequently contain demyelinating antibody to galactocerebroside (37a). Antibodies to other myelin components appear not to be myelinolytic (F. J. Seil, in (16)), although they might play a role in an antibody-dependent cell-mediated lytic event (discussed below). The neuroelectric blocking factor found in MS patients' circulating IgG is nonspecific, occurring as well in patients with other neurological diseases (C. L. Schauf, F. A. Davis, in (16); F. J. Seil, in (16)). The immune complexes present in MS patients' blood and CSF contain lipids (38) and antibody against galactocerebroside and GM4 ganglioside (38a).

The situation, with respect to cell-mediated immune responses, is equally uncertain. MS patients' peripheral T lymphocytes stimulated with MBP were reported to undergo blast transformation, and this finding has been repeated (39). On the other hand, other early reports of "specific" interactions of myelin antigens with lymphoid cells, leading to changes in cell surface charge and electrophoretic mobility, proved to be impossible to reproduce. More recently stimulation of MS lymphocytes with MBP or with various myelin glycolipids was reported to produce a significant increase in "early" or "active" E-rosette forming cells (40, 41). The antigenic specificity of this reaction has not been clearly demonstrated and the biological implications of the phenomenon itself are unclear. Circulating T cells reactive with MBP have been reported in 75% of MS patients, but also in 50% of other neurological disease controls (42).

One may wonder whether sensitized lymphocytes specific for neural antigen(s) would remain in the circulation for a significant period of time. Certainly in acute EAE, the wave of sensitized T cells generated in lymph nodes draining an immunization site can be found in the blood only for a few days. They presumably disappear into the CNS. Thus current attention is focused on the cells in the CSF of MS patients, which may represent a population in transit from the blood to the CNS. Since these are limited in number, investigators are using T-cell cloning techniques to obtain larger quantities of uniform cells which can be characterized as to their phenotype and immunologic specificity (43–46). No results are in as yet.

A tangential but relevant group of observations concerns the release of neural antigens into the blood and cerebrospinal fluid, both under circumstances where immunization (autoimmunization) might take place (35) and as part of the ongoing disease process (2, 22, 36, 47) (J. N. Whitaker, D. S. Synder, in (19)). While most observations have been concentrated on MBP, the presence of this antigen in the CSF suggests that myelin antigens in general are being released as a consequence of tissue damage; indeed proteolipid (48), MAG-reactive material (49) and low levels of gangliosides (50) have all been demonstrated in MS patients' CSF. Conversely MBP fragments may be present in the circulation of young individuals at the time when myelin is laid down in the CNS, and it is thought that these serve as temporary tolerogens (2). Lipids in the plasma appear to reflect dietary intake rather then events in the nervous system (51).

2. Role of Infection. In cases of apparent autoimmunity, the immunizing stimulus is usually unknown. It is almost conventional, in discussions of this subject, to list as possible stimuli infectious or traumatic lesions of the target tissue itself (with release of tissue antigens) and, alternatively, cross-reacting antigenic stimuli provided by viral or bacterial infection. Traditional epidemiologic studies strongly support the hypothesis that the MS process is triggered in genetically predisposed individuals by exogenous factors, most frequently viral infection. The evidence includes the fact that MS prevalence varies with latitude; that migrants between low- and high-prevalence areas carry their prevalence with them, if they migrate after puberty; the existence of foci of very high prevalence; and the occurrence of MS epidemics, that occurring

in the Faeroe islands after the arrival of British troops in 1940 being the best documented (52, 53). At the same time, evidence that childbirth can also initiate the MS process in some cases seems fairly compelling (54, 54a).

More sophisticated recent studies support these findings. In families with multiple cases of MS, the frequency and timing of second cases in relation to a first case can best be explained by exposure to common exogenous factors (55, 56). In a recent study of monozygotic twins discordant for MS, retrospective analysis showed that the affected twins had undergone many more major infections in the first 15 years of life than their unaffected sibs (57). In pairs of twins concordant for the disease, early onset was associated with early severe infection, either viral or bacterial, or occasionally with severe operative traumas or childbirth. In a careful study of an established MS population (58), individual exacerbations showed a significant relation to antecedent upper respiratory and gastrointestinal viral infections, as well as to childbirth.

Attempts to isolate a unique virus from neural tissue of MS patients have by and large met with failure, although there have been a dozen unconfirmed reports of putative causal agents (see (14, 15)). An unusual agent (59) resembling that found in subacute myelo-opticoneuropathy, has been found in many MS CSF samples but also in controls with other neurologic disorders.

The use of nucleic acid hybridization has permitted demonstration of persistent measles and herpes simplex virus genomic material in about half of MS brains and control brains as well (60, 61). As further specific probes are developed for other common viruses, we may learn that many brains, both of diseased and normal individuals, contain a significant and perhaps diverse flora of genomic material foreign to the host. On the other hand, no antigens of either measles or herpes appear to be expressed in MS brain (see (15, 17)). Thus the finding may represent "molecular archeology" testifying to past infection (and a possible role in autoimmunization) but not to an ongoing role in immunologic stimulation. A relative increase in antibody titers against common viruses is found in MS, and the patients' CSF may contain multiple antiviral antibodies (62, 63) (K. P. Johnson et al., in (19)), but these are commonly ascribed to polyclonal stimulation locally of preprogrammed B lymphocytes, which enter MS lesions nonspecifically, and to the apparent defect of immune regulation shown by MS patients. T lymphocytes reactive against measles virus are difficult to demonstrate in MS patients' peripheral blood ((64, 65), but see (44)), but are found in CSF (66).

The importance of conventional infection with the viruses which cause childhood diseases as a trigger of autoimmunization has received strong support from recent reports. Doherty, in studies of influenza and vaccinia virus infections of the murine CNS, showed that unprimed T cells enter the CNS and CSF, where they may freely interact with the products of local tissue damage (P. Doherty, in (4)). Johnson, in a study of measles cases in Lima (35), showed that MBP appears early in the CSF, that there is pleocytosis in one-third of uncomplicated measles cases, and that obvious virus is present in the CSF cells. Thus everything conspires to lead to rapid sensitization against neural antigens. In fact lymphocytic reactivity to MBP appeared in about 15% of uncomplicated measles or measles with pneumonia and in over half of cases complicated by encephalitis. In the chronic, relapsing, demyelinative disease produced by Theiler's murine encephalomyelitis virus in SJL mice (67, 68), there is clear evidence of sensitization to myelin antigens (34). Attempts to transfer the disease from affected animals to normal syngeneic recipients by simple transfer of lymphoid cells have, however, failed thus far. Several unrelated viruses infecting the CNS can produce similar inflammatory demyelinating disease in SJL mice (68); in other words, a unique agent is not required. An adoptive transfer of what appears to be autoimmune demyelinative disease without transfer of virus has also been achieved in Lewis rats infected with JHM, a strain of murine hepatitis virus (69). This lesion, by the way, is to be sharply distinguished from that produced in mice by JHM virus, which appears to be based on a simple infection and killing of oligodendrocytes (70).

A question which has not been addressed, either in human subjects or animal models,

concerns the possible role of virus in supplying an antigenic stimulus to helper T cells, which can then facilitate the response of other effector T and B cells to neural antigens. Certainly T-cell help is essential to most biologically important immune responses, and this may be the most important aspect of the triggering event. It is significant, in this regard, that the virus infections commonly followed by post-infectious encephalomyelitis involve enveloped viruses in the myxo-, paramyxo-, herpes-, and poxvirus groups. The incorporation of host antigen(s) into the viral envelope must favor this process. At the same time, an alternative role is not ruled out of microbial antigens which happen to cross-react with neural constituents. For example, measles antibody appears to show a weak cross-reaction with MBP (K. P. Johnson et al., in (19)).

3. **Immune Regulation.** While a great deal has been said about abnormal immune regulation in diseases like MS, rheumatoid arthritis, juvenile diabetes, and systemic lupus erythematosus, solid evidence for such faulty regulation as a causative factor in any of these diseases is far from persuasive.

The case is perhaps strongest in relation to the animal models. Thus the acute monophasic EAE, readily produced in a variety of species and strains of laboratory animals, becomes a chronic, relapsing or progressive disease only in certain susceptible strains of animals, such as the strain 13 guinea pig and the SJL and PL strains of mice, in particular with immunization at about the time of weaning (4–8). Ths SJL mouse characteristically exhibits early loss of normal suppressor T-cell function, early resistance to induction and/or maintenance of specific immunologic tolerance, and consequently exaggerated autoimmune phenomena (N. M. Ponzio, in (4)). Suppressor T cells play a major role in preventing development of EAE in some rat and mouse strains and terminating the individual EAE attacks in others (71, 72). Ablation of these cells with cyclophosphamide intensifies individual attacks of EAE and the number of recurrences in SJL mice (F. D. Lublin, in (4)). Thus the susceptibility gene in these animals, which is linked to genes in the immune response region of H-2 (the murine homologue of the D region in HLA), affects the rate of loss of suppressor T-cell function and this in turn controls the establishment or reestablishment of specific immune responses associated with lesion formation. One presumes, since this has not been formally demonstrated, that the same defect facilitates development and maintenance of an autoimmune response and chronic encephalomyelitis in SJL mice infected with Theiler's or other neurotropic viruses (68). EAE is also restricted by genes at additional loci governing other aspects of lesion formation, such as vasoamine sensitivity of the CNS vasculature (73).

MS in human subjects clearly occurs on a background of genetically determined predisposition. Some races of men are relatively or completely insusceptible to this disease (Bantu, Inuit, American Indian, Yakut, Gypsy, Hutterite) (74). Conversely families with multiple cases of MS demonstrate the existence of one or more "susceptibility genes" (75). HLA typing has established moderately strong linkage disequilibrium between a susceptibility gene (in Caucasians of Northern European origin) and markers encoded in chromosome 6: HLA-A3, B7, and particularly DW2 (DR2) (55, 76). The new loci related to D have not been studied as yet in MS. A weaker linkage is found of MS to certain Gm allotypes encoded in chromosome 14: Gm1 and 17 (expressed as IgG1 allotypes) and Gm 21 (expressed on IgG3) (77, 78).

These linkages, which are not found in acute monophasic illness comparable to acute EAE, imply that susceptibility to MS is determined by regulation at the T-cell level and perhaps, as well, by certain antibody responses. One may speculate that DW2 (DR2) or a gene closely linked to it controls the genesis of the recurrent lesions characteristic of MS by its effect on suppressor T cells, as has been suggested for D-locus-associated susceptibility genes in other chronic "autoimmune diseases." An interesting proposal, which calls for a good deal of further work, is that it may be possible to relate the disease pattern, i.e., recurrent bouts of mild–moderate new lesion formation separated by periods of remission *versus* relentless progression, to specific HLA haplotypes (79) and, by implication, to specific patterns of immunoregulatory function.

Table I summarizes a few of the points made thus far. An entirely similar table could be drawn comparing monophasic autoimmune

TABLE I. DEMYELINATIVE DISEASES OF CNS

Diseases studied	ADE[a]	EAE	MS	R-EAE	V-EAE[b]
Genetic predisposition					
Radical preference	0	0	+	+	+
Restriction at MHC	0	0	+	+	+
Restriction at other loci	?	+	+	+	?
Faulty immune regulation	0	0	+	+	?
Initiation of disease					
Enhanced susceptibility at puberty	0	0	+	+	?
Factors initiating disease[c]	M, V	M	V, C	M	V
Role of autoimmunization					
Virus causes autoimmunization, e.g., to MBP	+	NA	?	NA	+
Relation of autoimmunization to disease	+	+	±[d]	+	+
Immunosuppression arrests disease	0	+	+	+	+

[a] ADE: Acute disseminated encephalomyelitis, postvaccinal and postinfectious encephalomyelitis; also sporadic encephalitis, optic neuritis, transverse myelitis, neuromyelitis optica.
[b] V-EAE: R-EAE-like disease, induced with Theiler's murine encephalomyelitis virus or other neurotropic virus diseases.
[c] M: Immunization with myelin. V: Infection with enveloped and other viruses. C: Childbirth.
[d] T-Lymphocyte cloning from blood, CSF, and CNS lesions in progress.

and virus-induced polyneuritis in man and experimental animals with chronic relapsing inflammatory polyneuropathy in genetically restricted hosts.

It is not clear that recently described peculiarities of the known subpopulations of mononuclear cells in the peripheral blood and CSF of MS patients ((18, 20, 21), B. G. W. Arnason, in (19)) reflect the fundamental problem in immune regulation described above. Five findings stand out among many which have been reported.

First, active blasts are present in the peripheral blood and CSF (S. A. Armentrout and S. van den Noort, unpublished data), and these may or may not correspond to the $T\gamma\mu$ cells also found there (80, 81). Virtually all peripheral T cells in patients with active MS carry phenotypic markers of "activated" T cells (82a). A high proportion of CSF T cells are cycling, even in "inactive" MS (82).

Second, a brief surge of T cells carrying the T4 marker, characteristic of the helper–inducer class of T lymphocytes, is seen in the CSF at the onset of an exacerbation of MS ((83), B. G. W. Arnason, in (19)).

Third, suppressor T cells, stimulated to suppress by mitogens like concanavalin A and characteristically carrying the markers T5 and T8 as well as an Fc receptor for IgG (so-called $T\gamma$ cells), decrease or disappear from the blood

immediately before an exacerbation and return to normal or above normal levels with remission (84–86). This finding has not been completely reproducible, and it appears pertinent to this reviewer to wonder about the uniformity of commercially produced monoclonal antibodies used in various laboratories for what should be identical tests. A similar drop in suppressor cells is seen in many but by no means all cases of chronic progressive MS (87). A variety of other techniques has been used to demonstrate the drop in suppressor cell activity. It is accompanied by, and may be in part responsible for, evidence of polyclonal activation of peripheral and CSF B cells (e.g., (98)).

The fourth finding is a fall in natural killer cell activity, in the lymphoid cells of both blood and CSF (88–90) (see also P. A. Neighboor, B. R. Bloom in (19)) and a corresponding loss of the ability to produce interferon in response to viral or mitogenic stimulation. This change is seen in about one-third of MS patients, and is not well correlated with disease activity. Again, it has not been seen by all observers.

Fifth and finally, during periods of disease activity, one finds in the peripheral blood activated monocytes, which contain proteolytic enzymes (90a) and which produce and release substantial amounts of prostaglandin E2 (91).

These more or less "specific" changes in MS are accompanied by an overall drop in "early" or "avid" T cells (rapidly binding large numbers of sheep erythrocytes) (92). However all the findings are nonspecific, both in the immunologic sense (they are observed without reference to any specific antigen) and in the broader medical sense (they are observed in other diseases such as lupus). They may have a trivial explanation, in that the activated monocytes—one must perhaps regard these as a spillover into the blood and CSF from the site of lesion development in the CNS—produce PGE2, which can modulate NK cells so that their phenotypic markers and cytotoxic activity are temporarily lost (81). Research is underway to determine if PGE2 can modulate the phenotype and suppressor activity of T8+ cells. The finding that T8 is present on cultured sheep oligodendrocytes (93) suggested the theory that an autoimmune response directed at T8 might damage these cells, in the brain, causing myelin breakdown, and simultaneously cause the disappearance of T8+ lymphocytes from the blood. This proposition was supported by the finding that MS serum contains a lymphocytotoxic factor (93a) and the finding that antibody to T8 caused modulation (disappearance) *in vitro* of both T8 and suppressor activity (94). However, T8 has not been found on human oligodendrocytes by several competent observers, and this theory has been temporarily shelved. If peripheral lymphocytes from MS patients with active disease are held *in vitro* for 24–48 hr, T8 and suppressor activity appear (see B. G. W. Arnason, in (19)); this suggests that modulation indeed does take place *in vivo*, whatever its mechanism may be.

Some of these "specific" changes may have another explanation, in that large numbers of T8+ cells are found in the MS plaques in the brain and spinal cord, especially in perivascular cuffs but also in the parenchymal cell infiltrate (95). Thus they may be actively withdrawn from the blood as part of lesion formation.

In either case, modulation or active disappearance, one can visualize the loss of suppressor activity as contributing to prolongation of a lesion-inducing immune response. However, this is not in any sense a genetically determined inadequacy of suppressor function,

like that identified in SJL mice, and it is possible that the regulatory defect which permits the evolution of the chronic immunologic process underlying MS has not yet been uncovered.

A brief comment is in order about other *in vitro* findings in MS, for which specificity has been claimed. Alterations in surface properties of lymphocytes defined by charge, agglutinability, and adherence to virus-infected cells or to myelin (listed in (18, 96)) can be rather simply accounted for by the shift in lymphocyte subsets noted above and by the active monocyte-dependent production of E-series prostaglandins (91). Cultures of MS patients' peripheral lymphocytes with various antigens show enhanced (unregulated?) production of cytophilic antibody (also demonstrable by RIA or ELISA techniques) (97, 98). Thus in tests with measles antigens or MBP, such antibody may provide a recognition element leading to further monocyte activation, prostaglandin production, and nonspecific adherence of blasts to any target presented. MS patients' plasma appears to contain MBP fragments (36), immune complexes (99), elevated levels of certain hormones (ACTH, prolactin) (100), and altered levels of zinc (101) and of certain fatty acids (51), all of which may contribute to deviations of lymphocyte behavior *in vitro* and of red cell surface charge (electrophoretic mobility) (102, 103), platelet aggregation (104), and leukocyte adherence to glass (105).

4. Roles of Cell-Mediated Immunity and Antibody. The immunopathologic mechanisms which may play a role in the lesions of MS fall into the same categories as those which underlie disease in other organs, and can be studied in well-known model systems (for detailed reviews, see (2, 3, 14–20, 106)). Again investigation of the inflammatory and demyelinative process in experimental animals has been pushed further than the investigation of MS itself.

The best known encephalitogen, MBP, induces EAE in several species and elicits delayed type skin reactions and *in vitro* lymphocytic reactions closely correlated with the disease process (107, 108). The disease can be adoptively transferred by transfer of T cells from sensitized donors (see (2, 3)), and transfer is enhanced by exposure of these cells to mitogen or to MBP *in vitro* (109, 110). It has

thus been customary to regard the acute EAE lesion as a pure T-cell-mediated reaction (CMI), and this view is strongly supported by the fact that EAE can be induced with small MBP peptides which induce CMI without any trace of antibody formation (111). A parallel but less well worked out series of observations has been made in rabbits and guinea pigs injected with PLP (27, 29, 31). The basic CMI lesion in turn, as studied in simpler models, consists of primary effector T-cell activation at or near the vessel wall, followed by a massive parenchymal invasion by activated nonspecific monocytes (macrophages) and smaller numbers of both specific and nonspecific T and B cells (B. H. Waksman, in (106)). This is what is actually seen in morphologic studies of acute EAE (P. W. Lampert, in (19), (5-7, 112, 113)). That the initial T-cell reaction occurs at the level of the vessel wall, presumably after "dual recognition" of MBP and of an appropriate major histocompatibility complex antigen seems likely if, as reported, MBP does in fact make its way to the luminal surface of the endothelium of brain vessels (see (12)) and endothelial cells carry Ia (114).

In spite of the attractive simplicity of this formulation, we must recognize the possibility that two different immunologic responses, directed to different myelin antigens, might be required to generate the complete EAE lesion. This hypothesis was developed to explain the observation that there is little demyelination in acute EAE of guinea pigs sensitized with MBP and a great deal in animals sensitized with whole myelin. The hypothesis receives support from the following experiments. In the eye of rabbits injected intravitreally with lymphokine-containing supernatants from activated lymphocytes, mononuclear cell infiltration appears around vessels in the myelinated nerve fiber layer of the retina but little breakdown of myelin is seen. If antibody to myelin constituents is injected simultaneously, demyelination may be extensive ((115), see also (12)). Antibody alone does not demyelinate. Thus antibody-dependent cellular cytotoxicity (ADCC) may be superimposed on the inflammation resulting from T-cell-mediated immunity when whole myelin serves as the immunizing agent. In similar experiments, a typical T-cell-mediated lesion is produced in dorsal nerve roots of tuberculin sensitized rats injected locally with tuberculoprotein (PPD), but there is demyelination only if the animals also possess antibody against galactocerebroside (115a).

No such analysis has yet been carried out of the early or chronic lesion of MS. A detailed study of the participating cell populations with the use of monoclonal antibodies and immunofluorescence (95) shows a predominance of T8+ cells (cytotoxic/suppressor phenotype) in perivascular cuffs and both T4+ (helper/inducer) and T8+ cells infiltrating the white matter parenchyma together with large numbers of Ia-bearing cells (presumably macrophages and some B cells). Thus the picture corresponds to the conventional picture of a CMI lesion, except for the unexpectedly large proportion of T lymphocytes bearing the T8 marker. One may object that the lesions studied, even though "early" from the traditional pathologist's viewpoint, must actually be several days–several weeks old; thus what is seen includes secondary and tertiary events at the cellular level.

A recurrent question concerns the possibility that oligodendrocytes (oligos) may be the primary target of viral or immune attack in MS, demyelination occurring only as a secondary manifestation of damage to these cells. Oligos are diminished or absent in established MS plaques, and there is a failure of remyelination during periods of remission. Primary lesions of oligos produced by viral infection (70) or by simple chemicals like biscyclohexanone oxaldihydrazone (Cuprizone) (116) produce primary demyelinative lesions with considerable resemblance to those of MS. Also antibody specific for oligos is found in MS patients' sera, but in sera from patients with other neurological disorders as well (117). Cultured ovine oligos carry T8 (93), and it is easy to believe that they may serve as a target of the attack that also ablates T8+ lymphocytes in the circulation.

Nevertheless this proposition has never been popular, since oligos are numerous in gray as well as white matter; if they are the primary target in MS, the lesions should not be limited to white matter. Attempts to induce a disease like EAE by immunizing animals with purified or cultured oligos have failed repeatedly (117a). What may be the coup de grace for this theory is Raine's recent observation that

oligos within fresh MS lesions, in which there is active myelin breakdown, are normal in number and appearance (118). In conventional EAE lesions there is little damage of oligos and remyelination is brisk after the acute disease has subsided. For the moment, we must accept the conclusion that oligo damage in older MS plaques is secondary to the primary effects of disease, i.e., either to the inflammatory process in which they are enveloped or to the myelin breakdown itself.

A second recurrent theme is the possible significance of edema in early MS lesions. That such edema actually is present has been demonstrated by the technique of computerized axial tomography (CAT) with enhancement: injection of radiopaque dye intravenously shortly before scanning clearly shows the rapid leakage of macromolecules from affected vessels and its suppression by corticosteroid hormones (119). Nuclear magnetic resonance, used at frequencies which "see" water, reveals more than five times as many lesions as CAT scanning (120).

Similarly in acute EAE, it has been possible to identify vascular leakage by staining tissue sections for fibrin (121) or by measuring extravasation of radiolabeled macromolecules (122). This edema can of course be that which commonly accompanies intense T-cell-me-diated reactions or, alternatively, may be due to an immune complex lesion of the vessel wall, with triggering of the complement cascade. The inhibition of acute EAE lesion formation by protease inhibitors (M. Smith, in (3); (123)) and what may be a similar inhibition of MS (124) speak in favor of the latter hypothesis. Again the implication is that the conventional CMI lesion may have an added component due to antibody formation. One thinks of the possible involvement not only of complement but also of the plasmin or clotting systems in the vascular process (125); in fact inhibitors of coagulation also inhibit EAE.

It is important to recognize that even this picture is simplistic. As suggested in Table II, activated T cells recruit various inflammatory cells by release of lymphokines (B. H. Waksman, in (106)). While activated monocytes (macrophages) are the predominant population of secondary cells and usually dominate the histologic picture, other inflammatory cells may also be recruited and activated, both by lymphokines and by antigen–antibody complexes (126). These activated cells produce a broad range of mediators which affect vascular permeability as well as the behavior of the other cells in the total infiltrate. As indicated earlier, increased prostaglandin production is seen in the stimulated monocytes which make

TABLE II. INFLAMMATORY MEDIATORS IN MS LESIONS

Activated cells producing mediators	Mediators	Local effects	Effects in circulating blood
T Cells	Lymphokines	Vasodilation	Activated monocytes
Monocytes[a,b]	Lysosomal enzymes	Vascular permeability	Modulation of T-cell
Mast cells, basophils[a,b]	Monokines	increase	subsets
Polymorphonuclears[b]	PGE$_2$[d]	Adherence and activation	Adhesiveness of T
Platelets[b,c]	TXA$_2$[d]	of monocytes (and other	lymphocytes
Endothelium[a,b,c]	PGI$_2$[d]	cells)	Decreased NK[e]
	LTC$_4$[d]	Chemotaxis and diapedesis	activity
	Histamine		
	5-HT		
	Superoxide		
(C-Cascade[b])	(Bradykinin)		

Note. Distinct sites of action of polyunsaturated fatty acids, steroids, nonsteroidal anti-inflammatory drugs, zinc, superoxide dismutase, interferon.

[a,c] Activation primarily by: (a) lymphokines; (b) antigen–antibody complexes; (c) other mediators.

[d] Derived from membrane phospholipid by action of phospholipase A$_2$, to give arachidonic acid, and the cyclooxygenase and lipoxygenase pathways: PGE$_2$, prostaglandin E$_2$; TXA$_2$, thromboxane; PGI$_2$, prostacyclin; LTC$_4$, leukotriene C$_4$; 5-HT, 5-hydroxytryptamine (serotonin).

[e] NK, natural killer cell.

their way into the circulation. Thus in addition to producing local effects, they may influence both the phenotype and the behavior of circulating T cells and NK cells. Thromboxanes, prostacyclin, and leukotrienes have yet to be studied in MS lesions, as well as the macromolecular lymphokines, monokines, and enzymes. Needless to say, the production and functional effects of all these mediators provide tempting targets for therapeutic intervention with new agents, a few of which are listed in the footnote to the table.

It seems likely that an important component of the rapidly reversible functional loss in acute bouts of MS is due to edema rather than to demyelination. Edema fluid may affect conduction simply by increasing local pressure or, possibly, by separating the myelin layers from each other and from the axon, or even by altering the ionic environment in the vicinity of nodes of Ranvier (Discussion in (16)). In EAE, it seems clear that the acute symptomatology is in fact related to the vascular leakage rather than to the cellular infiltrative lesion or to demyelination (121).

One must, at the same time, recognize the possibility that part of the acute functional loss is due to neuroelectric blocking factors. Such factors are present in MS and appear to represent autoantibody (IgG) directed against certain presynaptic components of the synapse (C. U. Schauf, also F. J. Seil, in (16)). They are found in other neurologic diseases as well as in MS; thus, the degree to which they contribute to the specific symptomatology of MS remains conjectural. Equally conjectural is the possible effect of locally released macromolecular mediators and neurotransmitters, listed in Table II, on conduction. A final element contributing to early recovery, in particular recovery from myelin loss, is reorganization of the axonal membrane, with an increase in the number of well-distributed sodium channels and recovery of the ability to conduct in the absence of myelin.

5. **Conclusions.** Most available evidence suggests that infection with enveloped viruses of the myxo-, paramyxo-, herpes-, and poxvirus families may occasionally induce immunization to neural antigens, myelin antigens in particular, and a consequent encephalomyelitis localized to the white matter. In individuals with a genetically determined abnormality of immune regulation, this process may not be suppressed and may give rise to the recurrent or long-lasting periods of new lesion formation which we call multiple sclerosis. Exacerbations may be provoked by further virus infections or by childbirth. The responsible white matter antigen(s) have not been firmly identified and the immunoregulatory abnormality is unknown. The character of the lesions appears to be determined by multiple simultaneous immune responses to different antigens and multiple superimposed immunopathologic effects.

Much of what is presented in the present review may require revision as the further application of monoclonal antibody techniques (127) and the new techniques of cloning, fusing, or otherwise immortalizing T cells (128) reveals previously unsuspected neural or viral antigens in white matter and effector molecules and/or cells reactive with these antigens. Thus, in mouse experiments Reovirus strains infecting the pituitary and pancreas have been shown to produce intense immunization to a variety of autoantigens in these organs (M. Haspel, in (4)). The range of actual responses was uncovered only by carrying out fusions with infected animals' spleen cells and studying the hybrids thus obtained. Similarly continuous "monoclonal" lines of T cells specific for a single myelin antigen are being studied for their ability to produce EAE (129). At least seven laboratories in the United States and several abroad are hybridizing B cells and cloning the two principal classes of T cells, helper/inducer and cytotoxic/suppressor, from MS patients' blood and CSF, and the clones are being examined for reactivity with neural and viral antigens. One may hope that within a few more years the nature of the significant antigens and of the immunologic reactants which produce multiple sclerosis will be clear.

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