Inflammation of the central nervous system (CNS) may be the result of both innate and adaptive immune responses. In Alzheimer’s disease (AD) an innate immune response is triggered by local production of amyloid β-protein (Aβ), whereas in multiple sclerosis (MS) an adaptive immune response directed against myelin components initiates inflammation in the CNS (Table 1). Adaptive immune responses involving antibody- or cell-mediated responses have differential effects in AD and MS, and in animal models of these diseases. In addition, the recent appearance of encephalitis in individuals with AD that have been immunized with Aβ has parallels to underlying mechanisms of cell-mediated adaptive immune responses in MS, in which pro-inflammatory T-cell responses seem to drive the disease. These features of inflammation, which are outlined for AD and MS in Table 1, are reviewed here in terms of both disease pathogenesis and therapy.

Multiple sclerosis
Multiple sclerosis is an inflammatory disease of the central nervous system characterized by perivascular cuffs of mononuclear cells that include both lymphocytes and macrophages. This infiltration leads to damage of the myelin sheath and the underlying axon. Activation of microglia and astrocytes occurs in MS, but it is secondary to infiltrating lymphocytes. In the initial stages of the disease, the inflammation that occurs in MS is episodic and associated with discrete attacks of neurological dysfunction followed by recovery, which may leave residual neurological damage. Subsequently the disease often becomes more progressive, developing to a stage where there is less inflammation and nervous system damage is caused by a degenerative process initiated by the inflammation.

The episodic inflammation that is classic of MS is clearly visualized by magnetic resonance imaging (MRI) scans of the brain after administration of the contrast material gadolinium. Gadolinium crosses an open blood–brain barrier created by the inflammation and highlights discrete areas of inflammation. The duration of enhanced inflammation in individuals receiving weekly MRI scans is 4–8 weeks, and virtually all new lesions enhance in their earliest phases. When the acute inflammation resolves, it leaves a scar and tissue damage. This can be seen in the three-dimensional MRI images in Fig. 1, which were recorded over a 1-yr period in a single individual affected with MS. The inflammatory process of MS is associated with a complex cascade of inflammatory molecules and mediators, including chemokines, adhesion molecules associated with activated endothelial cell walls and matrix metalloproteases.

The cause of the recurrent inflammation in MS is now generally accepted to be autoimmune in nature, that is, a cell-mediated autoimmune attack against the white matter sheath. An alternative explanation for the episodic and chronic inflammation that is the hallmark of MS is the presence of a virus or infectious agent that has persistently infected the nervous system. But although infectious agents have been extensively sought in MS, none has been isolated. Viruses and infectious agents are, however, thought to be important in triggering the immune system and the immune attack on the nervous system. Given the inflammatory nature of the pathological process and the...
the adaptive immune system can be classified broadly into cellular and humoral (antibody)-type responses. Among cellular responses, different types or classes of cellular immune responses have been identified that are essential for understanding the mechanisms of the inflammatory process in MS and for devising strategies to control it. As discussed below, the different classes of cell-mediated immune response have important implications for attempts to develop a vaccination strategy not only for MS but also for AD.

Cellular immune responses can be classified as TH1-type or TH2-type responses (Fig. 2), depending on how they differentiate from TH0 precursors. TH1 (or pro-inflammatory) responses are induced when T cells differentiate in the presence of interleukin 12 (IL-12), and TH1 cells are characterized by the secretion of interferon-γ (IFN-γ) and inflammatory mediators such as tumour necrosis factor-α (TNF-α). TH1-type responses are important in fighting viral infections, and MS seems to be a cell-mediated autoimmune disease of a TH1 type. Anti-inflammatory T-cell responses include both TH2 responses and T cells that have been classified as ‘regulatory cells’. TH2 responses are induced when T cells differentiate in the presence of IL-4, and TH2-type cells secrete anti-inflammatory cytokines such as IL-4 and IL-10. TH2-type responses are important in fighting parasitic infections, and TH1 and TH2 responses may cross-regulate each other.

Another class of T cells comprises regulatory cells that can downregulate TH1-type inflammatory processes. Different types of regulatory cell have been described. TH3 cells act primarily through the secretion of transforming growth factor-β (TGF-β) and are preferentially induced at mucosal surfaces. TH3 cells (T regulatory cell 1) act primarily through the secretion of IL-10 (ref. 17). CD4+CD25+ regulatory cells are T cells that express CD25 (IL-2 receptor) and exert potent regulatory function through cell contact and also through cytokines such as IL-10 and TGF-β (ref. 18). If MS is a TH1-type cell-mediated autoimmune disease, it might be possible to regulate the TH1 responses by the induction of regulatory cell populations.

The induction of TH1-type myelin-reactive cells and their migration into the nervous system is shown in Fig. 2a. It is postulated that T[P (T precursor) myelin-reactive T cells are induced to differentiate into myelin-reactive TH1 cells when an antigen that crossreacts with a myelin antigen is presented to a TH1 cell by an antigen-presenting cell in the context of IL-12 and co-stimulatory molecules. It is generally thought that viruses with structures that crossreact with myelin antigens act as crossreactive antigens. TH1 T cells that react with myelin antigens, such as proteolipid protein (PLP), myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), cross the blood–brain barrier where the myelin antigens are represented to the T cell by antigen-presenting cells in the brain (microglia cells), and an inflammatory cascade is triggered with the release of inflammatory mediators that cause damage to the myelin sheath and ultimately the underlying axon.

One of the primary animal models for MS, experimental allergic encephalomyelitis (EAE), is induced by immunizing different mouse or rat strains with a myelin autoantigen (such as MBP, PLP or MOG) given in complete Freund’s adjuvant, which induces a TH1-type cell-mediated response against the myelin antigen. In EAE, myelin-reactive TH1-type CD4+ T cells migrate from the periphery into the CNS, where they also initiate a cascade of immune-mediated damage (Fig. 2a). In animals, EAE can be induced by the adoptive transfer of TH1-type CD4+ cells specific for one of the myelin proteins.

The hypothesis that MS is a TH1-type disease is supported by several observations. First, it has been shown directly by the effects of γ-interferon, the prototypic T H1 cytokine, which when administered to individuals with MS caused clinical exacerbations. Second, individuals affected with MS have TH1 bias, as indicated by increased concentrations of IL-12 (refs 21, 22) and IL-18 (ref. 23), both of which induce IFN-γ and increase TH1-type chemokine receptor expression. Last, IL-12-secreting cells in the peripheral blood are linked to inflammation in the CNS, as measured by gadolinium enhancement on MRI imaging. Increased numbers of IL-12-secreting cells in the blood are associated with gadolinium enhancement, and chemokine deficiency decreases the number of IL-12-secreting cells, which is linked to clinical response.

In addition to IL-12, it has been shown recently that osteopontin is important in TH1 differentiation in autoimmune demyelinating disease. The most widely used immunomodulatory drug in MS, β-interferon, seems to have two broad mechanisms of action: it decreases γ-interferon secretion by cells in the peripheral blood and blocks the migration of T cells across the blood–brain barrier.

Vaccination
The term ‘vaccination’ stems from the original observation of Jenner and his use of subcutaneous administration of cowpox to prevent the subsequent development of smallpox. Since then, the term vaccination has acquired a broader meaning. According to current immunological theory, vaccination is no longer restricted to administering infectious agents but applies to manipulating the immune system in a...
manner that regulates or suppresses inflammatory and even non-inflammatory processes that can cause tissue damage. Thus, one can redefine vaccination as "the generation or induction of an immune response that is beneficial to the host in halting a pathological process", irrespective of whether that process is immune-mediated, autoimmune or even inflammatory.

Thus, vaccination involves not only the use of the immune system itself to correct or to alter abnormal immune responses that cause damage, but the immune system may be used to affect beneficially pathological processes that are neither autoimmune nor inflammatory. A striking example is represented by reports of the effectiveness of vaccine-induced cell-mediated immune mechanisms, such as stroke or trauma, may have a secondary protective or beneficial role. In an extensive series of studies, Schwartz and co-workers have shown that T-cell autoimmunity against myelin antigens can be beneficial in animal models of central nervous system damage caused by crush injury of the optic nerve or spinal cord contusion. Thus, an "immunological response" directed against nervous system tissue also has the potential to have a protective or beneficial role.

Antigen-specific vaccination in MS

Antigen-specific modulation of the immune system is presumed to be the most specific and potentially least toxic way in which to manipulate the immune system in disease and represents the classic model of vaccination, that is, the induction of an antigen-specific beneficial immune response. For MS, a T<sub>1</sub>-type cell-mediated disease, the strategy is to induce T<sub>1</sub>2 or antigen-specific regulatory cells (Table 1 and Fig. 2b).

Numerous approaches using antigen-specific therapy have been successful in the murine EAE model and some of these have been tested in individuals with M S. The most successful so far has been the use of glatiramer acetate or copolymer 1, which is now an approved therapy for M S. Glatiramer acetate is a random copolymer of four amino acids that was designed to mimic M B P and thus induce EAE. It does not have encephalitogenic properties but instead works effectively in what seems to be an antigen-specific manner to suppress EAE by regulating or suppressing epitope spread, in which damage caused by one T cell specific for one myelin antigen induces reactivity to another myelin antigen. This conundrum seems to have been resolved by the phenomenon of bystander suppression, in which antigen-specific myelin-reactive regulatory cells are induced that secrete anti-inflammatory cytokines such as IL-10 and TGF-β (ref. 37). Such regulatory cells secrete anti-inflammatory cytokines when they encounter the autoantigen in the target tissue and thus suppress inflammation in the CNS caused by T cells of a different specificity. Thus, in the EAE model, one can suppress PLP-induced EAE by glatiramer acetate, by mucosal administration of M B P or by the use of altered peptide ligands of M B P, all of which induce anti-inflammatory regulatory T cell responses (T<sub>1</sub>2, T<sub>1</sub>3). Of note, in immune-deficient mice, T<sub>1</sub>2-type responses can induce a form of EAE.

But therapeutic vaccination is not without potential risks. Both in M S and in AD. In the early 1980s, Jonas Salk and colleagues attempted to treat individuals with M S by injecting large amounts of M B P subcutaneously to 'vaccinate' against putative harmful T-cell responses to M B P. They could induce both cellular and humoral (antibody) immune responses to M B P, but obtained no consistent positive clinical effects and even some suggestion that the injections might have been harmful.
**Alzheimer's disease**

Alzheimer's disease is the most common form of age-related cognitive failure in humans. It is characterized neuropathologically by the progressive accumulation of the 42-residue Aβ peptide in limbic and association cortices, where some of it precipitates to form a range of amorphous and compacted extracellular plaques.

**Human trials of Aβ vaccination in AD**

The finding that active vaccination with Aβ peptide in an animal model led to early clinical trials in which an Aβ synthetic peptide was administered parenterally showed that the peptide has a primary role in the vaccine-mediated clearance of Aβ from the brain, because passive transfer of Aβ antibodies has shown similar beneficial neuroprotective effects.

**Figure 3 Inflammation and immune mechanisms in Alzheimer's disease.**

Accumulation of Aβ leads to stimulation of the innate immune response, including activation of microglia and astrocytes, release of cytokines such as TNF-α and IL-β, complement activation and free-radical formation. This innate immune activation is a two-edged sword, because it can promote the inflammatory pathways that are important in the neuropathological damage that occurs in AD, unlike M. The inflammation in AD seems to arise from inside the CNS with little or no involvement of lymphocytes or monocytes beyond their normal surveillance of the brain.

The inflammatory cytopathology (microglia, astrocytosis, complement activation, increased cytokine expression and acute phase protein response) is thought to represent a secondary response to the early accumulation of Aβ in the brain (Fig. 3). This innate immune response that occurs in the brain, which is presumably secondary to amyloid deposition, leads to the accumulation of inflammatory mediators such as TNF-α, IL-1, IL-6, free radicals and microglial activation.

To what degree this activation of microglia and other potential antigen-presenting CNS cells and secretors of cytokines is involved in the progressive neurodegenerative process is not yet clear, although it has been generally assumed to do more harm than good. Studies of transgenic mice that overexpress an AD-causing mutant form of human amyloid precursor protein (APP) and develop amyloid deposits have shown, however, that crossing such mice with mice overexpressing a natural inhibitor of complement C3 results in a worsening of Aβ plaque load and more neuronal loss.
discontinued shortly after its initiation when roughly 5% of the treated participants developed what seemed to be an immunological reaction involving IL-4, IL-10 and TGF-β. These anti-immunological responses may themselves help the pathologic process by suppressing inflammation and microglial activation, which are believed to contribute to the CNS dysfunction in AD. Furthermore, cells secreting TGF-β may themselves aid in the clearance of Aβ. Such anti-inflammatory T cells would act in the CNS only at sites where Aβ is involved in the inflammatory process and thus would not be expected to interfere with normal physiology.

Aβ as an autoantigen

We have found recently that APP transgenic mice, which produce robust quantities of Aβ in the brain, have a form of immunological tolerance in which they show significantly lower T-cell responses when immunized with Aβ than do wild-type mice. This deficit can be overcome in part by providing T-cell help to the animal. Thus, the presence of abundant Aβ in the brain may not only cause local neuronal and glial damage but also hinder the generation of a therapeutic immune response, whether innate or induced.

Very recently, we have begun to extend such analyses to humans and, by using sensitive short-term cloning techniques, have found heightened in vitro reactivity of peripheral T-cells against Aβ in some elderly individuals and people with AD. Early studies did not find lymphocyte proliferation in response to APP peptides in individuals with AD. The likelihood of seeing this T-cell hyperreactivity in humans increased with age but was not observed in all individuals with AD or all aged normal individuals. Our results raise the possibility that endogenous T-cell reactivity in a host may relate to the progression of the cytopathic process of AD. In addition, such data suggest that it may be useful to test individuals for their intrinsic T-cell reactivity to Aβ before offering them any immunotherapeutic approach based on Aβ.

Beneficial versus deleterious T-cell responses

The issue of beneficial versus deleterious T-cell responses in vaccine trials with a humanized monoclonal antibody to Aβ expressed in mice vaccinated with Aβ peptide plus pertussis. Efforts are underway to determine the basis for the adverse inflammatory reaction induced by Aβ, and to attempt to model it in animals. No abnormal effects have been documented in APP transgenic mouse models in which Aβ antibodies have been administered, and such mice have shown robust clearing of brain Aβ deposits and even improvements in behavioral deficits. This is in contrast to the EAE model in which administration of antibody to MOG worsens the progression of EAE. There is therefore an interest in conducting trials with a humanized monoclonal antibody to Aβ as the next step in the clinical evaluation of the immunotherapeutic approach to AD. It may also be possible to immunize with portions of Aβ to generate only antibodies that target N-terminal residues.

to relate to the generation of immune response against MOG, but to the type of immune response. In the SJL mouse there is infiltration of cells expressing γ-interferon in the brain and a predominately helper T-cell response, whereas in the B10.M mice there is a Th2 and Th3 response that seems to prevent disease. Thus, the immune repertoire of the host before vaccination may determine the outcome of vaccination.

It seems that vaccination strategies both in AD and in MS will be dependent on skewing the immune response in such a way that it is not detrimental to the host. In this regard, we have found in the APP mouse model of AD that nasal administration of Aβ induces antibody responses in association with an ‘anti-immunological’ cellular immune response involving IL-4, IL-10 and TGF-β. These anti-immunological responses may themselves help the pathologic process by suppressing inflammation and microglial activation, which are believed to contribute to the CNS dysfunction in AD. Furthermore, cells secreting TGF-β may themselves aid in the clearance of Aβ. Such anti-inflammatory T cells would act in the CNS only at sites where Aβ is involved in the inflammatory process and thus would not be expected to interfere with normal physiology.