Multiple sclerosis (MS) remains an enigmatic disease (or syndrome), reluctant to give up its secrets: visualised on MRI, an inflammatory vapour trail in the cerebrospinal fluid, characteristic in its clinical manifestations and now partially responsive to therapeutic intervention. However, the exact causality (genetic/environmental) remains hidden behind the curtain. One way to try to coax it out of its hiding place is to look for a direct cause, whether genetic or environmental. The experimental stage chosen was 220 and 225. Plaques were the most common around the lateral ventricles: anterior, inferior and posterior horns.

The study concluded that to an extent, all areas of the cerebrum were vulnerable once regional size was accounted for. Although the white matter plaques were most conspicuous, they were seen junctionally and in the internal nuclei. However, ‘stand-out’ areas were periventricular in the lateral ventricle (as opposed to the third ventricle, say), and in detail, these were the supero-lateral angles of the anterior horns, bodies of the lateral ventricles, inferior and posterior horns (but not the inferomedial aspects). However, there seemed to be some sparing of certain large periventricular areas: caudate nucleus, thalamus and corpus callosum.

Apart from the beautiful microscopic detail, which resonates with MRI work decades later, what pathogenic insights did the authors discuss?

First, they felt that the asymmetry in the deeper recesses of the para-ventricular structures mitigated against soluble diffusing factors. They did however support the concept of a vascular basis which had been put forward and then debated in 1863 (for), 1942 (against) and 1950 (against) in particular. Their stand was nuanced against a large vasculopathy, but they felt that there was ‘some more subtle peculiarity of the circulation in certain cerebral areas’. What they especially highlighted was that these periventricular areas were situated on boundary zones between major cerebral arteries and that these were relatively avascular. For example, the white matter at the lateral angle of the lateral ventricle was at the limits of supply of two large rivers: anterior and middle cerebral; or the lateral angle of the posterior horn (anterior, middle and posterior cerebral). They contrast this with regions which although adjacent to the lateral ventricles have adequate supply and were not unduly susceptible, for example, thalamus, caudate nucleus and hippocampus. The thesis also extended to the junction of the cortex and white matter.

Their work was dedicated and exhaustive. Their conjectures are stimulating. How did the next half-century of medical scientists view their contributions? One
way is to consider how the top five articles which cite this work, frame their contribution.

Kutzelnigg et al highlight cortical pathology... ‘the presence of cortical demyelination ...has been previously recognised [from this work].’7 Trapp and Nave consider the grey matter involvement and say...’while recent reports of cortical demyelination were a surprise to many in the MS community, cortical demyelination has been reported in the MS literature for decades [from this work].’6 Peterson et al use this work to point out that ...’while the density of myelin in the cortex is less than in the white matter, demyelinated lesions have been identified in the cerebral cortex of MS brains [from this work].’7 Magliozzi et al cite Brownell and Hughes ...’previous neuropathological studies have shown the presence of demyelination, axonal damage and neuronal loss, in the cortical and deep grey matter of multiple sclerosis patients’.8 Kidd et al describe in some detail the distribution of the lesions given in this paper in their introduction to their work on cortical lesions.9

A different compass to use is McAlpine’s Multiple Sclerosis and its progeny, with a roll call of distinguished MS investigators over half a century. The original was published prior to this publication (1955) and the 1965 and 1972 editions carry little in the way of comment. It is in 1985 that a full chapter is devoted to neuropathology and our paper is well described in a rich section on plaque topography. Five years later, the essence of the work is again well detailed, with Ian McDonald’s chapter (1998)10 pointing out that the later accumulation of disability probably reflects the multiplicity of lesions involving the cortex as described by this work. The most recent edition in 2005 highlights again the original contribution in demonstrating that demyelinated plaques may be present in all areas of the grey matter.

Modern MRI techniques are increasingly being used to visualise grey matter pathology and the current McDonald classification of MS specifically highlights cortical lesions to enable dissemination in space, as well as the other characteristic topographies described in this paper.11

It is appropriate now to honour the two individuals who carried out this work by briefly describing their lives.

Betty Brownell (figure 1) was born in Dublin of Huguenot descent. She had an illustrious pathological career centred on Bristol and Oxford as well as deep involvement in the Royal College of Pathologists, especially related to training and the establishment of neuropathology as a subspecialty. Her research work was wide: muscle, peripheral nerve, Creutzfeldt-Jakob disease and spinal cord.12

Trevor Hughes talks about his life in a number of specially recorded videos.13 He had an extremely busy neuropathological career in Oxford and Stoke Mandeville, culminating in his book the Pathology of the spinal cord. But it was also hugely varied: from a love of natural history (spiders in particular) to high-level University and Hospital administration (he was the Senior Bursar and then acting Warden of Green Templeton College) to biography (Thomas Willis).

The legacy was immense and is, and was, a fundamental clue to the task of trying to edge closer to a truer understanding of the hidden secrets of MS. We remain truly grateful to the insights from the work of Brownell and Hughes.

Funding: The author has not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: None declared.

Patient consent for publication: Not required.

Provenance and peer review: Commissioned; internally peer reviewed.

Author note: A final symmetry to this paper was their marriage, but sadly Betty Brownell died only a few years later.

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