Revisiting *The Pathogenesis of Multiple Sclerosis Revisited*

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Uncertainty breeds speculation. First, multiple sclerosis (MS) is said to be a sexually transmitted disease – childhood onset cases representing examples of child abuse. Now, the concept of MS as an inflammatory disorder has been sidelined. Does it matter that affected individuals are repeatedly exposed to untested new ideas concerning aetiology and disease mechanisms; that lay organizations spend time setting straight the record – as they and their advisers see it; that journalists prowling for news are seen to have over-blown their stories; that yet more raw hypotheses are spawned by the oxygen of this publicity; or that original research is discredited by these neurological *borborygmi*? After all, these claims and counter-claims provided copy for the *New Scientist* (A Coglan, *Have We Got It Horribly Wrong*? 16 November 2002) and national radio in the UK covered both stories. Antivivisectionists spotted an open goal and wrote to the newspapers. Journalists waved the 'freedom of speech' flag and an institution was criticized for distancing itself from the sex-abuse author.

Scientific debate is healthy but should all the laundry be washed in public, or is there a responsibility on authors and editors to get it right in advance of publication? These and related issues are raised by the review of PO Behan, A Chaudhuri and BO Roep entitled *The Pathogenesis of Multiple Sclerosis Revisited* (*J R Coll Physicians Edinb* 2002; **32:** 244–265).

Briefly, they propose that the concept of MS as a focal inflammatory and autoimmune disease is based on erroneous extrapolation from animal models, thereby promulgating confused strategies for treatment and causing patients unnecessary morbidity and mortality. Rather, MS is a neurodegenerative and clinically progressive trait in which expression of a gene encoded on chromosome 17 (among others), influenced by sunlight and vitamin D activity, promotes generalized astrocyte proliferation with secondary damage to the blood–brain barrier and metabolic defects – plaques merely representing focal areas of maximum compromise. Those who offer hypotheses exercise the luxury of picking facts that suit from the entire corpus of knowledge – with all its vicissitudes. In the end, however, the facts must be individually credible, faithfully displayed, and collectively coherent in support of the new claim. The case made by Behan *et al.* turns on eight main points:

'… it is inaccurate to extrapolate the findings (in experimental autoimmune encephalomyelitis [EAE]) to the pathogenesis of human MS'

The acute monophasic course of EAE, as originally described, does (as Behan *et al.* stress) best mimic acute disseminated encephalomyelitis (ADEM) and acute haemorrhagic leucoencephalitis (Hurst's disease) in humans, but – in order to see the big picture – readers of the *J R Coll Physicians Edinb* might reasonably have expected critical analysis of protocols for EAE developed since the 1970s which address the issues of relapse, chronicity, axonal loss and remyelination.

'… lesions of MS have… scant or even absent inflammatory reactions… such infiltrates lack aggressiveness…'

Behan *et al.* lean mainly on the writings of J Dawson, C Lumsden and C Adams. Dawson (1916) considered that '… disseminated sclerosis is a subacute… encephalomyelitis' and made the distinction between '… processes which are from the beginning distinguished by inflammatory… cell infiltration and those which begin as degenerations and only in their further course are connected with… [inflammatory cell infiltration]'. Lumsden (1955) initially took the position that '… there is… little inflammatory cellular reaction even during the acute phases of plaque development… the disease is a

toxi-degenerative process…', but his last word was that '… it is a disorder of the myelin sheath-oligodendroglial cell complex. The evidence that this is… due to specific anti-myelin antibodies is… almost inescapable… small to moderate numbers of plasmacytotoid lymphocytes are regularly present at all stages of actively demyelinated plaques…'. While recognizing that the intensity of lymphocyte infiltration varies with evolution of the lesion and rarely approaches that seen in ADEM, that unidentified events trigger the inflammatory process, and that intrinsic properties may render the central nervous system (CNS) unduly vulnerable in people who develop MS, revisions of Lumsden's account by R Weller, I Allen and H Lassmann do not deviate from the immunological flavour of his final position. Building on Dawson, it is hard to read Adams (1977) as anything other than an exposition of the important role played by infiltrating lymphocytes in the pathogenesis of MS: 'I have put forward evidence that perivenous cuffing may precede formation of the perivenous plaque and that a probing finger of lymphocytic infiltration (Dawson's finger) pushes along the vein in advance of demyelination'.

'*No one specific [immunological] abnormality has ever been found and confirmed… the many claims (for humoral immunity) have not stood the test of time nor have the many studies on immunoglobulin abnormalities found in the cerebrospinal fluid*'

The presence of oligoclonal bands, reflecting intrathecal synthesis, is sufficiently routine to be part of diagnostic criteria for MS. It could be argued that failure to identify antigen-specific immunological abnormalities constitutes absence of evidence, not evidence of absence. Behan *et al.* do not review technical advances and results obtained since the early 1990s. Also, in dismissing the significance of oligoclonal bands, the authors may miss a more fundamental point – namely, that failure to demonstrate antigen specificity reflects a polyclonal abnormality of B-cell activation.

'*Clearly no association of autoimmune disease with MS occurs… and no true association exists*'

Behan *et al.* disregard three large epidemiological surveys showing an increase in the prevalence of autoimmunity among relatives of probands with MS – one on the fallacious grounds that it reports a reduction in autoimmunity among relatives. Instead, attention is drawn to a review by Behan concluding that 'no such association with autoimmune diseases and correlations with histocompatibility antigens… were found in MS'. Readers may wonder whether the same disease is being studied as the one they know unambiguously to be associated with HLA-DR15.

'*Immunosuppression has failed to have any consistent effect on prognosis or disease progression… the data… show predominantly a powerful placebo effect*'

The natural history of MS includes relapses, fixed disability and slow progression – each dependent on differences in the extent of inflammation, demyelination and axonopathy. Behan *et al.* must be alone in concluding that the difference in relapse rate between interferon-treated patients and controls 'is a placebo effect'; presumably the statement that 'these trials should be considered as single- rather than double-blind' is the authors' perspective. On mechanistic interpretations of how these drugs act, is the conclusion that 'such an explanation defies belief and lies more in the realm of science fiction' reasoned scientific argument?

'*Epidemiological studies… have shown that certain diseases are associated with MS… classically, these are malignant glioma, neurofibromatosis type 1 (NF1) and hypertrophic peripheral neuropathy*'

The association with glioma depends on 34 case reports culled from six studies offering two examples, and two papers describing three patients, the rest being single case reports. The story with respect to NF1 amounts to 10 cases published in five separate papers (the largest series being five) supplemented by three personal examples. Cases of MS and peripheral neuropathy are well described but rare; the largest and best series is not quoted by Behan *et al.* Anecdote is not epidemiology.

'*… generalized glial proliferation accounts for the globally reduced [magnetic resonance spectroscopy] anisotropy;… metabolic changes contribute to the formation of plaque in areas of maximum compromise*'

Whereas most analysts take a centrifugal view of the diffuse histological, radiological and spectroscopic changes seen in MS – structural,

functional and metabolic effects radiating out in directions determined stochastically and by boundaries within the CNS from a nidus of the disease process, Behan *et al.* propose a centripetal process. Is this not the horse's tail wagging the cart?

'*Neurological diseases... found in association with MS... share a common genetic influence mainly from genes on chromosome 17 affecting cell proliferation*'

Those who check the primary literature quoted in support of the claim that genes for glioblastoma multiforme, MS and Charcot Marie Tooth disease map to the region of NF1 at 17q11.2 find only secondary sources or a reference that is simply wrong. Inaccurate proof-reading may also explain why a paper on concordance for disability in sibling pairs is cited as evidence 'from scholars of MS that the disease is toxic metabolic in origin'. Even after correctly lining up text and citations, however, readers will struggle to understand why concordance for disability in affected sibling pairs is evidence for MS being a progressive neurodegenerative disorder.

Setting the scene with selective and inaccurate citations from the literature, bending the reader's ear with hyperbole, and confining the argument to evidence that fits without presenting the whole story, are tired tactics for decorating a maverick hypothesis. Setting out one's stall with a quotation from Bertrand Russell, 'the fact that an opinion has been widely held is no evidence that it is not utterly absurd; indeed in view of the silliness of the majority of mankind, a widespread belief is more likely to be foolish than sensible,' risks the riposte that 'it is undesirable to believe a proposition when there is no ground whatever for supposing it true' (Russell, 1928).

Diary Dates

The Society of Neurological Surgeons 2003 Annual Meeting
Cincinnati, Ohio, USA
18–20 May 2003
For further details contact:
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Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA
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2nd Dubrovnik International Conference on Multiple Sclerosis
Dubrovnik, Croatia
21–24 May 2003
For further details contact:
Zelijka Petelin, MD
Tel: +385 1 2388 342
Fax: +385 1 2421 846
E-mail: ms@mef.hr

Consortium of MS Centers Annual Meeting
San Diego, CA, USA
28 May–1 June 2003
For further details contact:
Consortium of MS Centers, Gimbel MS Center,
718 Teaneck Road, Teaneck, NJ 07666, USA
Tel: +1 201 837 0727/+1 877 700 CMSC (toll-free USA)
Fax: +1 201 837 9414
E-mail: info@mscare.org

13th Meeting of the European Neurological Society
Istanbul, Turkey
14–18 June 2003
For further details contact:
ENS 2003, c/o AKM Congress Service, Clarastrasse 57,
PO Box, CH-4005 Basel, Switzerland
Tel: +416 1686 7711
Fax: +416 1686 7788
E-mail: info@akm.ch

6th IBRO World Congress of Neuroscience
Prague, Czech Republic
10–15 July 2003
For further details contact:
The Secretariat, GUARANT Ltd, Opletalova 22,
110 00 Prague 1, Czech Republic
Tel: +420 2 2421 0650
Fax: +420 2 2421 2103
E-mail: ibro2003@biomed.cas.cz
www.ibro2003.cz

7th Congress of the European Federation of Neurological Societies
Helsinki, Finland
30 August–3 September 2003
For further details contact:
EFNS Head Office, University Campus, Courtyard 1,
Alser Strasse 4, A–1090 Vienna, Austria
Tel: +43 1 889 05 03
Fax: +43 1 889 05 03/13
E-mail: headoffice@efns.org
www.kenes.com/efns2003

19th Congress of the European Committee for Treatment and Research in MS (ECTRIMS)
Milan, Italy
17–20 September 2003
For further details contact:
Professor Dr Giancarlo Comi,
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