Meeting report

Rapid progress in the field of infectious and autoimmune disorders of the nervous system*

In recent years, there has been significant progress in the understanding of inflammatory diseases of the CNS. The use of novel immunological and molecular biological approaches is a major driving force for this development. This report summarizes the key contributions of an international symposium entitled 'Recent Developments in the Pathogenesis of Inflammatory CNS Disorders', which was recently held in Bonn, Germany, to highlight this rapidly expanding field.

Inflammatory diseases of the CNS pose major clinical problems worldwide, since many of them are still associated with a high mortality rate and permanent neurological deficit. These disorders are caused by infectious organisms or by autoimmune reactions in the nervous system. Complex interactions between infectious agents or the autoantigen, the immune system, and the nervous system are involved in their pathogenesis. Among the infectious agents, bacteria, parasites, viruses including HIV, and prions are of particular importance, whereas multiple sclerosis still represents the major challenge in the field of autoimmune disorders.

In order to develop more effective therapeutic strategies, the nature of the pathogens and their interactions with the host as well as basic mechanisms of immune reactions in the nervous system have to be elucidated.

Parasitic infections

Among parasitic infections of the CNS, malaria and toxoplasmosis have received considerable attention. G. Grau (Geneva, Switzerland) described novel aspects of the pathogenesis of experimental cerebral malaria. He presented the hypothesis that cytokine-induced *de novo* expression of cell adhesion molecules on cerebral endothelial cells mediates adhesion of blood cells to endothelia. This may induce plugging of cerebral blood vessels and cause sudden death. Inflammatory perivascular infiltrates are consistently absent. A similar mechanism is likely to operate in the pathogenesis of

human cerebral malaria, since the histopathological findings in the human brain are virtually identical. The survival of experimental animals in cerebral malaria following injection of antibodies to the leucocyte function associated antigen LFA-1 and to TNF- α , which triggers expression of cell adhesion molecules on cerebral endothelial cells, strongly supports this model.

Toxoplasma encephalitis has gained much interest in the last decade due to its high incidence in AIDS patients, where it represents the most common opportunistic infection of the brain. M. Deckert-Schlüter (Bonn, Germany) introduced several animal models of *Toxoplasma* encephalitis and analysed the impact of host genetic factors on the regulation of the intracerebral immune response to *Toxoplasma (T.) gondii*. A role for both genes within the major histocompatibility complex (MHC) and MHC-unrelated genes was demonstrated in congenic strains of mice. Irrespective of the genetic background of the animals, common prognostic indicators could be identified. High numbers of intracerebral CD4⁺ and CD8⁺ T cells as well as high intracerebral TNF- α and IFN- γ levels correlated with a favourable outcome. In addition, there was a strong activation of microglial cells. In *T. gondii*-infected rats, microglia exhibited an induction of CD4 antigens, which may be of key relevance for the understanding of HIV-associated CNS manifestations in AIDS patients.

Bacterial infections

Despite the impressive arsenal of modern antibiotics, the outcome of bacterial CNS infections is still poor. H. W. Pfister (Munich, Germany) introduced the hypothesis that components of the bacterial wall such as teichoic and lipoteichoic acid in Gram-positive bacteria and lipopolysaccharide in Gram-negative bacteria induce cerebrovascular complications, brain oedema and hydrocephalus. Cytokines and other immune mediators in the CSF may contribute to this mechanism. This cascade may even be enhanced by the release of bacterial cell wall components during aggressive antibiotic therapy. To counteract these mechanisms, Pfister proposed corticosteroids in combination with antibiotics for the treatment of bacterial meningitis. Partial amelioration in an experimental model of bacterial meningitis in rabbits was also achieved by injection of an antibody to cell

*The meeting was held in Bonn, Germany, on May 25–27, 1995. It was organized by M. Deckert-Schlüter, D. Schlüter, H. Hof, and O. D. Wiestler and sponsored by the Deutsche Forschungsgemeinschaft and the Ministerium für Wissenschaft und Forschung des Landes Nordrhein-Westfalen.

adhesion molecules (CD18), which reduces the severity of the inflammatory reaction in the subarachnoid space.

Involvement of bacterial components in the pathogenesis of meningitis was studied by E. Tuomanen/B. Spellerberg (New York, USA/Aachen, Germany). The chemical structure of the polysaccharide capsule determines the virulence of pneumococci, and cell wall components are important stimulators for the recruitment of leucocytes to the subarachnoid space. This group was able to identify sugar moieties in bacterial polysaccharides with the potential to open the blood-brain barrier. These findings do not only highlight the role of bacterial cell wall components in pneumococcal meningitis, but also point to a novel mode of drug delivery in various CNS disorders.

Listeria (L.) monocytogenes preferentially affects children, pregnant women, and immunocompromised patients. K. Frei (Zürich, Switzerland) and D. Schlüter (Mannheim, Germany) analysed experimental murine *L. monocytogenes* infection of the CNS. K. Frei focused on cytokine production in this disease and showed that interleukin (IL)-10 is detectable in the CSF of patients with bacterial meningitis and in mice with *L. monocytogenes* infection. IL-10 may contribute to the down-regulation of the immune response in the CSF, since IL-10 dose dependently impaired the listericidal activity of IFN- γ -activated macrophages, and antibodies to IL-10 abrogated bacterial growth in macrophages *in vitro*. These observations may provide an explanation for the insufficient killing of bacteria in the CNS. D. Schlüter identified ependymal cells, plexus epithelial cells, and neurons as targets for *L. monocytogenes* in the brain. Protection against the fatal course of the disease was achieved by immunization which induced an early recruitment of CD4⁺ and CD8⁺ T cells to the brain and an accelerated production of protective cytokines. A decisive role of CD4⁺ and CD8⁺ T cells for the immunity to *L. monocytogenes* was demonstrated in cell depletion experiments.

Viral infections

Measles virus infections still pose an important problem in Africa and Asia. V. ter Meulen (Würzburg, Germany) identified a defective measles virus as the pathogenic agent of subacute sclerosing panencephalitis (SSPE) of childhood. These mutants lack viral budding and show a

reduced expression of the viral envelope proteins. Significant spread of these mutants in the CNS occurs in the presence of a strong anti-measles immune response. This indicates that the viral mutants escape detection by the immune system. V. ter Meulen's group has also analysed the interaction between virus and host. He presented strong evidence that two cellular membrane proteins, the membrane cofactor protein CD46, and moesin, a membrane-organizing external spike protein, are functionally associated with measles virus infectivity of cells.

A wide spectrum of intracerebral immune responses upon viral infections was illustrated in contributions on experimental Sindbis virus, lymphocytic choriomeningitis virus (LCMV), and coronavirus infection of the CNS. Antibodies are particularly important for the clearance of Sindbis virus, which elicits a strong TH2 cytokine response in the brain (D. Griffin, Baltimore, USA).

J. Löhler (Hamburg, Germany) presented LCMV infection, a classical example for a CD8⁺ T cell mediated immune reaction. This virus primarily infects structures of the circumventricular organs in mice. The infection is terminated solely by specifically activated CD8⁺ T cells. Studies with genetically manipulated β_2 -microglobulin-deficient mice, which lack CD8⁺ T cells, revealed that the virus cannot be eliminated from the brain of these animals. Infusion of immune spleen cells from syngeneic wild type mice results in viral clearance. This interesting observation indicates that LCMV-infected murine cells can effectively present viral antigen to CD8⁺ effector T lymphocytes together with MHC class I molecules in the absence of β_2 -microglobulin.

The course of coronavirus-induced encephalitis in the rat is significantly influenced by host genetic factors (R. Dörries, Mannheim, Germany). In BN rats, an early T and B cell response results in rapid clearance of the virus from the brain. In contrast, Lewis rats show a delayed immune response, and this allows the virus to infect a significant number of parenchymal cells, predominantly oligodendrocytes. Therefore, in Lewis rats immune-mediated viral clearance is associated with a significant neurological sequel.

HIV infection

The major challenge in the field of HIV encephalitis is to determine pathogenic mechanisms underlying the development of this common encephalopathy in AIDS

patients. This question still remains unresolved despite intense research efforts over almost a decade. C. A. Wiley (Pittsburgh, USA) noticed that AIDS dementia now occurs more frequently than in the early years of the AIDS epidemic, since AIDS patients have an improved survival due to effective therapy of opportunistic infections. With the viral burden as a parameter of severity of HIV encephalitis it was shown that all patients with clinical signs of AIDS dementia had significant amounts of viral genome in their brains. In AIDS dementia, analysis of the regional distribution of HIV DNA in the CNS revealed a high affinity of the virus for the deep grey matter. This appears to indicate that HIV-associated encephalopathies are not restricted to the white matter. Immunohistochemistry, antigen capture assay, and *in situ* hybridization techniques showed that the majority of AIDS patients had evidence of CNS infection at the time of autopsy.

S. Lipton (Boston, USA) presented a model of HIV-related neuronal injury and proposed a common final pathway of neurotoxicity for disorders as diverse as HIV infection, stroke, trauma and epilepsy. He suggested that HIV-infected macrophages/microglial cells are activated by gp120 to produce neurotoxic agents including nitric oxide, arachidonic acid and its metabolites. These factors can lead to increased glutamate release or decreased glutamate re-uptake. In addition, activated macrophages produce increased amounts of the glutamate-like agonist quinolinate. Activation of voltage-dependent Ca^{2+} channels and NMDA receptor-associated channels lead to a significant Ca^{2+} increase in neurons. Excessive intracellular Ca^{2+} is thought to contribute to the formation of free radicals, cellular necrosis, and, possibly, apoptosis. Attempts to interfere with this neurotoxic pathway using NMDA antagonists are currently in progress.

Prion diseases

Prion diseases have gained considerable attention due to the fascinating nature of the scrapie agent and due to the bovine spongiform encephalopathy (BSE) epidemic in Great Britain. In his key note address, C. Weissmann (Zürich, Switzerland) highlighted the current status of the prion hypothesis. Elegant studies in prion protein (PrP)-deficient mice have clearly demonstrated the requirement of normal cellular prion protein (PrP^C) for the development of scrapie. Transplantation experiments between PrP-deficient and PrP⁺-animals may open a

new avenue to analyse the pathogenesis of these disorders. Major issues which remain to be elucidated include the mechanism of formation of the pathogenic PrP^{Sc} isoform and the mechanism of PrP^{Sc}-induced neurotoxicity.

Autoimmune diseases

One session was mainly devoted to demyelinating disorders of the central and peripheral nervous system.

M. Brahic (Paris, France) covered the topic of Theiler's virus infection as a viral model of CNS demyelination. Inbred strains of mice differ greatly in their susceptibility to this infection. The DA strain of Theiler's virus causes a persistent infection of the white matter with chronic inflammation and primary demyelination in susceptible animals, whereas resistant mice do not develop inflammatory lesions. The genetic control of resistance could be mapped to the H-2D region of the murine MHC and to the IFN- γ gene. Furthermore, his group could demonstrate that in IFN- α/β -receptor- and IFN- γ -receptor-deficient mice, IFN- α/β and IFN- γ play distinct roles in the course of the immune response to Theiler's virus. There is also evidence that different viral strains determine the pattern of disease.

H. Wekerle (Martinsried, Germany) gave an overview of the model of experimental allergic encephalomyelitis (EAE), the classical animal model for multiple sclerosis (MS). He summarized basic neuroimmunological reactions in this model. Fascinating new data on MHC class I expression on neurons may well end a longstanding debate on this matter and may have a great impact on our understanding of neural degeneration. Under normal conditions, astrocytes actively suppress MHC class I expression on neurons. However, this suppression is lost in irreversibly damaged, electrically silent neurons, which may now be immunologically recognized and destroyed by CD8⁺ T lymphocytes.

H. Lassmann (Vienna, Austria) presented oligodendrocyte neuropathology in various stages of MS lesions in a rare set of human brain biopsies. Loss of oligodendrocytes was only marginally related to the stage of demyelinating activity within the lesions. It was also shown that in an early stage of the disease, oligodendrocytes may be largely preserved in some patients, whereas in others oligodendroglial loss is already pronounced.

H. P. Hartung (Würzburg, Germany) illustrated various forms of the Guillain-Barré syndrome (GBS), a

clinically important demyelinating disease of the peripheral nerve. Its aetiology is still unknown. Recent data indicate that the GBS is associated with *Campylobacter (C.) jejuni* infection. According to the concept of molecular mimicry, *C. jejuni* and peripheral nerve share epitopes, which are recognized by *C. jejuni*-specific T cells and induce an autoimmune reaction in the peripheral nerve. Studies in experimental allergic neuritis (EAN), a rat model for the GBS, showed autoreactive T lymphocytes specific for the myelin antigens PO and P2 as well as circulating antibodies to these antigens as pathogenic factors involved in autoimmune neuritis.

This meeting with 150 scientists from both basic and clinical neurosciences and immunology has produced an intense exchange of current views and concepts on

the pathogenesis of inflammatory CNS disorders. The organizers are convinced that interdisciplinary research between neurologists, neuropathologists, virologists, microbiologists, immunologists, and molecular biologists will considerably advance the field and may well result in novel and more successful therapeutic strategies.

M. Deckert-Schlüter, D. Schlüter, H. Hof* and*

O. D. Wiestler

Institut für Neuropathologie,

Universitätskliniken Bonn,

Bonn, Germany and

**Institut für Medizinische Mikrobiologie und Hygiene,*

Universität Heidelberg,

Fakultät für Klinische Medizin Mannheim,

Mannheim, Germany