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# A reappraisal of the roles of glial and vascular elements in the development of white matter necrosis in irradiated rat spinal cord

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In patients, white matter necrosis can be an incapacitating and possibly fatal complication of radiotherapy involving brain or spinal cord. White matter necrosis in the cervical spinal cord of the rat occurs between 4 and 8 months after single doses of X-rays greater than approximately 20 Gy. Lesions which are clearly vascular in nature occur following lower radiation doses and at times longer than 1 year post-irradiation. Over the last decade, white matter necrosis in rat spinal cord has been used as an endpoint in a number of studies to establish dose-time-fractionation relationships for both low and high LET radiations (e.g. see van der Kogel, 1983 for review). Up to 15 or 20 years ago a considerable effort was put into identifying the nature of the pathogenesis occurring in the central nervous system (CNS) during the latent period prior to the onset of necrosis and into the identification of the target cell lineages involved. Two distinct hypotheses emerged: (1) The view taken by many radiobiologists that white matter necrosis is caused by damage to the glial cells and more specifically to the cells responsible for myelination in the CNS, the oligodendrocytes. (2) The view taken by many neuropathologists that damage, in one form or another, to the vasculature is responsible. In this presentation, the opposing views are reappraised and the role of oligodendrocyte damage in the development of white matter necrosis has been critically assessed.

## The 'Glial' hypothesis

The observations implicating the oligodendrocyte as the primary target cell lineage in the formation of white matter necrosis can be summarized under four main headings:

*Focal demyelination* is observed early in the pathology. The functional role of the oligodendrocyte dictates that damage to this cell type would be demyelinating in nature. Primary demyelination, i.e. demyelination due directly to oligodendrocyte injury leaving naked intact axons, has only been described in association with necrosis in one report (Blakemore & Palmer, 1982), and in this case, always on the edges of small infarcts. Much of the demyelination which is commonly reported is secondary, occurring as a result of Wallerian-type degeneration or retrograde degeneration of axons and their myelin sheaths. The loss of tissue architecture so typical of the white matter necrosis lesion results from a coalescence of foci of necrosis rather than of foci of primary demyelination. Transient myelin pathology has been observed at early times following irradiation (Mastaglia *et al.*, 1976) but was thought by the authors to be unrelated to the later-occurring necrosis.

*The lesion has a predilection for white matter* White matter contains long tracts of myelinated axons and it is the large component of myelin which has been used to link oligodendrocyte injury with necrosis. However, white matter also contains all other CNS tissue elements except nerve cell bodies and thus a predilection for white matter does not necessarily imply primary damage to any particular cell type. In addition, the lesion may occur in grey matter, e.g. the dorsal horns, as shown in Figure 1.

*Vascular pathology* While it is the case that some authors have reported little or no vascular pathology associated with white matter necrosis (e.g. Mastaglia *et al.*, 1976) many other reports describe clear vascular lesions in both human (Jellinger & Sturm, 1971) and animal (Caveness, 1977; Martins *et al.*, 1979; Blakemore & Palmer, 1982) material. Oedema, haemorrhaging, telangiectasia and endothelial cell pathology have all been observed in association with white matter necrosis.

*Alterations in glial cell kinetics* Alterations in glial cell labelling at early times following irradiation (Hornsey *et al.*, 1981) may be more closely related to the transient myelin pathology reported by Mastaglia *et al.* (1976). The relationship between later glial cell changes (e.g. Zeman, 1963; Zeman *et al.*, 1964; Hubbard & Hopewell, 1979) and the onset of necrosis is unclear (Haymaker *et al.*, 1968). However, as a general conclusion Zeman (1966)

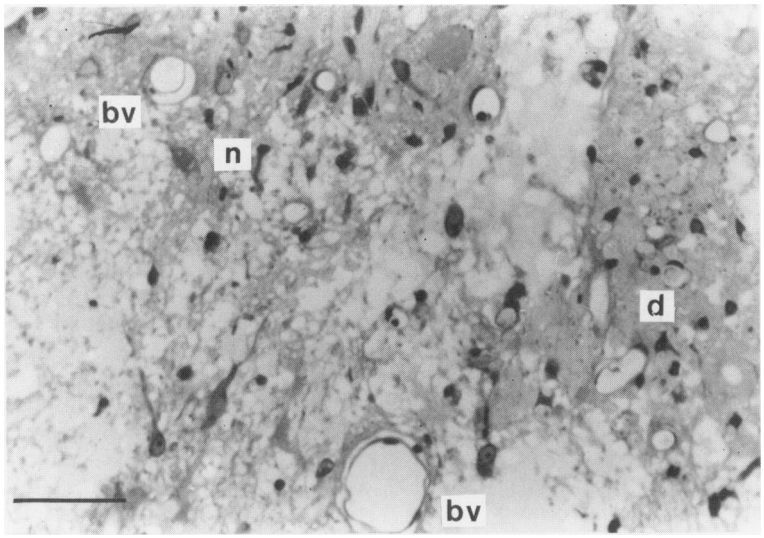


**Figure 1** Transverse section of rat cervical spinal cord, $5\frac{1}{2}$ months following 24.5 Gy X-rays. Necrosis in the dorsal horn adjacent to the dorsal column (d). Generalised oedema and a cellular reaction are evident. Some vessels (bv) have swollen perivascular spaces; neurons (n) undergoing ischaemic necrosis are visible. Bar represents 100 $\mu$m.

noted that selective blood vessel involvement predominates in the development of white matter necrosis in mature animals.

In general, it must be concluded that there is no pathological pathway by which damage to oligodendrocytes alone could lead to massive tissue necrosis. Blakemore & Patterson (1978) have demonstrated, using the demyelinating agent lysolecithin, that local demyelination of irradiated spinal cord does not induce axonal degeneration or necrosis in the cat or rat.

## The 'Vascular' hypothesis

No coherent 'vascular' hypothesis may be drawn from a review of the existing literature. However, as a result of our own examination of the histopathological features which characterise a necrotic lesion, i.e. oedema, extravasation of red blood cells, astrocyte and macrophage reaction, endothelial cell pathology and neuronal loss (see Figure 1), we concur with the conclusion of Blakemore & Palmer (1982) that the necrosis lesion arising between 4 and 8 months post-irradiation is typical of infarction in the CNS. Recent work by Tamaki *et al.* (1984) on spontaneously hypertensive rats has given us a possible mechanism by which this infarction could occur. They showed that the ischaemic necrosis seen in the brains of their animals arose as a direct result of severe oedema causing reduced blood flow. The oedema occurred as a consequence of blood–brain barrier breakdown.

Disruption of the blood–brain barrier prior to the development of white matter necrosis has been recorded by a number of workers (e.g. Clemente & Richardson, 1962; Caveness, 1977; Martins *et al.*, 1979). It is thus possible that increased permeability of the blood–brain barrier brought about by radiation damage to either endothelial cells alone or by an interaction between more than one damaged tissue element, could give rise to oedema and consequent ischaemia.

A serial histopathology study of irradiated rat CNS is at present underway, animals being sacrificed just prior to and during the range of times in which symptoms would be expected to arise. Preliminary findings indicate that the first pathology to occur consistently (prior to the onset of clinical signs) is oedema and extravasation of red blood cells (see Figure 2). These lesions occur in white and grey matter, the latter predominantly in the dorsal horns. In our rats, we most commonly observe white matter necrosis in the dorsal columns of the white matter and the adjacent dorsal horns. These two regions of white and grey matter are supplied by a common arterial plexus. Lazorthes (1972) has cited this zone of blood supply to the cord as being the most vulnerable to ischaemia. Thus, a lesion in blood supply is implicated in the pathogenesis of white matter necrosis in the spinal cord.

## Conclusions

(1) Radiation damage to oligodendrocytes alone is unlikely to cause white matter necrosis.
(2) White matter necrosis following irradiation may be due to infarction.

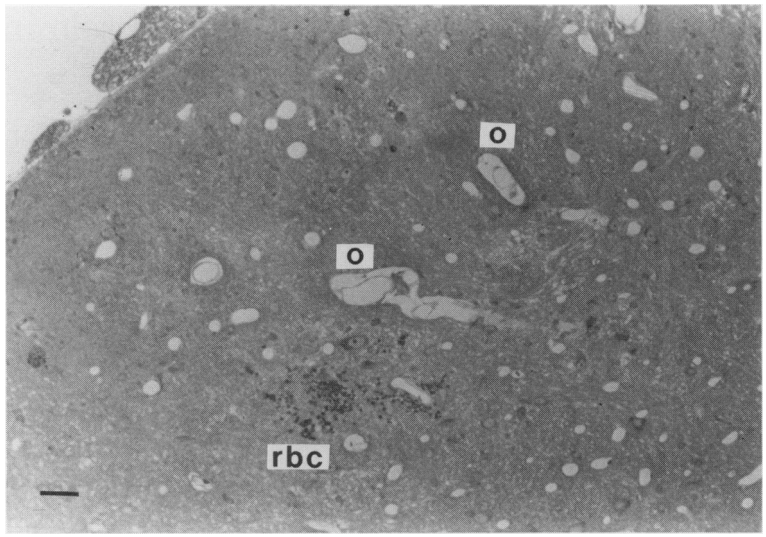


**Figure 2** Transverse section of rat cervical spinal cord, 5 months following 30 Gy X-rays. Dorsal horn of rat prior to onset of clinical signs. Evidence of oedema is seen in the enlarged perivascular spaces (o). A large number of extravasated red blood cells (rbc) are visible. Bar represents 100 $\mu$m.

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