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PATHOGENESIS OF VIRUS-INDUCED DEMYELINATION

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I. Introduction

A. Demyelinating Diseases of Humans

Demyelination is the loss of myelin, the lipid sheath surrounding the neuronal axon. Myelin loss can occur following direct damage of the myelin (primary demyelination) or secondary to neuronal damage

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and axonal loss (secondary demyelination). Myelin is produced by oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS). The biochemistry of these two forms is different.

Demyelination is a component of several viral diseases of humans. The best known of these are subacute sclerosing panencephalitis (SSPE) of children, produced by measles virus, and progressive multifocal leukoencephalopathy (PML), produced in adults and children by JC papovavirus. Both are rare conditions, SSPE being a late onset complication of measles and PML occurring in association with immunosuppression. In addition to these two well-described examples of viral demyelination there are several other demyelinating diseases of possible viral etiology. These include the best known of human demyelinating diseases: multiple sclerosis (MS), for which circumstantial evidence has suggested an infectious etiology (reviewed by Acheson, 1972; Nathanson and Miller, 1978), and Guillain-Barré syndrome, which has been described following both viral infection and immunization (Johnson, 1983; Schonberger *et al.*, 1979).

In the last few years it has become apparent that one of the major manifestations of acquired immunodeficiency syndrome (AIDS) is neurological disease. In addition to AIDS-related dementia, lesions of demyelination in the CNS have been described (reviewed by Johnson *et al.*, 1988), as has peripheral neuropathy (Lipkin *et al.*, 1985; Cornblath *et al.*, 1987). The cause of the CNS demyelination remains speculative, and may be complex because immunosuppression in these patients allows numerous secondary infections and reactivation of latent viruses. A clear role is evolving for a related virus, human T leukemia virus type I (HTLV-I), which has been associated with tropical spastic paraparesis in the Caribbean and myelopathy in Japan (Gessain *et al.*, 1985; Osame *et al.*, 1986). Both diseases involve CNS demyelination and are clinically similar to MS. Indeed, it has been suggested that a virus closely related to HTLV-I is the causative agent in MS (Koprowski *et al.*, 1985).

Encephalomyelitis with demyelination has been described following several well-known virus infections, including measles, vaccinia, smallpox, mumps, rubella, influenza, herpes, and Epstein–Barr infections (Miller *et al.*, 1956; DeVries, 1960; Marsden and Hurst, 1932; Hart and Earle, 1975; Townsend *et al.*, 1976; Hoult and Flewett, 1960; Gudnadottir *et al.*, 1964; Grose *et al.*, 1975). Postvaccinal encephalomyelitis with demyelination was first seen in the last century with the use of Pasteur's attenuated rabies vaccine. This was prepared from animal neural tissue and resulted in direct sensitization to CNS

components. The eponymous vaccine virus, vaccinia, although successfully used to eradicate smallpox, was also associated with numerous cases of demyelinating encephalomyelitis (Miller, 1953; DeVries, 1960).

In addition to the well-known viruses detailed above, there are many viruses localized to discrete geographic regions that produce neurological disease in humans. These viruses are endemic and occasionally epidemic in tropical regions, and whereas the viral etiology is known, the neuropathology often remains undescribed. It is possible that demyelination is a component of many of these infections. There are also a number of other variously described, idiopathic human demyelinating conditions such as polyneuritis, optic neuritis, and transverse myelitis of unknown etiology.

B. Animal Models of Viral Demyelination

There are a number of naturally occurring virus infections of animals that involve demyelination, and many of these serve as instructive models for human demyelinating diseases. These include visna in sheep, caprine encephalitis-arthritis in goats, canine distemper of dogs, a paramyxovirus of cats, and Marek's disease of fowl. In addition to the naturally occurring diseases, many viruses have been shown to be capable of producing demyelination in experimental situations. Some of these viruses are not neuroinvasive and must be inoculated intracerebrally; others are neuroinvasive variants or mutants of naturally occurring viruses. Viruses associated with natural and experimental demyelinating diseases are listed in Table I.

To discuss virus-associated demyelinating disease it is first necessary to review the architecture and functional organization of the CNS. It is also necessary to consider what is known of the interaction of viruses with CNS cells. Much of our knowledge here comes from studies of nondemyelinating neurotropic viruses. It is also necessary to understand the immunology of the CNS, which differs in several important aspects from that of the rest of the body. Much that is known of the immunology of the CNS has been learned from studies of experimental allergic encephalomyelitis (EAE), a CNS inflammatory disease induced by extraneural injection of myelin antigens. The relevant aspects of each of these areas will be considered in turn before considering experimental models of viral-induced demyelination. As will be seen, viruses capable of producing demyelinating disease have no common taxonomic features; they include both DNA and RNA viruses, enveloped and nonenveloped viruses. This is followed by an

TABLE I

DEMYELINATING VIRUSES

Family	Virus
Alphavirus	Semliki Forest virus
	Ross River virus
	Venezuelan equine encephalitis virus
Coronavirus	Mouse hepatitis virus
Herpesvirus	Herpes simplex I virus
	Marek's disease virus
Paramyxovirus	Measles
	Canine distemper virus
Papovavirus	JC virus
Picornavirus	Theiler's virus
Retrovirus	Visna
	HTLV-I
	HIV
Rhabdovirus	Vesicular stomatitis virus
	Chandipura virus

attempt to summarize the important factors influencing viral demyelination, their common features, and possible mechanisms.

C. *The Target Organ*

The CNS consists of the brain, the spinal cord, and the optic nerves. It is a continuous system selectively insulated from the circulatory system by the blood–brain barrier. The important cells are the neurons, oligodendrocytes, astrocytes, microglia, and cerebral endothelial cells. The CNS differs from the PNS in several respects. The myelin-forming cells in the PNS are Schwann cells, the myelin is biochemically different, and astrocytes, oligodendrocytes and microglial cells are absent in the PNS.

Central nervous system neurons are morphologically and functionally diverse. All neurons produce neurofilament protein, neuron-specific enolase, and stain with silver. Much effort has been invested to differentiate subpopulations of neurons based on their neurotransmitter systems (reviewed by Gombos and Aunis, 1982). It is likely that many viruses infect specific subpopulations of neurons; indeed, this has been shown to be the case for a few viruses. Lymphocytic choriomeningitis virus (LCMV) persists in somatostatin but not cholecystokinin-producing neurons (Lipkin *et al.*, 1988). Poliovirus infects

predominantly motor neurons in the spinal cord and brainstem (Bodian, 1949). Rabies virus preferentially infects pyramidal cells of the hippocampus and Purkinje cells of the cerebellum (Johnson, 1965; Murphy, 1977). Variants of reovirus specifically localize to hippocampal and other neurons of the limbic system (Spriggs *et al.*, 1983). For many viruses the neuron is an ideal target cell. Neurons are metabolically active but nondividing, long-lived, and communicate directly and distantly throughout the body with many other neuronal and nonneuronal cells. Viral infections of neurons include acute, latent, and persistent infections; see Table II.

Astrocytes have been divided into two groups based on their reactivity with the antibody A2B5 (Raff *et al.*, 1983a,b). The intermediate filaments of astrocytes contain glial fibrillary acid protein (GFAP) and this is used as a characteristic marker of these cells (reviewed by Eng, 1982). Astrocytes are found around the cerebral blood vessels, where their "foot processes" make contact with the basal surfaces of endothelial cells. The functions of astrocytes are not completely understood, but they are known to respond (astrocytic hypertrophy) to CNS injury (Bignami and Dahl, 1976). Probable functions include a role in supplying the metabolic requirements of neurons, regulation of neurotransmitter production by neurons (Kimelberg and Norenberg, 1989), and response to hormones and control of immune responses in the CNS (see Section I,D). Viruses that infect astrocytes *in vivo* include visna virus, canine distemper virus, herpes simplex, JC papovavirus, and mouse hepatitis virus (see Table II).

Oligodendrocytes are the cells of the CNS that form the myelin sheath that surrounds axons. They are found throughout the CNS, but predominate in the white matter, where chains of oligodendrocytes are a characteristic feature. For a review on the biology of oligodendrocytes see Bartlett and Mackay (1983) and Bologna (1985). The cell lineage relationships of CNS cells have been the subject of much research. Oligodendrocytes and type 2 astrocytes appear to be derived from a common precursor cell (O2A) which carries a marker recognized by the A2B5 and O4 antibodies (Raff *et al.*, 1983b; Trotter and Schachner, 1989). Maturation of this bipotential progenitor cell is under the control of platelet-derived growth factor produced by type 1 astrocytes (Raff *et al.*, 1988). The O series of monoclonal antibodies, O4, O1, and O10, define increasingly more mature stages of oligodendrocyte differentiation (Sommer and Schachner, 1981; Schachner, 1982). Evidence also exists from neurogenesis studies in the cerebral cortex for a common precursor cell for neurons and oligodendrocytes (B. P. Williams *et al.*, 1991). The markers galactocerebroside and sulfatide are both expressed on the cell surface of oligodendrocytes a few

days prior to myelination (Abney *et al.*, 1981). Other surface markers include myelin basic protein (MBP) and sialosylgalactosyl cerebroside GM4 (Yu and Iqbal, 1979). Oligodendrocytes and astrocytes also produce the enzymes carbonate dehydratase and 2′,3′-cyclic-nucleotide 3′-phosphodiesterase, the latter a marker of oligodendrocyte differentiation (for reviews on marker enzymes of glial cells, see Schousboe, 1982; Giacobini, 1987). Oligodendrocytes vary in size and support different numbers of internodes; small cells probably myelinate internodes on several small-diameter axons, while large cells may myelinate a single or a few internodes on large-diameter axons (Bunge, 1968; Blakemore,

TABLE II

VIRAL INFECTIONS OF CENTRAL NERVOUS SYSTEM CELLS *in Vivo*

Cells	Virus
Neurons	Lymphocytic choriomeningitis virus
	Theiler's virus
	Herpes simplex virus
	Varicella zoster virus
	Visna virus
	Rabies virus
	Vesicular stomatitis virus
	Mouse hepatitis virus
	Reovirus 3
	Measles
	Semliki Forest virus
Oligodendrocytes	Measles
	JC papovavirus
	Mouse hepatitis virus, JHM, ts8
	Theiler's virus
	Semliki Forest virus
	Ross River virus
	Eastern equine encephalitis virus
	Venezuelan equine encephalitis virus
	Visna virus
	Herpes simplex virus
Astrocytes	Canine distemper virus
	Visna virus
	JC papovavirus
	Herpes simplex
	Mouse hepatitis virus, JHM
Microglia	Canine distemper virus.
	Visna virus
	HIV

1982). The fact that one oligodendrocyte can myelinate many axonal internodes is an important consideration in CNS demyelinating disease, because destruction of a single oligodendrocyte can result in the demyelination of many internodes. In contrast, the loss of one Schwann cell in the peripheral nervous system results in demyelination of a single internode. Under normal conditions oligodendrocytes are long-lived, nonproliferating cells, with a large turnover of cellular membranes. Like neurons, oligodendrocytes are targets for several viral infections; see Table II.

Oligodendrocytes produce myelin by wrapping and compacting specialized extensions of their plasma membrane in concentric multiple lamina around the axon. The major protein components of myelin are proteolipid protein (PLP), myelin-associated glycoprotein (MAG), myelin basic protein (MBP), and glycolipids such as galactocerebroside. The myelin protein genes have now been cloned and sequenced. The MBP gene in the mouse has at least five differentially spliced forms (de Ferra *et al.*, 1985; Newman *et al.*, 1987). The rat MAG gene has two differentially spliced forms, one of which is expressed in myelinating, suckling rats, the other in fully myelinated adult rats (C. Lai *et al.*, 1987). Each MAG message produces a distinct size of protein. The signals that control and regulate the differential splicing of these myelin genes are not clear. Further studies may lead to an understanding of developmentally regulated events in primary myelination and in myelin repair following demyelination.

Of the major cell types in the CNS probably the least in known about microglial cells. During development in the rat, two types of microglia can be recognized: ameboid microglia (brain macrophages) which differentiate into ramified microglia, characteristic of the adult brain. This differentiation, at least *in vitro*, appears to be regulated by the relative levels of the extracellular matrix proteins laminin and fibronectin (Chamak and Mallat, 1991). In the resting adult rat brain, microglia have also been divided into two populations, the ramified microglia situated within the CNS parenchyma and the perivascular (adventitial or perithelial) microglia situated around small blood vessels (Mato *et al.*, 1985). Studies on bone marrow chimeras indicate that at least the perivascular microglia are bone marrow derived (Hickey and Kimura, 1988). Following damage to the CNS at sites of neuronal destruction or inflammation, ameboid brain macrophages reappear. These cells are derived from the resident microglia (Graeber *et al.*, 1989), are phagocytic (Streit and Kreutzberg, 1988), produce cytokines that can stimulate astrocytes and neurons, express macrophage monocyte markers (Graeber *et al.*, 1990), and are involved in the initiation of immune responses (see Section I,D).

Cerebral endothelial cells differ from those of other tissues by their tight junctions, low levels of cytoplasmic vesicles, presence of transferrin receptors, and absence (in the rat) of the OX43 antigen that is present on other endothelial cells (Jefferies *et al.*, 1984; Robinson *et al.*, 1986). At the anatomical level, the barrier between the blood and the brain is formed by the tight junctions between the endothelial cells of the cerebral capillaries and the cells of the arachnoid meninges and choroid plexus. The cerebrospinal fluid (CSF) is generated mostly at the choroid plexi by selective filtration. Selectivity is high because total protein in the CSF is about 0.4% the level in serum. No organized lymphatic tissue is demonstrable within the CNS, although it has been suggested that the CSF drains to the deep cervical lymph nodes via a lymphatic channel possibly arising in the region of the carotid foramen (Bradbury and Cole, 1980).

Viruses can enter the CNS by a variety of methods, including retrograde transport along the axons of peripheral nerves, as occurs with rabies, reovirus, and herpes simplex viruses; and infection of olfactory neurons, as has been demonstrated with neurotropic influenza viruses, some alphaviruses, and mouse hepatitis virus (Cook and Stevens, 1973; Tyler *et al.*, 1986; Nir *et al.*, 1965; Perlman *et al.*, 1989). Most blood-borne viruses enter the CNS across the cerebral vascular endothelial or choroid plexus cells. Others, such as mumps and visna virus, infect choroid plexus cells (Wolinsky *et al.*, 1976; Brahic *et al.*, 1981a), or may be transported through endothelial cells in pinocytotic vesicles (Brightman, 1968). This seems to be the case with the alphaviruses Semliki Forest virus, and eastern equine encephalitis virus (Pathak and Webb, 1980; Murphy and Whitfield, 1970), and is probably the most common route of CNS infection. Viruses may also cross the blood–brain barrier within normally recirculating or inflammatory mononuclear cells, as has been suggested for canine distemper virus, cytomegalovirus, and human immunodeficiency virus (HIV) (Summers *et al.*, 1978; Wiley and Nelson, 1989).

D. Immunology of the Central Nervous System

The tight junctions of the cerebral endothelial cells, the low level of CSF immunoglobulins (1/500 serum), the absence of lymphatic organization, low to undetectable levels of major histocompatibility (MHC) molecules, and the failure to detect lymphocytes in the CNS have all contributed to the long-held concept that this organ is an immunologically privileged site. However, recent research indicates that this view is open to reinterpretation. Intravenous transfer of isotopically labeled T cell clones to naive, syngeneic rats has demonstrated that

cloned, activated T cells can normally cross the blood–brain barrier but that only cells that encounter antigen remain localized to initiate an inflammatory response (Wekerle *et al.*, 1987; Cross *et al.*, 1990).

The precise sequence of events that occur in the initiation, expansion, and specific localization of CNS immune responses remains unclear. Recognition of antigens in association with MHC molecules is required in both the inductive and effector phases of the immune response. This recognition places constraints on responses against CNS pathogens because cells of the CNS express low or undetectable levels of MHC molecules in the resting state. It has become clear, however, that various signals can enhance constitutive low levels of MHC class I expression and induce MHC class II expression on CNS cells.

At the interface between the brain and circulating lymphocytes are the cerebral endothelial cells. Presentation of viral antigens by MHC molecules displayed on the luminal surface of endothelial cells could be important in recruiting T cells into the CNS at the sites of infection. In culture, MHC class I expression can be enhanced, and MHC class II induced, on these cells by treatment with interferon γ (Male *et al.*, 1987). This effect can in turn be modulated by infection with virus (see Section II,A). There is some debate as to whether endothelial cells can function as efficient antigen-presenting cells (McCarron *et al.*, 1985; Pryce *et al.*, 1989). *In vivo*, the inducibility of class II on cerebral endothelial cells is controversial. Some studies of inflammatory disease find these cells express MHC class II (Traugott and Raine, 1985; Sobel *et al.*, 1984), others find them negative (Matsumoto *et al.*, 1986; Vass *et al.*, 1986). *In vivo*, cerebral endothelial cells constitutively express a high-affinity form of LFA-1 (Dustin and Springer, 1989). Morphological changes in cerebral endothelial cells have been observed at sites of CNS inflammation (Cross *et al.*, 1990), as has expression of a marker of high endothelial venules recognized by the antibody MECA-325 (Cannella *et al.*, 1990). In chronic relapsing experimental allergic encephalomyelitis (see Section I,E), which is characterized by episodes of CNS inflammation, increased expression of MHC class II, ICAM-1, and MECA-325 on cerebral vessels correlates with influx of inflammatory cells (Sakai *et al.*, 1986; Cannella *et al.*, 1990).

A role seems to be emerging for perivascular microglial cells as important antigen-presenting cells in the initiation of CNS inflammatory reactions (Hinrichs *et al.*, 1987; Hickey and Kimura, 1988; Cross *et al.*, 1991). Perivascular microglia and, at sites of injury or inflammation, parenchymal microglia (see Section I,C), have been observed to express several macrophage and monocyte markers, including MHC class I and II, CD4, OX42 (CR3), ED1, ED3, and low levels of

CD45 (Matsumoto *et al.*, 1986; Hickey and Kimura, 1988; Graeber *et al.*, 1990; Sedgwick *et al.*, 1991). These cells can also secrete interleukins (Woodroofe *et al.*, 1991). Perivascular microglia constitutively express MHC class II (Perry and Gordon, 1988; Mattiace *et al.*, 1990), can function as antigen-presenting cells for the induction of experimental allergic encephalomyelitis (EAE) (Hickey and Kimura, 1988), and have been suggested to be the key cell in the initiation of CNS immune responses (Cross *et al.*, 1991).

Closely associated with endothelial cells and the surrounding perivascular microglia are extensions of astrocytes known as astrocytic foot processes. Astrocytes also appear to have an important role in regulating CNS immune responses. Both type I and type II astrocytes (see Section I,C), have been shown *in vitro* and *in vivo* to increase expression of MHC class I and to express MHC class II in response to interferon γ (Hirsch *et al.*, 1983; Wong *et al.*, 1984; Male *et al.*, 1987; Calder *et al.*, 1988), and *in vitro* to function as antigen-presenting cells for the presentation of MBP to T cell lines (Fontana *et al.*, 1984a). Interferon γ can also induce the expression of ICAM-1 on cultured human astrocytes and interferon β has been found to inhibit interferon γ-induced expression of class II MHC at the transcriptional level (Ransohoff *et al.*, 1991). Astrocytes and gliomas in culture produce the cytokines interleukins 1 and 3 (IL-1, IL-3), and IL-1 production has been demonstrated in the brains of mice treated with endotoxin (Fontana *et al.*, 1982, 1983, 1984b; Frei *et al.*, 1986). These findings have led to the suggestion that astrocytes and endothelial cells mediate immune responses in the CNS by functioning as antigen-presenting cells and form an immune control system in the brain (Fontana and Fierz, 1985); this suggestion must now be modified to include a role for microglial cells.

Induction of Ia molecules on cultured astrocytes by interferon is strain dependent in both rats and mice. Astrocytes from Lewis rats express much higher levels of Ia in response to interferon than astrocytes from BN rats (Massa *et al.*, 1987a). Similarly, SJL and BALB/c mice are high and low responders, respectively. These findings correlate with the severity of EAE seen in these animals. Lewis rats and SJL mice are highly susceptible to EAE, and BN rats and BALB/c mice are resistant to EAE (Wege *et al.*, 1986). Mouse strains (B10.S and B10.ASR2) susceptible to CNS demyelination following Theiler's virus infection also express Ia on astrocytes, oligodendrocytes, and endothelial cells in the spinal cord (Rodriguez *et al.*, 1987a) but no expression was observed in mice (B10.S[9R]) resistant to the disease.

There is also evidence for direct viral induction of MHC molecules on cultured astrocytes. Expression of Ia molecules is induced on rat

astrocytes by the binding of live or inactivated mouse hepatitis virus JHM (Massa *et al.*, 1986), and both class I and class II MHC molecules are induced by live or inactivated measles virus (Massa *et al.*, 1987b). Levels of Ia expression on astrocytes are amplified by addition of tumor necrosis factor (TNF) (Massa *et al.*, 1987b), a cytokine whose release is stimulated by virus infection (Wong and Goeddel, 1986). In contrast, mouse astrocytes infected with mouse hepatitis virus (strain A59) express class I but not class II MHC and a soluble factor released by the astrocytes induces class I expression on oligodendrocytes (Suzumura *et al.*, 1986, 1988).

Neurons and oligodendrocytes differ from endothelial cells, astrocytes, and microglia in their expression of MHC molecules. *In vitro*, neither cell type constitutively expresses MHC class I or class II. Class I but not class II molecules are inducible on both cells by treatment with interferon γ (Hirsch *et al.*, 1983; Wong *et al.*, 1984; Suzumura *et al.*, 1986; Calder *et al.*, 1988; Joly *et al.*, 1991). *In vivo*, class I molecules can also be induced on neurons by direct intracerebral inoculation of interferon γ (Wong *et al.*, 1984). In oligodendrocytes, interferon-inducible expression of MHC class II is lost on differentiation from the oligodendrocyte–type II astrocyte (O2A) common precursor (Calder *et al.*, 1988).

E. Nonviral Experimental Demyelination

In addition to infection, demyelination may also result from immunization with various combinations of CNS antigens or from exposure to chemicals. These models yield additional information that is relevant to a consideration of viral demyelination.

Experimental allergic encephalomyelitis (EAE) was first produced in monkeys in the 1930s, and has since been demonstrated in many animal species. Experimental allergic encephalomyelitis is characterized by intense focal perivascular inflammation and demyelination in the brain and spinal cord, in response to peripheral inoculation of CNS antigens. Severity of disease corresponds to the degree of delayed-type hypersensitivity to CNS antigens, but not with the levels of circulating anti-brain antibodies. Because disease could be transferred with suspensions of lymph node cells, or purified T cells, it was concluded that this inflammatory condition and associated demyelination were dependent on the presence of CNS antigen-specific T cells (Thomas *et al.*, 1950; Paterson, 1960; Ortiz-Ortiz *et al.*, 1976). Indeed, it is now well established that extraneural immunization with purified MBP or specific (encephalitogenic) peptides of MBP can induce MBP-specific, class II-restricted T cells that cross into the CNS to produce

the characteristic perivascular infiltrates observed in this disease. Furthermore, this inflammatory disease can be initiated by the adoptive transfer of MBP-specific T cell lines and clones (Ben-Nun *et al.*, 1981; Sakai *et al.*, 1986).

Experimental allergic encephalomyelitis produced by inoculation of purified brain components such as MBP, peptides of MBP, or transfer of MBP-specific T cell clones must be separated from that produced by inoculation of whole white matter. The disease resulting from inoculation of purified MBP or peptides derived from it is not as severe as that produced by inoculation of whole white matter. Sera from animals immunized with whole white matter contain demyelinating activity, but sera from animals inoculated with MBP alone do not (Bornstein and Appel, 1961; T. Saida *et al.*, 1978). Inoculation of purified oligodendrocytes can also produce EAE, with production of serum antibodies that demyelinate cerebellar tissue cultures and lymphocyte proliferation responses to oligodendrocytes, but not to MBP (Podusolo *et al.*, 1976; McDermott *et al.*, 1977; Raine *et al.*, 1977; Abramsky *et al.*, 1977).

The demyelinating activity in the sera of animals inoculated with whole white matter or oligodendrocytes correlates with the titer of antibody to the glycolipid galactocerebroside (T. Saida *et al.*, 1977a, 1979; K. Saida *et al.*, 1978), and sera from rabbits inoculated with purified galactocerebroside demyelinates CNS tissue cultures (Dubois-Dalcq *et al.*, 1970; Fry *et al.*, 1974; Saida *et al.*, 1977b). Further, direct inoculation of anti-galactocerebroside antibody into the optic nerve of cats resulted in destruction of oligodendrocytes and demyelination (Carroll *et al.*, 1985) and inoculation of rabbits with bovine brain gangliosides initiated demyelinating encephalitis (Konat *et al.*, 1982).

Demyelination can be separated from inflammation on the basis of studies of T cell clones. Transfer of syngeneic, MBP-reactive T cell clones to naive rats results in a CNS inflammatory disease with minimal demyelination, whereas transfer of both MBP-reactive clones and antibody to the oligodendrocyte surface antigen myelin/oligodendrocyte glycoprotein (MOG) results in a more intense inflammatory response with extensive demyelination (Linington *et al.*, 1988; Lassmann *et al.*, 1988; Fierz *et al.*, 1988). It seems likely that although MBP-specific T cells initiate the CNS inflammatory response, the extent of demyelination is related to the production of antibodies to components of oligodendrocytes such as MBP or MOG.

Damage to myelin, including demyelination, can be induced by a variety of chemicals (reviewed by Blakemore *et al.*, 1983). Chemicals inducing demyelination by destruction of oligodendrocytes include ethidium bromide, lysolecithin, and cuprizone (Spencer and Schaum-

burg, 1980; Hall, 1972). Mice fed on a diet containing cuprizone show pyknotic oligodendrocytes and subsequent demyelination in specific white matter tracts (Blakemore, 1973a). Degenerating myelin is removed by macrophages. Processes from hypertrophic astrocytes then surround the demyelinated axons, new oligodendrocytes appear, and, on withdrawal of cuprizone, mediate remyelination (Blakemore, 1973b; Ludwin, 1978). Some chemicals will also destroy astrocytes producing CNS lesions of demyelination void of glial cells. Remyelination of these lesions is slower. Oligodendrocytes reappear within or around the lesion but remyelination does not occur in the absence of astrocytes (Blakemore, 1975).

II. Animal Models of Viral Demyelination

A. *Mouse Hepatitis Virus*

Mouse hepatitis virus (MHV) is a member of the Coronaviridae. These viruses contain a single-stranded message sense genome in excess of 32 kb. Transcription from a full-length replicative intermediate produces a set of 3′ coterminal messenger RNAs. The unique 5′ sequence of each mRNA is translated. Seven genes have been clearly identified and are numbered 1 to 7, 5′ to 3′. Additional open reading frames are present in some viruses but not others and have been designated 2A or 2B, and so on. By far the largest gene at 23 kb (Pachuk *et al.*, 1989) is gene A, the putative viral RNA polymerase. The envelope spike glycoprotein, S, is encoded by RNA 3, the matrix protein, M, by RNA 6 and the nucleoprotein, N, by RNA 7. Gene 2 encodes a hemagglutinin protein that is expressed only in selected strains of MHV. The envelope glycoprotein, S (previously E2), encoded by RNA 3, is post-translationally cleaved into two 90-kDa glycoproteins known as S1 and S2 (previously E2, 90B and 90A). This glycoprotein contains the major viral neutralizing epitopes and mediates viral receptor binding and fusion. For reviews on the molecular virology of coronaviruses see Siddell *et al.* (1983), Spaan *et al.* (1988), and Lai (1990).

Strains of MHV cause a spectrum of diseases from hepatitis and enteritis to encephalomyelitis with demyelination. Demyelinating strains include MHV-4, A59, and JHM. As with all viruses, pathogenesis and severity of disease are dependent on host and viral genetics and the route and dose of inoculation. The influence of viral and host genetics on the outcome of disease is always complex but is particularly so with MHV. This has been dramatically demonstrated by studies of different laboratory strains, their temperature-sensitive

mutants, monoclonal antibody neutralization-resistant variants, and *in vivo* and *in vitro* isolates. Several pathogenic, biochemical, and genetic differences have been observed among the different laboratory strains of MHV and as we will discuss although nominal strain designations may be identical, differential viral properties can evolve in the process of both *in vivo* and *in vitro* laboratory passage (Taguchi *et al.*, 1985; Morris *et al.*, 1989; Gallagher *et al.*, 1990).

Monoclonal antibody-resistant variants of MHV with altered neurovirulence have been generated by several laboratories. One example is variant V5A13.1 (Dalziel *et al.*, 1986), selected from wild-type (wt) MHV-4 using a neutralizing monoclonal antibody. The parental MHV-4 wt is highly neurovirulent ($LD_{50} < 0.5$ pfu) following intracerebral inoculation, whereas the variant is avirulent ($LD_{50} > 1800$ pfu). Others have described similar attenuated neutralization-resistant variants, including JHM wt B35 (Wege *et al.*, 1983) and JHM-DL 2.2-V-1 (Fleming *et al.*, 1987). In all of these variants, the neurovirulence of the parental wild-type virus is attenuated but the capacity to induce chronic white matter disease remains.

In situ hybridization studies have demonstrated that both MHV-4 wt and its V5A13.1 variant predominantly infect neurons (Fazakerley *et al.*, 1992). Following intracerebral inoculation MHV-4 wt was first detected in neurons of the deep cortical layers. The virus spread rapidly and by 3 days was present throughout the deep cortical areas, in occasional foci in the outer cortex, caudate, olfactory lobe, rhinencephalon, hypothalamus, pons, brainstem, and in the midcerebellar nuclei. The outer layers of the cortex, thalamus, and most of the cerebellum remained largely uninvolved. The infection was almost exclusively neuronal. Meninges, choroid plexi, endothelial cells, and glial cells were rarely infected. This widespread infection was associated with death of the animals within 4 days of inoculation and probably resulted from direct viral destruction of infected neurons. The V5A13.1 variant spread at a slower rate to infect the same areas but with involvement of fewer neurons. The slower rate of spread presumably allowed intervention of the immune response before infection of a lethal number of neurons, and the mice survived to develop a chronic demyelinating disease in which virus persisted in glial cells of the white matter (Dalziel *et al.*, 1986; Fazakerley *et al.*, 1992).

The JHM-DL strain of MHV also predominantly infects neurons while its derivative, monoclonal antibody-resistant variant 2.2-V-1, infects both neurons and glial cells. Another variant, 2.2/7.2-V-2, infects only glial cells. These variants are avirulent and produce a subacute demyelinating disease (Fleming *et al.*, 1987). A change from acute lethal encephalitis to subacute demyelinating disease has also been observed between JHM wt and its B35 variant (Wege *et al.*, 1988).

Demyelination is also seen in animals surviving inoculation with parental MHV-4 of JHM, and in MHV-4-infected animals protected by passive administration of neutralizing monoclonal antibodies (Buchmeier *et al.*, 1984; Perlman *et al.*, 1987). In the latter case one possibility is that neutralization-resistant variants with avirulent, demyelination-inducing phenotypes are generated *in vivo*. Selection of demyelinating variants *in vivo* may also occur in rats infected with JHM wt. In one study (Taguchi *et al.*, 1985, 1986), intracerebral inoculation of parental JHM wt virus into 4-to-5-week-old Lewis rats and analysis of the brain virus after several days of replication demonstrated an increase in the size of mRNAs 2 and 3 and of the nonglycosylated S glycoprotein (product of mRNA 3). In contrast to the previously described MHV-4 V5A13.1 and JHM-DL 2.2-V-1 variants, the large S, brain-derived JHM variant was more virulent than the parental JHM wt virus (Taguchi *et al.*, 1985, 1986). In another study (Morris *et al.*, 1989), a variant isolated from the spinal cord of infected rats synthesized an S glycoprotein smaller than that produced by the inoculum virus.

Interpretation of these data is complex but has been partially clarified by sequencing studies (Schmidt *et al.*, 1987; Luytjes *et al.*, 1987; Parker *et al.*, 1989). The longest S protein is that of MHV-4 (1376 amino acids). By comparison, the other strains and variants all have deletions in the same region. Differences between the S proteins of MHV-4 and MHV-A59 are seen not only at the level of the sequence but also in the epitopes defined by monoclonal antibodies (Talbot and Buchmeier, 1985; Fleming *et al.*, 1983). From coronavirus sequence studies it is clear that the genomes of these viruses are highly variable and that a region of hypervariability exists in the S glycoprotein. This hypervariable region undergoes a high frequency of recombination (Banner *et al.*, 1990). A scheme of polymerase jumping has been proposed to account for these events (M. M. C. Lai *et al.*, 1987).

The influence of host (rodent) genes on the pathogenesis of MHV infection has also been studied. Intracerebral infection of most mouse strains with MHV-4 or A59 is lethal, but SJL mice survive. Genetic studies indicate that resistance is governed by a single autosomal recessive gene on chromosome 7 that is not linked to the MHC locus (Knobler *et al.*, 1981). Other studies have suggested that two genes govern susceptibility. A major determinant of susceptibility appears to be a 110-kDa membrane-associated glycoprotein that serves as a cellular receptor for MHV (Boyle *et al.*, 1987). This molecule, related to the carcinoembryonic antigen family of proteins, is expressed in hepatocytes and brush-border cells of susceptible mice (R. K. Williams *et al.*, 1991) and has been cloned and shown to be a member of the immunoglobulin supergene family (Dveksler *et al.*, 1991). Human and ham-

ster fibroblast cells, normally resistant to MHV infection, are susceptible when transfected with this gene.

Host genes are also important at other stages of the virus infection. The molecular basis of age-related susceptibility to MHV remains, as for other viruses, an incompletely understood phenomenon. An age-related susceptibility of rats to the JHM strain correlates with the differentiation state of oligodendrocytes. Replication of virus in primary cultures of oligodendrocytes is inversely related to the levels of 2′,3′-cyclic-nucleotide 3′-phophodiesterase, a marker of oligodendrocyte differentiation and myelination (Beushausen and Dales, 1985). In primary rat CNS cultures, virus replication appears to be confined to a discrete intermediate stage in oligodendrocyte differentiation between the O2A precursor cells and fully differentiated oligodendrocytes, which are both resistant to infection (Wilson *et al.*, 1986; Pasick and Dales, 1991).

Another area of virus–host gene interaction is at the level of the immune response. The role of the immune response in protection and pathogenesis during MHV infection is incompletely understood and controversial. Results vary between laboratories (strains of the virus), rats and mice, and strains of rats and mice. Strain variation is well demonstrated by differences in the pathogenesis of MHV JHM in Lewis and BN rats. Weanling Lewis rats aged 30 to 35 days inoculated intracerebrally with JHM develop either acute encephalitis or subacute demyelinating disease. In contrast, infected weanling BN rats remain clinically healthy (Watanabe *et al.*, 1987). Virus replicates in the brains of both strains but markedly different pathologies result. In the first few weeks of infection, Lewis rats have large inflammatory plaques throughout the white matter, whereas clinically healthy BN rats have small nodular plaques of demyelination that are associated with astrocytic hypertrophy and an influx of plasma cells. Several weeks postinfection Lewis rats show areas of remyelination but no new plaques of demyelination, whereas BN rats show both remyelination and new plaques of inflammatory demyelination. Viral antigens are present in these late demyelinating lesions.

The difference in these pathologies appears to reside in the immune response. Spread of CNS infection in BN rats is controlled by locally produced antibody (Dorries *et al.*, 1987). A similar accumulation of plasma cells is not observed in Lewis rats. However, infected Lewis rats demonstrate *in vitro* lymphoproliferative responses to both virus and MBP. In contrast, these are absent in the BN rats (Watanabe *et al.*, 1983, 1987), which are also refractive to MBP-induced EAE (Wege *et al.*, 1986). The basis for T cell unresponsiveness to MBP in both MHV infection and EAE in the BN rat appears to reside at the initiation of

the CNS immune response. MHC class II, Ia molecules can be induced on astrocytes by either JHM virus or interferon γ in Lewis but not BN rats (Massa *et al.*, 1987a,b). In mice, reduction in brain virus titers during acute MHV JHM infection is also associated with the influx of inflammatory cells and correlates with high levels of $CD8^+$ T cells and natural killer (NK) cells (Williamson *et al.*, 1991). Protection from a lethal intracerebral dose of MHV-4 can be mediated by adoptive transfer of antibodies, virus-specific $CD4^+$ T cells, or virus-specific $CD8^+$ T cells (Buchmeier *et al.*, 1984; Stohlman *et al.*, 1986; Yamaguchi *et al.*, 1991), indicating that more than one immunological mechanism is protective. In mice, MHC class I but not class II could be detected on cultured mouse astrocytes following infection with MHV A59 (Suzumura *et al.*, 1986). In a further complication of MHV, MHC interactions, MHV-4 infection of cultured cerebral enothelial cells has been observed to down regulate H2K and up regulate H2D (both class I MHC molecules) and to block, at the transcriptional level, interferon γ-induced expression of class II molecules (Joseph *et al.*, 1989, 1991).

The relative roles of direct viral destruction and the immune response in generating the lesions of demyelination appear to vary with the system studied. In rats, lesions of demyelination are observed in infected animals and in infected animals that are immunosuppressed or immunodeficient (Sorensen *et al.*, 1982, 1987). In contrast, in one study of C57BL/6J mice infected with MHV JHM DL or 2.2-V-1, immunosuppression prevented development of demyelinating lesions. Lesions could be partially restored by adoptive transfer of naive or MHV-sensitized, MHC-matched, nylon wool-nonadherent spleen cells (Wang *et al.*, 1990). This is in contrast to previous studies on mice with MHV-4, which concluded that demyelination was directly viral mediated (Weiner, 1973; Lampert *et al.*, 1973). The possibility that MHV infection generates autoimmune T cell reactions that have a role in the production of demyelinating lesions is raised by the finding of MBP-specific T cells in rats infected with MHV JHM (Watanabe *et al.*, 1983). As in EAE (see Section I,E), transfer of these cells to naive animals results in perivenular, CNS inflammatory, but not significantly demyelinating, lesions. In summary, even for this extensively studied virus we still cannot relate with certainty the mechanism of demyelination; indeed it is likely that this varies and is dependent on a combination of virus and host genetics.

Research is now under way to unravel the events that lead to the CNS remyelination that occurs after MHV-induced demyelination. Changes have been observed in the composition of glial cell populations (Godfraind *et al.*, 1989; Armstrong *et al.*, 1990) and the transcription of glial cell genes (Jordan *et al.*, 1989).

B. Theiler's Virus

Theiler's murine encephalomyelitis virus (TMEV), like MHV, is a natural, enteric infection of mice. The virus was originally described in 1934 by Theiler following its isolation from a mouse with hind limb paralysis. The virus belongs to the cardiovirus genus of the Picornaviridae. The virions are small (28 nm), nonenveloped, and contain a single positive strand of genomic RNA that is translated to give a single polyprotein. The genome and the polyprotein can be divided into three main regions, which are preceded by a leader protein L. P1 contains the four structural capsid proteins designated 1A, 1B, 1C, and 1D (also known as VPs 4, 2, 3, and 1). The P2 region contains three proteins (2A, 2B, and 2C) of unknown function and the P3 region contains proteins 3A, 3B, 3C, and 3D, which function in RNA replication (3B), proteolytic cleavage of the polyprotein (3C), and as the RNA polymerase (3D). For reviews on Theiler's virus see Friedmann and Lorch (1985), Rodriguez *et al.* (1987b), and Nash (1991).

Isolates other than Theiler's original isolate (TO) have been obtained from around the globe and investigated experimentally. These include strains DA, GDVII, BeAn, Yale, and WW. In mice, strains GDVII and FA produce an acute encephalitis and are virulent when inoculated intracerebrally, intranasally, or orally. These strains have been shown to produce epizootics of encephalitis (Thompson *et al.*, 1951). The other strains are comparatively avirulent in adult mice, although all kill neonatal mice.

Theiler passed the original isolate (TO) into weanling mice, reproducing the paralysis (Theiler, 1934). Inflammatory lesions were present in the brain and spinal cord, being most prominent in the latter. The spinal cords also demonstrated neuronal necrosis, particularly of anterior horn cells, and this poliomyelitis was originally studied as a mouse model of polio (Olitsky and Schlesinger, 1941). Histopathologically it is characterized by areas of neuronal necrosis, neuronophagia, and microglial proliferation, which are seen throughout the CNS, in the absence of white matter disease. Mice that survive this early poliomyelitis develop a persistent CNS infection with lesions of inflammatory demyelination in the spinal cord (Daniels *et al.*, 1952). This biphasic disease is characteristic of most of the avirulent brain isolates and passages of Theiler's virus. Strains TO, DA, BeAn, and WW are all capable of inducing a chronic demyelinating disease following intracerebral inoculation.

The nominally avirulent (TO) group viruses are in fact more or less virulent depending on the virus strain, passage history, mouse strain, and the route and dose of the inoculum (Lipton, 1975; Lehrich *et al.*,

1976; Lipton and Dal Canto, 1979a; Powell *et al.*, 1977; Dal Canto and Lipton, 1982). Adaption to growth in cell culture selects attenuated viruses that in some cases no longer induce the acute poliomyelitis seen with the original brain isolates, although the subsequent chronic demyelination may be more intense (Lipton, 1978; Lipton and Dal Canto, 1979b). Comparison of DA virus passaged and isolated directly from mouse brain with virus passaged and isolated *in vitro* demonstrated greater heterogeneity in the *in vivo* genotype, indicating that specific variants are selected by *in vitro* passage (Roos and Whitelaw, 1984). The presence within the CNS of a population of viruses with related but variant genomes is a complicating factor in studying the pathogenesis of all the demyelinating RNA viruses and has been discussed for MHV in Section II,A.

Despite the genetic variability that probably exists *in vivo* during infection, genetic studies on representative, cloned genomes and genetically engineered recombinants have begun to elucidate the viral genetic loci responsible for virulence, persistence, and demyelination (reviewed by Brahic *et al.*, 1991). Complete nucleotide sequences of several different clones of GDVII, DA, and BeAn have now been determined (Ozden *et al.*, 1986; Ohara *et al.*, 1988; Pevear *et al.*, 1987, 1988; Tangy *et al.*, 1989; McAllister *et al.*, 1989; Roos *et al.*, 1989; Fu *et al.*, 1990). GDVII, DA, and BeAn are 90% identical in their nucleotide sequences and 95% identical in their amino acid sequences. In the GDVII virus, neurovirulence is controlled by at least two loci, one variously mapped to the VP1, L/VP1, or 1B(VP2)/2C region (Brahic *et al.*, 1991; Calenoff *et al.*, 1990; Fu *et al.*, 1990) and one 5′ of this region (Brahic *et al.*, 1991; Fu *et al.*, 1990) that may be the 5′ noncoding region alone (Lipton *et al.*, 1991). The 5′ noncoding region has been found to be a major determinant of neurovirulence in two other picornaviruses, polio virus and mengo virus (La Monica *et al.*, 1987; Duke *et al.*, 1990). In the studies of Lipton and colleagues (1991), attenuated recombinants of GDVII that contained only the BeAn 5′ noncoding sequences did not persist and could produce only small, early, localized lesions of demyelination, suggesting that chronic, persistent, demyelinating disease is not the inevitable consequence of avirulence. This view is shared by Brahic and colleagues, who have mapped persistence and demyelination to the VP1 region of DA (McAllister *et al.*, 1990; Tangy *et al.*, 1991; Brahic *et al.*, 1991). In contrast, Roos and colleagues suggest that all strains of the virus are capable of persisting and initiating a demyelinating disease if the infection is nonlethal and that there are multiple determinants of persistence and demyelination (Fu *et al.*, 1990; Rodriguez and Roos, 1992). The importance of VP1 in demyelination is further illustrated by the reduced replication rate and

fewer lesions observed following infection with a DA virus with a single amino acid change at residue 101 of VP1 (Zurbriggen and Fujinami, 1989; Zurbriggen *et al.*, 1991).

As with many viral systems, the extent of the pathology depends not only on the virus, but also on the mouse strain. The most severe demyelinating disease is observed in SJL/J mice, CBA and Swiss mice show an intermediate susceptibility, and AKR, DBA, and BALB/c mice show minimal lesions (Lehrich *et al.*, 1976; Lipton and Dal Canto, 1979a). Genetic studies have indicated that susceptibility to demyelination is linked to the MHC class I gene, *H2D* (Rodriguez *et al.*, 1986) and two non-MHC genes, one on chromosome 6, close to the T cell receptor β chain locus and one on chromosome 3, near the carbonate dehydratase-2 locus (Melvold *et al.*, 1987, 1990). The MHC-linked susceptibility does not result from a failure to generate virus-specific, $CD8^+$, cytotoxic T lymphocytes because these can be isolated from the CNS in both resistant and susceptible mice (Lindsley *et al.*, 1991). The non-MHC-linked susceptibility loci could represent, for example, the virus receptor. Both GDVII and BeAn virus have been shown to bind to a 34-kDa membrane-associated protein on susceptible cells (Kilpatrick and Lipton, 1991).

The pathology of the demyelinating disease is well documented. Inflammatory cell infiltrates, predominantly monocytes, lymphocytes, and plasma cells, are first seen in the leptomeninges and as perivascular cuffs in the spinal cord. In the chronic phase of the disease these are associated with lesions of demyelination that expand throughout the white matter. In the lesions of demyelination axons appear to be preserved, there is marked astrocytic hypertrophy and gliosis, and normal oligodendrocytes can be found. Electron microscopic studies have demonstrated stripping of myelin lamellae by mononuclear cells (Dal Canto and Lipton, 1975), and macrophages containing myelin debris are present within and around the lesions. With time, the inflammatory response subsides and astrocytic gliosis is the most prominent feature. Remyelination is first apparent shortly after demyelination, increases with time, and is mediated by Schwann cells (Dal Canto and Lipton, 1980).

In one series of ultrastructural studies of chronic demyelination associated with DA and WW virus infections, macrophages were the cells most heavily infected; infection of astrocytes and other inflammatory cells was also seen, but no infection of (or pathological changes in) oligodendrocytes or remyelination by Schwann cells was observed (Dal Canto and Lipton, 1979, 1982; Dal Canto, 1982). In contrast, WW virus was observed to replicate in oligodendrocytes in mouse CNS organ cultures (Wroblewska *et al.*, 1979) and has been demonstrated to

persist in glial cells by *in situ* hybridization studies (Brahic *et al.*, 1981b; Stroop *et al.*, 1981, 1982). By electron microscopy, DA and BeAn viruses have also been observed to infect oligodendrocytes during the chronic phase of disease (Rodriguez *et al.*, 1983; Blakemore *et al.*, 1988). In a study of DA virus infection of SJL/J mice, in which virus infection was determined by *in situ* hybridization and cell types by immunostaining, approximately 25 to 40% of the infected cells were oligodendrocytes, 5 to 10% were astrocytes, and 10% were microglia or macrophages (Aubert *et al.*, 1987).

Neutralizing antibodies are detectable in the serum within a week of infection and rise slowly (Lipton, 1975). Intrathecal antibody production occurs (Lipton and Gonzalez-Scarano, 1978). T cells specific to the virus are detectable early in infection and remain throughout the persistent infection (Rabinowitz and Lipton, 1976). Both viral antibody titers, viral-specific T cell proliferative responses, and delayed-type hypersensitivity responses are maximal at times of maximum demyelination (Clatch *et al.*, 1985). Virus-specific, $CD8^+$ cytotoxic T lymphocytes are generated (Pena Rossi *et al.*, 1991; Lindsley *et al.*, 1991). Despite the presence of high titers of neutralizing antibody and antiviral T cell activity, virus can persist in the CNS for at least a year (Lipton *et al.*, 1984). Virus can be isolated from the spinal cords of mice with paralysis and demyelination but not from clinically healthy infected mice (Welsh *et al.*, 1990).

To determine the role of the immune response in viral clearance and protection, various manipulations of the immune system of infected mice have been undertaken. In DA-infected SJL mice, cyclophosphamide or anti-thymocyte serum potentiated the acute grey matter disease, leading to higher brain virus titers, greater dissemination of virus, increased neuronal necrosis, rapid onset of clinical symptoms and increased mortality (Lipton and Dal Canto, 1977). BeAn infection of thymectomized, $CD4^+$-depleted, CBA mice increased the mortality to 100% by 4 weeks postinfection (Welsh *et al.*, 1987). Depletion of $CD8^+$ cells made little difference to survival but did decrease virus clearance from the CNS. Depletion of $CD4^+$ T cells was associated with an inability to produce anti-viral antibody, suggesting that the protective effect of the immune response in the early polio phase of this disease is mediated by anti-viral antibodies. In support of this, both CD4-depleted and athymic *nu*/*nu* mice can be protected from infection by transfer of anti-viral antibody (Welsh *et al.*, 1990; Fujinami *et al.*, 1989). However, in another study, both $CD4^+$ and $CD8^+$ T cells were suggested to be important in protecting mice from the acute infection. Increased mortality was observed in DA-infected C57BL/10SNJ mice depleted of $CD3^+$, $CD4^+$, or $CD8^+$ T cells (Rodriguez *et al.*, 1991).

The immune response appears to play an important role in development of the demyelinating lesions, although its role is still contentious. In support of an immune component, demyelinating lesions are absent, or at least reduced, in mice surviving immunosuppression with cyclophosphamide, anti-lymphocyte serum, or cyclosporin A (Lipton and Dal Canto, 1977; Roos *et al.*, 1982; Rodriguez and Quddus, 1986). Furthermore, demyelination has been reduced by treatment with anti-Ia antibodies (Friedmann *et al.*, 1987), depletion of $CD4^+$ T cells in thymectomized mice (Welsh *et al.*, 1987), and treatment with anti-CD3, -CD4, or -CD8 monoclonal antibodies (Rodriguez and Sriram, 1988; Rodriguez *et al.*, 1991). In contrast, infected, athymic, *nu*/*nu* mice have been reported to develop demyelinating lesions (Rosenthal *et al.*, 1986; Love, 1987). In support of an immunological basis to the demyelination, an investigation of spatial and temporal relationships between viral RNA and changes in CNS-specific transcripts such as MBP and PLP did not indicate any direct correlation (Yamada *et al.*, 1990).

The possible role of autoimmune responses in the demyelinating lesions is, as with other aspects of Theiler's virus immunology, inconclusive. In one study, neither serum nor splenocytes from infected SJL mice with demyelinating lesions had any effect on myelinated CNS cultures, nor did these cells demonstrate proliferation responses to MBP or spinal cord, nor could they transfer disease to naive recipients (Barbano and Dal Canto, 1984). In contrast, antibodies and delayed-type hypersensitivity (DTH) responses to myelin and antibodies to MBP have been observed in CBA mice infected with BeAn virus (Welsh *et al.*, 1987; Rauch *et al.*, 1987). The levels of antibodies to MBP correlated with clinical signs. Antibody cross-reactivity between virus and another myelin/oligodendrocyte component, the glycolipid galactocerebroside, has also been reported (Fujinami *et al.*, 1988), although it is not immediately apparent why these nonenveloped virions should cross-react with an antibody to a glycolipid; one possibility is a conformational mimicry (Oldstone, 1987).

C. Semliki Forest Virus

Semliki Forest virus (SFV) is an alphavirus found in Africa (Bradish *et al.*, 1971). The virology and molecular biology of the virus have been reviewed by Atkins *et al.* (1985). The virion is small (50 nm) and the genome consists of a single 11-kb molecule of positive-sense RNA (42S) that acts directly as a message. A smaller subgenomic (26S) message coding for the structural proteins is transcribed from a

negative-sense replicative intermediate. The prototype strain has been cloned and sequenced (Garoff *et al.*, 1980). The structural proteins consist of the capsid protein (C) and three surface glycoproteins (E1, 2, and 3). The glycoprotein spikes of the virus are composed of three copies each of E1 and E2. The envelope structure of the virus has been visualized at 3.5-nm resolution by reconstruction cryoelectron microscopy (Vogel *et al.*, 1986). The virus enters cells by receptor-mediated endocytosis. Fusion occurs in the endosome. The virus has been reported to bind to the class I MHC molecule (Helenius *et al.*, 1978), although this finding has not been repeated. The closely related virus, Sindbis, has been demonstrated to bind to a developmentally regulated neuronal protein (Ubol and Griffin, 1991), which appears to be a laminin receptor.

Several isolations of SFV from mosquitoes are documented and from these, strains of different passage histories have been derived. Experimental infections of mice, rats, guinea pigs, and rabbits have been reported (Bradish *et al.*, 1971). The natural host for the infection is unknown. Following much use in many laboratories, SFV was thought to be unable to infect humans. However, this appears to be strain dependent, as a case of fatal human encephalitis has been reported in a scientist working with the Osterrieth strain of the virus (Willems *et al.*, 1979). Presently the virus appears to be responsible for an outbreak of febrile illness in central Africa. Symptoms include severe, persistent headaches and myalgia (Mathiot *et al.*, 1990). Infection of the mouse has been the most studied and here the virus strains can be designated as virulent (L10, V13) or avirulent [A7, A7(74), A8] in the adult animal (Bradish *et al.*, 1971). Other strains include the strain sequenced by Garoff and colleagues and designated by them the prototype strain (Garoff *et al.*, 1980), the avirulent, MRS MP 192/7 strain (Henderson *et al.*, 1970), and a series of nitrosoguanidine-induced mutants of the L10 strain (Barrett *et al.*, 1980).

The outcome of infection in mice depends on the strain of the virus and the age and strain of the mice. All strains of virus that have been tested are virulent in neonatal and suckling mice by all routes of inoculation (Bradish *et al.*, 1971). Replication, predominantly in neurons, results in destruction of these cells (Woodward *et al.*, 1978; Pathak and Webb, 1978). Central nervous system infection of adult mice with L10 virus results, as in the neonatal and suckling mice, in neuronal destruction and death. In contrast, infection of adult mice with A7(74) virus results in a subacute, demyelinating meningoencephalomyelitis with minimal neuronal destruction, followed by remyelination and complete recovery. Defective interfering viruses have

been observed in culture and when inoculated into mice can protect against infection with a lethal dose of virus (Bruton and Kennedy, 1976; Crouch *et al.*, 1982; Barrett and Dimmock, 1984).

Despite high virus titers in the brains of SFV A7(74)-infected adult mice, electron microscopic studies reveal no maturation of virus and no advanced stages of virus replication, only accumulation of viral nucleocapsid material, predominantly in neurons (Pathak and Webb, 1978, 1988). This apparent contradiction remains unresolved. Treatment of adult mice with the drug sodium aurothiomalate induces physiological changes in neurons. Infection of such mice with SFV A7(74) results in complete replication of virus within neurons, neuronal destruction, and death (Pathak and Webb, 1983). It appears that replication of the A7(74) strain is blocked within differentiated adult mouse neurons but not in the differentiating neurons of neonatal or suckling mouse brains. Neuronal maturity has also been demonstrated to be an important determinant of susceptibility in rats infected with another alphavirus, Japanese encephalitis virus (Ogata *et al.*, 1991).

Following intraperitoneal infection of adult mice with the A7(74) strain, virus replicates in smooth and skeletal muscle, resulting in a plasma viremia that is present from the first to the third day of infection (Pusztai *et al.*, 1971). Virus enters the brain by passage across the cerebral endothelial cells (Pathak and Webb, 1974, 1980), and is detectable in the CNS by infectivity assay from day 1 to 11 (Jagelman *et al.*, 1978; Fazakerley and Webb, 1987a), and by immunocytochemistry for up to 6 months (Khalili-Shirazi *et al.*, 1988). Virus also persists for many months in the CNS of athymic *nu*/*nu* mice unable to produce anti-viral IgG or T cell responses (Fazakerley and Webb, 1987b).

Following intraperitoneal infection, disturbance of the blood–brain barrier, as measured by the IgG index of the CSF, occurs until 7 or 8 days postinfection (Parsons and Webb, 1982a). This is associated, between days 4 and 10, with a transient pleocytosis (Parsons and Webb, 1982b). On restoration of the blood–brain barrier, anti-viral antibody synthesis continues locally within the CNS (Parsons and Webb, 1982a). Demyelination, observed in the brain (Kelly *et al.*, 1982), spinal cord (Pathak *et al.*, 1983), and optic nerves (Illavia *et al.*, 1982), is first apparent 9 days postinfection and is maximal at day 14. Remyelination occurs and is apparent by 21 days. Demyelination has been observed in several strains of mice (Suckling *et al.*, 1980). Electrophysiological studies indicate abnormal visual evoked responses (Tremain and Ikeda, 1983), changes in axonal transport in demyelinated optic nerve fibers (Pessoa and Ikeda, 1984; Jenkins and Ikeda, 1991), and abnormalities in retinal neurons (Tansey and Ikeda, 1986). There are changes in the levels of neurotransmitter precursors (Bar-

rett *et al.*, 1986) and behavioral changes in infected mice (Webb *et al.*, 1979).

Virus infection stimulates both humoral and cellular immunity. Mice immunized with inactivated SFV demonstrate protective, delayed-type hypersensitivity responses that can be transferred to naive animals by lymph node but not spleen cells (Kraaijeveld *et al.*, 1979a,b). Virus can replicate in macrophages (Van der Groen *et al.*, 1976) and macrophages produce interferons α and β in response to infection (Blackman and Morris, 1984). Late in the infection, spleen cells produce interferon γ. Anti-viral, cytotoxic T lymphocytes are present in infected mice from day 3 to 10 postinfection (Blackman and Morris, 1984) and can destroy SFV-infected, MHC-positive, primary, murine brain cell cultures (Morris *et al.*, 1987). Both neutralizing and nonneutralizing monoclonal antibodies directed against the E1 or E2 envelope glycoproteins can protect mice against a lethal dose of infection (Boere *et al.*, 1983, 1985).

Neuropathological studies of adult mice infected intraperitoneally with the avirulent A7(74) strain demonstrate a predominantly mononuclear cell inflammatory response in the meninges and around vessels. Foci of inflammation and associated demyelination are apparent throughout the brain, but predominate in the cerebellum (Suckling *et al.*, 1977). There is little or no destruction of neurons, but astrocytic hypertrophy and gliosis are apparent (Chew-Lim *et al.*, 1977; MacKenzie *et al.*, 1978; Kelly *et al.*, 1982). A detailed electron microscopic study of the development of demyelinating lesions (Pathak *et al.*, 1983) demonstrates early infiltration of lymphocytes, which associate closely with astrocytes, oligodendrocytes, and myelinated axons. In older lesions macrophages can be observed removing the damaged myelin. The axons remain intact. Accumulation of viral nucleocapsids is apparent in neurons (Pathak and Webb, 1988), and viral antigens are detectable on neurons, particularly in the hippocampus, and on glial cells in the cerebellum (Khalili-Shirazi *et al.*, 1988).

The inflammatory neuropathology is suggestive of an immune-mediated demyelination and this is supported by immunological studies. Athymic *nu*/*nu* mice have neither changes in axonal transport, lesions of demyelination, nor neuronal pycnosis, despite persistently high brain virus titers (Jagelman *et al.*, 1978; Fazakerley and Webb, 1987b; Jenkins *et al.*, 1988). Adoptive transfer of syngeneic spleen cells to infected *nu*/*nu* mice restores the lesions of demyelination, and these occur earlier following the transfer of SFV-primed lymphocytes. Intraperitoneal transfer of anti-SFV immune serum does not restore the lesions (Fazakerley *et al.*, 1983; Fazakerley and Webb, 1987b). Immunosuppression by cyclophosphamide (Suckling *et al.*, 1977), total body

irradiation (Fazakerley and Webb, 1987c), or cycloleucine (Amor and Webb, 1987) delays or prevents demyelination, although demyelination is not prevented by treatment with cyclosporine (Fazakerley and Webb, 1987a). This drug probably does not cross the blood–brain barrier (Palestine *et al.*, 1985; Fazakerley and Webb, 1987a).

Possible mechanisms of demyelination include a T cell response either to viral determinants on the cell surface, or to an autoantigen. Virus-specific, cytotoxic T cells are present in the first 2 weeks of infection (Blackman and Morris, 1984). At 7 days, lymph node cells respond to MBP in a proliferation assay (Mokhtarian and Swoveland, 1987). Interestingly, C57Bl/6 mice that have recovered from SFV A7(74) infection are susceptible to MBP-induced EAE, whereas previously uninfected mice are not (Mokhtarian and Swoveland, 1987). Semliki Forest virus is an enveloped virus and, as with any such virus, takes its envelope lipids from the membranes of the host cell. If virus is grown in mouse brain cell cultures, the envelope contains myelin glycolipids, including galactocerebroside (Webb *et al.*, 1984; Khalili-Shirazi *et al.*, 1986; Evans and Webb, 1986).

In addition to the well-studied A7(74) and L10 strains of SFV two mutant viruses, M9 and M136, have been described (Sheahan *et al.*, 1981, 1983). The mechanism of demyelination here appears to be different: these mutants destroy G26-24 oligodendroglioma cells in culture and produce demyelination in adult mice by direct destruction of oligodendrocytes (Sheahan *et al.*, 1981, 1983; Atkins and Sheahan, 1982).

Two related alphaviruses, Ross River virus (RRV) and Venezuelan equine encephalitis viruses (VEEV), also produce experimental demyelination in mice (Seay and Wolinsky, 1982, 1983; Dal Canto and Rabinowitz, 1981a). Extraneural inoculation of the T48 strain of RRV produces focal lesions of inflammatory demyelination and necrosis throughout the brainstem, cerebellum, and spinal cord (Seay and Wolinsky, 1982). Electron microscopy demonstrates that oligodendrocytes are the primary site of viral replication, but virus is also found in subpopulations of neurons and in invading polymorphonuclear leukocytes and macrophages. Demyelination occurs within 3 days of infection, increases with increasing brain virus titer, is not prevented by immunosuppression with cyclophosphamide, and probably results from either a direct effect of the virus on the oligodendrocytes, or the virally induced release of toxic factors. Remyelination occurs and is not mediated by migrating Schwann cells (Seay and Wolinsky, 1982, 1983). The situation with VEEV is different and more akin to that described for the A7(74) strain of SFV. Venezuelan equine encephalitis virus produces inflammatory lesions of primary de-

myelination in the spinal cord of infected mice. Lesions are absent in *nu/nu* mice, suggesting an immune-mediated demyelination (Dal Canto and Rabinowitz, 1981a).

D. Visna Virus

Visna virus belongs to the lentivirus group of retroviruses. The name of the virus derives from the Icelandic name given to the wasting, demyelinating neurological disease it causes in sheep. The infectious visna virus is an enveloped RNA virus, but the viral life cycle also involves a DNA proviral stage. The provirus is detectable within an hour of infection (Haase *et al.*, 1982). Different strains of visna and the closely related caprine arthritis encephalitis virus (CAEV) have been sequenced (Sonigo *et al.*, 1985; Saltarelli *et al.*, 1990; Querat *et al.*, 1990; Sargan *et al.*, 1991; Staskus *et al.*, 1991a). The viral genome is a positive strand of polyadenylated RNA of approximately 9 kb that contains three structural genes, *gag*, *pol*, and *env*, 5′ to 3′. In addition there is a series of small open reading frames between and overlapping these genes that code for regulatory proteins. The *gag* gene is translated into a polyprotein that is cleaved to give the three components of the virus core. The *env* gene appears to code for a 90 to 100-kDa precursor envelope glycoprotein that is processed and highly glycosylated to produce the major surface glycoprotein gp135. (Vigne *et al.*, 1982; Sonigo *et al.*, 1985). Visna virus appears to bind to the cell surface sheep MHC class II molecule (Dalziel *et al.*, 1991). The *pol* gene product, as with other lentiviruses, encodes the viral reverse transcriptase (Sonigo *et al.*, 1985).

The virology of visna virus has been reviewed by Nathanson *et al.*, (1985), Haase (1986), Narayan *et al.* (1988), Clements *et al.* (1988), and Cheevers and McGuire (1989). Natural infection is by the respiratory route, by which the virus also causes the more common chronic pulmonary disease of sheep, known in Iceland as *maedi* and in North America as progressive pneumonia. Infection of lambs also occurs through colostrum. There is no evidence of germ-line transmission. Visna normally occurs in Icelandic sheep as a neurological complication of maedi. The disease is rarer in sheep of other breeds. Epidemics in Icelandic sheep have been related to the confined, close housing of animals (Gudnadottir, 974). The closely related CAEV is found world wide in goats, and produces both arthritis and demyelination. Serological studies indicate that infection may be as high as 80–85%, with estimates for the prevalence of clinical disease varying from low to about 25% of the seropositive population (Adams and Gorham, 1986; East *et al.*, 1987). Clinical disease is commonly apparent 2 years or

more after infection and results in death, usually within a year (Sigurdsson, 1954; Oliver *et al.*, 1981).

Visna was originally isolated from Icelandic sheep (Sigurdsson *et al.*, 1960), but subsequent isolations have been made from sheep in several countries. The different isolates differ somewhat in their properties. The prototype virus isolated by Sigurdsson *et al.* and a North American isolate (Cutlip and Laird, 1976) replicate to high cell-free titers and are cytolytic in a sheep choroid plexus cell line *in vitro*, whereas most North American field isolates establish persistent, syncytium-forming infections with low or undetectable levels of cell-free virus (Narayan *et al.*, 1982). Addition of macrophages or monocytes to cultures of persistently infected, sheep choroid plexus cells results in productive, cytolytic infection of the latter (Narayan *et al.*, 1982; Anderson *et al.*, 1983).

Persistent infection occurs *in vivo* and virus can be found in several organs, throughout life, despite the presence of neutralizing antibody. For example, *in situ* hybridization has been used to detect polymerase chain reaction (PCR)-amplified viral sequences in fixed tissues, including bronchiolar epithelial cells and alveolar macrophages (Staskus *et al.*, 1991b). Infection of monocytes and macrophages is particularly important in the pathogenesis of visna as monocytes are the likely mechanism of virus distribution between tissues (Gendelman *et al.*, 1986). The maturation of virally infected monocytes to macrophages is associated with an increase in viral gene expression. Migration of infected monocytes across the blood–brain barrier is a likely mechanism of virus entry into the CNS. Another mechanism of viral entry into the CNS is via the choroid plexi. *In situ* hybridization studies of choroid plexus cells infected *in vivo* indicate the presence of proviral DNA in up to 3% of cuboidal epithelium cells. Immunofluorescence studies detect only rare positive cells in the choroid plexus, and comparison of the levels of DNA and RNA in these cells indicates that viral expression is blocked in these cells at a transcriptional level (Haase *et al.*, 1977, 1982; Brahic *et al.*, 1981a).

Maedi has been characterized as a lymphoproliferative interstitial pneumonia. The alveolar septae contain numerous inflammatory cells, which in severe cases can form germinal centers. Likewise, neurological disease (visna) involves a predominantly mononuclear cell meningoencephalomyelitis with infiltration of cells around the vessels and formation of germinal centers in the choroid plexus (Sigurdsson *et al.*, 1962; Oliver *et al.*, 1981). Neurons are rarely destroyed. Astrocytic gliosis and demyelination are apparent.

The course of infection and the neuropathogenesis of visna virus have been studied experimentally in Icelandic sheep (reviewed by

Nathanson *et al.*, 1985). Intracerebral inoculation results in a persistent, cell-associated viremia, first detectable at 2 to 4 weeks postinfection (Petursson *et al.*, 1976). Virus is present in very few cells. Isolation of virus by cocultivation with sheep choroid plexus cells indicates that as few as 1 in 1 million cells, lymphocytes, and macrophages actively produces infectious virus (Petursson *et al.*, 1978; Narayan *et al.*, 1982). Cocultivation studies indicate that virus also persists throughout life in the lungs, lymphoid tissues, and CNS (Petursson *et al.*, 1976). The difficulty of virus isolation suggests that virus persists in the proviral state and that very little infectious virus is produced. Neutralizing serum antibodies first appear 2 to 3 months postinfection and persist for life (Petursson *et al.*, 1976). Oligoclonal, neutralizing antibody, predominantly IgM, is produced by plasma cells in the CSF (Georgsson *et al.*, 1977; Nathanson *et al.*, 1979; Martin *et al.*, 1982).

Within a few weeks of the experimental, intracerebral infection of Icelandic sheep, a subclinical meningoencephalomyelitis is apparent. This correlates in severity with that of a mononuclear cell pleocytosis, first detectable within months of infection (Nathanson *et al.*, 1979). The early lesion consists of infiltrating lymphocytes, monocytes, macrophages, and plasma cells, in which neuronal destruction, necrosis, and demyelination are rare (Georgsson *et al.*, 1976, 1977, 1982). There is a correlation between the infecting dose of virus, the CNS titer at times postinfection, and the severity of the early inflammatory response (Petursson *et al.*, 1976). Clinical signs, usually progressive paresis, first appear from 3 months to 8 years and may depend on the strain of the virus (Petursson *et al.*, 1978; Lutley *et al.*, 1983). Clinically affected animals have focal lesions of primary demyelination in the brain and spinal cord (Georgsson *et al.*, 1982). These vary in their degree of inflammation and gliosis and probably represent the difference between young and old lesions.

Unlike demyelinating virus infections of the rat and the mouse, it has not been possible in the sheep to separate the role of the virus and that of the immune response in the pathogenesis of the disease. However, Nathanson and co-workers (1976) were able to suppress the early, nondemyelinating inflammatory lesions using anti-thymocyte serum. This did not change the frequency of virus isolation, nor in the absence of T cell immunity was there any evidence of direct virus-induced destruction of CNS cells, indicating that the early inflammatory response probably confers no benefit, only damage. This finding suggests that demyelination does not result from direct destruction of oligodendrocytes; however, the immunosuppression experiments address only the early lesions, and the situation may change as the pathology progresses to include demyelination.

Infection of oligodendrocytes has been shown by *in situ* hybridization of a visna virus-specific probe to cells stained with anti-oligodendrocyte antibodies (Stowring *et al.*, 1985). The number of infected cells does not correlate with the extent of the demyelinated lesions, leading to speculation that infection of oligodendrocytes may induce and maintain an immune response to these cells (Nathanson *et al.*, 1985). Lymphocytes taken from sheep up to 2 years postinfection demonstrate normal responses to mitogens, but no response to myelin basic protein by proliferation assay (Panitch *et al.*, 1976). Neither do these sheep have antibodies to galactocerebroside. The composition of the inflammatory lesions in whole brain-induced EAE in the sheep is similar to that seen in visna, but the distribution of the lesions is different, and lymphocyte proliferation to MBP and antibodies to galactocerebroside are present (Panitch *et al.*, 1976). The mechanism of demyelination in visna remains to be determined but results to date are more suggestive of an immune-mediated mechanism than of direct virus destruction.

E. Canine Distemper Virus

Canine distemper and old dog encephalitis are natural, demyelinating diseases of dogs produced by the same virus (Imagawa *et al.*, 1980). Canine distemper virus is a member of the morbillivirus group of the Paramyxoviridae and as such is related to measles. Like visna virus in sheep, canine distemper has been studied experimentally. Animals can be infected intraperitoneally or intranasally. The course and outcome of infection are variable. Neurological signs may present within days to months, the time of onset appearing to correlate with age. Inflammatory and noninflammatory lesions of demyelination are observed and the type of lesion is probably related to the degree of virus-induced immunosuppression. Immunosuppression has been observed in some animals as a decrease in lymphocyte responses to mitogens (Krakowka *et al.*, 1980; Vandevelde *et al.*, 1982a; Cerruti-Sola *et al.*, 1983) and a severe lymphocytopenia is sometimes observed (McCullough *et al.*, 1974; Krakowka *et al.*, 1975, 1980). Nevertheless, some dogs are able to mount a rapid immune response, preventing widespread viral dissemination in the CNS. This results in no or small focal lesions of demyelination that may or may not be inflammatory; such animals quickly recover (Appel *et al.*, 1982; Cerruti-Sola *et al.*, 1983). Animals with persisting immunosuppression and chronic noninflammatory demyelination have also been observed (Cerruti-Sola *et al.*, 1983). Between these two extremes are animals with varying degrees of immu-

nosuppression; they may or may not develop early noninflammatory lesions of demyelination, but progress to lesions of inflammatory demyelination of varying severity (Krakowka *et al.*, 1980; Appel *et al.*, 1982; Cerruti-Sola *et al.*, 1983; Summers *et al.*, 1987). An important question has been the role of the immune response in these late inflammatory lesions. The outcome in such dogs ranges from viral clearance, recovery, and remyelination (McCullough *et al.*, 1974; Vandevelde *et al.*, 1985) to severe demyelination and white matter necrosis.

The early plaques of demyelination are focal, periventricular, often noninflammatory, and are suggestive of a direct effect on glial cells (Raine, 1976; Summers *et al.*, 1979; Vandevelde *et al.*, 1982b, 1983, 1985). Viral infection, viral inclusions, probably nucleocapsids, and the expression of all four four viral structural proteins (N, P, F, and H) have been observed in astrocytes, neurons, macrophages, meningeal, ependymal, and choroid plexus cells, as well as in invading lymphocytes (Wisniewski *et al.*, 1972; Mitchell *et al.*, 1991), but not, or rarely (Raine, 1976), in oligodendrocytes. Consistent with this finding is the infection of astrocytes but not oligodendrocytes in primary brain cell cultures (Zurbriggen *et al.*, 1986). However, destruction of both cell types occurred in these cultured explants, leading to the suggestion that destruction of oligodendrocytes in this disease is mediated by the release of toxic factors from other CNS cells (Zurbriggen *et al.*, 1986). Demyelination has been suggested to result from infection and perturbation of astrocyte functions, leading to edema and ballooning of myelin sheaths (Summers and Appel, 1987), and astrocyte hypertrophy early in disease has been described (Summers *et al.*, 1979; Summers and Appel, 1987).

In most animals progressing to chronic disease, and in some animals with subacute disease, the demyelinating lesions are inflammatory and invading mononuclear cells strip myelin lamellae from axons and phagocytose myelin debris (Wisniewski *et al.*, 1972). Disturbance of the blood–brain barrier and intrathecal antibody synthesis occur in dogs with inflammatory demyelinating lesions (Vandevelde *et al.*, 1986). Antibodies to virus and myelin are present in both serum and CSF (Krakowka *et al.*, 1973, 1975; Vandevelde *et al.*, 1982a, 1986). Bound antibody has been demonstrated in lesions of demyelination. Levels of MBP in the CSF correlate with the clinical and pathological course of the inflammatory disease (Summers *et al.*, 1987).

In addition to the humoral response, a cellular immune response to the virus occurs (Appel *et al.*, 1982) and in some experimentally infected dogs a cellular response to myelin antigens is also present (Cerruti-Sola *et al.*, 1983). Both the cellular and the humoral immune

responses to myelin occur in dogs with and without visible lesions of demyelination, leading to the suggestion that immune responses to myelin in this disease are epiphenomena (Cerruti-Sola *et al.*, 1983). A comparison of the neuropathology of canine distemper and canine EAE also led to the suggestion that autoimmunity to myelin is not an important component of this disease, because the distribution and composition of the lesions differ in these two conditions (Summers *et al.*, 1984).

F. Other Experimental Virus-Induced Demyelinations

A paramyxovirus also causes demyelinating disease in cats. A natural, subclinical, inflammatory, demyelinating disease has been observed in 7% of stray domestic cats examined in Perth, Australia (Cook, 1979; Cook and Wilcox, 1985). Focal lesions of demyelination of various size are present throughout the brain and optic nerves. Oligodendrocytes on the edge of lesions have vesiculation of the rough endoplasmic reticulum, and paramyxovirus-like nucleocapsids have been described within glial cells (Cook, 1979; Cook and Wilcox, 1985). The same inclusions were seen in indicator cells cocultivated with CNS tissue from cats with lesions of demyelination (Wilcox *et al.*, 1984). Such cultures became persistently infected with little cytopathic effect. Antibodies raised to the purified cytoplasmic inclusions stained similar inclusions in MS plaques (Cook *et al.*, 1986).

Herpes viruses are ubiquitous DNA viruses found in association with neural tissues throughout the vertebrate animals. The viruses are large and complex and have in excess of 70 genes, with a genome in excess of 150 kb (McGeoch *et al.*, 1988). Several of these viruses have been associated with demyelinating disease. Demyelination associated with herpes simplex virus type I (HSV-I) has been studied in both mice and rabbits (Townsend and Baringer, 1976; Kristensson and Wisniewski, 1978). Herpes simplex virus type II also produces demyelination in mice following direct intracerebral or genital infection, with lesions in the brain, spinal cord, and optic nerves (Martin, 1982; Martin and Stoner, 1984). Marek's disease of fowl is characterized by peripheral nerve demyelination following infection with a herpes virus (reviewed by Payne, 1982).

In mice, footpad, corneal, facial, or pinna infection with HSV-I results in focal demyelination of axons in the corresponding root entry zone in the CNS (Baringer and Swoveland, 1973; Townsend and Baringer, 1976, 1978; Kristensson *et al.*, 1978, 1979; Hill, 1983). The virus spreads intraaxonally without producing demyelination or any other damage in the transporting peripheral nerves (Cook and Stevens,

1973; Kristensson *et al.*, 1979). Schwann cells in the region of the ganglia, but not those within the nerve itself, can become infected but do not release mature virus (Rabin *et al.*, 1968; Cook and Stevens, 1973). However, in one report, replication and release of mature virions from Schwann cells and lesions of inflammatory demyelination were observed after direct microinjection of virus into the sciatic nerve (Townsend and Collins, 1986).

On reaching the CNS, HSV-I replicates in and destroys astrocytes in the root entry zone (Townsend, 1981; Itoyama *et al.*, 1991) and necrotic, hemorrhagic, inflammatory, demyelinating lesions are produced (Townsend and Baringer, 1976). Viral destruction of oligodendrocytes may occur (Kristensson *et al.*, 1979) and virus has been shown to replicate in these cells *in vitro* (Kastrukoff *et al.*, 1987). Schwann cell remyelination occurs in the demyelinated lesions on the CNS side of the root entry zone (Townsend, 1983). Virus can become latent within the trigeminal or dorsal root ganglion (Kristensson *et al.*, 1979; Stroop *et al.*, 1984).

Experimental infection of mice with temperature sensitive (ts) mutants of two rhabdoviruses, Chandipura virus and vesicular stomatitis virus (VSV), has been shown to produce CNS demyelination. The ts472 strain of Chandipura virus and the tsF41 and G32 strains of VSV produce extensive inflammatory demyelination in the spinal cords of infected mice (Dal Canto *et al.*, 1979). In both cases, no demyelinating lesions are present in *nu*/*nu* mice, although high brain virus titers, foci of necrosis, and extensive gray matter degeneration occur (Dal Canto *et al.*, 1979; Dal Canto and Rabinowitz, 1981b).

III. Human Demyelinating Diseases

A. Postinfectious Encephalomyelitis

The use of live attenuated measles virus vaccines has resulted in virtual elimination of this virus in the United States (reviewed by Hinman, 1982). However, measles remains a major health problem in many other countries. Encephalomyelitis is an important complication of measles, occurring in about 1 in 1000 cases (Johnson *et al.*, 1978). Neurological signs follow acute infection within days to weeks. This postinfectious encephalomyelitis is characterized by a perivenular mononuclear cell inflammation and demyelination. The neuropathology resembles that seen in EAE. Myelin basic protein levels in the CSF correlate with disease progression, and lymphocyte proliferation responses to MBP are present in some patients (Lisak *et al.*, 1974;

Johnson, 1982). The likely autoimmune nature of this disease is reinforced by the failure to detect measles virus, measles antigens, or measles antibody in the CNS (Johnson *et al.*, 1984; Gendelman *et al.*, 1984).

Postinfectious encephalitis with perivenular demyelination also occurs as a rare complication of vaccinia, varicella, and rubella infections (Spillane and Wells, 1964; Griffith *et al.*, 1970) and probably also occurred in smallpox (Marsden and Hurst, 1932). In contrast to the situation with measles virus, vaccinia and varicella have been recovered from brains and CSF (Angulo *et al.*, 1964; Brooks *et al.*, 1979; Peters *et al.*, 1978). Central nervous system demyelination has also been documented following mumps, influenza, and Epstein–Barr virus infections (Schwarz *et al.*, 1964; Hoult and Flewett, 1960).

B. Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is found worldwide and predominates in young males. It is a rare disease affecting perhaps 1 in 1 million children per year. There is no association with HLA type (Aysun *et al.*, 1983). The disease occurs years, sometimes many years, after acute measles encephalitis. The average age of onset is between 7 and 8 years, and the disease is fatal within months to years (Detels *et al.*, 1973). Pathologically the disease is characterized by a mild meningitis, perivascular cuffing, gliosis, and varying degrees of demyelination. Eosinophilic inclusion bodies are seen in several cell types but particularly oligodendrocytes, which contain measles nucleocapsids (Greenfield, 1950; Bouteille *et al.*, 1965). Measles virus antigens are detectable in both neurons and glia (Connolly *et al.*, 1967), and measles virus has been isolated from some biopsies by cocultivation with nonneural cells (Horta-Barbosa *et al.*, 1969; Payne *et al.*, 1969; Katz and Koprowski, 1973). Measles inclusion body encephalitis (MIBE), a clinically similar disease with a shorter incubation time, is associated with immunosuppression (Roos *et al.*, 1981). In SSPE but not MIBE there are high serum antibody titers to all the measles virus proteins except the matrix (M) protein and the CSF contains oligoclonal IgG and elevated titers to measles virus (Wechsler and Fields, 1978; Hall *et al.*, 1979; Dorries *et al.*, 1988). Measles virus antibody complexes have been detected on CNS cells, myelin, and in cerebral blood vessels, CSF, sera, renal glomeruli, and skeletal muscles (Dayan and Stokes, 1972; Jenis *et al.*, 1973; Perrin and Oldstone, 1977; O'Regan *et al.*, 1979; Sotrel *et al.*, 1983). Anti-viral antibody may modulate the immune response by removing viral antigens from the surface of infected CNS cells (Fujinami and Oldstone, 1979).

Persistence of measles virus in SSPE and MIBE is associated with defective viral gene expression. Infected cells do not express all viral proteins. The most common finding is absence of M protein expression (Hall and Choppin, 1981; Baczko *et al.*, 1984; Liebert *et al.*, 1986). Altered protein expression is associated with changes in levels of viral-specific transcripts within infected cells (Baczko *et al.*, 1988). In one study, sequencing of clones of measles virus genes from SSPE and MIBE brains demonstrated that mutations occurred in most genes with a frequency as high as 2% of all bases although the most dramatic changes were seen in the M gene (Cattaneo *et al.*, 1988, 1989).

Measles virus infection of the rat CNS has proved to be a good model system for elucidating the molecular changes that give rise to restricted viral gene expression. Restricted expression of viral genes has been demonstrated both in rat brains and in primary rat brain CNS cell cultures and is associated with polarized attenuation of transcription (Schneider-Schaulies *et al.*, 1989, 1990). Interestingly, passive transfer of anti-hemagglutinin antibodies to rats has been shown to modulate viral gene transcription within infected cells and convert the disease from acute to subacute encephalitis (Liebert *et al.*, 1990a). The mechanism of this action remains unknown but is of interest given the high levels of measles virus antibodies present in SSPE.

The mechanism of demyelination in SSPE remains unknown but given that there is restricted viral replication in oligodendrocytes and that T cell responses to measles are normal in SSPE, viral perturbation of oligodendrocyte cell function, cell destruction as a consequence of occasional productive bursts of complete virus replication, and T cell-mediated destruction of infected oligodendrocytes are all possibilities. In rats, measles virus infection can generate T cell responses to MBP (Liebert *et al.*, 1990b).

C. Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), first described in 1958, is a rare opportunistic human demyelinating disease associated with immunosuppression and lymphoproliferative diseases such as Hodgkin's lymphoma and chronic lymphocytic leukemia. The disease is found worldwide. Two related papovaviruses, JC and simian virus 40 (SV40), have been isolated from PML brains (Padgett *et al.*, 1971; Weiner *et al.*, 1972) although JC virus appears to be responsible for the majority of cases (Walker, 1978). Most populations have a high incidence of JC virus antibodies although this ubiquitous virus has not been associated with any other disease. In PML, high numbers of viral particles are present in the brain (Dorries *et al.*, 1979). Viral nucleic

acid has been detected in oligodendrocytes, astrocytes, and cerebral endothelial cells by *in situ* hybridization (Dorries *et al.*, 1979). Focal lesions of demyelination result from destruction of oligodendrocytes (Astrom *et al.*, 1958; Walker, 1978; Johnson, 1983). This appears to be a direct consequence of virus infection because abnormal astrocytes and oligodendrocytes around the periphery of lesions contain large inclusion bodies and are positive for viral nucleic acid (Dorries *et al.*, 1979; Shapshak *et al.*, 1986). It has not proved possible to study the disease experimentally. JC virus produces no disease in mice (Tooze, 1981), although the virus produces cerebral tumors in hamsters (Padgett *et al.*, 1977). However, dysmyelination was observed in mice transgenic for JC virus early region genes under the control of the viral promoter. This was associated with high levels of viral T antigen mRNA in the brain, raising the possibility that early viral gene products impair the function of oligodendrocytes such that they fail to produce myelin (Small *et al.*, 1986).

D. Acquired Immunodeficiency Syndrome

Approximately 10% of all AIDS patients present with a neurological disorder. Peripheral neuropathy has been noted in up to 20%, encephalopathy is clinically apparent in over 50%, and at autopsy in 75% of patients (Anders *et al.*, 1986; Parry, 1988; Dalakas *et al.*, 1988). Clinical symptoms and pathological findings are many and varied but include both peripheral and CNS demyelination (Lipkin *et al.*, 1985; Cornblath *et al.*, 1987; Hollander and Stringari, 1987). Human immunodeficiency virus has been isolated from peripheral nerves and demonstrated by electron microscopy in peripheral nerve axons (Ho *et al.*, 1985).

In the CNS, HIV is found predominantly within macrophages, microglial cells, and multinucleate giant cells, occasionally in endothelial cells and possibly, but rarely, in glial cells. Neuronal infection does not occur (Epstein *et al.*, 1984; Sharer *et al.*, 1985; Koenig *et al.*, 1986; Gray *et al.*, 1987; Wiley and Nelson, 1988; Kure *et al.*, 1990). Human immunodeficiency virus can be isolated from the cerebrospinal fluid (Ho *et al.*, 1985). Studies on the CSF have also demonstrated intrathecal oligoclonal immunoglobulin synthesis with antibodies to HIV gp41 and p24 (Ho *et al.*, 1985; Resnick *et al.*, 1985; Goudsmit *et al.*, 1987). In one study of AIDS patients (Wiley *et al.*, 1988), HIV was detected by immunocytochemistry with a monoclonal antibody to gp41 in 37 of 93 brains examined. Three brains also showed JC virus in oligodendrocytes by *in situ* hybridization. These brains had severe lesions

of demyelination and other changes characteristic of PML. Of the 93 brains examined, 31 were positive for cytomegalovirus (CMV) by immunocytochemistry; 22 of these were also positive for HIV. Coinfection of individual CNS cells by these two viruses has been demonstrated (Nelson *et al.*, 1988). Other opportunistic CNS infections seen in AIDS patients include herpes simplex, toxoplasmosis, and cryptococcosis. Onset of neurological symptoms in AIDS can occur at various times from the presenting symptom in otherwise asymptomatic infections to late in the disease (Snider *et al.*, 1983; Nielsen *et al.*, 1984; Navia *et al.*, 1986). At autopsy brains show a minimal inflammatory response that is predominantly perivascular and composed mostly of macrophages often infected with HIV. Multinucleate giant cells are characteristic and probably result from fusion of infected macrophages and microglia. Microglial nodules, which may be associated with CMV infection, are also present (Wiley and Nelson, 1989).

Central nervous system demyelination is not a consistent finding in AIDS patients, although vacuolation of white matter is a more common finding (Shaw *et al.*, 1985; Petito *et al.*, 1985). The amount of HIV detected in the CNS by nucleic acid probes or antibodies is not proportional to the neuropathology, leading to suggestions that the latter results from factors in addition to the direct effect of HIV. Immunological mechanisms, release of cytokines, and blood–brain barrier changes have been postulated to be involved in the pathogenesis (Wiley and Nelson, 1989; Robbins *et al.*, 1987). Human immunodeficiency virus infection of mononuclear cells results in their production of various cytokines, including interleukins 1, 6, and 8, TNF-α and β, and granulocyte–macrophage colony-stimulating factor (GM-CSF) (Merrill *et al.*, 1989; Nakajima *et al.*, 1989; Vyakarnam *et al.*, 1990). Interleukin1 and TNF-α have been demonstrated to damage and destroy oligodendrocytes and myelin in culture (Selmaj and Raine, 1988). The mechanism of demyelination is not at all clear at this time. JC virus is clearly present in a minority of cases and produces a typical PML disease with demyelination resulting from JC virus destruction of oligodendrocytes. It is possible that JC virus is present in a larger number of patients and is responsible for much of the demyelination seen in AIDS patients. Similarly, the glial nodules could result from CMV infection of the CNS following immunosuppression. Microglial nodules associated with CMV are seen in the CNS following other forms of immunosuppression (Wiley and Nelson, 1989). One possibility is that HIV-infected macrophages infiltrate the CNS in response to other infections such as JC, CMV, or HSV, and contribute little directly to the neuropathology (Wiley and Nelson, 1989).

E. Human T Cell Leukemia Virus Type I-Associated Demyelination

Another retrovirus that has been associated with human demyelinating disease is HTLV-I. This virus is asymptomatic in most infected individuals but is also the cause of adult T cell leukemia and the demyelinating disease HTLV-I-associated myelopathy (HAM), also known as tropical spastic paraparesis (TSP). These diseases are found in HTLV-I endemic areas, including Japan, the Caribbean, South America, and central Africa. For a review on this virus see Cann and Chen (1990). Lesions of inflammatory demyelination that include fiber loss have been observed in the spinal cord and optic nerves (Moore *et al.*, 1989). The close clinical resemblance of HAM and TSP to MS has led to a search for related retroviruses in this disease. In MS, HTLV-I and HIV sequences are absent both by *in situ* hybridization and PCR. Antibodies to HTLV-I envelope proteins are also absent (Epstein *et al.*, 1987; Hauser *et al.*, 1986; Ehrlich *et al.*, 1991).

F. Multiple Sclerosis

Much research into virus-induced demyelination of the CNS has been aimed at understanding the human demyelinating disease multiple sclerosis (MS), and many of the features observed in the experimental animal systems are seen in this disease. The epidemiology of MS is suggestive of an environmental factor, possibly a virus, and numerous viruses have been associated with this disease by serology, isolation, or pathological study of CNS tissue. Susceptibility is linked to the MHC, specifically the DR2 locus (Dupont *et al.*, 1977; Batchelor *et al.*, 1978). As with the virus models discussed above, MS is characterized by inflammatory lesions of CNS demyelination with no involvement of the peripheral nervous system. Antibodies and T cell responses to a number of viruses and to CNS antigens have been widely reported. No single virus has been consistently associated with this disease either by isolation or serology.

IV. Important Factors in Virus-Induced Demyelination

A. The Importance of Virus and Host Genetics

The above descriptions of experimental animal systems of virus-induced CNS demyelination indicate the important determinants of disease, which include factors controlled by the genetics of the virus, the genetics of the host, and the environment. The strain of the virus,

the route and dose of exposure, and interaction with numerous host genes are all important and we will consider each in turn.

The importance of the virus genetics in determining the outcome of CNS disease is well illustrated by attenuated vaccine viruses such as that for polio, which produces a subclinical infection rather than the paralysis associated with natural infection. Sequencing of the entire genome of poliovirus type 3 has demonstrated that change of a single nucleotide from cytosine to uracil in the 5′ noncoding region abolishes the ability of this virus to replicate in mouse brain and renders the infection avirulent (La Monica *et al.*, 1987). Similarly, single nucleotide changes affecting neuropathogenesis have been reported for the CVS strain of rabies virus, reovirus type 3, and the SA AR86 strain of Sindbis virus (Seif *et al.*, 1985; Bassel-Duby *et al.*, 1986; Russell *et al.*, 1989).

The genetic differences between demyelinating and nondemyelinating, often virulent, strains of the animal model viruses discussed above are not completely clear in any case. The best understood is Theiler's virus, where the availability of infectious clones of the different strains and the ability to engineer recombinants with this small positive-sense genome has allowed mapping of some of the determinants of neurovirulence, although even in this system some debate remains (Calenoff *et al.*, 1990; Fu *et al.*, 1990; Brahic *et al.*, 1991; Lipton *et al.*, 1991). Mouse hepatitis virus variants have been mostly selected by their resistance to neutralization with monoclonal antibodies. Given this selection pressure, it is likely that genetic changes between variant and parental virus are to be found within the envelope glycoproteins. The coronaviruses have two glycoprotein spikes, HE and S, encoded by genes 2 and 3, respectively. Direct RNA sequencing of the S gene in MHV-4 and its V5A13.1 variant have determined that the variant has a deletion, relative to the parental virus, of 142 amino acids in the S1 molecule (Parker *et al.*, 1989). While it is likely that this change in gene 3 influences the outcome of infection from rapidly lethal encephalitis to subacute demyelination, the effect of other changes in this large (> 32 kb) and highly changeable genome cannot be ruled out. To date infectious clones of this long genome are not available for sophisticated genetic studies. Analysis of the genetic basis of the difference in neurovirulence between strains of SFV is impeded by the lack of sequence data and infectious clones of the most studied virulent (L10) and avirulent, demyelinating [A7(74)] strains. Unfortunately, the pathogenesis of the sequenced prototype strain has been little studied.

Sequencing studies of cloned measles virus transcripts isolated from two patients with SSPE demonstrated change of 2% of the nucleotides

in the structural genes (M, F, and HN), relative to the reference Edmonston strain (Cattaneo *et al.*, 1988). Variation between clones derived from the same brain was 0.16% of the nucleotides. Changes found during persistent measles virus infections include altered ratios of viral transcripts, changes in the reading frame of the fusion gene, sequence deletions, decreased expression of hemagglutinin, fusion, and matrix proteins, and absence of matrix protein (Lin and Thormar, 1980; Hall and Choppin, 1981; Norrby *et al.*, 1985; Liebert *et al.*, 1986; Cattaneo *et al.*, 1987, 1988). It is not clear which, if any, of these phenomena are responsible for changing the pathogenesis of measles infection from a systemic to a CNS infection, or indeed if they are the cause or the consequence of measles virus persistence in the CNS during SSPE. It is likely that most reflect changes that are permissible in the measles virus genome during persistent CNS infection.

RNA genomes undergo rapid change (reviewed by Holland *et al.*, 1982; Smith and Inglis, 1987). The frequency of mutations in RNA genomes is estimated to be on the order of 10^{-3} to 10^{-4} changes per base. Given that the titer of virus in an infected brain can exceed 10^8 pfu, a single brain could contain on the order of 10^4 different genotypes, and for a genome of 11 kb (e.g., alphavirus), genotypes with base changes at every possible site would likely be present. The possibility must be considered that variants with a demyelinating phenotype arise and are selected *in vivo*, and in this way many common viruses can occasionally produce neurological, including demyelinating, disease. The isolation from the brains of rats with demyelinating disease of variants of mouse hepatitis virus with changes in gene 3, relative to the inoculum virus, may be an example of *in vivo* selection of virus with an altered demyelinating phenotype (Morris *et al.*, 1989). *In vivo* generation of variant viruses has also been observed with LCMV, visna, and HIV (Ahmed and Oldstone, 1988; Clements *et al.*, 1988; Hahn *et al.*, 1986). Clearly, demyelination, as with any other viral-associated pathology, is determined by the viral genotype and changes as small as one nucleotide could result in a demyelinating disease as opposed to systemic or acute lethal CNS disease. The possibility that occasional viruses with a demyelinating phenotype are selected from a population of *in vivo*-generated genotypic variants derived from a nondemyelinating phenotype must be considered.

The phenotype of a virus that results in demyelinating disease is complex. Important properties are likely to include an ability to replicate extraneurally, spread to the CNS, attach to, enter, and replicate in CNS cells, and destroy or perturb the functioning of these cells. Interaction with the immune response will also be of much importance. Change at any stage of any of these processes as a result either

of a change in viral genotype (variant selection, as discussed above) or change in the host could result in demyelination by a virus otherwise unassociated with this pathology.

The virus must first gain access to the host and initiate an infection. This stage will depend on the dose of the virus and the mechanism of exposure. Epidemics of demyelinating disease are well known. Visna virus produces epidemics in Icelandic sheep, and these have been related to the confined, close housing of animals and the spread of aerosol virus in respiratory exudates (Gudnadottir, 1974; Narayan and Cork, 1985). Marek's disease herpes virus, a demyelinating virus of fowl, can decimate poultry farms (Purchase, 1975). Chickens become persistently infected and release virus from the feather-follicle epithelium, in feces, and in respiratory exudates (reviewed by Payne, 1982). Epidemics of human demyelinating disease are also known and include the well-known outbreaks of multiple sclerosis, a disease of possible viral etiology, in the Faroe Islands after British troops were stationed there during the Second World War (Kurtzke and Hyllested, 1979), and in Key West, Florida (Sheremata *et al.*, 1985). Many cases of HAM/TSP have been described in Japan and the Caribbean and are associated with HTLV-I infection (Gessain *et al.*, 1985; Osame *et al.*, 1986). More recently, demyelination has been reported in association with the AIDS epidemic.

Throughout the process of initiation of infection, spread to the CNS, and infection of CNS cells the genetics of the host are important. Host genetic determinants of infection include the presence of appropriate cell surface receptors, and many factors present in the internal cellular environment necessary for all the stages of viral replication, assembly, and release and the immune response. Important internal cellular factors could include endosomal fusion mechanisms, intracellular pH gradients, host transcriptional factors required by the viral polymerase, and protein translation, translocation, and processing factors. These may all vary from cell to cell and in given cell types with differentiation and activation states.

Progress is being made in elucidating receptors for viruses associated with demyelinating disease. Mouse hepatitis virus binds to a 110-kDa carcinoembryonic antigen, glycoprotein (Boyle *et al.*, 1987; Dveksler *et al.*, 1991). The resistance of adult SJL mice to infection may represent a polymorphic difference between mouse strains at the site of virus binding. The receptor for HIV, CD4, is well known and the receptor for the closely related visna virus appears to be the sheep MHC class II molecule (Dalgleish *et al.*, 1984; Maddon *et al.*, 1986; Dalziel *et al.*, 1991). Semliki Forest virus has been reported to bind to class I MHC molecules (Helenius *et al.*, 1978). Theiler's virus binds to a

34-kDa membrane-associated glycoprotein (Kilpatrick and Lipton, 1991).

The genetic control of the immune response is complex but includes among others the genes of the MHC and those encoding antibody and T cell receptor specificities. The susceptibility of the rat to MHV and the mouse to Theiler's virus-induced demyelinating disease has been linked to the induction of MHC molecules on astrocytes (Massa *et al.*, 1987a; Rodriguez *et al.*, 1987a). In Theiler's virus infection, SJL mice are susceptible and C57Bl/6 mice resistant and this differential susceptibility has been mapped to the *H2D* locus (Lipton and Melvold, 1984; Clatch *et al.*, 1985; Rodriguez *et al.*, 1986).

Once an infection has been initiated, in order to produce a CNS demyelinating disease the virus must usually gain access to the CNS and infect CNS cells. This was discussed in Section I and can occur by a variety of routes. Once in the CNS many viruses associated with demyelinating disease infect neurons. Strains of Theiler's, MHV, SFV, and canine distemper virus have all been reported to infect and destroy neurons. In the mouse and rabbit models, herpes simplex virus also infects neurons, although mostly those of the peripheral nerves and without producing damage. Neuronal infection by visna and HIV is rare. In adult mice, the FA and GDVII strains of Theiler's virus, high doses of MHV-4 or A59, and the L10 strain of SFV all infect and destroy CNS neurons, leading to rapid death of the animal. The brain-derived WW, TO, and DA strains of Theiler's virus also infect and destroy CNS neurons, leading to an acute paralytic disease and death of some animals. Most mice survive and develop a chronic demyelinating disease. Similarly, some mice given low doses of MHV-4 or A59 survive to develop demyelinating disease. The V5A13.1 variant of MHV infects and destroys neurons but spreads at a slower rate than the parental virus, allowing intervention of the immune response and limitation of the infection before it reaches a lethal distribution (Fazakerley *et al.*, 1992). The mice survive and progress to a subacute demyelinating disease. The A7(74) strain of SFV, like the L10 strain, infects neurons, but unlike the L10 strain does not destroy them (Pathak and Webb, 1978). The infection is unproductive, and again the mice survive to develop a subacute demyelinating disease. Thus the extent of neuronal destruction and the interplay of the rate of viral spread and its control by the immune response are important in determining the early outcome of all these infections, with surviving animals in each case progressing to demyelinating disease.

Tissue culture passage of the avirulent TO-like strains of Theiler's virus (Lipton, 1978) results in strains that no longer produce the acute neuronal phase of the disease, but still give rise to the second phase of

chronic demyelination (Lipton and Dal Canto, 1979b). These viruses infect glial cells but not neurons (Stroop *et al.*, 1982). Similarly, MHV-4 predominantly infects neurons, while its ts8 mutant infects predominantly glial cells (Dubois-Dalcq *et al.*, 1981; Knobler *et al.*, 1982). A similar relationship is seen between MHV-DL and its variant 2.2/7.2-V-2 (Fleming *et al.*, 1987), and between the L10 strain of SFV and its M136 and M9 mutants (Atkins and Sheahan, 1982). The genetic differences involved in these changes of tropism are as yet unknown. In the case of the brain-passaged, avirulent strains of Theiler's virus, the V5A13.1 variant of MHV, and the A7(74) strain of SFV, which produce acute neuronal infection followed by demyelination, it is not clear whether these viruses initially infect both neuronal and glial cells, or if glial cell infection is dependent on *in vivo* generation and selection within the CNS of appropriate gliotropic variants.

B. Mechanisms of Demyelination

Possible explanations for viral-induced demyelinating disease include, (1) direct viral destruction of oligodendrocytes, (2) direct viral lysis of persistently infected oligodendrocytes or their precursor cells in response to cell activation or differentiation, (3) infection of oligodendrocytes and immune-mediated destruction of these cells by an antiviral immune response, (4) immune-mediated destruction of oligodendrocytes as a result of virus-induced autoimmune responses, (5) destruction of oligodendrocytes by the release of toxic factors from surrounding cells as a result of an antiviral or autoimmune response, and (6) an autoimmune response resulting from a perturbation of immunological tolerance and independent of viral infection of the CNS.

An example of the first mechanism is JC papovavirus, which infects and directly destroys oligodendrocytes, leading to PML. Here the immune response is normally protective as this disease is seen only in association with immunosuppression (Walker, 1978; Johnson, 1983; Dorries *et al.*, 1979, 1984; Aksamit *et al.*, 1985).

Experimental immunosuppression, depletion of lymphocyte subpopulations, and infection of athymic *nu/nu* mice have demonstrated that the demyelination induced by the A7(74) strain of SFV is immune mediated, and that induced by the TO-like strain of Theiler's virus is at least in part immune mediated (Lipton and Dal Canto, 1977; Jagelman *et al.*, 1978; Roos *et al.*, 1982; Fazakerley *et al.*, 1983; Fazakerley and Webb, 1987b; Rodriguez and Quddus, 1986; Welsh *et al.*, 1987). The A7(74) strain of SFV rarely infects oligodendrocytes during the acute infection but by immunocytochemistry viral antigens can be detected weeks after infection in occasional astrocytes and oligodendrocytes

(Khalili-Shirazi *et al.*, 1988). By electron microscopy, immunocytochemistry, and *in situ* hybridization, it has been well established that strains of Theiler's virus can infect and persist in oligodendrocytes (Brahic *et al.*, 1981b; Stroop *et al.*, 1981, 1982; Rodriguez *et al.*, 1983; Rodriguez, 1985; Aubert *et al.*, 1987). The presence of virus in oligodendrocytes in these two systems where demyelination is immune mediated would be consistent with demyelination as a result of immune destruction of virally infected oligodendrocytes. It is also likely that demyelination in the late inflammatory lesions of canine distemper is immune mediated (Appel and Gillespie, 1972; Krakowka *et al.*, 1973, 1975; Appel *et al.*, 1982). Early lesions in this disease, often noninflammatory, probably result from direct viral effects on glial cells and may result from oligodendrocyte destruction by toxic factors released from infected astrocytes (Zurbriggen *et al.*, 1986). In distemper, infected oligodendrocytes are never or rarely observed by electron microscopy (Wisniewski *et al.*, 1972; Raine, 1976; Summers *et al.*, 1987). Oligodendrocytes are clearly infected by visna virus (Stowring *et al.*, 1985); however, the numbers are few relative to the extent of the demyelination, and it has been suggested that immune responses may be involved in the demyelination (Nathanson *et al.*, 1985). The early, nondemyelinating encephalitis can be suppressed with anti-thymocyte serum (Nathanson *et al.*, 1976), but the role of the immune response in the later demyelinating lesions remains unclear.

In SFV, MHV-JHM, and Theiler's virus, demyelination has been shown to, or in the case of visna is likely to, involve the immune response and the virus has been demonstrated to infect oligodendrocytes. At first sight, it would appear that an immune response to viral antigens would suffice to destroy these virally infected cells and produce lesions of demyelination. However, there are several details that must not be overlooked. First, the infected oligodendrocytes would have to produce viral proteins, and for cytotoxic T lymphocyte-mediated destruction, peptides of these proteins would have to be presented on the cell surface in association with MHC molecules. Second, the host would require appropriate B and T cell specificities to recognize the viral protein or viral peptide–MHC complex. The situation may be complex.

As regards the expression of viral proteins during a persistent infection, this may be selective or blocked. For example, the visna virus genome can be detected by *in situ* hybridization in choroid plexus cells but viral protein expression is rarely observed, and it has been suggested that protein production is blocked in these cells at the level of transcription (Haase *et al.*, 1977, 1982). In the case of LCMV, cells acutely infected *in vivo* express both viral glycoprotein and nucleopro-

tein. In contrast, in the persistent infection, glycoprotein expression is significantly reduced and may be undetectable, whereas nucleoprotein expression remains high (Oldstone and Buchmeier, 1982). Expression of the hemagglutinin protein of the MBS strain of measles virus is selectively inhibited during persistence in adult hamster neurons (Swoveland and Johnson, 1989). A similar finding has been observed in the neurons of rats persistently infected with the CAM/R40 strain of measles virus (Schneider-Schaulies *et al.*, 1989). In these cases, selective expression of viral proteins is associated with reduced virus production and this is linked to the differentiation state of the host cell. Neonatal or suckling animals infected with the MBS or CAM/R strains of measles virus described above succumb to a rapidly fatal encephalitis, in which all viral proteins and mature virions are produced in neurons (Johnson and Byington, 1971; Liebert and ter Meulen, 1987). Cultured neuroblastoma cells can be productively infected with measles virus in their undifferentiated state, but virus production is significantly reduced on induction of differentiation (Miller and Carrigan, 1982). Similarly, the A7(74) strain of SFV infects and destroys neurons in neonatal and suckling mouse brain but produces nonproductive infection in adult mouse neurons (Pathak *et al.*, 1976; Pathak and Webb, 1988). The same phenomenon may occur when this virus infects oligodendrocytes.

Oligodendrocytes are more difficult to study *in vivo* than neurons, but a study of the JHM strain of MHV in rats suggests that virus interaction with oligodendrocytes may also depend on differentiation state. JHM virus infection of primary brain cell cultures appears to be confined to a discrete intermediate stage in oligodendrocyte differentiation between the O2A precursor cells and fully differentiated oligodendrocytes, both of which are resistant to infection (Wilson *et al.*, 1986; Pasick and Dales, 1991). In the case of Theiler's virus, persistently infected cells in the white matter of the spinal cord (probably oligodendrocytes) have been shown by *in situ* hybridization to contain low copy numbers of viral RNA. By immunoperoxidase staining no viral capsid production can be detected in these cells (Cash *et al.*, 1985). It would appear that RNA viruses can persist in CNS cells without expressing all their viral proteins, that is, neurons can restrict the replication of some RNA viruses. The molecular events involved remain to be elucidated.

A second feature necessary for viral-specific T cell destruction of virally infected cells is expression of MHC molecules. In mice persistently infected with LCMV, MHC class I molecules are not expressed on neurons (Mucke and Oldstone, 1992). This may be the case for other neuronal infections. In the course of persistent LCMV infec-

tion, neuronal infection may be transient and cyclical, that is, at any given time different neurons may be infected. In this scenario of persistent LCMV infection, individual neurons would first be infected from a productive, perhaps extraneural source, and then as a result of restriction of replication within the neuron, few or no mature virions would be produced, the cell would survive the infection, and any accumulated viral genetic material would be degraded (Fazakerley *et al.*, 1991). This and the failure of these cells to express MHC molecules and thus avoid direct cytotoxic T lymphocyte (CTL) lysis would explain why following transfer of LCMV-specific CTLs to persistently infected mice (Oldstone *et al.*, 1986) virus is rapidly cleared from most tissues, but only slowly from the CNS.

As discussed in Section I, uninfected oligodendrocytes do not express MHC molecules. *In vitro*, MHC class I, but not class II, expression can be induced by interferon γ or by soluble factors released from astrocytes (Suzumura *et al.*, 1986, 1988; Calder *et al.*, 1988). The expression of MHC molecules by infected oligodendrocytes *in vivo* remains unclear. A situation similar to that described for LCMV in the neuron may exist. Failure of MHC class I expression could allow viral genetic material to persist. Occasionally, on activation or differentiation, cells could become MHC positive, resulting in immune-mediated destruction. Alternatively, change in activation or differentiation could result in complete virus replication and cell destruction.

Even if MHC expression occurs on infected CNS cells and some viral proteins are produced, responses may be limited by the availability of a T cell epitope. Cytotoxic T lymphocytes may respond to only one or two epitopes on a glycoprotein and these differ according to the MHC type. It has been estimated that for a single MHC molecule there is an average of only one CTL epitope per 1500 amino acids of virus protein (Whitton and Oldstone, 1989). For example, mice of the $H2^b$ haplotype produce a CTL response to the glycoprotein of lymphocytic choriomeningitis virus, but no T cell epitopes are recognized on this molecule by $H2^d$ mice (Whitton *et al.*, 1988). Selective protein expression in persistently infected cells may therefore significantly decrease the chances of a CTL immune response to these cells. Although apparently straightforward because both antibody and T cell reactivity to viral antigens have been demonstrated in experimental and human demyelinating diseases, viral-specific, MHC-restricted, immune-mediated destruction of virally infected oligodendrocytes remains to be proved as a mechanism of demyelination.

There is no *a priori* reason to invoke autoimmune mechanisms of demyelination in viral-associated demyelinating disease. Nevertheless, autoreactivity has now been widely observed. Antibody and T cell

responses to myelin antigens have been reported for rats infected with MHV or measles virus, mice infected with Theiler's virus or SFV, dogs infected with canine distemper, and cases of human measles encephalomyelitis (Krakowka *et al.*, 1973; Vandevelde *et al.*, 1982a; Cerruti-Sola *et al.*, 1983; Watanabe *et al.*, 1983; Johnson *et al.*, 1984; Rauch *et al.*, 1987; Welsh *et al.*, 1987; Mokhtarian and Swoveland, 1987; Liebert *et al.*, 1988). The level of these responses sometimes correlates with the extent of the demyelinating disease, as observed for myelin antibody titers in some dogs with distemper (Krakowka *et al.*, 1973; Cerruti-Sola *et al.*, 1983) and in some mice infected with Theiler's (DA) virus (Rauch *et al.*, 1987). In other cases no correlation is apparent, because high titers of anti-myelin antibody are also observed in dogs with distemper that have no lesions of demyelination (Cerruti-Sola *et al.*, 1983), and SJL mice infected with Theiler's virus can develop lesions of demyelination in the absence of immune responses to MBP or PLP (Miller *et al.*, 1990).

It is not yet clear whether CNS autoimmune responses in viral-associated demyelinating disease are important in the pathogenesis or are epiphenomena. The transfer of inflammatory CNS disease to uninfected animals with immune cells, as has been reported with MBP-specific T cells from JHM-infected Lewis rats to naive uninfected rats (Watanabe *et al.*, 1983), must be interpreted with caution because it is not clear that the recipients developed lesions of demyelination. Central nervous system perivenular inflammation as a result of the transfer of MBP-specific T cells is to be expected. The subacute demyelinating disease seen in Lewis rats infected with this virus is likely to result from a more complex pathogenesis. The role of immune responses to viral antigens, antibody to autoantigens, and their synergistic effects with this MBP-specific T cell response must be considered.

Transfer of MBP-specific T cells to naive rats usually results in an inflammatory CNS disease with minimal demyelination. Lesions of demyelination can be significantly increased by the additional transfer of anti-oligodendrocyte antibody (Linington *et al.*, 1988). As discussed in Section I, anti-oligodendrocyte antibodies, and particularly those to the glycolipid galactocerebroside, have been previously determined to produce demyelination. In this context it has been proposed that glycolipid in the envelope of viruses budding from oligodendrocytes may be immunogenic and initiate immune responses to glycolipids such as galactocerebroside (Webb and Fazakerley, 1984). Demyelination could depend on both generation of T cell-mediated inflammatory reactions, to either viral or CNS antigens and production, perhaps locally by plasma cells recruited into these lesions, of anti-oligodendrocyte antibodies.

Autoreactivity to CNS antigens could result from a breaking of tolerance in response to the release of large amount of CNS antigens (e.g., MBP) during the acute, highly destructive phase of many of these CNS diseases. The levels of MBP in the cerebrospinal fluid of dogs with distemper is related to the severity of the disease (Summers *et al.*, 1987).

Another mechanism for the viral induction of autoimmune responses is cross-reactivity between viral and host cell proteins, termed molecular mimicry (Notkins *et al.*, 1984; Oldstone, 1987). The polymerase protein of hepatitis B virus contains a motif of six amino acids also found in the rabbit encephalitogenic site of MBP. A peptide containing these six amino acids and the flanking amino acids in the hepatitis B sequence when inoculated into rabbits produces CNS inflammation, and antibody and T cell responses that cross-react with MBP (Fujinami and Oldstone, 1985). However, this appears to be of little relevance, because with the exception of a case of peripheral neuropathy involving demyelination (Tsukada *et al.*, 1987) in which cross-reactivity to CNS MBP is not relevant, hepatitis B virus infection has not been associated with lesions of demyelination. Sequence similarities of various lengths and numbers of identical residues have now been reported for CNS antigens and many viruses (Jahnke *et al.*, 1985; Shaw *et al.*, 1986). At present, the significance of these to CNS disease remains uncertain.

Much of the impetus for studying virus-associated demyelination has derived from the view that MS is likely to have an infectious etiology. Demyelination in this disease could occur by any of the mechanisms observed in the experimental animal models following infection by an as yet unidentified virus. Perhaps more likely is that demyelination in MS can be initiated by infection with one of several viruses, possibly even acting by different mechanisms to produce lesions of CNS demyelination. After all, MHV, SFV, and Theiler's virus all produce inflammatory, demyelinating lesions in the mouse CNS that are histopathologically difficult to tell apart.

Whatever the mechanism of demyelination in MS, little or no significant remyelination occurs. This is in contrast to the situation in many of the animal models in which extensive remyelination is often observed. Understanding the molecular events that control remyelination should be a major component of future research in virus-induced demyelinating disease.

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