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## The immune system response to viral infection of the CNS

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*In immunological terms the CNS is at a severe disadvantage in its ability to respond to infection by virus. First, both glial and neuronal cells normally do not express molecules of the major histocompatibility complex. Second, the most efficient cells for stimulating an immune response (leucocyte dendritic cells) are not present in the healthy CNS; and third, there is no specialized lymphatic drainage from the CNS to lymph nodes to enable the immune system to be quickly informed of the presence of an infection. Nevertheless, the immune system apparently copes with the vast majority of viral infections in the CNS. This is clearly evidenced by the reactivation of latent CNS viral infections in some immunosuppressed patients and the dramatic increase in the severity of CNS disease in young or otherwise immunologically incompetent experimental animals infected with neurotropic viruses. The routes by which the CNS and the immune system may communicate and the varied ways in which an immune response may affect the outcome of a viral infection of the CNS are discussed.*

**Key words:** central nervous system / viral encephalomyelitis / antigen presentation / immunity / lymphocytes / viral persistence

THE IMMUNE SYSTEM has evolved in higher vertebrates into a complex, multi-factorial surveillance mechanism designed to limit both the spread of infectious organisms as well as the outgrowth of neoplastic cells. There appear to be few, if any, body compartments that are not patrolled by the immune system. The central nervous system (CNS) is, however, compared to most other sites, normally lacking in the essential elements and conditions known to lead to a rapid and affective immunological response. The paucity of immune elements in the CNS and the consequent lack of immune interactions that occur obviously has important consequences for the way in which viral infections of the CNS are handled.

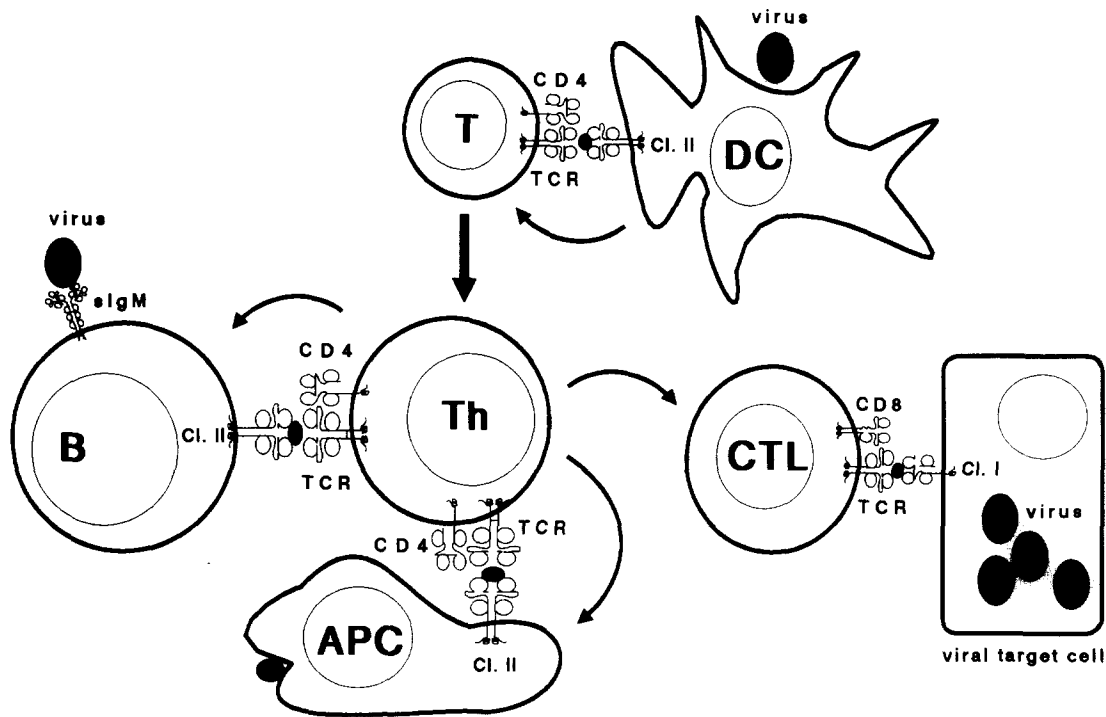
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Recent experimental evidence indicates that the 'immunological privilege' of the CNS is by no means absolute and that there are some forms of communication between the immune and central nervous systems. Indeed, the immune surveillance of the CNS appears to be sufficient in most cases to control or eliminate most viral infections. Here we briefly describe those components of the immune system which are fundamental for effective defence against viral infection and illustrate why the normal CNS is considered to be so immunologically deficient. The possible mechanisms that enable the immune system to respond to a CNS viral infection are discussed and brief examples given of the way in which the course of infection may be altered by the action of the immune system.

### The major histocompatibility complex and T and B lymphocytes

Studies in the 1970s and subsequently (reviewed in ref 1) established the nature of the specific recognition requirements necessary for the immune system to respond to a given antigen and, in particular, for cytotoxic T lymphocytes to recognize and destroy virus-infected cells (Figure 1). Most T lymphocytes can be subdivided into two non-overlapping populations expressing distinct surface molecules known as CD4 and CD8. The former subset predominantly exhibit helper/inducer function, whereas the latter is the most active in terms of cytotoxic capacity.<sup>2</sup> Both subsets also express a T cell-specific receptor which recognizes peptide antigen (for example, derived from a virus present in an infected cell), only when it is bound to and displayed on the cell surface in the context of a major histocompatibility complex (MHC) class I or class II molecule. CD8<sup>+</sup> cells almost exclusively react with antigen presented by MHC class I molecules, whereas CD4<sup>+</sup> T cells react with antigen in the context of MHC class II molecules (reviewed in ref 3). MHC class I molecules are present on virtually all cells of the body (with important exceptions—see below) but expression of



**Figure 1.** Basic mechanisms of T and B lymphocyte activation following viral infection. Unprimed  $CD4^+$  (T) lymphocytes are activated following interaction with leucocyte dendritic cells (DC) which are a specialized and highly efficient type of antigen-presenting cell (APC). DC may provide factors (indicated by the small arrow) which assist in this process. T lymphocytes use a specific T cell receptor (TCR) to recognize peptide forms of (viral) antigen which are presented to the T cell in the context of MHC class II molecules (Cl II) on the DC. DC are not normally present in the CNS and so this step probably first occurs outside the CNS. The activated, primed  $CD4^+$  T helper lymphocyte (Th) may now interact with a variety of APC, which could include macrophages, astrocytes, microglia and vascular endothelial cells. B lymphocytes can bind virus and also act as APC for  $CD4^+$  Th lymphocytes. The Th cells produce factors (indicated by small arrows) that allow B lymphocytes to differentiate into antibody-secreting plasma cells.  $CD8^+$  T lymphocytes (CTL) see virus-infected cells through viral peptides presented in the context of MHC class I molecules (Cl I). Th lymphocytes also provide factors which enable further differentiation of the  $CD8^+$  T cells into active cytotoxic T lymphocytes (CTL).

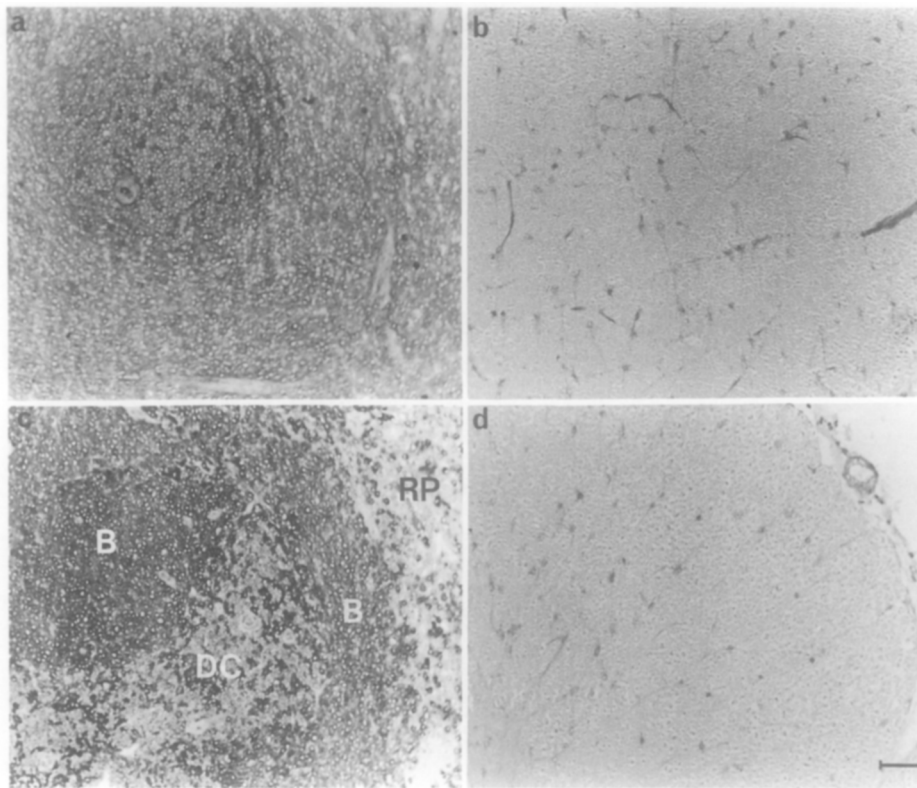
MHC class II molecules is significantly more restricted, being found predominantly on cells within lymphoid organs that have an important role as antigen presenting cells for  $CD4^+$  T lymphocytes.<sup>4</sup>

Cytotoxic T lymphocytes can recognize and kill any cells infected by virus because viral peptides will be presented by the almost ubiquitous MHC Class I molecules.<sup>1</sup> To do so, the cytotoxic T lymphocytes usually need the help of  $CD4^+$  T helper cells.<sup>5</sup> The  $CD4^+$  T cell subset also provides help for antigen-specific B lymphocytes resulting, ultimately, in their differentiation into antibody-secreting plasma cells. Antibody plays an important role in the immune response following infection, by preventing extra-cellular spread of virus. Thus, for effective control

of a virus infection, expression of both types of MHC molecules is usually needed (there are of course exceptions) as well as the presence of B lymphocytes and both types of T cells.

### MHC expression in the CNS

Figure 2 starkly illustrates the problems faced by the CNS when infected with virus. Compared with a spleen for example (Figure 2a,c), the normal CNS parenchyma is virtually devoid of MHC expressing cells (Figure 2b,d). The positive staining in Figure 2b is blood vessels expressing MHC class I. Other elements of the immune system such as T and B lymphocytes are also very difficult to detect.



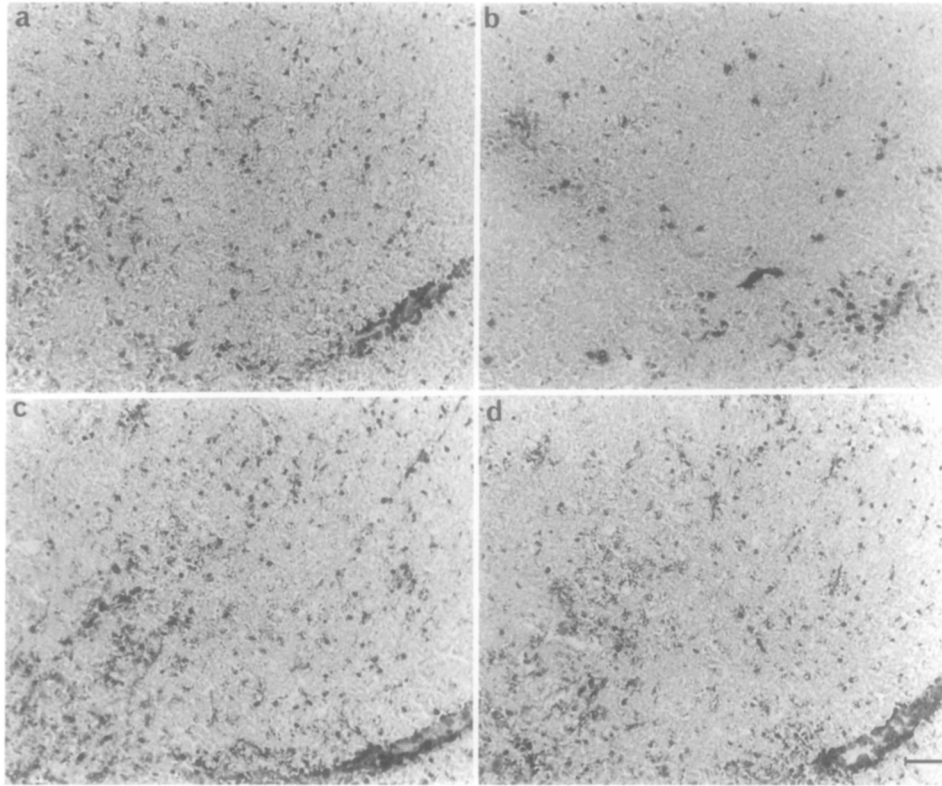
**Figure 2.** Low MHC expression in the CNS. Cryostat sections of spleen (a,c) and thoracic spinal cord (b,d) from a normal Lewis strain rat stained by the immunoperoxidase method for expression of MHC class I (a,b: monoclonal antibody (mAb), MRC OX18) or MHC class II (c,d: mAb, MRC OX6). All cells in spleen are MHC class I positive (a) whereas mainly B cells (B) and dendritic cells (DC) in the T cell area and scattered cells in the red pulp (RP) are MHC class II positive (c). Only endothelial cells of the spinal cord vasculature are MHC class I positive (b). A few cells in the meninges are MHC class II positive; scattered positive cells elsewhere in the tissue are usually intraluminal (d). All panels are the same magnification. Bar = 50  $\mu$ m.

Nevertheless, after viral infection, leucocytes, predominantly T lymphocytes and blood monocytes, may cross the blood-brain barrier and enter the parenchyma of the CNS. The appearance of these cells is usually accompanied by the upregulation of MHC expression on resident CNS cells and this is illustrated in Figure 3. Although there are relatively few infiltrating cells (in Figure 3b only infiltrating cells and not the CNS are stained), substantial MHC class I and II induction on the CNS itself results (Figure 3a,d). The MHC induction is probably due to secretion of cytokines such as interferon  $\gamma$ <sup>6</sup> by the infiltrating T lymphocytes.

### **CNS antigen presentation, lymphatic drainage and the blood-brain barrier**

In tissues other than the CNS (for example the skin), a specialized system exists to transport antigen

through afferent lymphatics to local lymph nodes where full activation of an appropriate immune response can occur. The efficiency of this system is at least partly related to the presence of dendritic antigen presenting cells in the skin, as in many other organs, that pick up antigen and transport it to the lymph nodes (reviewed in ref 7). The CNS is also deficient in this respect. First, no specialized dendritic antigen-presenting cells (see Figure 1) are present in the CNS.<sup>7</sup> Macrophage-like antigen-presenting cells are present<sup>8,9</sup> but most of these are not constitutively MHC class II positive. Moreover, there is also no evidence that these cells, or indeed any other resident CNS cells with potential to act as antigen-presenting cells, such as astrocytes,<sup>10</sup> can pick up antigen and pass to lymph nodes to allow sensitization of the immune system to occur. Second, the CNS has no specialized lymphatic drainage. The importance of this mode of antigen transfer to lymph



**Figure 3.** CNS MHC upregulation during viral infection. Lewis strain rats were irradiated and their bone marrow replaced with T cell-depleted marrow from BN strain rats. After 4 weeks, >90% of leucocytes were of donor (BN) origin. These chimeric rats were injected intracranially with coronavirus JHM and culled 2 weeks later when clinical disease was apparent. Serial cryostat sections of thoracic spinal cord were stained with monoclonal antibodies that recognize (a) MHC class I of both rat strains (mAb, MRC OX18), (b) MHC class I only of the donor (BN) strain (mAb, MRC OX27), (c) MHC class II of both strains (mAb, MRC OX6) or (d) MHC class II only of the host (Lewis) strain (mAb, MRC OX3). These experiments show that there are relatively few infiltrating cells (b) but these are nevertheless sufficient to induce high levels of MHC expression on resident CNS cells (a,c,d). Note that most of the MHC class II staining is accounted for by host CNS expression (d), rather than by infiltrating cells (c, showing MHC class II of donor cells and host CNS). All panels are the same magnification. Bar = 50  $\mu$ m.

nodes as a means of sensitizing the immune system has been clearly demonstrated by the observation that survival of skin allografts is prolonged if afferent lymphatic drainage is absent.<sup>11</sup> Finally, the endothelium of the CNS blood vessels is very tight creating a blood-brain barrier. Unlike most other endothelial surfaces, this barrier prevents the passage of most cells and small molecules into the CNS.<sup>12</sup>

### Informing the immune system that a CNS infection has occurred

The factors discussed above clearly illustrate the problems faced by the immune system in responding

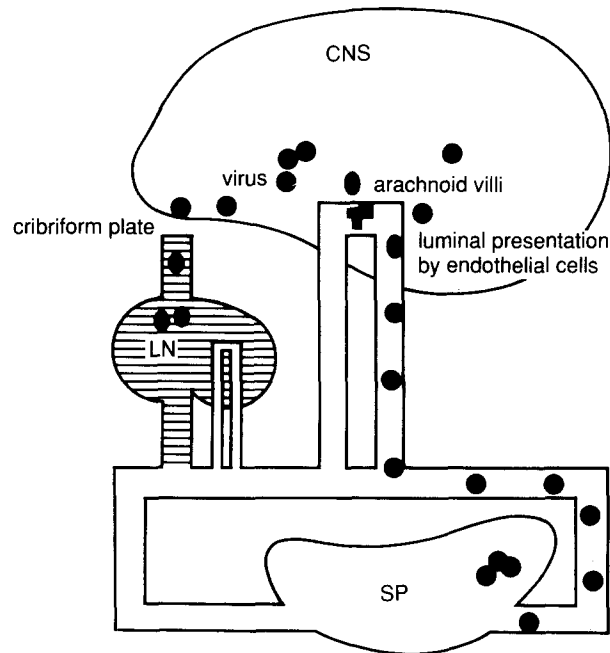
to a CNS viral infection. In most instances, however, it is likely that the immune system is already sensitized in the periphery before the virus ever reaches the CNS, as a result of infection of the primary target organ. A typical example is polio virus infection of the gut followed later by viremia and subsequent CNS infection (see Almond, this issue<sup>13</sup>). Nevertheless, once CNS infection has occurred, how is the immune system first informed that this region is infected and subsequently provided with re-sensitizing boosts of antigen? There are at least three possible ways, which include the movement of antigen into the blood through arachnoid villi, antigen passage to the cribriform plate and drainage by lymphatics into the cervical lymph nodes, and

presentation of antigen on the luminal surface of vascular endothelial cells (see Figure 4 for details). However, none of these routes are likely to be as efficient in this task as are the dedicated afferent lymphatics present in other organs and tissues.

### Passage of effector leucocytes into the CNS and antigen presentation

Once the immune system is sensitized there does not appear to be anything preventing the initiating of an inflammatory response within the CNS, despite its many immunological deficiencies. But exactly how leucocytes circulating in the blood know that they

should cross the brain vascular endothelium and enter the CNS is not definitely known. It seems likely that there is a requirement for some sort of non-specific adhesion to occur between circulating leucocytes and the brain vascular endothelium, as a first step in the process of extravasation of these cells from the blood into the parenchyma of the CNS. A complex array of molecules has now been described that have the specific task of binding cells together (reviewed in ref 16). The molecules LFA-1 on T cells and ICAM-1 on endothelial cells are important for interactions between these two cell types but other molecules are almost certainly involved. (See also *Seminars in the Neurosciences*, vol 2(6), 1990 and vol 3(4), 1991 for further information on such molecules.)



**Figure 4.** Communication between the CNS and the immune system. Most of the cerebrospinal fluid enters the blood by bulk flow through narrow channels in the arachnoid villi (sponge-like structures between subarachnoid space and superior sagittal sinus) so antigen in the cerebrospinal fluid may reach the spleen (SP) or lymph nodes (LN) by this route. Alternatively, antigen may traverse the olfactory nerves, leaving the brain by the cribriform plate, where it is collected and drained by afferent lymphatics into the cervical lymph nodes.<sup>14</sup> There is some evidence that antigen may be able to pass from brain to blood through the vascular endothelium.<sup>15</sup> Antigen recognition by T cells could then occur on the endothelial cells themselves. There is, theoretically, no requirement for transport of whole molecules by the latter pathway as T lymphocytes see only peptide antigens, which may more readily be processed and transported through the endothelial cells for presentation on the luminal surface of the vasculature.

The next step is unclear. It is possible that foreign antigen in the CNS is degraded and presented to the adhering T cells as peptides in the context of MHC molecules on the luminal face of the vascular endothelial cells. This could impart a signal to the T cells to initiate the process of extravasation or, alternatively, the T cells may directly damage the endothelial cells<sup>17</sup> allowing the rapid passage of many leucocytes into the CNS. The latter process certainly occurs during lymphocytic choriomeningitis virus infection in mice.<sup>18</sup>

It is possible that no antigen-specific recognition at the vascular endothelium is required at all. There is accumulating evidence that the CNS is routinely patrolled by the immune system, although the discussion above illustrates that this function must be performed by relatively few T cells at any one time, given their scarcity in the healthy CNS. Data are emerging that pre-activated but not resting T lymphocytes may preferentially pass from the blood into the CNS.<sup>19</sup> In this way, the immune system through its random surveillance of the CNS may become aware of the presence of foreign antigen. Which cell type(s) in the CNS present antigen to the extravasated T lymphocytes is not known but perivascular macrophages<sup>8</sup> or astrocytes<sup>10</sup> are likely candidates as both are intimately associated with the CNS vasculature. One point that keeps emerging in this discussion is that immune reactions may proceed in the CNS but only after the response has been initiated outside the CNS.

### **A local immune response**

Once specific T cells have interacted with CNS antigen, a relatively rapid accumulation of other, non-specific inflammatory cells may follow. Subsequently, the immune response can develop to some extent within the CNS as evidenced by high levels of, for example, specific anti-viral immunoglobulin in the cerebrospinal fluid and the restricted (oligoclonal) nature of this antibody.<sup>20</sup> There is also evidence that expansion of populations of T cells with restricted specificity may occur in the CNS.<sup>21</sup>

### **How the immune response may influence the outcome of viral infection**

Here we outline briefly examples of CNS viral infections to illustrate the variable ways in which an

immune response may affect the outcome of the infection.

### ***Prevention of CNS disease***

The protective nature of an effective immune response is illustrated by the course of CNS viral infection in immunologically immature or immunosuppressed hosts. Infection of immunologically incompetent neonatal rats or mice with the neurotropic coronavirus JHM causes acute lethal encephalitis.<sup>22,23</sup> In animals which are nursed by pre-immunized mothers the onset of neurological symptoms is delayed, indicating protection by transfer of maternal antibodies.<sup>24,25</sup> In the human neonate, disseminated infections involving the CNS may occur and are usually accompanied by high mortality or severe consequences for the survivors<sup>26</sup> (see also Coyle this issue<sup>27</sup>). Immunosuppression during experimental CNS infection in mice by corona virus JHM and Theiler's virus is associated with enlarged areas of histopathological change, spread of virus and increased incidence of fatal encephalitis.<sup>23,28</sup> In man, immunosuppressive treatment during organ transplantation may induce reactivation of chronic persistent virus infection resulting in, for example, lytic infection of oligodendrocytes and death, as seen during progressive multifocal leucoencephalopathy caused by polyomavirus JC.<sup>26</sup> Moreover, the acquired immunodeficiency syndrome (AIDS) is frequently complicated by opportunistic viral infections of the CNS including JC-, herpes and cytomegalovirus.<sup>29</sup>

In contrast, the immunocompetent host controls viral CNS infections by protective humoral and cellular effector mechanisms. Data from experimental corona virus and Theiler's virus infection in mice suggests that antibodies limit viral spread by neutralizing extracellular virus<sup>25,28</sup> whereas action of CD8<sup>+</sup> cytotoxic T lymphocytes is required for viral clearance from the brain.<sup>28,30</sup> These events usually parallel the recovery of the infected host from acute neurological disease or even prevent clinical manifestation of CNS infection.

### ***Enhancement of CNS disease***

The elimination of virus in the CNS by cellular immune-mediated mechanisms may also contribute to the severity of the disease. Direct evidence for the contribution of local virus-specific immunity

to CNS disease is seen following intracerebral infection of immunosuppressed mice by lymphocytic choriomeningitis virus. A persistent infection is established in these animals which remain healthy until they receive CD8<sup>+</sup> lymphocytes specific for the virus. These cells, in performing their task of viral clearance, ultimately induce so much damage to the CNS vasculature and other local tissue that the animals die.<sup>18</sup>

A rare and immunologically less understood complication is postinfectious encephalomyelitis which follows recovery from peripheral infection with some exanthema viruses.<sup>26</sup> Strong inflammation in the CNS accompanied by widespread primary demyelination in the absence of viral particles in brain and no detectable virus-specific immune response in the cerebrospinal fluid suggests an autoimmunological destruction of the CNS as a consequence of peripheral infection.

#### *Failure to eliminate virus from the CNS*

Failure of complete virus clearance from the brain by a competent immune system may end in persistent or latent infection of the CNS (see also Stevens, this issue<sup>31</sup>). In this context, viruses with strong tropism for neurons are of particular interest, because neurons are extremely resistant to induction of MHC class I and so viruses infecting neurons may escape elimination by MHC class I-restricted CD8<sup>+</sup> cytotoxic T lymphocytes. Lack of sufficient CD8<sup>+</sup> cytotoxic T lymphocyte activity in combination with a strong local antiviral antibody response may help to maintain the persistent state of the infection. Selection pressure put on the virus by these antibodies results in the generation of non-neutralizable virus variants, as seen in visna virus infection of sheep<sup>32</sup> (see also Zink and Narayan, this issue<sup>33</sup>). Alternatively, the viral strategy of replication is modified. RNA viruses, like measles, can shut off viral protein synthesis in the presence of high titers of neutralizing antibodies. However, the genetic information of the virus is still present in the target cell and synthesis of viral proteins can start again after the antibody titer has dropped beyond a certain threshold.<sup>34</sup> DNA viruses like polyoma virus JC reveal host cell dependent rearrangements of genomic control regions regulating replication.<sup>35</sup> In conjunction with constant monitoring of infected cell foci by the patrolling immune system, this probably results in subclinical infection over decades.

A lethal outcome is, however, still possible during severe immunosuppressive states (AIDS, leukemia, transplantation).

#### **Future directions**

Once immune sensitization outside the CNS has occurred, the immune system may then respond to antigen present in the CNS. Without prior sensitization, the ability to respond is much diminished.<sup>36</sup> Information briefly presented here provides possible mechanisms by which immune surveillance of the CNS may be achieved but further work is required before the relative importance of these 'communication' routes is defined.

The clear examples of reactivation of latent CNS viral infections when individuals are immunosuppressed illustrates that the immune system is generally effective in limiting the potentially damaging effects of uncontrolled viral spread in the CNS. How this is achieved is not understood, given that in such latent viral infections, many or most of the elements described above which are considered essential for the effective functioning of anti-viral immunity are usually absent. A substantial amount of work is required before these and other allied aspects of the immune-pathogenesis of CNS viral infections are clarified.

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