Although multiple sclerosis is commonly designated as an inflammatory demyelinating disorder of the central nervous system, historical and modern descriptions have underscored the involvement of axons and neuron cell bodies as germane to a more complete understanding of the pathophysiology of the disease (Raine and Cross, 1989; Ferguson et al., 1997; Trapp et al., 1998; Bitsch et al., 2000; Peterson et al., 2001; Lassmann, 2004; Bruck, 2005; Hauser and Oksenberg, 2006). Indeed, recent research has yielded evidence confirming neuronal apoptosis in multiple sclerosis plaque lesions, and signs of oxidative stress in cortex, hippocampus and deep grey matter structures (Peterson et al., 2001; Bo et al., 2003; Dutta et al., 2006). Several studies have suggested a correspondence between the magnitude of the disease burden within the cerebral cortex and the predilection for having a progressive phenotype of multiple sclerosis (Kutzelnigg et al., 2005; Lassmann et al., 2007). The recently established paucity of inflammatory cell infiltrates and glial cell activation in grey matter lesions suggests that the pathobiological underpinnings of tissue injury in grey matter may be distinctive from that of white matter. In particular, grey matter injury could principally be the derivative of a primary neuronal mechanism of pathology, or perhaps secondary to indirect influences such as axonal injury and transection, culminating in neuronal degeneration and humoral injury cascades including antibodies, cytokines, proteases, nitric oxide and glutamate (Rudick and Trapp, 2009; Steinman, 2009).

That multiple sclerosis neuronal pathology concomitantly exists in the eye and brain is also not a new principle, but rather has escaped extensive pathological re-exploration in the past few decades (Sharpe and Sanders, 1975; Fisher et al., 2006; Gordon-Lipkin et al., 2007; Sepulcre et al., 2007; Waxman and Black, 2007). The occurrence of inflammation in the eye, as manifested by retinal periphlebitis and uveitis in patients with multiple sclerosis, has been recognized for many decades, but was only recently related to nerve fibre layer injury and brain atrophy. It is of further interest that, although retinal axons are unmyelinated (with myelin as the putative target of the disease process in multiple sclerosis), inflammatory activity within the eyes of patients with multiple sclerosis corroborates the hypothesis that the immune response in this disorder may be directed against antigens other than myelin, and establishes a precedent to explore actively innovative approaches that will characterize more fully these novel immune response repertoires. There has been a recent resurgence of interest in the anterior visual pathway as a window on the brain. The increased application of high-resolution optical coherence tomography has revealed that retinal nerve fibre layer thinning is a common occurrence in multiple sclerosis and exists independent of a history of optic neuritis (Trip et al., 2005; Fisher et al., 2007; Gordon-Lipkin et al., 2007; Pulicken et al., 2007; Sepulcre et al., 2007; Henderson et al., 2008). Bolstering the contention that occult disease activity targets the eye in a fashion similar to tissue injury in the brain and spinal cord, patients with primary progressive multiple sclerosis (those without inflammatory demyelinating attacks of any variety) also exhibit abnormally thinned retinal nerve fibre layers; and longitudinal changes in retinal nerve fibre layer thickness can be measured over time both in patients with and without a history of optic neuritis (Pulicken et al., 2007).

In this issue of Brain, Green and colleagues report a post-mortem analysis of eyes from 82 cases of multiple sclerosis and 10 control patients with neurological disease. They report extensive retinal atrophy with shrunken neurons and dropout of both retinal ganglion cells in 79% of eyes, and inner nuclear layer (amacrine and bipolar cells) atrophy in 40% of eyes from people with multiple sclerosis. A subset of patients was examined by immunohistochemistry, which revealed human leucocyte antigen-DR reactive cells with a phenotype of microglia, and evidence of axonal loss and injury. There was also extensive glial fibrillary acid protein immunoreactivity consistent with astroglial cell activation. The severity of retinal atrophy was significantly associated with post-mortem brain weight and there was a trend towards an association with disease duration, suggesting that the observed pathology may be indicative of more global changes occurring in the brain over time. The conspicuous observation of frequent involvement of the iris in multiple sclerosis was also observed and associated with severity of the retinal pathology. None of these pathologic processes were observed in the control cases.

Limitations of this report include the categorical analysis of tissue pathology and skewing of samples for multiple sclerosis cases, with no central nervous system disease controls, and the limited number of cases examined for immunohistochemical staining (five cases providing a total of eight eyes). The absence of
detailed clinical histories and the less than optimal tissue preservation limited further clinicopathological correlation and ultrastructural analysis.

Nonetheless, this is the first description of inner nuclear layer cell loss in multiple sclerosis and is a reminder of the important lessons that can be learned from careful neuropathological examination. This report potentially represents a paradigm shift in our thinking about the mechanisms of neuronal disease, much in the way that the application of confocal microscopy strikingly revealed pervasive axonal transections and terminal ovoid profiles that rekindled interest in the relevance of axonal pathology in multiple sclerosis. While retinal ganglion cell dropout can be reconciled by understanding the relationship between optic nerve inflammation and consequent damage to nerve axons, the involvement of the inner nuclear layer is substantially more provocative. Specifically, the paucity of inflammatory mononuclear cells in the inner nuclear layer is worthy of further analysis in multiple sclerosis. The retinal nuclear loss in both the ganglion and inner nuclear cell layers in eyes from patients with a history of multiple sclerosis may reflect more global pathology in the central nervous system. Indeed, in one study, nerve fibre layer was associated with cerebral white matter volume but not grey matter volume (Gordon-Lipkin et al., 2007). Perhaps specific measurement of segmented nuclear cell layers will reflect cerebral cortical pathology better in specific subtypes of multiple sclerosis. A major caveat emphasized by the study of Green and colleagues is the presence of astroglial cells in the ganglion cell layer and microglial cells that extend down into the inner nuclear layer, which could confound measures of nuclear layer thickness.

Electroretinograms may also prove useful in examining for ganglion cell or inner nuclear layer pathology in multiple sclerosis. There are several old reports of abnormalities detected by electroretinography, but these were mostly in patients with optic neuritis and the abnormalities were attributed to retrograde degeneration (Persson and Wang, 1984; Falsini et al., 1999). Perhaps a more careful analysis could reveal cases in which there is evidence for primary retinal pathology.

Taken together, the findings by Green and colleagues of extensive retinal nuclear loss in both the ganglion and inner nuclear cell layers in eyes from patients with a history of multiple sclerosis provide clear documentation of neuronal pathology that in the case of the inner nuclear layer seems to be independent of classical mononuclear cell-mediated inflammation and myelin antigens. Resolving whether this is related to humoral mechanisms directly or indirectly targeting retinal neurons, or a manifestation of trans-synaptic degeneration, could provide major insights into the underpinnings of neuronal damage in multiple sclerosis.

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