Virus-Induced Autoimmune Reactions in the CNS

P.J. Talbot[1], D. Arnold[2], and J.P. Antel[2]

1 Introduction

Neurologic diseases are diverse and often not well-understood, despite the tremendous health care problems they pose, such as the estimated 22 million persons worldwide who suffer from dementia, a characteristic loss of mental capacities. Virus infections are an established contributor to development of an array of diseases of the central nervous system (CNS) and are implicated in a further spectrum of disorders in which the etiology is not yet formally established. For example, 60% of acquired immune deficiency syndrome (AIDS) patients suffer neurologic sequelae presumably caused by human immunodeficiency virus (HIV). Viruses can contribute to the development of neurologic disease via an array of direct and indirect mechanisms, as summarized in Table 1 and described in detail in this chapter. Direct mechanisms refer to neural cell injury arising as a

[1] Centre de recherche en santé humaine, INRS-Institut Armand-Frappier 531, boulevard des Prairies, Laval, Québec, Canada, H7V 1B7
e-mail: Pierre.Talbot@inrs-iaf.uquebec.ca
[2] Montreal Neurologic Institute, McGill University, 3801 University Street, Montreal, Québec, Canada, H3A 2B4

G. Gosztonyi (ed.), *The Mechanisms of Neuronal Damage in Virus Infections of the Nervous System*
© Springer-Verlag Berlin Heidelberg 2001

Table 1. Virus involvement in autoimmune disease of the CNS

	Effects on systemic immune response	Effects within CNS compartment
Induction or maintenance of antigen-restricted responses	Cross-reactivity of virus and CNS antigen – molecular mimicry	Response to viral antigens expressed in neural cells
	Response to CNS antigens transported to regional lymph nodes	Increased expression or release of neural antigens by virus infected cells: Sensitization to autoantigens – break in tolerance Expansion of antigenic targets – epitope or determinant spreading
		Antigen presentation by APCs within CNS to pre-sensitized lymphocytes
Non-antigen-restricted enhancement of immune response	Activation of APCs Changes in immune regulatory cells and cytokines Induction of molecules involved in lymphocyte trafficking	Blood–brain barrier: Induction of chemoattractant and adhesion molecules Activation of perivascular APCs
		Parenchyma: Activation of APC and immune regulatory capacity of microglia Enhance effector functions of glial cells: Effector cytokines, proteases, NO Antibody-dependent cell cytotoxicity

APCs, antibody-presenting cells; *NO*, nitric oxide.

consequence of the cells becoming infected with virus per se. Such infections can result in actual cell lysis, as in the case of poliomyelitis or herpes simplex encephalitis, or loss of cell function without cell death, a phenomenon termed loss of luxury function (Oldstone et al. 1982). Subacute sclerosing panencephalitis (SSPE) is an example of a chronic neurologic disease initially considered to be neurodegenerative but which is now established to be a result of a direct and persistent measles virus infection.

Indirect mechanisms of virus-induced neurologic disease would include those in which disease development is dependent on participation of non-viral mechanisms, which in the context of this chapter will be related to products of the immune system. Such indirect effector mechanisms could result from infection either outside or within the CNS. Infection of systemic lymphoid organs with virus could promote development of specific CNS antigen-directed immune responses by the process of molecular mimicry which implies that the neural-directed immune response arises because of antigenic homologies between viral and neural antigens (Oldstone 1987, 1998). The entity of acute disseminated encephalomyelitis, which follows immunization with neural tissue-containing vaccine such as the original Pasteur rabies vaccine, establishes the precedent that immune-mediated CNS demyelinating disease can occur, although in this condition the immune response is induced by non-viral antigens contained in the vaccine. Systemic virus infection can also alter immune regulatory activity so as to favor immune activation, which in turn would favor migration of the immune response into the CNS.

Virus infection within the CNS could trigger an immune response by an array of mechanisms. Infection of neural cells even with defective virus, such as with genetically engineered adenoviruses used in gene transfer paradigms, can evoke a viral antigen-directed immune response with harmful effects on host tissue. The Theiler's murine encephalomyelitis virus (TMEV) model of chronic immune-mediated CNS demyelination indicates that an immune response directed at myelin antigens can evolve over a prolonged time period, presumably as a result of a break in immune tolerance as such antigens become exposed or released consequent to the initial infection; this effect has been referred to as epitope or determinant spreading and is not dependent on molecular mimicry (LEHMANN et al. 1992; MILLER et al. 1997). Tissue injury can also result from release of effector molecules including cytokines from glial cells, particularly microglia, which become infected with virus or are activated by its presence; such an effect has been referred to as bystander injury (HORWITZ et al. 1998). This mechanism has been invoked to account for the neuronal injury associated with HIV encephalopathy (CONANT et al. 1998; KOLSON et al. 1998).

In this chapter, we will consider whether and how the direct and indirect consequences of viral infection can contribute to development of the human disease multiple sclerosis (MS), which is regarded as the prototype of a cellular immune-mediated CNS disorder. Whether an initial unique viral infection initiates the disease process remains speculative (TALBOT 1995). Since demyelination is the hallmark of MS, throughout this chapter, we will illustrate how virus-related immunopathogenic mechanisms can contribute to CNS demyelination. We will focus on coronaviruses to illustrate how experimental models have been used to characterize the immunopathogenesis of virally mediated CNS demyelinating disorders and how one can undertake a search for disease-related viruses in the human disease state. Although the immune system is regarded to be directed primarily at the myelin and its cell of origin, the oligodendrocyte in MS, there is increasing recognition that there is substantial axonal injury as well. We will consider in some detail the basis whereby such injury can result either as a primary or secondary event in the disease course and how it contributes to the extent of clinical neurologic disability.

Multiple sclerosis is a chronic debilitating neurologic disease that affects 0.1%–0.2% of the population in high-risk areas such as Canada and northern parts of the United States of America and of Europe. Both genes and environment have been brought to the "Supreme Court" of scientific suspicions, although a final judgment is still awaited and may be a long-time in coming, since several genes and several environmental factors may contribute to neuropathogenesis.

2 Viruses and Multiple Sclerosis

Even though the etiology of MS remains elusive, a working hypothesis is that it is a polygenic disease (SADOVNICK et al. 1997) in which an infectious agent or agents

play(s) a role, either in disease initiation and/or in its propagation and relapses. Interestingly, an infectious etiology was postulated when the disease was first described in the nineteenth century. Viruses would be the most likely infectious culprit in genetically predisposed individuals (KURTZKE 1993; COOK et al. 1995). Several viruses have been implicated in the last two decades, although not one has so far withstood the test of time or closer scrutiny, perhaps because several different viruses, acting through similar direct and/or indirect mechanisms, could be involved (TALBOT 1995). Neurotropic viruses recovered from patients include: measles, herpes simplex, parainfluenza, tick-borne encephalitis and rabies viruses, simian virus 5, coronaviruses and cytomegalovirus (JOHNSON 1985), and more recently a retrovirus (PERRON et al. 1997). A series of studies have used the findings of increased serum titers and/or local antibody synthesis against various viral agents within the CNS of MS patients as evidence for their participation in the MS disease process (SALMI et al. 1981). Measles, herpes simplex, and coronaviruses (SALMI et al. 1982) were again implicated, as were mumps, varicella, influenza C, rubella and vaccinia viruses. Findings regarding simian virus 5 are inconsistent (GOSWAMI et al. 1987; VANDVIK and NORRBY 1989). Epstein-Barr (BRAY et al. 1992; KINNUNEN et al. 1990) and human T lymphotropic (SHIRAZIAN et al. 1993) viruses are further examples. Analysis of viral antibodies in MS affected and non-affected twin pairs could only confirm elevated cerebrospinal fluid antibodies to rubella and vaccinia viruses (WOYCIECHOWSKA et al. 1985). In situ hybridization detected measles genomes in only a few MS patients (HAASE et al. 1981; COSBY et al. 1989). This technique was also used to detect murine-related coronaviruses in brains of 12 of 22 MS patients, with antigen detected by immunohistochemistry in two patients (MURRAY et al. 1992a). The development of the very sensitive polymerase chain reaction (PCR) technique led to the detection of human T lymphotropic virus genetic information in MS patients (REDDY et al. 1989), although other groups have failed to confirm this result (e.g., DEKABAN and RICE 1990), which has unfortunately given a bad reputation to the PCR-based search for MS-associated viruses, even when studies are very carefully performed.

A recent study attempting to link human herpes virus-6 with MS described an IgM response, suggestive of viral reactivation, but only in patients with the relapsing-remitting form of MS. PCR-based viral DNA detection in blood cells was positive in less than a third of MS patients tested (SOLDAN et al. 1997), which prompted words of caution (STEINMAN and OLDSTONE 1997). A further cautionary note is that detection of virus and disease causality are not necessarily linked. One need consider whether there is a normal viral flora in both the CNS and in the lymphoid system which may be more readily expressed in response to inflammatory conditions. Thus, a viral etiology for MS remains speculative, as do the pathogenic mechanisms that would lead from initial viral exposure in a genetically susceptible individual to chronic disease.

3 Coronaviruses and Multiple Sclerosis

Coronaviruses appear in the long list of viruses occasionally associated with MS. Human coronaviruses (HCoV) were first isolated in the mid-1960s from patients with upper respiratory tract disease (TYRRELL and BYNOE 1965; HAMRE and PROCKNOW 1966; MCINTOSH et al. 1967). Their characteristic morphological appearance led to the creation of a new virus family (TYRRELL et al. 1968). Serological studies distinguish HCoV into two groups, named 229E and OC43 after the initial isolates. Viral proteins have slowly been identified, either directly or through the cloning, sequencing, and expression of viral RNAs, and resemble proteins of other coronavirus strains (ARPIN and TALBOT 1990; MOUNIR and TALBOT 1992, 1993a,b; MOUNIR et al. 1994; LABONTÉ et al. 1995). These viruses are recognized respiratory pathogens involved in up to one-third of common colds and to which close to 100% of the population has been exposed, as shown by seroconversion (MYINT 1994).

The possible involvement of these viruses in neurologic disease such as MS remains an intriguing possibility that is sustained by several lines of evidence. Direct relevance of coronaviruses to MS was initially suggested by isolation of two coronaviruses from the CNS of two MS patients (BURKS et al. 1980). Even though a murine origin of these isolates was suggested from genomic (WEISS 1983) and antigenic (FLEMING et al. 1988) assessments, recent reports strengthen the possible importance of coronaviruses in MS. First, there was a preferential association of murine-like coronavirus genes with MS brain tissue, shown by in situ hybridization (MURRAY et al. 1992a). Second, susceptibility of primates to murine coronavirus-induced demyelinating disease, after intracerebral (MURRAY et al. 1992b, 1997), or even peripheral inoculation (CABIRAC et al. 1994) was demonstrated. This suggests that previous MS isolates may indeed have derived from infection by murine-like viruses. As in rodents, astrocytes were described as a site of viral persistence in primates (MURRAY et al. 1997) and virus could find its way to the CNS after a peripheral inoculation (CABIRAC et al. 1994). Other findings implicating coronaviruses in MS include intrathecal antibody synthesis (SALMI et al. 1982) and controversial ultrastructural observations (TANAKA et al. 1976). However, serological assessments failed to show increased levels of anti-HCoV antibodies in MS serum and/or cerebrospinal fluid (FLEMING et al. 1988; HOVANEC and FLANAGAN 1983; JOHNSON-LUSSENBURG and ZHENG 1987). One study did show a significant association of colds with MS exacerbations and an equally significant association of HCoV-229E infection in MS patients compared to controls (JOHNSON-LUSSENBURG and ZHENG 1987). Interestingly, in the first report on the association of viral infections and MS, it was commented that seasonal HCoV infection patterns do indeed fit the observed occurrence of MS exacerbations (SIBLEY et al. 1985).

More recently, molecular biologic approaches have been applied to resolving the relation between coronavirus infection and MS. An in situ hybridization study with cDNA synthesized from the RNA of HCoV-OC43 failed to detect this viral genome in four autopsy and one biopsy samples (SORENSEN et al. 1986). However, these authors speculated that more sensitive methods of detection may be required

in view of the probably low viral titers and the small number of infected CNS cells (Sorensen et al. 1986). Thus, we initiated a search for HCoV in human brains a few years ago with a more sensitive assay. Our initial pilot study did reveal the presence of HCoV-229E RNA in MS autopsy brain tissue (Stewart et al. 1992). Extremely stringent RT-PCR RNA amplifications followed by Southern blot hybridization and nucleotide sequencing were performed on coded tissue. After this was completed, codes were broken and we found the following from 90 donors: both strains of HCoV were surprisingly prevalent (44% for HCoV-779E and 23% for HCoV-OC43), without signs of preferential histological expression sites. A statistically significant higher prevalence of HCoV-OC43 was found in MS patients than in either neurologically normal controls or controls with other neurologic diseases (Arbour et al. 2000). These results are consistent with the neurotropic potential of HCoV but, as in any other such studies, relevance to MS cannot be directly inferred. The next phase of our HCoV detection study involves in situ detection of viral RNA and the identification of sites of persistence by double-labeling of virus and cell markers. We have obtained initial evidence for the expression of HCoV-OC43 in neural tissue, after demonstrating the relative abundance of viral material by Northern blotting (Arbour et al. 2000). Our studies are consistent with persistence of HCoV in vivo, which is indicative that these viruses could be part of a CNS viral flora that only become pathogenically significant under conditions that remain to be determined but may for example include the expression of susceptibility genes.

Persistent HCoV infections in vitro have been reported, as for example HCoV-229E in the L132 human fibroblast cell line (Chaloner-Larsson and Johnson-Lussenburg 1981) and HCoV-OC43 in human glioblastoma and rhabdomyosarcoma cells (Collins and Sorensen 1986). Our own work has demonstrated that cell lines of neural origin, including oligodendrocytes, are susceptible to persistent infection by both strains of HCoV (Arbour et al. 1999a,b, 1998). We further showed that CD13 is the cellular receptor for HCoV-229E on susceptible neural cell lines (Talbot et al. 1994; Lachance et al. 1998). Primary cultures of mouse CNS cells can also be infected with HCoV-OC43 (Pearson and Mims 1985). Neuronal cells produced infectious virus whereas astrocytes only produced viral antigens. Oligodendrocytes were apparently not infected in that study. Human fetal brain cells were also susceptible to HCoV-OC43 infection, although no infectious virus was detected, indicative of an abortive viral infection. Such abortive or incomplete viral replication cycles in neural cells could also have pathological consequences, for example by altering the "luxury" cellular functions or attracting an immune response to the CNS. Our own studies have also demonstrated the susceptibility of primary human microglia and astrocyte cultures to infection by both HCoV strains (Bonavia et al. 1997), and more recently oligodendrocytes (Viau et al. unpublished data). Moreover, it is known that murine and human coronaviruses can infect human brain endothelial cells (Cabirac et al. 1995), a potential route of entry into the CNS from peripheral blood, after viremia (Myint 1994), or infection of blood lymphocytes or macrophages (Bang and Warwick 1960; Lamontagne et al. 1989). Importantly, as shown in studies with

murine coronaviruses, replication in neuronal and glial cell cultures has correlated with in vivo susceptibility to infection and disease development (e.g. PASICK and DALES 1991; LAMONTAGNE et al. 1989), which adds credence to the possible in vivo relevance of in vitro studies. Thus, coronaviruses may provide more than animal models for demyelinating disorders, as described in the next section: they may be active participants in human disease (HOUTMAN and FLEMING 1996).

4 Murine Coronavirus-Induced Immune-Mediated CNS Disease

Like HCoV, murine coronaviruses are respiratory pathogens. However, they have also attracted attention as causal agents of liver infections, hence their name MHV, for mouse hepatitis virus. Neurotropism of murine coronaviruses was first reported in 1949, when the JHM strain of MHV was isolated from mice with disseminated encephalomyelitis with extensive demyelination (CHEEVER et al. 1949; BAILEY et al. 1949). The hemagglutinating encephalomyelitis virus of pigs represents another example of neurologic involvement in a coronavirus infection (WEGE 1995). Infection of rodents with MHV provides an excellent animal model for virus-induced demyelinating disease, as originally described for the JHM strain (WEINER 1973; LAMPERT et al. 1973). Infection of adult mice culminates in encephalomyelitis with infection of both glial and neuronal cells and over 95% mortality. The few survivors develop chronic white matter pathology characterized by focal CNS demyelinating lesions, with subsequent remyelination and recurrent demyelination. Demyelination was long thought to be a primary effect of virus infection and destruction of myelin-synthesizing oligodendrocytes. However, an immunopathological mechanism, as is observed in MS, was subsequently documented (WANG et al. 1990; HOUTMAN and FLEMING 1996). Genetic susceptibility to MHV-mediated CNS disease in mice correlates, both in vivo and in vitro, with the infection of neurons and macrophages and is controlled by a single autosomal dominant gene on chromosome 7 (KNOBLER et al. 1981).

Murine coronaviruses can access the CNS through anteroneuronal transport via the olfactory nerve (LAVI et al. 1988; BARNETT and PERLMAN 1993), although the possibility remains that infected macrophages (BANG and WARWICK 1960; KNOBLER et al. 1981) may carry virus to the CNS, as is observed with HIV. Coronavirus CNS persistence appears to involve mainly oligodendrocytes (KNOBLER et al. 1982) and astrocytes (PERLMAN and RIES 1987), with possible neuronal involvement (PASICK and DALES 1991). Possible infection of microglial cells has not been seriously investigated, which is surprising given the long-known macrophage susceptibility (BANG and WARWICK 1960) and the above-mentioned genetically determined susceptibility of neurons and macrophages to infection (KNOBLER et al. 1981).

The underlying mechanisms explaining why neurons are involved in the acute phase of MHV (and TMEV) disease but appear spared in the chronic infection are

not known but may involve resistance of glial cells to immune clearance (Buchmeier et al. 1984; Stohlman et al. 1995) or the appearance of putative glial cell-specific viral variants that are resistant to the action of cytotoxic T cells (Pewe et al. 1996) or to antibody neutralization (Dalziel et al. 1986; Fleming et al. 1986). Virus mutants, either thermosensitive (Haspel et al. 1978), small plaque (Erlich et al. 1987) or neutralizing monoclonal antibody (mAb)-selected (Dalziel et al. 1986; Fleming et al. 1986), show modified pathology with sparing of neurons and infection of oligodendrocytes. Passive transfer of neutralizing mAbs modulated disease from fatal encephalomyelitis to chronic recurrent demyelination (Buchmeier et al. 1984). Selective cell susceptibilities to infection could also relate to initial virus-cell interactions that may differ according to the cell type that is infected. A member of the carcinoembryogenic (CEA) family of antigens has been identified as a cellular receptor for MHV (Williams et al. 1991), and a CNS receptor from the same CEA family has also been identified (Chen et al. 1995a). A variety of co-factors are also required for viral penetration after receptor binding (Yokomori et al. 1993). It is conceivable to imagine that these early events in viral infection are less prone to immune intervention when glial cells are the viral target.

Observations applicable to possible viral-associated immune mechanisms underlying development of MS have been made with the MHV model. Immunosuppression prevents virus-induced demyelination. The disease can be adoptively transferred by spleen cells from virus-infected donors (Wang et al. 1990). Cellular sensitization to myelin basic protein (MBP) and adoptive transfer of encephalomyelitis with such cells, as is done in the classic experimental allergic encephalomyelitis (EAE) models, has been reported in rats infected with MHV-JHM (Watanabe et al. 1983). MHV-JHM infection of mice also induces self-reactive T cells (Kyuwa et al. 1991). Interestingly, MHV infection can enhance the course of EAE (Cross et al. 1987).

Various immunopathogenically relevant alterations are shown to occur within the CNS after MHV infection. Viral particles induce expression of class II major histocompatibility (MHC) antigens on astrocytes (Massa et al. 1986) and class I antigens on astrocytes and oligodendrocytes (Suzumura et al. 1986), which could presumably activate local immune responses within the CNS. Actual infection of astrocytes is essential for MHC class I induction (Gilmore et al. 1994). Infection of oligodendrocytes results in an initial down-regulation of mRNA for proteolipid protein (PLP) followed by necrotic death; demyelination continues even in the absence of detectable viral antigen with apoptosis becoming the prevalent mode of cell death (Barac-Latas et al. 1997). Infection of activated glial cells, astrocytes and microglia, releases various inflammatory mediators as also observed in MS, including nitric oxide (NO) synthase and NO (Grzybicki et al. 1997; Edwards et al. 2000), interleukin (IL)-6, tumor necrosis factor-(TNF)-α, IL-1β (Sun et al. 1995; Edwards et al. 2000), as well as macrophage chemoattractant protein-1 and matrix metalloproteinases (Edwards et al. 2000). Each of these could contribute to tissue injury.

5 Systemic Virus Infection and Autoimmunity: Virus-Initiated Neuropathogenesis by Activation of Self-Reactive Lymphocytes (Molecular Mimicry)

Myelin basic protein and PLP constitute the most abundant proteins in the CNS (HASHIM 1978; MIKOSHIBA et al. 1991). It is believed that MBP contributes to the compactness of myelin lamellae by fusing the cytoplasmic surfaces of oligodendrocytes into major dense lines. PLP is the primary constituent protein of myelin, and it represents 50% of the myelin membrane proteins. It bears covalently linked lipids, shows five strongly hydrophobic transmembrane domains and surface-exposed regions and is thought to play a crucial role in myelination in the CNS, probably by promoting the apposition of extracellular surfaces of the myelin lamellae (DIEHL et al. 1986). Myelin-associated glycoprotein (MAG) and myelin-oligodendrocyte glycoprotein (MOG) are minor protein constituents of myelin (SATO et al. 1989; MIKOL et al. 1990). We know that MAG is a heavily glycosylated membrane protein with a long extracellular domain and a structure characteristic of the immunoglobulin superfamily. Although it is a quantitatively minor component of myelin (about 1% of total myelin protein), it is believed to play a role in axon-myelinating cell interactions. Similarly, MOG is also a minor glycoprotein of myelin, detectable in white matter tracts. It is anchored in the outer leaflet of the oligodendrocyte membrane through a glycosylphosphatidylinositol lipid intermediate. The presence on MOG of a series of leucine-rich repeats and the association of the so-called HNK-1 carbohydrate adhesion marker suggests a function of the protein in adhesion and thus in myelination. It was also shown to be a member of the immunoglobulin superfamily (PHAM-DINH et al. 1993).

The amino acid sequences of MBP and PLP are well-conserved among several species (DIEHL et al. 1986; FRITZ and MCFARLIN 1989) and their injection, either whole or as specific peptides, into various animals causes EAE, a T cell-mediated neuro-autoimmune disease that shares many clinical and histopathological features with MS (SWANBORG 1995). Various encephalitogenic determinants of MBP have been described (FRITZ and MCFARLIN 1989; LENNON et al. 1970; HASHIM et al. 1991). Encephalitogenic determinants on PLP were also reported (LININGTON et al. 1990; GREER et al. 1996; TUOHY et al. 1995). Immunization with MOG also induces EAE, and this particular model demonstrates that antibody can also be a major determinant of the extent of demyelination that develops, presumably through an antibody-dependent cell-mediated cytotoxic mechanism (SCHLUESENER et al. 1987).

Several studies have indicated autoimmune reactivity to various myelin antigens in MS, although such reactivity is sometimes also found in normal individuals, albeit often at lower levels. The best-studied target myelin antigen is MBP (reviewed in WUCHERPFENNIG et al. 1991). Several target epitopes for HLA-DR-restricted T lymphocytes of MS and/or normal patients were identified on human MBP (JINGWU et al. 1990; PETTE et al. 1990; BURNS et al. 1991; LIBLAU et al. 1991; SALVETTI et al. 1993; MEINL et al. 1993; CHOU et al. 1994). Recent

evidence suggests that the response to human MBP is dominated in at least some subjects by expanded clones that may persist in vivo for long periods of time (WUCHERPFENNIG et al. 1994). A study of the reactivity of 15,824 short-term T cell lines from MS patients and controls indicated that epitope 84-102 of human MBP is immunodominant in DR2+ MS patients, suggesting that this may be the encephalitogenic antigenic determinant in these individuals (OTA et al. 1990). This epitope may also be immunodominant for B cell responses (WARREN et al. 1995). Importantly, circulating in vivo-activated T cells reactive to MBP were detected in MS patients (ALLEGRETTA et al. 1990; LODGE et al. 1996). Numerous studies have identified other myelin antigens as possible autoimmune targets in MS patients (e.g. CHOU et al. 1992; SUN et al. 1991; BAIG et al. 1991; DEROSBO et al. 1993; MARKOVICPLESE et al. 1995; CORREALE et al. 1995). We have also recently reported on the possible importance of antigen-specific humoral responses in the disease pathogenesis (QIN et al. 1998). Non-myelin autoantigens, such as members of the heat shock protein family, are also candidate autoantigens in MS (VAN NOORT et al. 1995).

Among the various mechanisms proposed for virus induction of autoimmune diseases, an intriguing hypothesis which has yet to be definitively associated with human pathology is molecular mimicry (OLDSTONE 1987, 1998). It is well known that viral proteins can share antigenic determinants with host cell proteins. Upon viral infection, these common epitopes could, at least theoretically, induce cross-reacting immune responses leading to autoimmune disease. The biological relevance of such a pathogenic mechanism has already been demonstrated in an animal model (FUJINAMI and OLDSTONE 1985). Computer searches showed the conservation of a six-amino acid stretch between a site of MBP known to be encephalitogenic in rabbits and the hepatitis B viral polymerase. The corresponding peptide was synthesized chemically and injected into rabbits, which produced both anti-virus and anti-MBP antibodies, generated cellular reactivity to the CNS antigen, and developed an EAE-like disease. In the TMEV model, a virus-directed monoclonal antibody was shown to react with the oligodendroglial galactocerebroside and enhance virus-induced demyelination (YAMADA et al. 1990).

Other striking homologies observed between viral proteins and CNS antigens include conserved domains between MBP and human T lymphotropic virus (LIQUORI 1991), cytomegalovirus (ROOTBERNSTEIN 1995), influenza virus and adenovirus (JAHNKE et al. 1985) and between PLP and adenovirus, polyoma virus, Epstein-Barr virus, influenza virus and human T lymphotropic virus (JAHNKE et al. 1985; SHAW et al. 1986). Some viruses, previously listed as having been implicated in the etiology of MS, do share common determinants with the myelin antigens MBP and PLP, although the significance of such observations remains to be elucidated, since molecular mimicry is not automatically involved in disease (OLDSTONE 1987; RICHTER et al. 1994).

It has now been shown that peptides containing only four native residues of MBP can stimulate MBP-specific T cells and that this sequence is found in a number of viruses, including coronaviruses (GAUTAM et al. 1992). Certainly the best evidence for the possible relevance of molecular mimicry in the pathogenesis of

autoimmune diseases such as MS was the recent demonstration of activation of several MBP-specific T cell clones established from MS patients to seven viral and one bacterial peptide which contained the predicted motifs for binding to HLA-DR2 (WUCHERPFENNIG and STROMINGER 1995). This publication revived interest in pathogen-myelin molecular mimicry as a possible trigger of MS pathology (STEINMAN 1996). Our own contribution describing HCoV and MBP cross-reactive T cells in MS patients was timely in showing possible clinical relevance (TALBOT et al. 1996). Indeed, a recent review article, which quoted the Wucherpfennig and Strominger study (WUCHERPFENNIG and STROMINGER 1995) commented that no data are available to suggest the reverse mechanism, which is actually required to explain the development of MS, i.e. recognition of CNS protein sequences by T cells originally activated by a naturally processed viral or bacterial pathogen (STEINMAN 1996), an observation that we did provide for eight of 16 MS patients studied (TALBOT et al. 1996). Our published studies have now been extended to show cross-reactivity at the T cell clone level between both strains of HCoV (229E and OC43) and MBP as well as with PLP (BOUCHER et al. 1998). The next phase of our study involves the elucidation of the molecular basis, MS specificity and CNS relevance of this T cell cross-reactivity between a common respiratory pathogen and major myelin antigens against which the immune system appears to be activated in MS.

Another important observation from the WUCHERPFENNIG and STROMINGER (1995) study was that, with one exception, activating peptides could not have been predicted by simple sequence alignment. Indeed, the concept has now emerged that apparently very dissimilar peptides can activate the same T cells. This was evident in the memory T cell response to antigenically different arenaviruses (SELIN et al. 1994) and suggests that this may be explained by the concept of "molecular shape mimicry" i.e. recognition by the T cell receptor of a three-dimensional structure formed by the MHC–peptide complex (BHARDWAJ et al. 1993; QUARATINO et al. 1995; GARZA and TUNG 1995; KERSH and ALLEN 1996).

6 Systemic Virus Infections: Induction of Non-Antigen-Specific Immune Activation

The development of target-directed cellular immune mediated disorders is dependent on migration of lymphocytes from the systemic circulation into the involved target site. The extent of migration of T cells into the CNS is determined by a range of factors acting either upon the immune cells or the target tissue, both of which can be influenced by viral infection. Under basal conditions there does seem to be a level of ongoing immune surveillance within the CNS carried out by T cells which enter and then rapidly depart or die. As will be discussed later, the endogenous neural cells contribute to migration by providing chemoattractant signals, by serving as partners in the process of cell adhesion, and by providing immune

accessory signals. The lymphocyte migration process is dependent on the state of activation of the immune cells in the systemic circulation. We have shown that the migration rate of T cells derived from MS patients in vitro through a fibronectin barrier is increased compared to controls (UHM et al. 1997; PRAT et al. 1998). This process is dependent on production by the T cells of matrix metalloproteinases which increases when the cells are activated (STUVE et al. 1996). T cells, when activated, also up-regulate adhesion molecules, which will promote interaction with neural cells at the blood–brain barrier (BBB). Systemic viral infections are one set of stimuli that can induce immune activation including production of cytokines, which in turn can up-regulate expression of adhesion molecules and production of proteases (reviewed in ANTEL and BECHER 1998). Perhaps this could explain why exacerbations of MS are linked to seasonal occurrence of viral infections (SIBLEY et al. 1985; PANITCH 1994).

7 Virus-Induced Immune Activity within the CNS: Antigen-Specific Responses

Within the CNS compartment, a number of endogenous cell types have varying capacity to serve as antigen-presenting cells (APCs). At the BBB, the perivascular microglia are shown to be competent APCs (reviewed in ANTEL and BECHER 1998). In chimeric animals, histocompatibility between these cells and encephalitogenic myelin-reactive T cells is required for development of EAE. Within the parenchyma of the CNS, the microglia are the cell type that most convincingly demonstrate the properties of competent APCs. A central issue in understanding the basis for development of chronic immune-mediated demyelinating disease of the CNS, including after initial viral infection, is whether there is ongoing immune sensitization to antigen release during the initial process of tissue injury. In both the TMEV and coronavirus infection models and in the chronic EAE model, there are data that indicate that determinant spreading has occurred and that myelin-reactive T cells can be recovered from the infected animals. In the TMEV model, molecular mimicry was apparently not involved (MILLER et al. 1997). In the case of MBP peptide-induced EAE, T cells reactive to other MBP peptide sequences and other myelin antigens (PLP) can be recovered over time (MILLER et al. 1995). One need consider that the determinant spreading immune responses could be generated either in the CNS or in the regional lymph nodes. As regards the latter, it is well-demonstrated that antigens released into the CNS will reach these structures.

Determinant spreading to cryptic determinants on the same antigen or to other myelin antigens after an original attack on a specific determinant on a myelin antigen, as shown in the previously discussed experimental models, and which may in some instances involve molecular mimicry, could explain the multitude of complementary or often contradictory studies on immune reactivity to myelin

antigens that have been reported in MS (McRae et al. 1995). The observations of myelin-autoreactive lymphocytes in apparently healthy individuals have caused difficulties in inferring a pathological relevance for these cells in MS patients. Evidence was provided that both MBP- and PLP-reactive T cells are in an activated state, both in the periphery and the CNS compartment, preferentially in MS patients and not in healthy donors or patients with other neurologic disorders (Zhang et al. 1994). This study strengthens the proposed involvement of myelin-reactive T cells in the pathogenesis of MS (reviewed in Hohlfeld et al. 1995), and gives hope for treatment of disease by induction of tolerance to the target antigen or specific elimination of autoreactive T cells (Chen et al. 1995b; Brocke et al. 1996; Steinman 1996). However, it does not address the mechanism of induction of these autoreactive T cells in the initiation and development of MS.

8 Virus-Induced Immune Reactivity within the CNS: Effects on Glial Cells

Activation of CNS glial cells, namely astrocytes and especially microglia, is becoming recognized as a hallmark of various neurologic disorders (Coyle 1996; Ludwin 1997; Benveniste 1997; Zielasek and Hartung 1996; Chao et al. 1996; Brown and Kretzschmar 1997), including MS (Sriram and Rodriguez 1997) and Alzheimer's disease (Barger and Harmon 1997). Viruses that enter the CNS and target these cells, such as HCoV (Bonavia et al. 1997; Arbour et al. 2000) and various retroviruses (Gravel et al. 1993; Dhibjalbut et al. 1994; Sharpless et al. 1992), are therefore prime candidate mediators of at least some of this neuropathologically relevant activation (Bilzer and Stitz 1996). The role of microglial cells in CNS biology has only recently become recognized, since it has been difficult to differentiate these brain-resident cells from infiltrating macrophages (Ulvestad et al. 1994). Activation of glial cells results in increased expression of the immune accessory molecules involved in the process of antigen presentation. As previously mentioned, activation is further characterized by the release of various pro-inflammatory molecules such as cytokines, chemokines, NO, and reactive oxygen intermediates (Zielasek and Hartung 1996). These mediators can contribute both to regulating the activity of lymphocytes which enter this compartment and to actually effecting target directed injury.

9 Axonal Injury in Multiple Sclerosis

Although MS is regarded as primarily a myelin- and oligodendrocyte-directed autoimmune disorder, there is increasing recognition that the extent of axonal

injury and loss may account for at least a component of the neurologic dysfunction (reviewed in MATTHEWS et al. 1998). Conversely, one need consider whether axonal compensatory responses to demyelination may be sufficient to permit continued, relatively unimpaired neurologic function. The early pathological description of MS lesions by Marie and Charcot does indicate an appreciation for the axonal loss component, although emphasis was placed on the relative preservation of axons compared to their myelin sheaths. More recent pathological studies indicate axonal disruption even in early active lesions (DE STEFANO et al. 1995). Clinical brain-imaging correlative studies indicate that axonal involvement can contribute both to reversible and irreversible neurologic deficits, which characterize the MS disease process. The advent of magnetic resonance spectroscopy (MRS), which is an MR technique that can suppress the dominant water signal that forms the basis for conventional MR imaging (MRI), permits quantitation of multiple other molecules in the CNS, including *N*-acetyl aspartate (NAA), an amino acid exclusively expressed in neurons and their axons in the mature CNS. NAA is the dominant peak seen using long-sequence ^{3}H-based MRS. NAA production is dependent on intact mitochondrial function. Although MRS does not have the spatial resolution of MRI because of the increased voxel sizes needed, whole-brain images can now be reconstructed with MRS imaging (MRSI), permitting analysis of individual lesions and normal-appearing white matter. An example of such spectra derived from a chronic MS lesion and a conventional MRI-defined normal-appearing white matter is presented in Fig. 1.

In initial prospective studies of MS patients, using selected large volumes of interest, we and others demonstrated that there was a significant, albeit imperfect, correlation between progressive loss of NAA and clinical neurologic disability scores (EDSS). Such correlations were less robust between conventional MRI defined lesion volumes and EDSS score (DE STEFANO et al. 1995; FU et al. 1998). In the EAE model, animals with the chronic form of the disease, with its associated, persistent neurologic sequel, are also recognized as having a significant extent of axonal injury (TAUPIN et al. 1997).

Using the MRSI technique, we have had the opportunity to examine NAA values in MS patients presenting with acute neurologic deficits (DE STEFANO et al. 1998). In a series of such patients, we documented initially reduced NAA values in MRI-defined lesions corresponding to the anatomic site that coincided with the effected neurologic function, namely motor function in our patients. In these cases, we observed gradual recovery of the NAA over time, with a strong overall correlation between NAA values and clinical function (DE STEFANO et al. 1998). The basis for this reversible pattern of NAA depression could reflect several non-exclusive mechanisms. The inflammatory mediators present in the acute MS lesion could directly act upon the neuron/axon, perhaps having greater access to those whose myelin covering is damaged. As mentioned, NAA production is dependent on intact mitochondrial function. In vitro, one can demonstrate that neuron expression of NAA can be reversibly down-regulated by manipulation of culture conditions, such as by serum deprivation. The clinical worsening that occurred in MS patients receiving the anti-CD4 CAMPATH 1H mAb, was shown to be

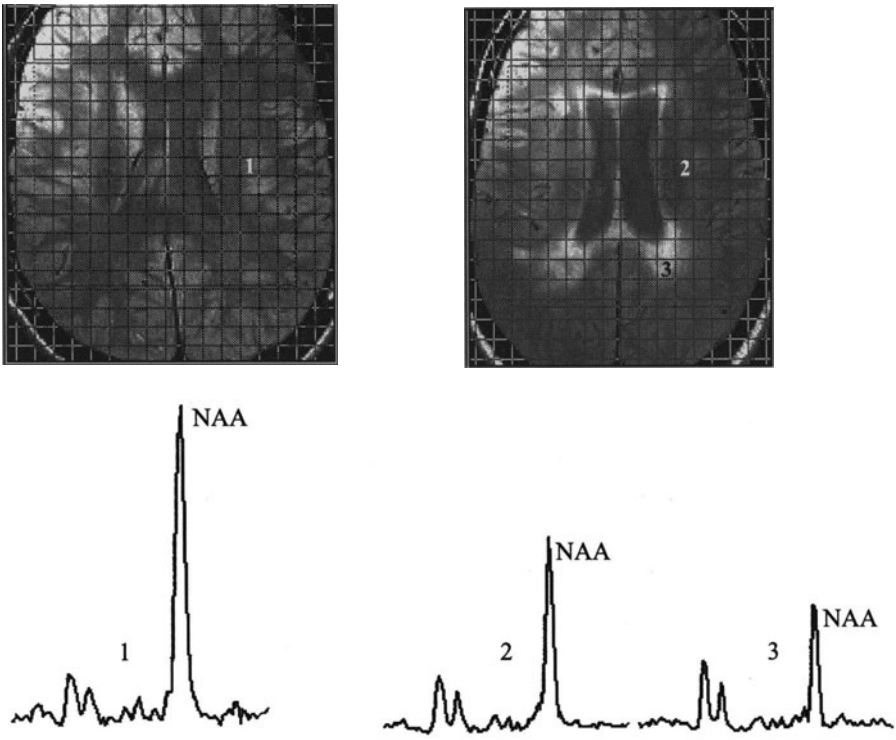

Fig. 1. Magnetic resonance spectroscopy profiles showing decrease in the peak of N-acetyl aspartate (*NAA*) in a chronic MS lesion and normal appearing white matter

dependent on axonal conduction block induced by NO, which in the active MS lesion would be produced by activated glial cells and probably infiltrating macrophages (WING et al. 1996).

The neuronal dysfunction in MS could also reflect an indirect effect of demyelination. Oligodendrocytes and astrocytes are likely important sources of trophic support for axons. The size of axons is known to be proportional to the extent of myelination. Depletion of myelin results in neurofilaments undergoing a change in their phosphorylation state, with subsequent effects on the entire axonal cytoskeleton. Axons in vitro show a propensity to grow on astrocyte substrates. Similarly, microglia can support axonal regrowth in selected injury paradigms (DAVID et al. 1990). One speculates whether the trophic vs destructive potential effect of these glial cells is shifted when such cells are activated in the inflammatory environment that characterizes MS.

Recent MRI pathologic correlative studies, have found that some MRI-defined lesions identified on post-mortem tissue specimens are not seen by gross visual inspection. Furthermore, studies using more specialized MRI techniques, such as magnetization transfer imaging and MRS have demonstrated abnormalities in what by usual MRI criteria is apparently normal tissue. These observations suggest

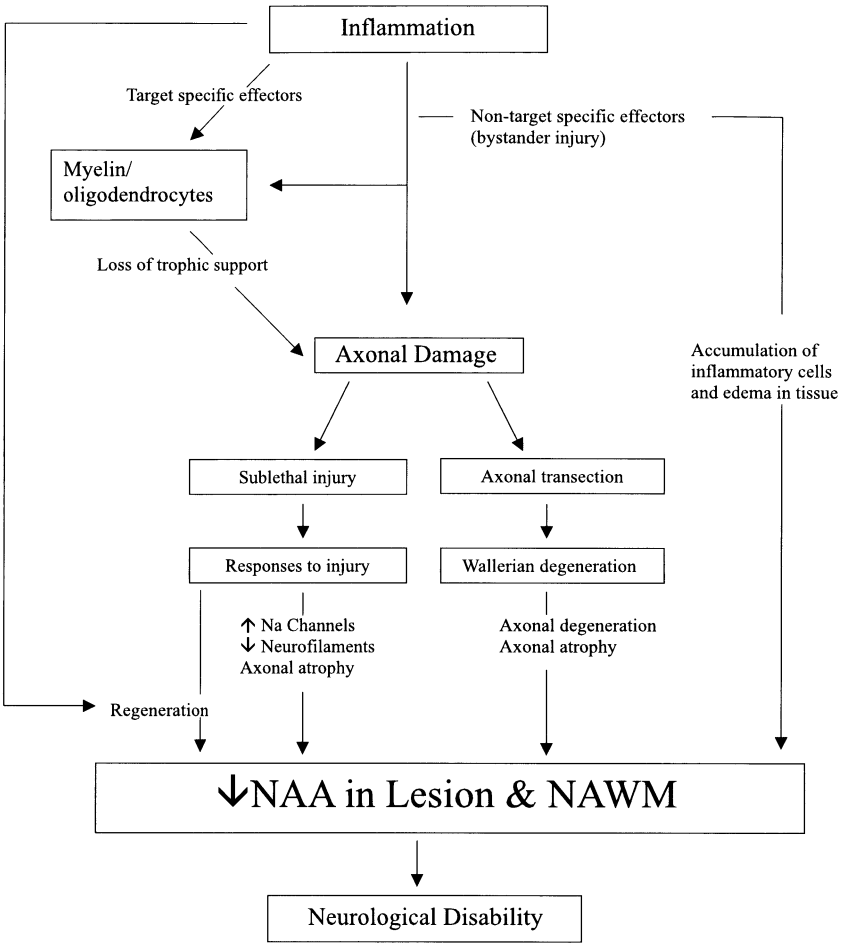

Fig. 2. Outline of basis of axonal injury and recovery in multiple sclerosis (*MS*),with resultant effect on *N*-acetyl aspartate (*NAA*) expression in lesions and normal appearing white matter (*NAWM*)

more widespread tissue abnormalities in MS than previously suspected. These could include dying back of axons transected at the remote lesion sites or diffuse tissue responses to pro-inflammatory cytokines. In this regard, focal stab-wound injury models in animals are shown to result in release of an array of cytokines which diffuse and induce reactive glial changes over a considerable distance (MOUMDJIAN et al. 1991). Such changes could make the normal appearing white matter more susceptible to subsequent injury.

Serial MRI studies of MS patients have documented that white matter lesions without apparent corresponding clinical deficits can also arise. These patients do not show the profound decreases of NAA within lesions in contrast to a symptomatic cohort. Short-echo-time MRS studies have also identified areas of myelin

destruction, as defined by free lipid release without evidence of NAA loss or clinical deficits. In the TMEV demyelination model induced in CD8 T cell-deficient animals, Rodriguez and colleagues demonstrated that extensive demyelination can occur without apparent functional neurologic deficits (Rivera-Quinones et al. 1998). The axons of these animals are shown to have compensated for their myelin loss by rearrangement of expression of Na^+ channels, so that such channels are now expressed throughout the course of the axon and are not restricted to the perinodal region. In this way, the animal can overcome the conduction block otherwise expected if only saltatory conduction over a relatively large distance (node-node) is the only means to maintain electrical conduction. Analysis of axons contained within active MS lesions indicates that such compensation also occurs in the human disease.

Additional compensatory mechanisms are now recognized to occur even in the mature CNS. Axonal sprouting would provide a means whereby an intact axon might replace the function of an adjacent injured one. Results from functional MRI studies suggest that functional reorganization within the CNS does occur following acute MS lesions. One raises the concern that over time these compensatory mechanisms may fail, either through ageing or additional lesions, and may account for the evolution of MS into a more chronic disorder as occurs in more than 50% of cases. The above considerations indicate that the axon is a central participant in the evolution of the MS disease process, both with regard to it being directly (immune-mediated) or indirectly (trophic support withdrawal) injured or, conversely, by providing a means to compensate for the primary myelin injury (see Fig. 2).

References

Allegretta M, Nicklas JA, Sriram S, Albertini RJ (1990) T-cells responsive to myelin basic protein in patients with multiple sclerosis. Science 247:718–721

Antel J, Becher B (1998) Central nervous system-immune interactions: contribution to neurologic disease and recovery. In: Antel J, Birnbaum G, Hartung H-P (eds) Clinical neuroimmunology. Blackwell Science pp 26–39

Arbour N, Day R, Newcombe J, Talbot PJ (2000) Neuroinvasion by human respiratory coronaviruses. J Virol 74:8913–8971

Arbour N, Côté G, Lachance C, Tardieu M, Cashman NR, Talbot PJ (1999a) Acute and persistent infection of human neural cell lines by human coronavirus OC43. J Virol 73:3338–3350

Arbour N, Ékandé S, Côté G, Lachance C, Chagnon F, Cashman NR, Talbot PJ (1999b) Persistent infection of human oligodendrocytic and neuronal cell lines by human coronavirus 229E. J Virol 73:3326–3337

Arbour N, Talbot PJ (1998) Persistent infection of neural cell lines by human coronaviruses. Adv Exp Med Biol 440:575–581

Arpin N, Talbot PJ (1990) Molecular characterization of the 229E strain of human coronavirus. Adv Exp Med Biol 276:73–80

Baig S, Olsson T, Yuping J, Hojeberg B, Cruz M, Link H (1991) Multiple sclerosis – cells secreting antibodies against myelin-associated glycoprotein are present in cerebrospinal fluid. Scand J Immunol 33:73–79

Bailey OT, Pappenheimer AM, Cheever FS, Daniels JB (1949) A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin. II. Pathology. J Exp Med 90: 195–212

Bang FB, Warwick A (1960) Mouse macrophages as host cells for the mouse hepatitis virus and the genetic basis of their susceptibility. Proc Natl Acad Sci USA 46:1065–1075

Barac-Latas V, Suchanek G, Breitschopf H, Stuehler A, Wege H, Lassmann H (1997) Patterns of oligodendrocyte pathology in coronavirus-induced subacute demyelinating encephalomyelitis in the Lewis rat. Glia 19:1–12

Barger SW, Harmon AD (1997) Microglial activation by Alzheimer amyloid precursor protein and modulation by apolipoprotein E. Nature 388:878–881

Barnett EM, Perlman S (1993) The olfactory nerve and not the trigeminal nerve is the major site of CNS entry for mouse hepatitis virus strain JHM. Virology 194:185–191

Benveniste EN (1997) Role of macrophages/microglia in multiple sclerosis and experimental allergic encephalomyelitis. J Mol Med 75:165–173

Bhardwaj V, Kumar V, Geysen HM, Sercarz EE (1993) Degenerate recognition of a dissimilar antigenic peptide by myelin basic protein-reactive T cells. J Immunol 151:5000–5010

Bilzer T, Stitz L (1996) Immunopathogenesis of virus diseases affecting the central nervous system. Crit Rev Immunol 16:145–222

Bonavia A, Arbour N, Wee Yong V, Talbot PJ (1997) Infection of primary cultures of human neural cells by human coronaviruses 229E and OC43. J Virol 71:800–806

Boucher A, Mercier G, Duquette P, Talbot PJ (1998) Clonal T cell cross-reactivity between myelin antigens MBP and PLP and human respiratory coronavirus in multiple sclerosis. J Neuroimmunol 90:33 (abstract)

Bray PF, Luka J, Bray PF, Culp KW, Schlight JP (1992) Antibodies against Epstein-Barr nuclear antigen (EBNA) in multiple sclerosis CSF and two pentapeptide sequence identities between EBNA and myelin basic protein. Neurology 42:1798–1804

Brocke S, Gijbels K, Allegretta M, Ferber I, Piercy C, Blankenstein T, Martin R, Utz U, Karin N, Mitchell D, Veromaa T, Waisman A, Gaur A, Conlon P, Ling N, Fairchild PJ, Wraith DC, Ogarra A, Fathman CG, Steinman L (1996) Treatment of experimental encephalomyelitis with a peptide analogue of myelin basic protein. Nature 379:343–346

Brown DR, Kretzschmar HA (1997) Microglia and prion disease: a review. Histol Histopathol 12: 883–892

Buchmeier MJ, Lewicki HA, Talbot PJ, Knobler RL (1984) Murine hepatitis virus-4 (strain JHM) – induced neurologic disease is modulated in vivo by monoclonal antibody. Virology 132:261–270

Burks JS, DeVald BL, Jankovsky LD, Gerdes JC (1980) Two coronaviruses isolated from central nervous system tissue of two multiple sclerosis patients. Science 209:933–934

Burns J, Littlefield K, Gomez C, Kumar V (1991) Assessment of antigenic determinants for the human T-cell response against myelin basic protein using overlapping synthetic peptides. J Neuroimmunol 31:105–113

Cabirac GF, Murray RS, McLaughlin LB, Skolnick DM, Hogue B, Dorovini-Zis K, Didier PJ (1995) In vitro interaction of coronaviruses with primate and human brain microvascular endothelial cells. Adv Exp Med Biol 380:79–88

Cabirac GF, Soike KF, Zhang JY, Hoel K, Butunoi C, Cai GY, Johnson S, Murray RS (1994) Entry of coronavirus into primate CNS following peripheral infection. Microbial Path 16:349–357

Chaloner-Larsson G, Johnson-Lussenburg CM (1981) Establishment and maintenance of a persistent infection of L132 cells by human coronavirus 229E. Arch Virol 69:117–129

Chao CC, Hu SX, Peterson PK (1996) Glia: the not so innocent bystanders. J Neurovirol 2:234–239

Cheever FS, Daniels JB, Pappenheimer AM, Bailey OT (1949) A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin. I. Isolation and biological properties of the virus. J Exp Med 90:181–194

Chen YH, Inobe J, Marks R, Gonnella P, Kuchroo VK, Weiner HL (1995a) Peripheral deletion of antigen-reactive T cells in oral tolerance. Nature 376:177–180

Chen DS, Asanaka M, Yokomori K, Wang FI, Hwang SB, Li HP, Lai MMC (1995b) A pregnancy-specific glycoprotein is expressed in the brain and serves as a receptor for mouse hepatitis virus. Proc Natl Acad Sci USA 92:12095–12099

Chou YK, Bourdette DN, Offner H, Whitham R, Wang RY, Hashim GA, Vandenbark AA (1992) Frequency of T cells specific for myelin basic protein and myelin proteolipid protein in blood and cerebrospinal fluid in multiple sclerosis. J Neuroimmunol 38:105–113

Chou YK, Jones RE, Bourdette D, Whitham R, Hashim G, Atherton J, Offner H, Vandenbark AA (1994) Human myelin basic protein (MBP) epitopes recognized by mouse MBP-selected T cell lines from multiple sclerosis patients. J Neuroimmunol 49:45–50

Collins AR, Sorensen O (1986) Regulation of viral persistence in human glioblastoma and rhabdomyosarcoma cells infected with coronavirus OC43. Microbial Path 1:573–582

Conant K, Garzino-Demo A, Nath A, McArthur JC, Halliday W, Power C, Gallo RC, Major EO (1998) Induction of monocyte chemoattractant proteon-1 in HIV-1 Tat-stimulated astrocytes and elevation in AIDS dementia. Proc Natl Acad Sci USA 95:3117–3121

Cook SD, Rohowskykochan C, Bansil S, Dowling PC (1995) Evidence for multiple sclerosis as an infectious disease. Acta Neurol Scand 91:34–42

Correale J, McMillan M, McCarthy K, Le T, Weiner LP (1995) Isolation and characterization of autoreactive proteolipid protein-peptide specific T-cell clones from multiple sclerosis patients. Neurology 45:1370–1378

Cosby SL, McQuaid S, Taylor MJ, Bailey M, Rima BK, Martin SJ, Allen IV (1989) Examination of 8 cases of multiple sclerosis and 56 neurological and non-neurological controls for genomic sequences of measles virus, canine distemper virus, simian virus-5 and rubella virus. J Gen Virol 70:2027–2036

Coyle PK (1996) The neuroimmunology of multiple sclerosis. Adv Neuroimmunol 6:143–154

Cross AH, McCarron R, McFarlin DE, Raine CS (1987) Adoptively transferred acute and chronic relapsing autoimmune encephalomyelitis in the PL/J mouse and observations on altered pathology by intercurrent virus infection. Lab Invest 57:499–512

Dalziel RG, Lampert PW, Talbot PJ, Buchmeier MJ (1986) Site-specific alteration of murine hepatitis virus type 4 peplomer glycoprotein E2 results in reduced neurovirulence. J Virol 59:463–471

David S, Bouchard C, Tsatas O, Giftochristos N (1990) Macrophages can modify the nonpermissive nature of the adult mammalian central nervous system. Neuron 5:463–469

Dekaban GA, Rice GPA (1990) Retroviruses and multiple sclerosis. 2. Failure of gene amplification techniques to detect viral sequences unique to the disease. Neurology 40:1254–1258

Derosbo NK, Milo R, Lees MB, Burger D, Bernard CCA, Ben-Nun A (1993) Reactivity to myelin antigens in multiple sclerosis – Peripheral blood lymphocytes respond predominantly to myelin oligodendrocyte glycoprotein. J Clin Invest 92:2602–2608

De Stefano N, Matthews PM, Antel JP, Preul M, Francis G, Arnold DL (1995) Chemical pathology of acute demyelinating lesions and its correlation with disability. Ann Neurol 38:901–909

De Stefano N, Matthews PM, Fu L, Narayanan S, Stanley J, Francis GS, Antel JP, Arnold DL (1998) Axonal damage correlates with disability in patients with relapsing-remitting multiple sclerosis. Results of a longitudinal magnetic resonance spectroscopy study. Brain 121:1469–1477

Dhibjalbut S, Hoffman PM, Yamabe T, Sun D, Xia J, Eisenberg H, Bergey G, Ruscetti FW (1994) Extracellular human T-cell lymphotropic virus type I tax protein induces cytokine production in adult human microglial cells. Ann Neurol 36:787–790

Diehl HJ, Scharch M, Budzinski RM, Stoffel W (1986) Individual exons encode the integral membrane domains of human myelin proteolipid protein. Proc Natl Acad Sci USA 83:9807–9811

Edwards J, Denis F, Talbot PJ (2000) Activation of glial cells by human coronavirus OC43. J Neuroimmunol 108:73–81

Erlich SS, Fleming JO, Stohlman SA (1987) Experimental neuropathology of chronic demyelination by a JHM virus variant. Arch Neurol 44:839–842

Fleming JO, El Zaatari AK, Gilmore W, Berne JD, Burks JS, Stohlman SA, Tourtelotte WW, Weiner LP (1988) Antigenic assessment of coronaviruses isolated from patients with multiple sclerosis. Arch Neurol 45:629–633

Fleming JO, Trousdale MD, El-Zaatari F, Stohlman SA, Weiner LP (1986) Pathogenicity of antigenic variants of murine coronavirus JHM selected with monoclonal antibodies. J Virol 58:869–875

Fritz RB, Mc Farlin DE (1989) Encephalitogenic epitopes of myelin basic protein. In: Sercarz E (ed) Antigenic determinants and immune regulation chem immunol. Karger, Basel pp 101–125

Fu L, Matthews PM, De Stefano N, Worseley KJ, Narayanan S, Francis GS, Antel JP, Wolfson C, Arnold DL (1998) Imaging axonal damage of normal-appearing white matter in multiple sclerosis. Brain 121:103–113

Fujinami RS, Oldstone MBA (1985) Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 230:1043–1045

Garza KM, Tung KSK (1995) Frequency of molecular mimicry among T cell peptides as the basis for autoimmune disease and autoantibody induction. J Immunol 155:5444–5448

Gautam AM, Pearson CI, Smilek DE, Steinman L, McDevitt HO (1992) A polyalanine peptide with only 5 native myelin basic protein residues induces autoimmune encephalomyelitis. J Exp Med 176: 605–609

Gilmore W, Correale J, Weiner LP (1994) Coronavirus induction of class I major histocompatibility complex expression in murine astrocytes is virus strain specific. J Exp Med 180:1013–1023

Goswami KKA, Randall RE, Lange LS, Russell WC (1987) Antibodies against the paramyxovirus SV5 in the cerebrospinal fluids of some multiple sclerosis patients. Nature 327:244–247

Gravel C, Kay DG, Jolicoeur P (1993) Identification of the infected target cell type in spongiform myeloencephalopathy induced by the neurotropic Cas-Br-E murine leukemia virus. J Virol 67: 6648–6658.

Greer JM, Sobel RA, Sette A, Southwood S, Lees MB, Kuchroo VK (1996) Immunogenic and encephalitogenic epitope clusters of myelin proteolipid protein. J Immunol 156:371–379

Grzybicki DM, Kwack KB, Perlman S, Murphy SP (1997) Nitric oxide synthase type II expression by different cell types in MHV-JHM encephalitis suggests distinct roles for nitric oxide in acute versus persistent virus infection. J Neuroimmunol 73:15–27

Haase AT, Ventura P, Gibbs CJ, Tourtelotte WW (1981) Measles virus nucleotide sequences: detection by hybridization in situ. Science 212:672–674

Hamre D, Procknow JJ (1966) A new virus isolated from the human respiratory tract. Proc Soc Exp Biol Med 121:190–193

Hashim G (1978) Myelin basic protein: structure, function and antigenic determinants. Immunol Rev 39:60–107

Hashim G, Vandenbark AA, Gold DP, Diamanduros T, Offner H (1991) T-cell lines specific for an immunodominant epitope of human basic protein define an encephalitogenic determinant for experimental autoimmune encephalomyelitis-resistant LOU/M rats. J Immunol 146:515–520

Haspel MV, Lampert PW, Oldstone MBA (1978) Temperature-sensitive mutants of mouse hepatitis virus produce a high incidence of demyelination. Proc Natl Acad Sci USA 75:4033–4036

Hohlfeld R, Meinl E, Weber F, Zipp F, Schmidt S, Sotgiu S, Goebels N, Voltz R, Spuler S, Iglesias A, Wekerle H (1995) The role of autoimmune T lymphocytes in the pathogenesis of multiple sclerosis. Neurology 45:S33–S38

Horwitz MS, Bradley LM, Harbertson J, Krahl T, Lee J, Sarvetnick N (1998) Diabetes induced by Coxsackie virus: initiation by bystander damage and not molecular mimicry. Nature Med 4:781–785

Houtman JJ, Fleming JO (1996) Pathogenesis of mouse hepatitis virus-induced demyelination. J Neurovirol 2:361–376

Houtman JJ, Fleming JO (1996) Dissociation of demyelination and viral clearance in congenitally immunodeficient mice infected with murine coronavirus JHM. J Neurovirol 2:101–110

Hovanec DL, Flanagan TD (1983) Detection of antibodies to human coronaviruses 229E and OC43 in the sera of multiple sclerosis patients and normal subjects. Infect Immun 41:426–429

Jahnke U, Fischer EH, Alvord EC (1985) Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. Science 229:282–284

Jingwu Z, Chou CHJ, Hashim G, Medaer R, Raus JCM (1990) Preferential peptide specificity and HLA restriction of myelin basic protein-specific T-cell clones derived from MS patients. Cell Immunol 129:189–198

Johnson RT (1985) Viral aspects of multiple sclerosis In: Koetsier JC (ed) Handbook of Clinical Neurology Demyelinating Diseases. Elsevier, Amsterdam pp 319–336

Johnson-Lussenburg CM, Zheng Q (1987) Coronavirus and multiple sclerosis: results of a case/control longitudinal serological study. Adv Exp Med Biol 218:421–429

Kersh GJ, Allen PM (1996) Essential flexibility in the T-cell recognition of antigen. Nature 380:495–498

Kinnunen E, Valle M, Piirainen L, Kleemola M, Kantanen ML, Juntunen J, Klockars M, Koskenvuo M (1990) Viral antibodies in multiple sclerosis – a nationwide co-twin study. Arch Neurol 47:743–746

Knobler RL, Haspel MV, Oldstone MBA (1981) Mouse hepatitis virus type 4 (JHM strain) – induced fatal central nervous system disease. I. Genetic control and the murine neuron as the susceptible site of disease. J Exp Med 153:32–843

Knobler RL, Lampert PW, Oldstone MBA (1982) Virus persistence and recurring demyelination produced by a temperature-sensitive mutant of MHV-4. Nature 298:289–281

Kolson DL, Lavi E, Gonzalez-Scarano F (1998) The effects of human immunodeficiency virus in the central nervous system. Adv Virus Res 50:1–47

Kurtzke JF (1993) Epidemiologic evidence for multiple sclerosis as an infection. Clin Microbiol Rev 6:382–427

Kyuwa S, Yamaguchi K, Toyoda Y, Fujiwara K (1991) Induction of self-reactive T-cells after murine coronavirus infection. J Virol 65:1789–1795
Labonté P, Mounir S, Talbot PJ (1995) Sequence and expression of the ns2 protein gene of human coronavirus OC43. J Gen Virol 76:431–435
Lachance C, Arbour N, Cashman NR, Talbot PJ (1998) Involvement of aminopeptidase N (CD13) in infection of human neural cells by human coronavirus 229E. J Virol 72:6511–6519
Lamontagne L, Descôteaux JP, Jolicoeur P (1989) Mouse hepatitis virus 3 replication in T and B lymphocytes correlate with viral pathogenicity. J Immunol 142:4458–4465
Lampert PW, Sims JK, Kniazeff AJ (1973) Mechanism of demyelination in JHM virus encephalomyelitis. Acta Neuropathol 24:76–85
Lavi E, Fishman PS, Highkin MK, Weiss SR (1988) Limbic encephalitis after inhalation of a murine coronavirus. Lab Invest 58:31–36
Lehmann PV, Forsthuber T, Miller A, Sercarz EE (1992) Spreading of T cell autoimmunity to cryptic determinants of an autoantigen. Nature 358:155–157
Lennon VA, Wilks AV, Carnegie PR (1970) Immunologic properties of the main encephalitogenic peptide from the basic protein of human myelin. J Immunol 105:1223–1230
Liblau R, Tournierlasserve E, Maciazek J, Dumas G, Siffert O, Hashim G, Bach MA (1991) T-cell response to myelin basic protein epitopes in multiple sclerosis patients and healthy subjects. Eur J Immunol 21:1391–1395
Linington C, Gunn CA, Lassmann H (1990) Identification of an encephalitogenic determinant of myelin proteolipid protein for the rabbit. J Neuroimmunol 30:135–144
Liquori AM (1991) Myelin basic protein (MBP) displays significant homologies with GAG core proteins of HTLV retroviruses. J Theor Biol 148:279–281
Lodge PA, Johnson C, Sriram S (1996) Frequency of MBP and MBP peptide-reactive T cells in the HPRT mutant T-cell population of MS patients. Neurology 46:1410–1415
Ludwin SK (1997) The pathobiology of the oligodendrocyte. J Neuropathol Exp Neurol 56:111–124
Markovicplese S, Fukaura H, Zhang JW, Alsabbagh A, Southwood S, Sette A, Kuchroo VK, Hafler DA (1995) T cell recognition of immunodominant and cryptic proteolipid protein epitopes in humans. J Immunol 155:982–992
Massa PT, Dörries R, ter Meulen V (1986) Viral particles induce Ia antigen expression on astrocytes. Nature 320:543–546
Matthews PM, De Stefano N, Narayanan S, Francis GS, Wolinsky JS, Antel JP, Arnold DL (1998) Putting MRS studies in context: axonal damage and disability in multiple sclerosis. Semin Neurol 18:327–336
McIntosh K, Becker WB, Chanock RM (1967) Growth in suckling mouse brain of "IBV-like" viruses from patients with upper respiratory tract disease. Proc Natl Acad Sci USA 58:2268–2273
McRae BL, Vanderlugt CL, DalCanto MC, Miller SD (1995) Functional evidence for epitope spreading in the relapsing pathology of experimental autoimmune encephalomyelitis. J Exp Med 182: 75–85
Meinl E, Weber F, Drexler K, Morelle C, Ott M, Saruhandireskeneli G, Goebels N, Ertl B, Jechart G, Giegerich G, Schonbeck S, Bannwarth W, Wekerle H, Hohlfeld R (1993) Myelin basic protein specific T lymphocyte repertoire in multiple sclerosis – complexity of the response and dominance of nested epitopes due to recruitment of multiple T cell clones. J Clin Invest 92:2633–2643
Mikol DD, Gulcher JR, Stefansson K (1990) The oligodendrocyte-myelin glycoprotein belongs to a distinct family of proteins and contains the HNK-1 carbohydrate. J Cell Biol 110:471–479
Mikoshiba K, Okano H, Tamura T, Ikenaka K (1991) Structure and function of myelin protein genes. Annu Rev Neurosci 14:201–217
Miller SD, Mcrae BL, Vanderlugt CL, Nikcevich KM, Pope JG, Pope L, Karpus WJ (1995) Evolution of the T-cell repertoire during the course of experimental immune-mediated demyelinating diseases. Immunol Rev 144:225–244
Miller SD, Vanderlugt CL, Begolka WS, Pao W, Yauch RL, Neville KL, Katz-Levy Y, Carrizosa A, Kim BS (1997) Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. Nature Med 3:1133–1136
Moumdjian RA, Antel JP, Yong VW (1991) Origin of contralateral reactive gliosis in surgically injured rat cerebral cortex. Brain Res 547:223–228
Mounir S, Talbot PJ (1992) Sequence analysis of the membrane protein gene of human coronavirus OC43 and evidence for O-glycosylation. J Gen Virol 73:2731–2736
Mounir S, Talbot PJ (1993a) Molecular characterization of the S protein gene of human coronavirus OC43. J Gen Virol 74:1981–1987

Mounir S, Talbot PJ (1993b) Human coronavirus OC43 RNA 4 lacks 2 open reading frames located downstream of the S gene of bovine coronavirus. Virology 192:355–360

Mounir S, Labonté P, Talbot PJ (1994) Characterization of the nonstructural and spike proteins of the human respiratory coronavirus OC43: comparison with bovint enteric coronavirus. Coronaviruses and their diseases. Adv Exp Biol Med 342:61–68

Murray RS, Brown B, Brian D, Cabirac GF (1992a) Detection of coronavirus RNA antigen in multiple sclerosis brain. Ann Neurol 31:525–533

Murray RS, Cai GY, Hoel K, Zhang JY, Soike KF, Cabirac GF (1992b) Coronavirus infects and causes demyelination in primate central nervous system. Virology 188:274–284

Murray RS, Cai GY, Soike KF, Cabirac GF (1997) Further observations on coronavirus infection of primate CNS. J Neurovirol 3:71–75

Myint SH (1994) Human coronaviruses – a brief review. Rev Med Virol 4:35–46

Oldstone MB, Sinha YN, Blount P, Tishon A, Rodriguez M, von Wedel R, Lampert PW (1982) Virus-induced alterations in homeostasis: alteration in differentiated functions of infected cells in vivo. Science 218:1125–1127

Oldstone MBA (1987) Molecular mimicry and autoimmune disease. Cell 50:819–820

Oldstone MBA (1998) Molecular mimicry and immune-mediated diseases. FASEB J 12:1255–1265.

Ota K, Matsui M, Milford EL, Mackin GA, Weiner HL, Hafler DA (1990) T-cell recognition of an immunodominant myelin basic protein epitope in multiple sclerosis. Nature 346:183–187

Panitch HS (1994) Influence of infection on exacerbations of multiple sclerosis. Ann Neurol 36: S25–S28

Pasick JMM, Dales S (1991) Infection by coronavirus JHM of rat neurons and oligodendrocyte-type-2 astrocyte lineage cells during distinct developmental stages. J Virol 65:5013–5028

Pearson J, Mims CA (1985) Differential susceptibility of cultured neural cells to the human coronavirus OC43. J Virol 53:1016–1019

Perlman S, Ries D (1987) The astrocyte is a target cell in mice persistently infected with mouse hepatitis virus strain JHM. Microbial Path 3:309–314

Perron H, Garson JA, Bedin F, Beseme F, Paranhos-Baccala G, Komurian-Pradel F, Mallet F, Tuke PW, Voisset C, Blond JL, Lalande B, Seigneurin JM, Mandrand B (1997) Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. Proc Natl Acad Sci USA 94:7583–7588

Pette M, Fujita K, Wilkinson D, Altmann DM, Trowsdale J, Giegerich G, Hinkkanen A, Epplen JT, Kappos L, Wekerle H (1990) Myelin autoreactivity in multiple sclerosis – recognition of myelin basic protein in the context of HLA-DR2 products by lymphocytes-T of multiple-sclerosis patients and healthy donors. Proc Natl Acad Sci USA 87:7968–7972

Pewe L, Wu GF, Barnett EM, Castro RF, Perlman S (1996) Cytotoxic T cell-resistant variants are selected in a virus-induced demyelinating disease. Immunity 5:253–262

Pham-Dinh D, Mattei MG, Nussbaum JL, Roussel G, Pontarotti P, Roeckel N, Mather IH, Artzt K, Lindahl KF, Dautigny A (1993) Myelin/oligodendrocyte glycoprotein is a member of a subset of the immunoglobulin superfamily encoded within the major histocompatibility complex. Proc Natl Acad Sci USA 90:7990–7994

Prat A, Weinrib L, Becher B, Duquette P, Couture R, Antel J (1998) Expression of brabykinin B1 receptor on lymphocytes from MS patients. Neurology 50:A151

Qin Y, Duquette P, Zhang Y, Talbot PJ, Poole R, Antel J (1998) Clonal expansion and somatic hypermutation of VH genes of B cells from cerebrospinal fluid in multiple sclerosis. J Clin Invest 102:1045–1050

Quaratino S, Thorpe CJ, Travers PJ, Londei M (1995) Similar antigenic surfaces, rather than sequence homology, dictate T-cell epitope molecular mimicry. Proc Natl Acad Sci USA 92:10398–10402

Reddy EP, Sandberg-Wollheim M, Mettus RV, Ray PE, DeFreitas E, Koprowski H (1989) Amplification and molecular cloning of HTLV-1 sequences from DNA of multiple sclerosis patients. Science 243:529–533

Richter W, Mertens T, Schoel B, Muir P, Ritzkowsky A, Scherbaum WA, Boehm BO (1994) Sequence homology of the diabetes-associated autoantigen glutamate decarboxylase with coxsackie B4-2C protein and heat shock protein 60 mediates no molecular mimicry of autoantibodies. J Exp Med 180:721–726

Rivera-Quinones C, McGavern D, Schmelzer JD, Hunter SF, Low PA, Rodriguez M (1998) Absence of neurological deficits following extensive demyelination in a class I-deficient murine model of multiple sclerosis. Nature Med 4:187–193

Rootbernstein RS (1995) Preliminary evidence for idiotype antiidiotype immune complexes cross-reactive with lymphocyte antigens in AIDS and lupus. Med Hypoth 44:20–27
Sadovnick AD, Dyment D, Ebers GC (1997) Genetic epidemiology of multiple sclerosis. Epidemiol Rev 19:99–106
Salmi A, Reunanen M, Ilonen J (1981) Possible viral etiology of multiple sclerosis. In: Katsuki S, Tsubaki T, Toyokura Y (eds) International Congress Series Neurology. Excerpta Medica, Amsterdam pp 416–431
Salmi A, Ziola B, Hovi T, Reunanen M (1982) Antibodies to coronaviruses OC43 and 229E in multiple sclerosis patients. Neurology 32:292–295
Salvetti M, Ristori G, Damato M, Buttinelli C, Falcone M, Fieschi C, Wekerle H, Pozzilli, C (1993) Predominant and stable T cell responses to regions of myelin basic protein can be detected in individual patients with multiple sclerosis. Eur J Immunol 23:1232–1239
Sato S, Fujita N, Kurihara T, Kuwano R, Sakimura K, Takahashi Y, Miyatake T (1989) cDNA cloning and amino acid sequence for human myelin-associated glycoprotein. Biochem Biophys Res Comm 163:1473–1480
Schluesener HJ, Sobel RA, Linington C, Weiner HL (1987) A monoclonal antibody against a myelin oligodendrocyte glycoprotein induces relapses and demyelination in central nervous system autoimmune disease. J Immunol 139:4016–4021
Selin LK, Nahill SR, Welsh RM (1994) Cross-reactivities in memory cytotoxic T lymphocyte recognition of heterologous viruses. J Exp Med 179:1933–1943
Sharpless NE, Obrien WA, Verdin E, Kufta CV, Chen ISY, Dubois-Dalcq M (1992) Human immunodeficiency virus type-1 tropism for brain microglial cells is determined by a region of the env glycoprotein that also controls macrophage tropism. J Virol 66:2588–2593
Shaw SY, Laursen RA, Lees MB (1986) Analogous amino acid sequences in myelin proteolipid and viral proteins. FEBS Lett 207:266–270
Shirazian D, Mokhtarian F, Herzlich BC, Miller AE, Grob D (1993) Presence of cross-reactive antibodies to HTLV-1 and absence of antigens in patients with multiple sclerosis. J Lab Clin Med 122:252–259
Sibley WA, Bamford CR, Clark K (1985) Clinical viral infections and multiple sclerosis. Lancet 1: 1313–1315
Soldan SS, Berti R, Salem N, Seccherio P, Flamand L, Calabresi PA, Brennan MB, Maloni HW, McFarland HF, Lin H-C, Patnaik M, Jacobson S (1997) Association of human herpes virus 6 (HHV-6) with multiple sclerosis: increased IgM response to HHV-6 early antigen and detection of serum HHV-6 DNA. Nature Med 3:1394–1397
Sorensen O, Collins AR, Flintoff W, Ebers G, Dales S (1986) Probing for the human coronavirus OC43 in multiple sclerosis. Neurology 36:1604–1606
Sriram S, Rodriguez M (1997) Indictment of the microglia as the villain in multiple sclerosis. Neurology 48:464–470
Steinman L (1996) A few autoreactive cells in an autoimmune infiltrate control a vast population of nonspecific cells: a tale of smart bombs and the infantry. Proc Natl Acad Sci USA 93:2253–2256
Steinman L, Oldstone MBA (1997) More mayhem from molecular mimics. Nature Med 3:1321–1322
Steinman L (1996) Multiple sclerosis: a coordinated immunological attack against myelin in the central nervous system. Cell 85:299–302
Stewart JN, Mounir S, Talbot PJ (1992) Human coronavirus gene expression in the brains of multiple sclerosis patients. Virology 191:502–505
Stohlman SA, Bergmann CC, van der Veen RC, Hinton DR (1995) Mouse hepatitis virus-specific cytotoxic T lymphocytes protect from lethal infection without eliminating virus from the central nervous system. J Virol 69:684–694
Stuve O, Dooley NP, Uhm JH, Antel JP, Francis GS, Williams G, Yong VW (1996) Interferon beta-1b decreases the migration of T lymphocytes in vitro: effects on matrix metalloproteinase-9. Ann Neurol 40:853–863
Sun JP, Olsson T, Wang WZ, Xiao BG, Kostulas V, Fredrikson S, Ekre HP, Link H (1991) Autoreactive T-cell and B-cell responding to myelin proteolipid protein in multiple sclerosis and controls. Eur J Immunol 21:1461–1468
Sun N, Grzybicki D, Castro RF, Murphy S, Perlman S (1995) Activation of astrocytes in the spinal cord of mice chronically infected with a neurotropic coronavirus. Virology 213:482–493
Suzumura A, Lavi E, Weiss SR, Silberberg DH (1986) Coronavirus infection induces H-2 antigen expression on oligodendrocytes and astrocytes. Science 232:991–993
Swanborg RH (1995) Animal models of human disease: experimental autoimmune encephalomyelitis in rodents as a model for human demyelinating disease. Clin Immunol Immunopathol 77:4–13

Talbot P (1995) Implication of viruses in multiple sclerosis. Med Sci 11:837–843
Talbot P, Jouvenne P (1992) Neurotropic potential of coronaviruses. Med Sci 8:119–125
Talbot PJ, Ékandé S, Cashman NR, Mounir S, Stewart JN (1994) Neurotropism of human coronavirus 229E. Adv Exp Med Biol 342:339–346
Talbot PJ, Paquette JS, Ciurli C, Antel JP, Ouellet F (1996) Myelin basic protein and human coronavirus 229E cross-reactive T cells in multiple sclerosis. Ann Neurol 39:233–240
Tanaka R, Iwasaki Y, Koprowski HJ (1976) Intracisternal virus-like particles in the brain of a multiple sclerosis patient. J Neurosci Res 28:121–126
Taupin V, Renno T, Bourbonnière L, Peterson AC, Rodriguez M, Owens T (1997) Increased severity of experimental autoimmune encephalomyelitis, chronic macrophage/microglial reactivity, and demyelination in transgenic mice producing tumor necrosis factor-alpha in the central nervous system. Eur J Immunol 27:905–913
Tuohy VK, Thomas DM, Haqqi T, Yu M, Johnson JM (1995) Determinant-regulated onset of experimental autoimmune encephalomyelitis: distinct epitopes of myelin proteolipid protein mediate either acute or delayed disease in SJL/J mice. Autoimmunity 21:203–213
Tyrrell DAJ, Almeida JD, Berry DM, McIntosh K (1968) Coronaviruses. Nature 220:650
Tyrrell DAJ, Bynoe ML (1965) Cultivation of a novel type of common-cold virus in organ cultures. Brit Med J 1:1467–1470
Uhm, Joon H, Dooley, Nora P, Stuve O, Francis G, Duquette P, Antel JP, Yong VW (1997) Migratory behaviour of T lymphocytes isolated from MS patients undergoing treatment with β-interferon (IFN-β1b). Neurology 48:A80
Ulvestad E, Williams K, Mork S, Antel J, Nyland H (1994) Phenotypic differences between human monocytes/macrophages and microglial cells studied in situ and in vitro. J Neuropathol Exp Neurol 53:492–501
van Noort JM, van Sechel AC, Bajramovic JJ, Elouagmiri M, Polman CH, Lassmann H, Ravid R (1995) The small heat-shock protein alpha B-crystallin as candidate autoantigen in multiple sclerosis. Nature 375:798–801
Vandvik B, Norrby E (1989) Paramyxovirus SV5 and multiple sclerosis. Nature 338:769–771
Wang FI, Stohlman SA, Fleming JO (1990) Demyelination induced by murine hepatitis virus JHM strain (MHV-4) is immunologically mediated. J Neuroimmunol 30:31–41
Warren KG, Catz I, Steinman L (1995) Fine specificity of the antibody response to myelin basic protein in the central nervous system in multiple sclerosis: the minimal B-cell epitope and a model of its features. Proc Natl Acad Sci USA 92:11061–11065
Watanabe R, Wege H, ter Meulen V (1983) Adoptive transfer of EAE-like lesions from rats with coronavirus-induced demyelinating encephalomyelitis. Nature 305:150–153
Wege H (1995) Immunopathological aspects of coronavirus infections. Springer Sem Immunopathol 17:133–148
Weiner LP (1973) Pathogenesis of demyelination induced by mouse hepatitis virus (JHM virus). Arch Neurol 28:298–303
Weiss SR (1983) Coronaviruses SD and SK share extensive nucleotide homology with murine coronavirus MHV-A59 more than that shared between human murine coronaviruses. Virology 126:669–677
Williams RK, Jiang GS, Holmes KV (1991) Receptor for mouse hepatitis virus is a member of the carcinoembryonic antigen family of glycoproteins. Proc Natl Acad Sci USA 88:5533–5536
Wing MC, Moreau T, Greenwood J, Smith RM, Hale G, Isaacs J, Waldmann H, Lachmann PJ, Compston A (1996) Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin Invest 98: 2819–2826
Woyciechowska JL, Dambrozia J, Leinikki P, Shekarchi C, Wallen W, Sever J, McFarland H, McFarlin D (1985) Viral antibodies in twins with multiple sclerosis. Neurology 35:1176–1180
Wucherpfennig KW, Strominger JL (1995) Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 80:695–705
Wucherpfennig KW, Weiner HL, Hafler DA (1991) T-cell recognition of myelin basic protein. Immunol Today 12:277–282
Wucherpfennig KW, Zhang JW, Witek C, Matsui M, Modabber Y, Ota K, Hafler DA (1994) Clonal expansion and persistence of human T cells specific for an immunodominant myelin basic protein peptide. J Immunol 152:5581–5592

Yamada M, Zurbriggen A, Fujinami RS (1990) Monoclonal antibody to Theilers murine encephalomyelitis virus defines a determinant on myelin and oligodendrocytes, and augments demyelination in experimental allergic encephalomyelitis. J Exp Med 171:1893–1907

Yokomori K, Asanaka M, Stohlman SA, Lai MMC (1993) A spike protein-dependent cellular factor other than the viral receptor is required for mouse hepatitis virus entry. Virology 196:45–56

Zhang JW, Markovicplese S, Lacet B, Raus J, Weiner HL, Hafler DA (1994) Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. J Exp Med 179:973–984

Zielasek, Hartung HP (1996) Molecular mechanisms of microglial activation. Adv Neuroimmunol 6: 191–222