This multi-author book, like the first edition and despite the title, concentrates mainly on features of the inflammatory response in the CNS, its peculiarities and possible significance in the development of neuronal loss during disease and following trauma. Inflammation is a basic pathological process and its role in diseases of the CNS has always been of interest, in part because it is not quite the same as in the peripheral tissues. Peculiarities of the CNS—the blood–brain barrier, absence of lymphatics, high density of endogenous down-regulated myeloid cells (microglia) and small extracellular space—all contribute to the characteristics of inflammation in this tissue. But there has also been an increasing awareness that inflammation in chronic degenerative diseases involving neuronal loss may not just be a response to the degeneration but may also be contributory to the tissue damage. Inflammation is a response to the breaching of a tissue’s integrity, directly or as a consequence of invasion by other organisms, and the sequence of events in peripheral tissues is well known. In the CNS, some of the key cellular players are not so obvious, e.g. mast cells and there is limited invasion by polymorphonuclear leucocytes (PML), whereas the changes in vascular permeability are more dramatic because of the normally low permeability and the small extracellular space combined with a severe anatomical restriction to tissue swelling.

All of the chapters review information derived from basic research as well as from clinical and pathological studies and so are of general interest. Of four new chapters, three are particularly concerned with aspects relating to disease, viz. Neuroimaging of inflammation, Focal cerebral ischemia and the CNS response to inflammation in the periphery. Inflammation is of course an essential component of the adaptive immune response reflecting the activity of the innate immune system, but immune responses are not a major concern in this volume, excepting for the last chapter in which the latest experimental and therapeutic experiences relating to the transplantation of tissue and embryonic or stem cells for the treatment of Parkinsonism and Huntington’s disease are described. The enhanced survival of tissue grafts in the brain was the origin of the concept that this organ was ‘immune privileged’, although it has been known for a number of years that the degree of privilege enjoyed by a graft is very dependent on the grafting site and surgical skill employed; factors mentioned here but not fully explored since the graft site is predetermined by the diseases under consideration.

In a volume of this kind dealing with a single topic, the same ground may be covered by several authors, this is useful since each examines a problem from the viewpoint of his or her own speciality. This increases the appreciation of the complexity of the situation and can help in the critical evaluation of the findings. For example, Anthony and Campbell emphasise that invasion of the parenchyma by PMLs in the acute phase is a major factor in inflammatory damage, whereas in discussing focal ischemia, del Zoppo and Hallenbeck conclude that PML adhesion in the microvasculature is responsible for poor perfusion and a worse outcome. Thus, therapeutic agents aimed at PML involvement and which target their adhesion to the endothelium, could well be beneficial but would not help to distinguish between the two mechanisms.

The myeloid cells are key players in inflammation and attention is directed in several of the chapters to the role of endogenous myeloid cells, the microglia, perivascular macrophages and those present in the meninges. The microglia are clearly important, their numbers, morphology and distribution mean that nowhere in the CNS can damage occur without it impinging on these cells. Their normal morphology would suggest that they have limited motility and do not patrol the tissue, a possible explanation for their high density. Most of the authors refer to the fact that normally these cells appear to be heavily down-regulated with low expression of many normal macrophage receptors, and the activation of microglia is commonly equated with inflammation. This is the basis of the imaging of inflammation reviewed in Chapter 4, since on activation the level of the peripheral benzodiazepine binding site is greatly increased enabling the use of $^{11}$C-PK11195 for PET. This procedure has dramatically demonstrated the widespread activation of microglia in Alzheimer’s disease (Chapter 10). This technique has produced some fascinating results although, as pointed out by Banati, it is expensive and it is questionable as to whether it provides added value in clinical practice. This form of imaging could however provide a valuable additional means of monitoring drug action in therapeutic trials where the objective is to suppress inflammation. Differences in microglial and inflammatory responses with age are covered in the first chapter, although their role and the question of inflammation in foetal brain development during the period of massive neuronal death is not covered. During inflammation it is also quite clear that they are the most significant endogenous source of both pro- and anti-inflammatory cytokines. There is however a duality in the perceived role
of the individual molecules and the cellular processes in CNS inflammation, which is referred to in several of the contributions and in particular in the discussion of traumatic brain injury and of focal cerebral ischemia. Most experimental work suggests that the acute phase of inflammation is most likely damaging, however, its role in the later and more chronic situations is confusing. This problematic duality is seen clearly in the actions of cytokines and in particular of TNFα, IL-1β and IL-6, reviewed in Chapter 7. The physiological aspects of certain cytokines on brain function and the HPA-axis is well covered by Konsman and Luohesi who review current ideas relating to the fever, fatigue and anorexia associated with peripheral infection and inflammation. Again IL1β and IL-6 feature prominently in the discussion although precise mechanisms are not resolved. Therapeutic trials targeting different aspects of inflammation in different neurological diseases started years ago, particularly in MS, but these are increasing as new drugs are developed and used successfully in treating inflammatory diseases of peripheral tissues. However, the underlying duality of the effects of inflammation in the CNS can mean that the results are disappointing. Thus, in MS the use of anti-TNFα, successful in rheumatoid, has proved unsuccessful. Axonal loss is now recognised to be an important accumulating deficit in this disease (Cuzner and Woodroofe, Chapter 9), and although it is suspected that the loss is an acute response to inflammatory product(s) of macrophages, the guilty party has not yet been identified. One prominent suggestion arising in explanations for neuronal death and axon loss is that, because of its actions on astrocytes and oligodendrocytes, inflammation affects the tissue glutamate balance. Verkhratsky and Jones discuss the astrocytic syncitium and provide a comprehensive review of the response to inflammation and injury in these neural cells. In MS, the inflammation is considered to result from the autoimmune response, but in many other situations the origin of the inflammation is not known, but is most likely related to neuronal death and degeneration of axons, dendrites and presynaptic terminals as seen in Alzheimer’s disease and following toxin-induced neuronal death (Chapters 2, 8 and 10).

Inflammation is almost a prerequisite for the generation of an adaptive immune response, and the question of the generation or enhancement of autoimmunity during brain inflammation has long been considered a possibility. Clearly, immune responses against antigens in the CNS take place, but in the periphery, how and which cells carry antigen to the lymphatic organs is important. Possibly more important is the identity and site within the CNS of cells capable of presenting antigen to circulating primed T cells. This is covered in relation to the blood–brain barrier by Johansson who draws attention to the perivascular myeloid cells. Interestingly, recent approaches to the treatment of Alzheimer’s disease have involved active immunisation to provide antibodies against the proposed neurotoxic and pro-inflammatory β-amyloid thus opsonising these deposits and so aiding their removal by macrophages/microglia. Since the phago-

cytosis of antigen–antibody complexes would itself activate the phagocytic cell, this presents a difficulty in the argument. Recent histopathological findings (Nicol et al. Nat. Med. 2003; 9: 448–452) in one of a series of patients immunised against β-amyloid who developed meningoencephalitis, indicate that the treatment does possibly remove amyloid plaques but does not reverse the clinical status nor the presence of neurofibrillary tangles. A side effect of the treatment appeared to be a T cell immunisation, which may have also been directed against cerebral vascular amyloid and generated further inflammation. The influence of NSAID usage in inhibiting the development and progress of Alzheimer’s seems well founded, supporting the conclusion that inflammation is a factor in the promotion of this disease and possibly, as suggested by Rogers, Kovelowski and Strohmeyer, an anti-inflammatory treatment will need to be coupled with immunisation. Because of the dual effects of inflammation in the brain, it is likely that any anti-inflammatory treatment regime will need to take this duality into account.

Reading such a book can be useful in another way since it draws attention to those topics that are absent or where information is missing. So although the book has ‘the nervous system’ in the title, inflammation in the peripheral nervous system is not covered although acute and chronic inflammatory neuropathies are important clinically. Explanations or investigations into the normally down-regulated status of microglia has received little attention. Nor is there much information on the status and dynamics of neo-vascularisation in the brain which follows injury and inflammation in peripheral sites. Even so, this slim volume (amazingly it is the same size as the first edition) provides a clear, concise, informative, and most importantly, readable, collection of up-to-date essays on various aspects of inflammation in the CNS. Because of the diversity of the contributor’s view points, I think that it would provide a good introduction for those unfamiliar with inflammation or for those unfamiliar with the special problems relating to the nervous system.

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