Slow and Persistent Virus Infections of Neurones – A Compromise for Neuronal Survival

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1 Introduction

Infections of the central nervous system (CNS) with intracellular pathogens are different in many respects from infections in other parts of the body due to both the anatomical and functional properties of the brain and the biological basis of immune surveillance in the CNS. Damage to brain cells might have severe consequences for the entire body and, in many instances, would conceivably interfere with vital functions. The CNS is particularly vulnerable to pathological stimuli since it consists of highly differentiated cell populations with complex functionally integrated cell-to-cell connections and specialised cytoplasmic membranes. Furthermore, CNS tissue is unique in its high metabolic rate and relative lack of capacity to regenerate. While persistent infection by a non-cytopathogenic virus in cells of an organ with a low-energy requirement and a high rate of regeneration may be tolerated, in CNS tissue such infections may interfere with normal function, especially when neurones are affected (Johnson 1982). From this point of view, the paucity of lymphatic drainage and the lack of constitutive expression of immune-regulatory molecules, e.g. MHC class II and even class I, make sense. Fortunately, the participation of the CNS in a viral infection is relatively uncommon, but it may

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develop as a complication of many systemic viral infections. The special situation in CNS with its quasi-syncytium favours persistent infection without immediate destruction of the infected target cells. In the long run, however, functional deficits, progressive disease and eventually death of the individual ensue. The invasion of the brain by viruses does not result per se from a pathogen's specific tropism for neural tissue, since neurotropic viruses usually cause infections without involvement of this organ. Several viruses, such as herpes simplex (HSV) or mumps virus, usually result in rather mild illnesses that may become severe only when the CNS is infected, while other viruses, e.g. certain enteroviruses, lead to symptoms of disease only when the brain or the spinal cord is invaded. Many neurotropic viruses more readily invade the CNS of the young. The reasons for this are obvious: (a) immaturity of the immune response, (b) reduced capacity to produce interferon, (c) dependence of susceptibility to viral infection on the level of cell differentiation, and (d) age-specific distribution of receptor proteins. Thus the viral biology plays an important part in the establishment of CNS infections. However, it is not only the direct virus–host relationship that may affect brain function and integrity; in many instances the resulting damage is caused by the immune system rather than by the virus itself. Considering these general points, viral infections of the CNS represent a competitive process in which properties of the infecting virus and those of the host, i.e. cellular and immunological factors, interact simultaneously.

In cases of acute lytic virus infections of the CNS, a rapid and efficient elimination of the pathogenic agent is necessary because nerve cells lack the capacity for regeneration, and loss of the highly specialised neurones may rapidly reach the threshold beyond which survival of the individual is endangered. On the other hand, the chances for viruses to persist and at least temporarily escape immune surveillance are facilitated. In the long run, however, persistent infections of the CNS lead to cell death, disturbed brain cell function, immunopathological disease and, if vital structures of the brain are involved, to the death of the individual.

2 Virus–Cell Interactions in the CNS

Although the CNS complications are usually self-limiting, in rare instances they may be severe and even life threatening. Viral infections of the CNS are not the result of a direct viral tropism for neural tissue, since in most cases the CNS is not the primary site of viral replication. After multiplication in the periphery and the ensuing viraemia, viral particles reach the CNS by various pathways. The major route is via the bloodstream (Johnson 1982). The blood–brain barrier formed by endothelial cells of the cerebral capillaries, astrocyte foot-processes and the basal lamina usually prevents viral particles from entering the CNS directly. In contrast, the brain is relatively easily accessible to activated lymphocytes and macrophages, which, if infected, may serve as vehicles carrying viruses across the barrier. This transport mechanism for viruses, also referred to as the 'Trojan horse' mechanism,

is responsible for CNS infections with several viruses such as paramyxoviruses (APPEL et al. 1978; FOURNIER et al. 1985; WOLINSKY et al. 1976) and lentiviruses (HAASE 1986; NARAYAN and CLEMENTS 1989). Other viruses invade the CNS by direct infection of endothelial cells, a mechanism proposed for poliovirus (BLINZINGER et al. 1969), Sindbis virus (JOHNSON 1965), Semliki Forest virus (PATHAK and WEBB 1974) and murine retroviruses (SWARZ et al. 1981). Other viruses, e.g. mumps or eastern and western equine encephalitis virus, invade the CNS by direct infection of the stroma of the choroid plexus, or by passive transport into the cerebrospinal fluid, where ependymal cells of the ventricle walls provide the basis for further spread in the CNS (HERNDON et al. 1974; LIU et al. 1970).

The second major pathway of CNS infection involves infection of neurones at nerve endings in the periphery and subsequent retrograde axonal transport into the CNS. Particularly rabies virus (MURPHY and BAUER 1974; IWASAKI et al. 1985) has been shown to use the neural route of CNS invasion. In the case of herpes simplex virus (HSV) infection of human beings, the primary site of replication is the epithelial cells of the skin or mucosa before the virus enters the peripheral ganglia (MARTIN and DOLIVO 1983). Viruses remain hidden from the immune system during the entry process into the CNS via direct cellular connections until the CNS infection is established. It has been demonstrated that axonal transport of herpes and rabies viruses occurs also in tissue culture of primary neurones and can be specifically inhibited in vitro and in vivo (LYCKE et al. 1984; LYCKE and TSIANG 1987; KRISTENSSON et al. 1986).

The interaction of infectious viruses and susceptible cells leads in general to cell destruction, persistent infection or cell transformation. This is largely determined by the genetic constitution of the host and by the type of viral agent. After an infectious virus has reached the CNS, symptoms of disease develop only if sufficient numbers of susceptible cells are infected to cause brain dysfunction and virus spread within the CNS is accomplished.

2.1 Acute Infections

Acute cytolytic infections inevitably lead to the death of individual cells and the release of progeny virus. Cell destruction is induced by the products of the viral genome or their effect on the regulatory mechanism of the cell. For several viruses the molecular events taking place during a lytic infection have been thoroughly described in tissue culture systems, and it is assumed that similar processes occur in CNS infections. A classical example of destructive infection of CNS tissue is poliomyelitis, an Enterovirus that exists in three serotypes (MELNICK 1996). The portal of entry for poliovirus is the alimentary tract, as experimental studies in monkeys have shown. The virus replicates initially in tonsils, neck lymph nodes, and Peyer's patches of the small intestine. Viraemia subsequently develops, which can lead to infection of the spinal cord or brain. Alternatively, poliovirus may spread along the axons of peripheral nerves to the CNS, as has been demonstrated in experimental infection (LA MONICA et al. 1987; MELNICK 1996). Once poliovirus

has entered the CNS, neuronal damage and destruction ensues as the consequence of intracellular replication, particularly of anterior horn cells of the spinal cord. Poliovirus contains a genome of single-stranded, positive-sense RNA that closely resembles a cellular messenger RNA in structure and function (KITAMURA et al. 1981; SABIN and BOULGER 1973; TOYODA et al. 1984; HOGLE et al. 1985). The initial step of poliovirus replication is its binding to a specific cellular receptor, a typical transmembrane protein of the immunoglobulin superfamily (MENDELSOHN et al. 1989). Receptor mRNA can be detected in many tissues that do not bind poliovirus or support its replication. Since several alternatively spliced mRNAs of the receptor exist, it is conceivable that not all of them direct the translation of fully functional poliovirus receptors (KOIKE et al. 1990; MENDELSOHN et al. 1989). In addition, another surface molecule of human cells, CD44, is functionally associated with the susceptibility of cells for poliovirus, although poliovirus does not bind directly to CD44 (SHEPLEY et al. 1994).

In order to understand the neurovirulence of poliovirus, nucleotide sequencing and gene cloning were carried out to identify the genetic differences between wild-type virulent strains of poliovirus and the life-attenuated strains used as vaccines (ALMOND 1991). Significant changes were observed in the 5′ nontranslated region (NTR) at positions 480, 481 and 472 in poliovirus types 1, 2 and 3, respectively. These mutations were linked to the ability of the virus to replicate in mouse brain or in neuroblastoma cells in culture (LA MONICA et al. 1987). Detailed investigation of the structure and function of the mutated NTR region revealed that attenuating mutations in the vaccine strains act through the disruption of a stem structure in the region of positions 470–540. Computer-generated analysis suggested that the greater the disruption of the stem, the greater the temperature sensitivity and the extent of attenuation. The intracellular functions of these mutations have not yet been identified completely, but the data available suggest that the 5′ NTR interact with cellular factors influencing the tropism of the virus. Understanding the intracellular events may eventually provide an explanation as to why motor neurones are the specific target. The tissue tropism, neurovirulence and species specificity of the poliovirus infection are being studied in a transgenic mouse model (HORIE et al. 1994; REN et al. 1990). The control of polio infection depends on the humoral immune system. Although many details of the virus–cell interaction in this disease are well understood, the host factors that in the majority of cases prevent poliovirus from entering the CNS and infecting the neural tissue are still unknown.

2.2 Persistent Infections of the Nervous System

A variety of virus–cell and virus–host interactions may lead to chronic or persistent virus infections of the CNS. Firstly, latent viral infections are characterised by intermittent episodes of viral replication and formation of infectious virus (see the chapter by Borchers and Field, this volume). This process may either remain clinically silent or result periodically in clinical disease. In between such episodes, the virus remains in a quiescent form. Secondly, in chronic viral infections, virus

can be continuously recovered from the host. Overt clinical disease may or may not develop, and the ensuing symptoms are caused either by viral replication or by reaction of the immune system. Thirdly, in slow virus infections, after a long incubation period of months to years, a slowly progressive disease course develops that is usually fatal.

An example illustrating the fact that closely related viruses may induce acute as well as persistent CNS infections is Theiler's murine encephalomyelitis virus (TMEV) infection. This infection serves as a model to understand poliomyelitis and multiple sclerosis. TMEV belongs to the picornaviridae and has an RNA genome structure very similar to that of the polioviruses. There are two groups of isolates, which cause either acute, rapidly fatal encephalitis (virulent strains) or biphasic chronic persistent disease with demyelination (avirulent strains). Despite their distinct biological properties, both strains are highly homologous with 95% identity at the genome and 90% at the protein level (PEVEAR et al. 1987, 1988). Regions of the genome associated with neurovirulence and persistence are similar to those of poliovirus and have been mapped to the 5′ NTR and to the region coding for the VP1 capsid protein (CALENHOFF et al. 1990; MCALLISTER et al. 1990). Isolation of monoclonal antibody escape mutants with a single amino-acid change in the VP1 underline the importance of the protein for the viral phenotype (ZURBRIGGEN et al. 1989).

Acute infection with the virulent TMEV strains affects predominantly neurones in the cerebral cortex and the ventral horns of the spinal cord (as in poliovirus infections). The virus reaches the CNS primarily by axonal transport, but endothelial cell infection has also been shown. In contrast, a persistent infection of primarily oligodendrocytes develops in the majority of mice surviving the infection with avirulent strains of TMEV, where productive virus infection is associated with demyelinating lesions. The avirulent virus finds its access into the CNS via macrophages as a 'Trojan horse'. Macrophage-like cells constitute about 10% of infected cells in the brain. The mechanism of persistence depends on interferon-induced blockage of viral RNA replication at the level of negative-strand RNA synthesis, and the generation of antigenic variants by antibody escape. The susceptibility to TMEV infection is associated with MHC class I and two non-MHC genes encoded on chromosomes 3 and 6 (RODRIGUEZ et al. 1986; MELVOLD et al. 1990). $CD8^+$ T cells are involved in antiviral immunity during acute infection. They also play an important role in immune surveillance of persistently infected CNS cells, but they are not vital for recovery from acute infection (BORROW et al. 1992). Essential for the control of TMEV infection are $CD4^+$ T cells, as has been shown by depleting this cell type or by inhibiting its function in vivo using anti-CD4 or anti-Ia blocking MAbs, respectively (WELSH et al. 1987). Simultaneously, however, TMEV-specific $CD4^+$ T cells might lead to immunopathology and demyelination. There are essentially three possible explanations for the immunopathological response. Firstly, the $CD4^+$ cells directly damage MHC class II-expressing glial cells. Secondly, they induce mononuclear cell infiltration and activate macrophages, which damage myelinated nerve fibers in the so-called bystander effect. Thirdly, during the infection, T cells with autoimmune properties

against nerve cell antigens could be induced, which might exacerbate ongoing pathology or induce new lesions.

In the human CNS, chronic viral infections rarely develop but latent infections are common. The classical example of this type is the infection with herpes simplex virus (HSV). The pathology inflicted on the brain tissue is the consequence of HSV reactivation from a latent state leading to complete viral replication cycles after certain stimuli. The pathology depends on the effectiveness of host defence mechanisms. Extensive molecular biological studies have defined several regions on the viral genome as specific contributors to HSV neuroinvasiveness and neurovirulence (STEVENS 1993). HSV consists of a double-stranded DNA molecule that codes for 74 genes. Half of them have been deleted without interference of the viral capacity to replicate in cell cultures. These genes, referred to as "supplemental essential genes", are associated with virus entry, sorting and augmenting the precursor DNA pool, repair of DNA, and shut-off of host macromolecular metabolism. There is evidence that several of them are linked directly to neuroinvasiveness and neurovirulence. Expression of these genes allows the virus to invade the CNS, to replicate in different brain cells and to spread efficiently from cell to cell. For its survival in a human population, HSV requires only a restricted set of genes. Interestingly, those genes dispensable for HSV replication in dividing cells, such as the thymidine kinase gene, are required for infection of non-dividing cells. Marker rescue experiments also suggest a role for the viral DNA polymerase in neuroinvasiveness and neurovirulence (DAY et al. 1988). The majority of viral deletion mutants revealed a reduced capacity to invade the CNS and to replicate in brain cells. Further changes in genes coding for structural glycoproteins as well as in immediate early genes and the long terminal repeat region are involved (THOMPSON et al. 1989; CHOU et al. 1990). The infection of neurones results in two mutually exclusive processes. Only if immediate early genes that regulate the viral lytic cascade are repressed will destruction and death of neurones be prevented. The price that the infected neurone has to pay is the establishment of viral latency with the potential reactivation of viral multiplication. The establishment of the latent phase is a function controlled and executed by the neurone rather than by the virus itself. This is concluded from observations showing that viruses selected for their ability to replicate in vitro still establish latent infection; vice versa, mutants with a deletion of the immediate-early transcription regulator gene persist in neurones (SEDARATI et al. 1993). Although no infectious virus can be isolated during latency, viral genomes are detected as multiple extrachromosomal DNA copies characteristically represented as covalently closed circles associated with nucleosomes (ROCK and FRASER 1985; DESHMANE and FRASER 1989). The only viral RNA transcripts detected in neurones during latency are the so-called latency-associate transcripts (LATs) (FRASER et al. 1992). Open reading frames are present within LAT sequences and proteins may be expressed. Further analysis revealed that competence to replicate in tissue culture and to establish latent infections in vivo is not affected in viruses with mutated LAT genes. A functional role during reactivation has been suggested by showing that LAT minus mutants were reactivated normally from sacral ganglia, but only slowly from trigeminal ganglia (SAWTELL and THOMPSON

1992). The molecular events that trigger viral reactivation are largely unknown. Clinical observations have shown that recurrence is associated with physical or emotional stress, immune suppression, UV light, or nerve damage. The role of the immune system in controlling HSV infection is not entirely clear, because recurrences can be observed even in the presence of normal cell-mediated and humoral immune responses. While there is apparently no gross interference with nerve function during latency, reactivation of HSV leads to the destruction of infected neurones. Since reactivation of HSV is successful in only a very small proportion of neurones, functional defects are usually not observed.

Among the best-studied slow virus diseases of humans is subacute sclerosing panencephalitis (SSPE) (TER MEULEN et al. 1983; LIEBERT 1997). The disease develops on the basis of a persistent measles virus (MV) infection in brain cells months to years after acute measles. How and when the virus reaches the CNS remains unknown, as do the mechanisms that trigger the disease. The tropism of MV for human tissue including brain cells is determined by its receptor, the ubiquitously expressed complement receptor CD46 (DÖRIG et al. 1993; NANICHE et al. 1993). The persistent CNS infection is characterised by a restricted measles virus gene expression at several stages (BILLETER et al. 1991; SCHNEIDER-SCHAULIES et al. 1995; LIEBERT 1997). Electron microscopical studies revealed the presence of viral nucleocapsids in neurones and other cells of the CNS in the absence of viral budding from these cells. It was found that the viral envelope proteins are markedly underexpressed or absent in infected brain cells. Transcriptional efficiency of the corresponding mRNAs is reduced, leading to a steep expression gradient for the virus-specific monocistronic transcripts and an increase of bicistronic transcripts has been described. Mutations and hypermutations in various genes of cloned SSPE viruses were detected that prevent a complete replicative cycle of MV and hence might contribute to the establishment of persistence (HIRANO 1992; CECCALDI et al. 1993).

Additional mechanisms may contribute to the restriction of MV gene expression, supporting the establishment of persistence (SCHNEIDER-SCHAULIES and LIEBERT 1991). Firstly, high levels of intrathecal antibodies causing antibody-induced antigenic modulation; secondly, a brain cell-specific restriction of MV mRNA expression; and thirdly, the presence of IFN-α/β and interferon-inducible gene products in SSPE brains. In spite of the pathognomonic hyperimmune response against measles virus in SSPE, clearance of virus from the CNS is not observed. In tissue culture experiments and in the rat model, antibody-induced antigenic modulation with monoclonal antibodies to MV haemagglutinin induced the down-regulation of viral RNA and protein expression. Complete clearance of virus was not achieved, and removal of antibodies led to reactivation of the viral infection from low copy numbers of persisting viral genomes (BARRETT et al. 1985; LIEBERT et al. 1990b; SCHNEIDER-SCHAULIES et al. 1992). Similar results were generated in Sindbis virus-infected immunodeficient SCID mice, where infectious viral particles are cleared from the CNS by antiviral antibodies, but viral RNA can persist for months in mouse brains (LEVINE and GRIFFIN 1992; LEVINE et al. 1991). Intrinsic brain cell-specific mechanisms leading to a restriction of viral gene expression were

observed in the experimental rat model and in infected brain cell cultures (SCHNEIDER-SCHAULIES J et al. 1993; SCHNEIDER-SCHAULIES S et al. 1989, 1990). The induction of type-I interferon by MV infection of brain cells results in further antiviral activity (HOFMAN et al. 1991; FUJII et al. 1988) and might cause the selection of interferon-resistant MV strains that are able to persist in the brain (CARRIGAN and KNOX 1990). The interferon-inducible Mx protein inhibits the expression of MV in human monocytes and neural cells (SCHNEIDER-SCHAULIES et al. 1994). The viral restriction was shown to occur at the transcriptional or post-translational level.

3 Impact of Viral Infection on Specific Cell Functions

In response to infection, cytokines are secreted within the CNS either from infected brain cells or from the infiltrating lymphomononuclear cells. Cytokines serve as important factors in the stimulation of the humoral and cell-mediated immune response by acting on cells of the immune system as well as on surrounding brain cells, thereby inducing antiviral proteins such as Mx, or cell surface molecules such as MHC antigens (CAMPBELL 1991; PLATA-SALAMAN 1991). Several studies report on measuring cytokine levels in human diseased brain. For example, in SSPE elevated levels of IFN-α/β-, IFN-γ- and TNF-α-positive cells have been detected (COSBY et al. 1989; HOFMAN et al. 1991; SEDGWICK et al. 1993). In the brains of HIV-1-infected patients, where essentially CD4-positive microglial cells take up and propagate the virus, these cells have been found to be the source of intrathecal synthesis of IL-1, IL-6, GM-CSF, and TNF-α (JORDAN et al. 1991; MERRILL and CHEN 1991). TNF-α and IL-1 have pleiotropic effects including regulation of body temperature, sleep, stimulation of surface molecules, chronic inflammatory effects, and the stimulation of proliferation and differentiation of glial cells (GIULIAN and LACHMAN 1985; MARTINEY et al. 1992; MERRILL 1991; PLATA-SALAMAN 1991). Since these two cytokines and MHC class-II antigens were increased in gliotic areas of HIV brains, a potential role for the immune system in the pathogenesis of HIV encephalopathy has been suggested (TYOR et al. 1992). Furthermore, TNF-α, IFN-γ and IFN-β can contribute to selective virus elimination by interacting directly with infected brain cells (KARUPIAH et al. 1991; LUCCHIARI et al. 1993; SCHIJNS et al. 1991).

The data obtained from human brains reflect late or final stages of disease processes, and little is known about the expression of cytokines and their cellular sources during early phases of an infection, when virus is spreading in the brain. To study the role of cytokines in the development of CNS virus infections, animal models, particularly with RNA viruses, have been investigated with respect to cytokine expression. Induction of IL-1a, IL-2, IL-6, TNF-α, and IFN-γ mRNA synthesis has been found in Borna disease virus (BDV)-infected rat brain within 2 weeks after intranasal infection. IL-2 and IFN-γ mRNA expression correlated

with the appearance of $CD4^+$ and $CD8^+$ T lymphocytes during the early stages of BDV infection (SHANKAR et al. 1992). Cytokine expression is different in acute and persistent infections of the CNS. In the CSF of mice persistently infected with lymphocytic choriomeningitis virus (LCMV), significant levels of IL-6 were detected in high-responder (NMRI) but not in low-responder (CBA/J) mouse strains. In contrast, after acute intracerebral infection both strains contained high levels of IL-6 in CSF and serum (MOSKOPHIDIS et al. 1991). The source of IL-6 in mouse brains was identified to be astrocytes and microglial cells infected with LCMV or vesicular stomatitis virus (FREI et al. 1989). In tissue cultures of rat astrocytes, Newcastle disease virus has been shown to induce TNF-α and -β, IL-6, and IFN-α and -β shortly after primary infections (LIEBERMAN et al. 1989). Acute and persistent infection of human astrocytoma cells with measles virus results in transient expression of a similar set of cytokines, namely IL-1, IFN-β, IL-6 and TNF-α (SCHNEIDER-SCHAULIES S et al. 1993). Although TNF-α and IL-1β were hardly detectable in persistently infected cells their induction was not suppressed, and such additional stimuli as diacylglycerol and calcium ionophore induced overexpression of these genes (SCHNEIDER-SCHAULIES S et al. 1993). Additionally, chemokine expression in experimentally infected rodents strongly suggests that the induction of certain cytokines and chemokines plays an important role in the activation of the host antiviral immune responses and in the pathogenesis of viral CNS infection (SAUDER et al. 2000).

Virus infections can directly lead to, or increase the amount of, MHC class II expression on the surface of astrocytes and microglia in the absence of IFN-γ, as shown for murine JHM coronavirus (JHMV) or MV-infected astrocytes (MASSA et al. 1986, 1987). Interestingly, in the TMEV model MHC induction was IFN-γ dependent and did not result from mere TMEV infection. The susceptibility to immunopathology depends on the mouse strains. MHC class II was readily inducible in the susceptible SJL and CBA strains but not in the resistant Balb/c mice (NASH 1991). Similarly, BN rats live well with experimental persistent JHMV or MV infections. A constitutive high MHC class II expression was detected in BN brain, while immunopathological (autoimmune) processes were observed in a significant proportion of Lewis rats, in which MHC class II was expressed only as a consequence of viral infection. This illustrates that early presence of immunoregulatory molecules in the brain may serve a protective purpose, while the same process could lead to pathology and disease when MHC molecules are expressed several days or weeks later (SEDGWICK and DÖRRIES 1991). This is also largely true for MHC class I expression that can be induced only under certain conditions (NEUMANN et al. 1997). Generally MHC molecules are usually absent or expressed at low levels on neural cells. This is one of the prerequisites for efficient cell-mediated defence against intracellular pathogens in the brain. That this is not sufficient, however, to result in viral elimination is well illustrated by the observations in brain tissue from patients with progressive multifocal leukoencephalopathy, a slow papovavirus infection predominantly of oligodendrocytes with extensive demyelination and bizarre glial cell changes. Here, both MHC class I and II are expressed in the lesions, yet viral clearance does not occur, probably because

there are no reactive T cells generated and the patients are generally immunosuppressed. This may allow for the establishment of persistent and ultimately chronic viral infection with progressive disease (ACHIM and WILEY 1992).

Direct consequences of virus–cell interaction on the neural cell function proper may be severe, even if only restricted areas of the brain are involved and particularly when the functional integrity of the affected brain cells is vital for the host. The disturbance of neurone function has been extensively studied with rabies virus. The virus causes a nonlytic infection of brain cells that rapidly leads to the death of the infected individual. In contrast to the limited cythopathology, the death of the infected individual is apparently the result of interference with neuronal cell function(s) in vital centres of the brain regulating sleep, body temperature, and respiration (TSIANG 1993). In experimental rabies virus infections it was observed that uptake and release of gamma-amino-*n*-butyric acid (GABA) decreased in infected rat embryonic cortical neurons (LADIGANA et al. 1994) and that binding of 5-hydroxytryptamine to serotonin receptor subtypes is reduced in infected rat brains (CECCALDI et al. 1993). It is conceivable that disturbances of specialised receptor systems for neurotransmitter and neurohormone turnover, as well as for the generation of chemical signals and electrical potentials, is the major cause of death of the infected individual. In rat astrocytoma cells persistently infected with MV, the infection strongly reduces cAMP response following the addition of catecholamines. Furthermore, the density of β-adrenergic receptors is decreased by 50% and coupling of the receptor to G-protein is affected (HALBACH and KOSCHEL 1979; KOSCHEL and MÜNZEL 1980). The endothelin-1-induced Ca^{2+} signal was absent in cells persistently infected with MV, and 95% of the binding sites for endothelin-1 were lost (TAS and KOSCHEL 1991). Anti-MV antibodies, present in high concentrations in SSPE brain, influenced the inositol-phosphate signal transduction pathway in the cells (WEINMANN-DORSCH and KOSCHEL 1990).

4 Immune-Mediated Antiviral Mechanisms

The control of virus infection depends on the generation of both humoral and cell-mediated immune responses (see the chapter by Dörries, this volume). Antibodies, which attack predominantly extracellular virus particles released from infected cells, are essential to limit the spread of virus in the host (SISSONS and OLDSTONE 1985). However, the failure to clear viruses such as varicella zoster virus, cytomegalovirus, or MV infections in cell-mediated immunodeficiency states suggests that T-cell responses may be more important than antibodies in overcoming several virus infections (SMITH et al. 1992). The basis for any immune response to viral infections of the CNS is that it is probably initiated in peripheral lymphoid tissue and followed by the invasion of activated T cells into the cerebrospinal fluid, meninges, and brain parenchyma (SEDGWICK et al. 1991b). The investigation of these aspects of viral CNS infections requires appropriate animal model systems.

Since virtually all viral CNS infections are preceded by primary peripheral infection, it is clear that virus neutralisation and opsonisation during viraemia is one of the most efficient defence reactions that prevents viral entry into the CNS. Experimentally, the lethal encephalomyelitis induced by the JHMV in newborn or suckling rats is prevented by nursing the babies from JHMV-immunised mothers (WEGE et al. 1993; PERLMAN et al. 1987). Identical findings were published in a mouse model of murine retrovirus-induced neurological disease and in protection from LCMV-induced teratogenic effects in newborn mice (SAHA et al. 1994; BALDRIDGE et al. 1993). Moreover, experimental virus infections of the CNS in immunocompetent hosts remain regularly subclinical if a strong virus-neutralising antibody response is mounted (TYLER et al. 1989; JUBELT et al. 1991; RIMA et al. 1991; SCHWENDER et al. 1991).

Nevertheless, viruses sometimes escape neutralisation in the periphery and succeed in entering the CNS. During retrograde axonal transport, the virus is inaccessible to the immune system and the immune system is no longer aware of the invading agent. Neither virus-specific antibodies nor cytotoxic T lymphocytes (CTL) can interfere with the axonal transport of viruses to the CNS, especially because nerve cells most likely are unable to up-regulate MHC class I molecules upon viral infection (MOMBURG et al. 1986). In addition, by using monocytes as 'Trojan horses', viruses may escape neutralisation by antibodies and enhance their probability of reaching the perivascular space in the CNS, because perivascular microglial cells are frequently exchanged by peripheral monocytes (SEDGWICK et al. 1991a, 1993). After invading the brain, viruses replicate and spread within the CNS, as long as the infected host does not succeed in recruiting immune effector cells into the brain parenchyma. Among the effector cells, B and plasma cells home toward virus-infected areas, where they secrete virus-specific antibodies (DÖRRIES et al. 1991; SCHWENDER et al. 1991). Also virus-specific $CD4^+$ helper T cells enter the CNS and are detectable in infected brain regions (LIEBERT and KOLOKYTHAS 2000). To prevent the formation of secondary virus-infected foci following extracellular spread of virus, intracerebral secretion of virus-specific antibodies in close spatial arrangement to virus-infected cells is needed. In several animal models of virus-induced encephalitis, specific antibodies will significantly restrict extracellular viral spread in the CNS (PERLMAN et al. 1989; PATICK et al. 1990; SCHWENDER et al. 1991; YOKOMORI et al. 1992; FAZAKERLY et al. 1992; ATHERTON 1992). In addition, dissemination from cell to cell, e.g. by fusion, can be interrupted by antibodies, as shown for mice infected with rabies virus (DIETZSCHOLD et al. 1992). The underlying molecular mechanism is not fully understood, but it is suggested that upon uptake of antibody-complexed virus into the infected nerve cell, viral RNA transcription is severely disturbed. In line with this concept are data obtained in vitro and in vivo with antibody-induced antigenic modulation (BARRETT et al. 1985; LIEBERT et al. 1990; SCHNEIDER-SCHAULIES et al. 1992) which demonstrate abrogation of MV transcription by antiviral antibodies. Morphological studies by immune electron microscopy supported the view that viral replcation is disturbed on the transcriptional or translational level, because the typical arrangement of virus-specific proteins in perinuclear cytopathic vacuoles and the amount of rough

endoplasmatic reticulum was drastically reduced in antibody-treated neurones after virus infection.

The successful combat of viral CNS infections by the humoral immune response requires rapid recruitment of pre-existing virus-specific antibody-secreting cells into the brain parenchyma. This is usually achieved if viral CNS infection occurs concomitantly with the acute peripheral infection. In contrast, when viral CNS infection occurs late after primary infection or remains unrecognised by the immune system, the immune response has to be initiated in peripheral lymphatics such as the cervical lymph nodes. This gives the virus considerably more time to travel through the tissue, until humoral effector systems reach the brain parenchyma. Recruitment of antibody-secreting cells is determined by the genetic background of the host, as is clearly evident from studies of coronavirus JHM (JHMV)-induced encephalomyelitis in rats. While clinically resistant Brown Norway rats rapidly differentiate virus-specific $CD4^+$ T cells and recruit virus-specific antibody-secreting cells into virus-infected areas of the brain, this process is significantly delayed in highly susceptible Lewis rats (Schwender et al. 1991; Imrich et al. 1994). Furthermore, specificity and effectiveness of the recruited humoral response is important, as seen in severe acute Sindbis virus encephalitis in mice (Tyor and Griffin 1993). In the JHMV rat model, an individual plasma cell from the brain of infected but clinically healthy BN rats synthesises approximately five times more effective specific virus-neutralising antibodies, compared with a plasma cell from the CNS of infected and severely diseased Lewis rats (Schwender et al. 1991).

The effect of a late or a rather unspecific recruitment of humoral immunity to the CNS is followed by viral spread within the CNS and destruction of important neural cells. Moreover, large virus-infected areas will cause a more vigorous infiltration of virus-specific T cells, as is usually seen in cases of limited viral spread. This intimate relationship between virus-specific antibody response and T-cell-mediated immunopathology was observed in acute LCMV-induced encephalitis of mice. In this model, passive administration of MAbs between 1 day before and 2 days after viral infection resulted in protection of mice from lethal encephalitis. This was accompanied by a diminished CTL response and clearance of the virus from the brain with less tissue damage than usually seen in unprotected mice (Wright and Buchmeier 1991). Similar results were obtained in the measles encephalitis model in rats and mice (Liebert and Finke 1995). Here, the induction of MV-neutralising antibodies may completely suppress the development of disease in weanling animals (Malvoisin and Wild 1990; Brinckmann et al. 1991) and maternal antibodies transferred during gestation are protective in newborn animals. These findings are consistent with the resistance to encephalitis observed in BN rats that mount an early high level of MV-specific humoral immune response (Liebert and ter Meulen 1987). The inevitably fatal acute disease can also be prevented by passive immunisation of newborn animals with neutralising monoclonal antibodies, however, at the price of converting the infection into one of a persistent nature (Rammohan et al. 1983; Liebert et al. 1990b). Thus, the presence of mere antibody, even if neutralising the infectivity of a virus, may be generally insufficient to

eliminate measles virus from the infected brain when there are not also MV-reactive T cells available. On the contrary, even without available virus-neutralising antibodies animals can be protected. This was demonstrated by immunisation with recombinant vaccinia viruses expressing either internal nucleocapsid protein, or haemagglutinin, or fusion glycoprotein that prevented the disease upon subsequent challenge with MV in nonimmunised rats (BANKAMP et al. 1991; BRINCKMANN et al. 1991). This was further shown in μMT mice that have an inherent defect for antibody production (KITAMURA et al. 1991; Liebert and Geißendörfer, unpublished data).

Although, in general, humoral immunity does not contribute to the pathology of viral CNS infection, indirect tissue destruction might occur during viral encephalitis. Activation of macrophages or microglia may be triggered by engagement of the FcR, which is expressed in high densities on these cells. Binding of immune complexes to the FcR of macrophages can stimulate these cells to release toxic substances that will cause severe bystander destruction of 'innocent' healthy cells in the surroundings of virus-infected areas. This assumption is supported by the observation in vitro of macrophage-dependent oligodendroglia cell degeneration in mixed glial cell cultures that were treated with immune complexes formed by canine distemper virus and CDV-specific antibodies (BOTTERON et al. 1992).

Incomplete elimination of virus from the CNS will result in chronic persistent infection. Usually, a long-lasting intrathecal antibody synthesis with specificity for viral proteins accompanies viral persistence (TER MEULEN et al. 1983; SONNERBORG et al. 1989; TYOR et al. 1992) and efficiently prevents reactivation of the infection (LEVINE and GRIFFIN 1992). Over time there is selection of the best-fitting antibody clones to the virus. Thus high-avidity antibodies prevail eventually, and the respective clones are preferentially recruited to the CNS. In this case, isoelectric focusing of cerebrospinal fluid specimens will show a restricted 'oligoclonal pattern' of antibody clones compared with the polyclonal distribution detectable in paired serum specimens. Presence of these oligoclonal bands can continue over decades after primary infection of the CNS and thus is used as a diagnostic marker of viral CNS infections (FELGENHAUER and REIBER 1992).

Besides the fact that intrathecal virus-specific antibody synthesis is a relevant indicator of viral CNS infection, long-lasting presence of these antibodies in high titres is supposed to interfere with viral replication, thereby probably contributing to selection of virus variants. Direct evidence for selection of neurotropic variants by antibodies has been provided by the demonstration of changes in the cell tropism of neurotropic JHMV when grown in the presence of virus-neutralising monoclonal antibodies (BUCHMEIER et al. 1984). When the neurotropic virus and the MAb were inoculated simultaneously, viral target cells were primarily oligodendrocytes, in contrast to animals inoculated with virus alone, where neurones were the major target. In the rat model of MV-induced encephalitis (LIEBERT and TER MEULEN 1987), MV-neutralising monoclonal antibodies modified the disease process when administered intraperitoneally, and MV variants emerged that were no longer neutralisable by the monoclonal antibody used for treatment, but by other monoclonal antibodies (LIEBERT et al. 1994). From these data it has to be

concluded that only rapid and effective elimination of virus-infected CNS cells will prevent long-lasting antibody-controlled persistence of the virus and thereby the potentially dangerous development of viral variants with altered neurotropism.

4.1 The Cell-Mediated Immune Response

In contrast to the effect of antibody-mediated antiviral mechanisms, which, at least in vivo, either act predominantly against the virus itself or interact with cell surface molecules without damaging the cell integrity, the T-cell immune protection is mediated generally by cell destruction, i.e. pathology (see also the chapter by Dörries, this volume). In experimental infection of mice with the lymphocytic choriomeningitis virus (LCMV), the number of infected brain cells has been shown to constitute an important factor directing beneficial or harmful effects mediated by effector lymphocyte activity (ALLAN and DOHERTY 1985). Since the timely T-cell immune response encounters a limited number of infected cells, the pathology inflicted should be little in most instances of acute viral encephalitis, and the beneficial effects will usually outweigh the harmful effects of the cell-mediated immune response. Paradoxically, the elaborate system of the host immune response to virus infection that may be protective outside the CNS can be destructive when operating within and may injure the host while helping to clear virus, particularly in a persistent infection. This also illustrates the importance of the balance between the kinetics of immune responses and the virus host interaction. The outcome of a viral infection is also determined in part by the type of neural cell infected. This is an important factor in the pathogenesis of disease, not only for the potential injury caused by viral infection per se but also for the potential interactions of the infected cells with the immune system. Thus the effect of even local damage can be dramatic when neurones are infected which are vital to host survival and cannot be replaced once injured or destroyed. In view of these considerations, the task of the immune response during CNS infection is to either quickly eliminate the viral agent or arrange to tolerate the infection within neural cells.

Although both $CD4^+$ and $CD8^+$ T cells can be relatively easily isolated and grown in culture from the CSF of patients with viral encephalitis and meningoencephalitis, their relative importance in, and contribution to, combating an infection is uncertain. From the observations made in several animal models it appears that the presence and function of $CD4^+$ rather than $CD8^+$ T cells is required to overcome viral CNS infections. This contrasts with the situation in other organs where, during acute and chronic viral hepatitis, cytotoxic MHC class-I-restricted $CD8^+$ T cells attack virus-infected hepatocytes and thus mediate protection as well as immunopathology or cell destruction.

The role of T cells in overcoming measles virus infection was analysed in the rodent MV-encephalitis model. For this purpose lymphocyte subpopulations were depleted by in vivo administration of MAbs directed against the CD4 or CD8 surface molecules of lymphocytes (BANKAMP et al. 1991; FINKE and LIEBERT 1994), or MV-primed T cells were intravenously transferred into MV-infected rats (REICH

et al. 1992; LIEBERT and GEISSENDÖRFER 2000). Both approaches demonstrated that $CD4^+$ cells are apparently indispensable for achieving viral clearance from the CNS, while $CD8^+$ cells were not vital for recovery from the acute infection. When $CD8^+$ T cells are depleted, rats are still completely protected by adoptive transfer of immune-primed viral antigen $CD4^+$ T cells without local production of neutralising antibody (LIEBERT et al. 1993). From these results it was concluded that neither $CD8^+$ T cells nor antibodies are necessary for efficient elimination of MV and protection from disease in the encephalitis model. The results were surprising, because the susceptibility of mice for MV encephalitis correlates with their ability to generate an MHC class-I (L^d)-restricted, $CD8^+$ T-cell-mediated cytotoxic immune response (NIEWIESK et al. 1993). Furthermore, the Balb/c^{dm2} mouse strain, that fails to express L^d but is otherwise genetically identical to MV-resistant Balb/c mice, also eliminates MV efficiently from the CNS, although no MV-reactive $CD8^+$ T cells are primed in these mice. The apparent explanation for the observation is that $CD8^+$ cells are unable to interact with neurones that lack MHC class-I expression after viral infection (MOMBURG et al. 1986; Müller, Löffler and Liebert, unpublished data). At this point it has to be remembered that the generation of virus-specific immune effector cells depends on the species infected, and even within a single species there is no unique T-cell subset used in the antiviral defence. In several virus infections of rodents, the importance of $CD8^+$ CTL for combatting infection has been consistently shown (AHMED et al. 1988; BENDER et al. 1992; MOSKOPHIDIS et al. 1987; OLDSTONE et al. 1986; NASH et al. 1987). In contrast, the $CD8^+$ T-cell-mediated clearance of JHMV from the CNS requires CD4 help (WILLIAMSON and STOHLMANN 1990; KÖRNER et al. 1991; FLORY et al. 1993; WEGE et al. 1993). In the protective immunity to retroviruses both $CD8^+$ and $CD4^+$ T cells were partially effective, but only the combination of both led to full protection (HOM et al. 1991). Recovery from acute murine cytomegalovirus infection can proceed in the absence of the $CD8^+$ subset and is mediated by $CD4^+$ T cells, which develop a compensatory protective activity that is absent in normal mice (JONJIC et al. 1990). $CD4^+$ T cells appear to be required for maintenance of the spontaneous recovery from Friend virus-induced leukaemia (ROBERTSON et al. 1992). These examples illustrate that there is no general assignment of a determinative role in vivo to either T-lymphocyte subset in the recovery from viral infections. Instead, a detailed examination is required for every virus infection in relation to its susceptible host, and hardly any prediction can be made even for related viruses. It appears, however, that in the CNS antiviral cell-mediated activity is dependent largely on $CD4^+$ T cells.

A detailed characterisation in vitro revealed that protective T cells in the experimental MV-encephalitis model produce high amounts of IL2, IFN-γ, and TNF-α, but not IL4 or IL6, defining them as TH_1 cells (REICH et al. 1992; FINKE et al. 1995). Interestingly, the predominant generation of TH_2 cells seen after both natural MV infection and vaccination against measles in human beings has led to the hypothesis that the lack of virus-specific TH_1 cells may contribute to the immunosuppression seen after infection or vaccination (WARD and GRIFFIN 1993). Data obtained in the mouse model are consistent with this concept, as from the

highly susceptible C3H mouse strain preferentially TH_2 $CD4^+$ T-cell lines can be isolated but not TH_1 cells. If cytokines secreted by TH_1 cells were important, two requirements would have to be fulfilled. Firstly, virus-primed T cells would have to invade the CNS and home toward sites of infection, and secondly, blocking cytokine function should abolish protection. By exploiting a genetic marker, it was shown in adoptive transfer experiments into MV-infected rats and mice that MV-specific $CD4^+$ T cells from a donor animal enter the brain of the host. These cells accumulated in infected areas, whereas in an immunocompetent animal they never comprised more than 5% of the infiltrating T cells (LIEBERT and KOLOKYTHAS 2000). It is unlikely that MHC class-II-restricted cytolysis plays a major role in eliminating MV from the brain, because the major cell population in the infected rodent brain is neurones. Rather, virus-specific MHC class-II-restricted lymphocytes – as shown before in the LCMV-infection model – induce immunopathological foci in the brain (MULLER et al. 1992). The observed paucity of virus-specific donor T cells in the brains of MV-infected mice and rats leads to the conclusion that recruitment of further cells is essential for combat of virus in an infected brain. Accordingly, the neutralisation of IFN-γ by administration of anti-IFN antibody rendered all mice susceptible to MV-induced acute encephalitis. Irrespective of the mouse strain, anti-IFN-treated animals died of infection, suggesting that cytokines may play an important role in the immune surveillance of the CNS. It was also shown that the infection of brain cells led to a differential induction of cytokines in primary and persistent MV-infection in human glial cell cultures and in rodent neurones (SCHNEIDER-SCHAULIES S et al. 1993; Mosch, Löffler and Liebert, unpublished data). The mechanism of cytokine action is conceivably to assist in the recruitment of effector cells into the CNS. For example, IFN-γ and TNF enhance the expression of VCAM-1 on brain endothelial cells to which stimulated T cells bind before they enter the brain and encounter viral antigen, which leads to further events of activation and the secretion of cytokines (BARON et al. 1993). The candidate prime source of IFN-γ and TNF-α in MV infection of the murine CNS are $CD4^+$ T cells and microglia. The potential contribution of other cytokines and the role of mononuclear phagocytes that are consistently present in infected foci have not yet been clarified.

In the murine TMEV model, the susceptibility to infection is MHC associated and maps to the class-I locus H-2D (NASH 1991). In susceptible strains of mice, $CD8^+$ T cells apparently fail to recognise viral antigens in the context of MHC class I, and so the virus persists and eventually causes disease. In in vivo depletion experiments using anti-CD8-antibody it was shown that virus clearance is delayed and demyelinating disease develops. These data show that $CD8^+$ T cells are not involved in immunopathology (i.e. demyelination) and are also not vital for recovery from acute infection. They may, however, contribute to antiviral immunity in acute infection and immune surveillance of persistently infected cells. Observations made in beta 2-microglobulin-deficient transgenic mice suggest that $CD8^+$ T cells may play a role in clearing viral persistence from glial cells (PULLEN et al. 1993). Similar to the measles model, $CD4^+$ cells are essential for controlling the early stages of infection. Depletion studies of $CD4^+$ cells in the TMEV model

suggest that the major role of $CD4^+$ T cells in Picornavirus infections is probably to provide help for B lymphocytes and thus enable the production of neutralising antibody (WELSH et al. 1987). Little is known about the possible antiviral activity of $CD4^+$ T cells in TMEV infection. However, experiments in which the MHC-II-restricted $CD4^+$ T cell function was suppressed have resulted in a reduction in the incidence of demyelinating disease. Following TMEV infection and initial T-cell infiltration into the CNS, MHC class-II induction on astrocytes is a key step allowing local antigen presentation and amplification of immunopathological responses within the CNS, and hence development of demyelinating disease (BORROW and NASH 1992). A bystander effect caused by the mononuclear cell infiltration and activation of macrophages, which in turn can lead to damage on myelin sheaths, is probably responsible for the observed immunopathology.

The price for evading persistent virus infection may be development of autoantibodies and autoreactive T cells. In rats infected with JHMV or MV, myelin basic protein (MBP)-reactive $CD4^+$ T cells have been detected that could transfer experimental allergic encephalomyelitis (EAE) to naive uninfected animals (WATANABE et al. 1983; LIEBERT et al. 1988). In rats rendered tolerant to MBP, not only EAE but also the precipitation of the autoimmune subacute measles encephalitis was suppressed (LIEBERT and TER MEULEN 1993).

4.2 Virus-Induced Cell-Mediated Autoimmune Reactions Against Brain Antigens

A co-factor role for MV in the development of EAE was suggested by early observations that showed that the course of EAE and its severity were potentiated in MV-infected hamsters (MASSANARI et al. 1979). Interestingly, after infection with measles virus some Lewis rats develop a disease process that is characterised by an inflammation in the CNS in the absence of MV antigen or viral nucleic acid. The lesions are very similar to those of naive rats receiving MBP specific $CD4^+$ T-lymphocytes. Oligoclonal immunoglobulins with restricted heterogeneity were detected in the cerebrospinal fluid of the animals, which probably react to brain antigens (DÖRRIES et al. 1988). Lymphocytes isolated from these animals were found to proliferate in vitro in the presence of MBP or PLP (LIEBERT et al. 1988). The intravenous transfer of MBP-reactive MHC class II-restricted $CD4^+$ T cell lines isolated from bulk cell populations induced a disease in naive syngeneic recipients with clinical and histopathological signs identical to T cell mediated EAE. The analysis of the antigenic fine specificity revealed that MBP-specific T cells from MV-infected as well as from MBP-challenged rats displayed an identical pattern of reactivity to a panel of synthetic peptides (LIEBERT et al. 1990a). The high degree of antigenic specificity was further supported by the failure of the T cell lines to proliferate in the presence of disrupted measles virions, isolated MV proteins, or other control antigens or peptide sequences. Vice versa, MV-specific T cell lines did not proliferate when MBP or synthetic MBP peptides were added to the cultures. The disease induced was clearly not due to activation of MV in the brain of

immunised Lewis rats, because virus could not be isolated from brain material and measles antigen was not detectable (LIEBERT and TER MEULEN 1993). The interaction between MBP-peptide and MV-infection was not observed when rats were infected intraperitoneally or when inactivated MV was used. Obviously, at least initially, some viral replication in the brain is required to enhance the vulnerability of the brain to autoimmune aggression. If autoimmune mechanisms participate in the pathogenesis of virus-induced encephalomyelitis, susceptibility to measles encephalitis and EAE should parallel in different rat strains depending on the genetic background. This is indeed the case, as Brown Norway rats that are resistant to EAE did not develop a subacute clinical disease, although they are generally able to replicate MV (LIEBERT and TER MEULEN 1987). The susceptibility of rats to the development of MV-induced CNS changes and disease is multifactorial, with the development of an MBP-specific CMI response representing a major factor.

5 Consequences of Viral Persistence in Neurones

In summary, establishment and maintenance or eventual elimination of persistent viral infections in the CNS is not the result of a single factor. Neither viral, nor host, nor immune defence functions alone are sufficient; it is rather the highly complex interrelation between those components that results in the temporary symbiosis of viruses and CNS cells. In many instances this leads to latent or slow viral infections with little or no specific immune response. The ongoing presence of viral proteins and/or nucleic acid, however, threatens to reactivate the viral replication process with the emergence of new symptoms and severe damage to brain substance and function. These symptoms may be the result of destructive virus–cell interaction or of the antiviral immune response in form of immunopathology. Since immune responses are generated in the periphery the combat of CNS virus infections is hindered. When neurones are infected, direct interaction of T cells with the infected host cell is not possible due to the lack of MHC expression. In any case, this would not be desirable, because immune responses, while being beneficial and effective in the periphery, inflict enormous pathology when attacking cells that lack the capacity to regenerate. Hence, a rapid elimination of virus (infected cells) is necessary, whereas a delayed immune response may allow the virus to spread in the CNS and, even if ultimately effective against the virus, may be destructive to the host. Because of this, precautions exist to prevent potentially damaging immune responses during persistent infections when, at least temporarily, the virus does not destroy its host cell. Obviously to the advantage of the host, a delicate balance is normally maintained between the requirements for the morphological and functional integrity of the CNS and the pretension of the immune system to combat virus and eliminate virus-infected cells.

From extensive studies in human and animal CNS infections the following facts have become clear: (a) The immune response to viral infections is initiated in

peripheral lymphoid tissues, followed by entry of activated end-differentiated T and B cells into the cerebrospinal fluid, meninges, and brain parenchyma. (b) During viral infections, the cytokines and chemokines induced vary between different strains of mice and in different cell types of the same mouse strain or human individual. (c) Interferon-induced proteins such as MA may contribute to the establishment of persistent infections, which are accompanied in certain cases by down-regulation of viral replication and/or restriction of viral gene expression. (d) During viral infections, MHC class antigens are expressed on astrocytes and oligodendrocytes and extensively on microglia that present viral antigen produced by infected cells. (e) In many viral infections T cells are required for viral elimination; sometimes clearance of virus also depends on the timely presence of virus-specific antibodies. (f) The synergistic interaction of all components of the adaptive immune system is required for both limitation of virus spread within the CNS and ultimate elimination of virus from brain cells. (g) However, in established persistent infection, immunopathology and/or autoimmunity may develop as a result of immune-mediated damage from inappropriate T-cell responses generated during attempted viral clearance.

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