Demyelinated lesions in the cerebral cortex and cortical atrophy have recently been recognized as important components of multiple sclerosis pathology. Although it has consistently been recognized in studies on the pathology of multiple sclerosis that demyelination may not only affect white matter but also the cortex and deep grey matter nuclei (Brownell and Hughes, 1962; Lumsden, 1970; Kidd et al., 1999; Cifelli et al., 2002), only the application of modern techniques for immunocytochemical detection of myelin antigen has revealed its extent, particularly in patients who died during the progressive stage of the disease (Peterson et al., 2001; Kutzelnigg et al., 2005). Three types of cortical lesions have been identified: combined cortico/subcortical lesions, perivascular intracortical lesions and band-like subpial lesions, which affect the cerebral cortex over several adjacent gyri and sulci (Bo et al., 2003a). In particular, the subpial lesions can be very extensive, affecting >60% of the cortical ribbon in the cerebrum (Kutzelnigg et al., 2005), the cerebellum (Kutzelnigg et al., 2007) and the hippocampus (Geurts et al., 2007).

In the early descriptions of cortical lesions in patients with progressive disease, it was emphasized that they differ from white matter lesions by the absence of perivascular and parenchymal infiltrates of T-and B-lymphocytes, vascular inflammation and blood–brain barrier disturbance (Bo et al., 2003b), whereas active demyelination and neurodegeneration was only associated with microglia activation. Thus, it was suggested that these lesions are due to neurodegenerative events that occur independently from inflammation. This view, however, has changed recently. Biopsies from patients with multiple sclerosis taken for diagnostic reasons showed that cortical demyelination is already present at early stages of the disease and, when this happens, the lesions show profound lymphocytic infiltration similar to that seen in active white matter lesions (Lucchini et al., 2011). In addition, even in patients with secondary progressive multiple sclerosis, there is profound inflammation in the meninges (Serafini et al., 2004; Magliozzi et al., 2007), which is topographically related to subpial demyelination in the underlying cortex (Kutzelnigg et al., 2005). Furthermore, the extent of active cortical demyelination and neurodegeneration correlated well with the severity of the inflammatory process in the meninges (Howell et al., 2011). Although these studies suggested that cortical lesions may also be associated with meningeal inflammation (Kutzelnigg et al., 2005) in primary progressive multiple sclerosis, a systematic investigation of the relationship between meningeal inflammation and cortical pathology in such patients has not been available. This topic is now addressed in detail in a study by Choi and colleagues (2012), published in this issue of Brain. The study makes use of the large collection of very well-characterized autopsy tissue from patients with primary progressive multiple sclerosis, which has been collected at the UK Multiple Sclerosis Society Tissue Bank at Imperial College, London. Here, the authors describe profound meningeal inflammation composed of T cells, B cells and macrophages in primary progressive multiple sclerosis, and show that the extent of meningeal inflammation correlates with microglia activation and the activity of demyelination or neurodegeneration in the underlying cortex. Furthermore, patients with extensive meningeal inflammation showed a more severe clinical course, shorter disease duration and younger age at death. In contrast to secondary progressive disease, no tertiary lymphoid-like structures were seen in the meninges of patients with primary progressive multiple sclerosis. These data further support the view that meningeal inflammation may drive tissue injury in the cortex, and that soluble factors, produced by activated lymphocytes within the meninges, may diffuse into the cortical tissue and induce demyelination and neurodegeneration either directly or indirectly through microglia activation (Choi et al., 2012).

However, the factors responsible for inducing demyelination and neurodegeneration in cortical lesions remain unresolved. Selective, plaque-like inflammatory demyelination is highly specific for multiple sclerosis and is not seen in other acute or chronic inflammatory diseases of the brain or meninges (Moll et al., 2007). In experimental studies, only two inflammatory mechanisms have been shown to lead to large scale primary demyelination typical of multiple sclerosis. These are either specific demyelinating antibodies, which reach the tissue in the context of a T-cell-mediated inflammatory process (Pomeroy et al., 2005; Merkler et al., 2006; Storch et al., 2006), or cytotoxic, major histocompatibility complex class I-restricted T cells, which are directed against oligodendrocyte or myelin antigens (Saxena et al., 2008). In cortical lesions, however, evidence for antibody and complement-mediated demyelination (Brink et al., 2005) or specific targeting of oligodendrocytes by activated cytotoxic T cells is currently lacking (Lucchini et al., 2011). However, absence of evidence is not...
evidence for absence, and the failure to detect antigen-specific mechanisms in the induction of cortical demyelination may be owing to the slow evolution of tissue injury in such lesions. Alternatively, induction of tissue injury in cortical lesions may be owing to other mechanisms which are, at present, unresolved.

In this respect, a second study published in this issue of Brain (Kolasinski et al., 2012) may help. In a very detailed investigation combining MRI and neuropathology, the authors found a significant correlation between neurodegenerative events between interconnected cortical areas, while white matter tracts and the thalamus. Thus, nerve cell or axonal loss in a given brain area appears to give rise to anterograde or retrograde degeneration in connected brain areas. Such neurodegeneration distant from the site of initial tissue damage will lead to microglia activation. This microglia activation may originally have beneficial effects by removing tissue debris and producing neurotrophic factors. However, microglia, pre-activated in the course of neurodegeneration, can be more easily converted into a cytotoxic phenotype when exposed to a pro-inflammatory cytokine milieu (Perry et al., 2010). In the context of cortical lesions, this could mean that cytokines produced by meningeal lymphocytes target microglia, which are already partially activated owing to anterograde or retrograde neurodegeneration, more efficiently by comparison with resting microglia, and stimulate their production of toxic effector molecules such as reactive oxygen or nitric oxide intermediates. As in other lesions, increased oxidative stress in such a scenario could play a major role in the induction of oligodendrocyte death and axonal and neuronal degeneration (Haider et al., 2011).

In conclusion, the two studies published in this issue of Brain add interesting new information to the enigma of cortical lesion pathogenesis in multiple sclerosis. The data support the view that meningeal inflammation plays an important role in the induction and propagation of cortical pathology in multiple sclerosis; but they also indicate that additional and, thus far, unknown mechanisms are necessary to trigger widespread demyelination and neurodegeneration in the cortex.

Hans Lassmann
Centre for Brain Research Medical University of Vienna, Vienna, Austria

Correspondence to: Hans Lassmann
Centre for Brain Research
Medical University of Vienna
Spitalgasse 4
A-1090 Vienna, Austria
E-mail: hans.lassmann@meduniwien.ac.at

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