Reviewing multiple sclerosis

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Introduction

In recent years, publishers have responded to the need for publications that summarize complex topics but formerly the review article was less popular, and students of neurological medicine then depended more on textbook accounts of diseases affecting the nervous system. No work has so dominated the 20th century and influenced neurologists in the English speaking world as Russell Brain's *Diseases of The Nervous System*. When John Walton took on the task of completing the 7th edition, published in 1969, 'Brain' had been continuously in print since 1933; he subsequently produced the 8th and 9th editions, in 1977 and 1985, respectively, and with colleagues is now preparing the 10th edition. Thus, Lord Brain and Lord Walton have reviewed developments in clinical neurology over a period in which more has been learned about the nervous system in health and disease than at any other time in history. One reviewer, opining that the 8th edition represented excellent new wine in an old and valued bottle, drew attention to the therapeutic shifts catalogued by 'Brain' down the 20th century. In 1933, the symptoms of Parkinson's disease could be alleviated by riding in a motor car; in 1992, this requires striatal transplantation of fetal mesencephalic neurones. The observations that have been made and the task of distinguishing fact from fiction so as best to document the accumulation of knowledge has probably been more difficult with respect to multiple sclerosis than for any other aspect of clinical neuroscience.

Quarterly Journal of Medicine: 1930

Having written a 'Critical review: disseminated sclerosis' in 1930¹ Dr Russell Brain was already an authority on multiple sclerosis when, as assistant physician to the London Hospital and to the Hospital for Epilepsy and Paralysis, Maida Vale,

his textbook was first published by Oxford University Press in 1933. Brain came straight to the point in his 'critical review'; drawing comparisons between the neurological manifestations of encephalitis lethargica and the encephalomyelitides that follow exanthematous disease and vaccination, he interpreted the pathological observations as having established disseminated sclerosis as an infective disease – a point of view first proposed by Marie in 1895.² Brain provided statistical evidence in favour of Guillain's assertion that disseminated sclerosis was second only to syphilis as the most frequent disease of the nervous system, and provided the first hospital- and population-based statistics, accurately defining the relationship between disease duration and rates for prevalence, incidence and mortality. Brain recognized that the geographical distribution of multiple sclerosis was uneven; he delineated regional trends that have subsequently been confirmed, and identified the innate susceptibility and resistance of northern Europeans and Blacks, respectively. Brain accepted that the disease occasionally occurred in sibling pairs but in line with his views on the cause, he was adamant that familial disseminated sclerosis arose from common environmental exposure and not the influence of genetic factors. Subsequent experience has shown that his views on the sex incidence were wrong, females being more commonly affected than males.

His reading of the pathological literature was sophisticated and very little of substance has since been added. Drawing heavily on the observations of Dawson,³ Brain described a sequence in which perivascular infiltration of lymphocytes and plasma cells is followed by phagocytosis of myelin, fibroglial overgrowth and some axonal loss; and he noted shadow plaques, now thought to be indicative of remyelination. In discussing the distribution of lesions throughout the nervous system, Brain emphasized the co-location of plaques and rich vascular networks around the ventricles, under the pial membranes and in the spinal cord.

In a scholarly section on the pathogenesis of disseminated sclerosis, Dr Brain restated the doctrine of neurobiology left by Cajal and his students

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del Rio Hortega and Penfield, describing the morphological and anatomical arrangements of fibrous and protoplasmic astrocytes, assigning a phagocytic role to microglia but confessing to ignorance on the function of oligodendrocytes. He pointed out that the early vascular lesion indicated invasion of the nervous system by a systemic and infective factor, capable of provoking the astroglial reaction that he regarded as the essential pathogenic feature of the disease. However, Russell Brain argued that factors distributed in the cerebrospinal fluid could as easily gain access to the brain parenchyma through the Virchow–Robin spaces, as could material crossing the vessel walls.

Section five of Brain's review dealing with 'experimental transmission and bacteriology' analysed a controversial episode. There had been many attempts to repeat the observations of Bullock⁴ that disseminated sclerosis could be transmitted to animals by inoculation of a spirochaete recovered from affected individuals. This culminated in the report by Chevassut that the organism 'spherula insularis', designated as a virus, could be cultured from the cerebrospinal fluid of more than 90% of patients with disseminated sclerosis but not controls.⁵ Brain quickly disposed of the spirochaetal theory of disseminated sclerosis but took a more reserved position with respect to Miss Chevassut, suggesting that technical factors may have made it difficult for her directly to visualize the organism in the spinal fluid or the nervous tissue itself; he was distinctly lenient on the failure to transfer this organism to monkeys – work that had been reported by Sir James Purves Stewart;⁶ notwithstanding uncertainty about the causal role of 'spherula insularis' in disseminated sclerosis, Brain extolled the virtues of using its detection as a diagnostic test. 'Spherula insularis' disappeared abruptly from interest following an incident at the Royal Society of Medicine, the details of which have been preserved through oral neurological history.⁷

In his clinical account of disseminated sclerosis, Brain identified typical manifestations of the disease, its common syndromes, and the clinical courses to be expected. His estimates for frequency of relapsing compared with primarily progressive disease would be consistent with contemporary views, as would the peak ages and extremes of onset; furthermore, he drew from personal experience in stressing that the course might evolve fully within a few months or remain stable over several decades. His clinical description was notable for its account of the mental state (spes sclerotica), the occurrence of convulsions, early descriptions of internuclear ophthalmoplegia, pupillary hippus (but not the Marcus Gunn abnormality), Lhermitte's phenomenon, trigeminal neuralgia, the useless hand of Oppenheim,

Brown–Sequard lesions, hyperaesthesia at the border of sensory levels, impaired colour vision, muscle wasting, and symptoms arising from affection of the conus medullaris; finally, he quoted statistics relating to the high frequency of disseminated sclerosis after an episode of optic neuritis.

Fever therapy, induced by malaria, typhoid vaccine and other organic or microbial pyrogens, featured prominently in Brain's account of treatment. There was no hint of adverse effects. The study in which Purves Stewart treated 70 cases of disseminated sclerosis with a vaccine derived from cultures of the putative 'spherula insularis' virus, and which he claimed would arrest the disease, alter the colloidal gold curve and eradicate the organism from the cerebrospinal fluid, was cited⁸ with the conclusion that removal of the organism from <10% of cases placed considerable difficulties in the way of therapeutic enthusiasm for Miss Chevassut's discoveries. Instead, the usual list of metal therapies – arsenic, silver, mercury and antimony – was given, and agents such as sodium salicylate or X-irradiation were mentioned; Brain concluded that the 'the multiplication of remedies is eloquent of their inefficacy'.

Russell Brain's first review of disseminated sclerosis ended where it began; after marshalling the evidence from 218 publications and detailing the clinical and pathological similarities between disseminated sclerosis and transitional forms of neuromyelitis optica, post exanthematous and vaccinal encephalomyelitis, and encephalitis periaxialis diffusa, he settled on the view that these demyelinating diseases differed only in the extent to which virulence of the initiating but as yet unidentified causative agent, and variations in host immunity, influenced the clinical phenotype. He regarded the syndrome of disseminated sclerosis as having a common pathogenesis with an inherent capacity for recovery throughout the course. Brain suggested that the tendency to relapse would, when fully understood, provide a clue to the nature of immunity and lead to a cure for the disease.

Brain's Diseases of the Nervous System, 1st Edition, 1933

In returning to this topic 3 years later,⁹ Russell Brain emphasized the clinical rather than biological aspects of the disease. Disseminated sclerosis was, not unreasonably, included in the chapter on infections of the nervous system, and treated separately from acute disseminated or post infectious forms of encephalomyelitis, and disseminated myelitis with optic neuritis. Not much had happened to reshape Brain's views on the aetiology or pathogenesis, although he now

preferred to consider the glial reaction as secondary, or at least sequential to the perivascular inflammation and demyelination; the aetiological status of the spirochaete and Miss Chevassut's virus – now described as a filtrable agent – remained uncertain and heredity was still not regarded as a risk factor. His description of the symptoms again emphasized the amyotrophic form and the occurrence of convulsions; a case of bilateral internuclear ophthalmoplegia had been observed, as had examples of Horner's syndrome, deafness, pathological laughter and crying, and trophic changes in the extremities. Brain's seven symptom groups included progressive spinal disease in older cases, onset with hemiplegia or conus lesions and the accelerated or Marburg form. A rather formal approach to differential diagnosis listed neurosyphilis and the hereditary ataxias, with special mention of the Drew family of Walworth,¹⁰ whose neurological disorder mimicked disseminated sclerosis (and is still attracting attention from neurologists), sub-acute combined degeneration of the cord, tumour and encephalitis lethargica. Both in the earlier review and in the 1933 edition, Brain commented on the special tendency for patients to exaggerate or entirely fake the manifestations of disseminated sclerosis.

Brain assigned a poor prognosis to young rather than middle aged patients, and those with brain-stem involvement by comparison with spinal disease. And he recommended the personal account of the disease written by Bruce Frederick Cummings under the pseudonym W.N.P. Barbellion, first published on 31 March 1923 as *The Journal of a Disappointed Man*.¹¹ Cummings was born at Barnstable on 7 September 1889 and died, aged 30, on 22 October 1919 at Gerrards Cross. He borrowed his pseudonym from the front of a sweet shop in Bond Street. Despite developing symptoms due to multiple sclerosis in early adult life, and dispirited by the example of his parents who both had paralytic neurological disorders, Cummings taught himself entomology and obtained a post at the Natural History Museum; Barbellion aped Mark Twain in ensuring that news of his death – 31 December 1917 – was prematurely announced so that he might enjoy reading notices of his book written in the belief that they would not reach the author's eyes. But his diary was declared 'an acerbic bid for immortality, written by a smart alec rotter' and sadly he only enjoyed the literary fantasy for 18 months; others have suggested that he even may have accelerated his departure by following contemporary advice to take arsenic and strychnine on a weekly basis. H.G. Wells identified the egoist in Barbellion but – himself an incurable scientific romantic – sympathized with the hopelessness of Barbellion's thwarted scientific dreams; 'not for him the Croonian lecture, the listening

Royal Society', although he did publish articles that justified the statement that in him biological science has lost one of the most promising of its recent recruits. Although Dr Brain devoted a few lines in the 1933 edition to a catalogue of tests that might be employed in assessing co-ordination of movement, he might have borrowed from Barbellion the child's satisfaction in coaxing a button to slip into its hole; 'all grown up people have forgotten how difficult and complex such operations are'. Sadly, nothing other than tact, judgement, metals and fevers could be offered by way of treatment 14 years after Barbellion's death; even the use of liver had disappointed Dr Brain.

Brain's discussion of the encephalomyelitides – which he believed all resulted from opportunistic infection secondarily affecting individuals immunocompromised by a primary agent – is interesting for its further evidence of Brain's adherence to the direct viral doctrine of demyelinating disease. Treatment was aimed at reducing intracranial pressure, by lumbar puncture or hypertonic glucose osmosis. These were common conditions and there had been a prolonged epidemic of post vaccinia encephalomyelitis in the 1920s so that Russell Brain re-iterated the advice of the Vaccination Order of 1929 that 'it is not generally expedient to press for the vaccination of persons of adolescent years who have not previously been vaccinated unless they have been in contact with a case of smallpox'. Immune serum from a previously vaccinated individual was recommended. Brain seemed a little uncomfortable in separating encephalomyelitis complicating measles from other forms and only gave it a special heading because of Ford's recent definitive review of the subject. In the 1930s, pain in the eyes occurring as part of Devic's disease could be treated with mustard leaves or leeches applied to the temples.

Uncertainty can be seen in Brain's discussion of encephalitis periaxialis diffusa; too many cases were familial, the term encephalitis suggested inflammation but this was presumptive, and the progressive paralysis and central visual failure were atypical of disseminated sclerosis – all of which indicated that these childhood disorders had a different aetiology from other forms of demyelinating disease. Subsequent editions of the textbook saw a gradual separation of these conditions into the group of leucodystrophies and related degenerative disorders

Brain's Diseases of the Nervous System, 2nd Edition, 1940

In writing a preface to the second edition of his textbook, in March 1940,¹² Dr Brain specified that

he had separated conditions that had become known as the demyelinating diseases.¹³ Illustrations were provided for the commoner diseases by Dr Dorothy Russell and Professor H.M. Turnbull; and references – many selected from the French and German literature – were appended to each section. Brain offered a classification that has survived all subsequent editions of the book with little modification. Small differences of emphasis were apparent in the largely unchanged accounts of the acute disseminated encephalomyelitides; Brain regarded spontaneous encephalomyelitis in adults as more common than the post exanthematous childhood forms and he separated the neurological complications of varicella from other childhood post exanthematous disorders on the basis of its clinical and pathological manifestations.

Significantly, he had noted the first description of experimental allergic encephalomyelitis in monkeys¹⁴ and so shifted abruptly to the view that demyelinating disorders were due to an allergic reaction in the brain and not direct viral infection. Significant changes were also made to the section on disseminated sclerosis which was defined as a disorder characterized by focal lesions early in the course later followed by progressive disease. His reading of the pathological papers of Dawson,³ Putnam¹⁵ and Greenfield¹⁶ presented a much clearer view of the sequence of perivascular lymphocytic infiltration, myelin ingestion by fat granule cells, myelin degeneration, fibroglial proliferation, and some axonal loss leading to the formation of the 'sclerotic plaque'. In an expanded account of the aetiology, Brain admitted the 'modern tendency to stress constitutional factors' and summarized the evidence on heredity from Curtius' monograph.¹⁷ He quoted a series, presumably of personal cases, in which exposure to a range of triggers – infections, pregnancy, surgical operations, electric shock, carbon monoxide poisoning and trauma – occurred shortly before presentation. Brain revised his figure for the frequency of disseminated sclerosis in the United Kingdom (200/million living people), noting that urban cases were more common than rural, that cases in childhood occurred rarely and that only 7% of patients developed the disease after the age of 50; the sex ratio was reversed 3:2 in favour of women. Brain's account of symptoms was based on a personal series of 100 consecutive cases, motor symptoms predominating over visual and sensory or miscellaneous manifestations. Again he emphasized the interval that may occur between optic neuritis and a subsequent episode – the longest survivor of his experience being 29 years from diagnosis; disease duration averaged 13.6 years. In 1940, Brain included encephalitis periaxialis diffusa (renamed Schilder's disease) in the section on 'diffuse sclerosis' and proposed this as an

example of an inherent defect in oligodendrocyte function.¹⁸ Analogies were made with swayback, known at that time to be treatable with copper.¹⁹

Major alterations to the 1940 edition were therefore the introduction of the term demyelinating disease, the attempt at classification, the recognition of experimental allergic encephalomyelitis, the emergence of ideas on the biology of the oligodendrocyte, the introduction of morbidity statistics, and the concept of immunological and inherited factors in the aetiology.

Brain's Diseases of the Nervous System, 3rd Edition, 1947

The third edition²⁰ introduced topics in which special experience had been gained during the second world war – in the main, descriptions of peripheral nerve injuries, nutritional disorders of the nervous system, and the introduction of penicillin. Sciatic neuritis was renamed prolapsed lumbar intervertebral disc, and affections of the brachial plexus and thoracic outlet were introduced. The psychological aspects of neurology received special attention.

The section on demyelinating disease contained very few changes. Hurst's hypothesis that myelin breakdown was mediated by enzymatic degradation, outlined in his G.E. Rennie lecture delivered to the Royal Australasian College of Physicians on 26 September 1941 in Melbourne, was included²¹ but not his descriptive paper separating acute haemorrhagic leucoencephalitis from the other encephalomyelitides.²² In his account of disseminated sclerosis, Dr Brain re-inserted a note on its history from his 1930 review concluding that Cruveilhier in 1835 and Carswell in 1838 first illustrated the lesions. This controversial matter of priority had been discussed by Putnam²³ in 1938 and since by others.²⁴ Russell Brain overlooked the important paper by Kabat²⁵ describing the quantification of immunoglobulin in the cerebrospinal fluid of patients with disseminated sclerosis; in several subsequent editions, only the colloidal gold curve was described – abnormalities of which merely reflect the antibody changes that Kabat had identified.

Brain's Diseases of the Nervous System, 4th Edition, 1951

Russell Brain had reconsidered his views on demyelinating disease when he returned to the topic in 1951;²⁶ he wished to emphasize that axon cylinders were often involved in the disease process and he felt ambivalent about the conclusion that myelin destruction was necessarily the primary

change. He sensed a growing belief that progress in understanding the demyelinating diseases would result from studies of the experimental models first mentioned in the second edition. Although intravenously injected antibodies recognizing constituents of the nervous system would not reproduce the pathological features of post infectious encephalomyelitis, Brain accepted as proven the claim that the human and experimental diseases were allergic. Spontaneous acute disseminated encephalomyelitis was no longer considered to be distinct from post infectious encephalomyelitis of childhood. Brain described the discussion that had taken place with respect to the relationship between the acute focal myelinoclasia of Marsden and Hurst (1932) but continued not to cite Hurst's paper;²² and his reading of the literature on experimental demyelination now made him uneasy about the suggested relationship between disseminated sclerosis and swayback.²⁷ The changes that could be detected in the cerebrospinal fluid were still not noted and he remained loyal to the memory of Barbellion now dead for 32 years; there were no new therapeutic suggestions.

Brain's Diseases of the Nervous System, 5th Edition, 1955

The title page of the 1955 edition,²⁸ barely keeping up with plain Dr Brain's progress, announced that Sir Russell (since 1952) had been created a baronet (in 1954). In the 5th edition, Brain identified important new work on acute disseminated encephalomyelitis resulting from publication of the influential paper from Newcastle in 1953;²⁹ and McAlpine's recommendations³⁰ for distinguishing acute disseminated sclerosis from acute disseminated encephalomyelitis – fever, bilateral optic neuritis, spinothalamic sensory loss and areflexia characterizing the latter, in which recurrences could occasionally be expected, were noted. It is in this section that Brain, following Miller,²⁹ first referred, albeit cautiously, to the use of corticosteroids in the treatment of demyelinating disease. Acute haemorrhagic leuco-encephalomyelitis earned a section of its own based on a somewhat delayed reading of the paper by Hurst²² and those of Brain's colleagues from the London Hospital.

Whilst the Newcastle group under the leadership of Henry Miller was collating cases of acute disseminated encephalomyelitis in preparation of the definitive papers of 1953 and 1956,^{29,31} Douglas McAlpine and his assistant (the E.G. Fearnside scholar of the University of Cambridge) were analysing 666 cases seen at the Middlesex Hospital; advance publication copies of their book³² were in circulation by January 1955 and Brain referred to

what is now known as 'McAlpine's Multiple Sclerosis' in the 1955 edition of his textbook, although this may have been added at proof stage since no details were included, and he did not follow McAlpine's nosological lead in adopting the term 'multiple sclerosis' despite this having been used in Germany and the United States since the end of the 19th century. But his account of the aetiology of disseminated sclerosis was much influenced by McAlpine and his colleagues: he quoted their rates for the frequency of familial disease (6.5%), and the 1952 paper on the natural history of disseminated sclerosis^{33,34} reporting that 14.4% of cases have a history of physical trauma in the 3 months preceding the onset of new symptoms and establishing a relationship between the part traumatized and the anatomical basis for new symptoms – guidelines not yet superseded and still used in exchanges between neurological specialists, solicitors and their clients. Based on the Middlesex Hospital study, Brain again up-dated his figures for prevalence to 1:2,400 (42/100,000) for England and Wales and 1:1,570 for Scotland (64/100,000) – establishing the latitudinal differential that remains unexplained to this day. After 32 years in which advice to clinicians on the differential diagnosis of disseminated sclerosis had not changed, Brain omitted encephalitis lethargica and introduced cervical spondylosis as a cause of ataxic weakness of the upper limbs with spastic paraparesis which might be confused with disseminated sclerosis.

Brain's Diseases of the Nervous System, 6th Edition, 1962

With the sixth edition,³⁵ Oxford University Press changed the format of Brain's *Diseases of the Nervous System*. The paper, print size and line spacing increased although the octavo format was maintained: the bigger book, no longer bound in red buckram with gold lettering on the spine and with the title blindstamped in black on the front cover, now appeared with a decorated spine in gold and black anticipating the elevation of its author to the peerage in 1964. A number of important changes were introduced in the section on disseminated sclerosis – a term which Brain continued to use; the detection of an abnormally high gamma globulin by paper electrophoresis was mentioned for the first time citing the work from Newcastle of Schapira and Park³⁶ but not Kabat's 20 year old report.²⁵ For several decades, Brain had drawn on personal anecdotes in assessing the prognosis for life and the interval between the presenting and subsequent attacks but he now found it convenient to quote from McAlpine on the average annual relapse rate (0.4/year), frequency of progression from onset, and average disease dura-

tion in fatal cases (20 years). Drawing once again on the experience of demyelinating disease from the Newcastle school, Brain accepted the clinical impression that corticotrophin might help in an acute exacerbation but he concluded that there was no convincing evidence for the value of maintenance treatment with prednisolone.³⁷

Brain had stuck with the 1940 classification of demyelinating disease listing encephalitis periaxialis diffusa (Schilder's disease), centrolobar sclerosis, encephaloleucopathia scleroticans, progressive degenerative subcortical encephalopathy, leucodystrophy, leuco-encephalopathia myeloclastica primitiva, encephalomyelomalacia chronica diffusa, concentric demyelination (Balo's disease) and the infantile varieties (Krabbe's, Scholz's and Pelizaeus-Merzbacher's diseases) as synonyms (not to mention tongue twisters) for diffuse sclerosis. This difficult group of diseases had recently been carefully scrutinized by J.G. Greenfield³⁸ and Brain inserted a paragraph which sought to improve on this descriptive soup. Greenfield had distinguished sudanophilic leucodystrophy (familial in childhood and sporadic in young adults – Schilder's disease), from Pelizaeus-Merzbacher (familial and childhood onset), Krabbe's disease with infantile onset and characteristic globoid cells, and metachromatic leucodystrophy – a condition which Brain and Greenfield had described in 1950³⁹ and which he now thought should be included in the chapter on the lipidoses.

Brain's Diseases of the Nervous System, 7th Edition, 1969

Lord Brain died on 29 December 1966, 2 years after he was elected to fellowship of the Royal Society, working to the last on the journal *Brain* which he had edited since 1954. Sir George Pickering, writing in the *Dictionary of National Biography*, credited him with four lasting discoveries – median nerve compression in the carpal tunnel, disc prolapse as a cause of cervical myelopathy, carcinomatous neuropathy, and endocrine exophthalmos. Apart from the description of metachromatic leucodystrophy he made no original discoveries relating to human demyelinating disease. However, his 1930 review of disseminated sclerosis is a classic paper; there was little need to alter many of his views over the next 30 years but, with only a few lacunes, he was alert to most developments as they occurred, being much influenced by work of the Newcastle school. It was therefore appropriate that his executors and publishers should invite John Walton, then Professor of Neurology in the University of Newcastle upon Tyne, to take re-

sponsibility for revising the premier neurological textbook of the day.⁴⁰

Dr Walton saw no need to alter Brain's classification of demyelinating disease although work from the Medical Research Council Demyelinating Disease Unit in Newcastle was incorporated; central pontine myelinolysis, described in 1959⁴¹ appeared in the table and with a brief textual account of four cases, three of whom were alcoholic. A few extra lines were included on relationships between the pathology of encephalomyelitis following vaccination against rabies; and acute cerebellar ataxia was re-instated as a variant of acute disseminated encephalomyelitis, complicating ECHO, Coxsackie and varicella infections. The nosological status of Devic's disease was again debated, Walton siding with opinion in the revised version of McAlpine's monograph⁴² and reverting to the position that neuromyelitis optica was simply a form of multiple sclerosis.

Disseminated sclerosis had become multiple sclerosis but no new insights could be offered on the aetiology, other than the suggestion that the disease arose from an auto-immune response in the central nervous system. Even though the risk of developing multiple sclerosis was increased by 15 times for the first degree relatives of an affected individual, nurture was deemed to be a more important aetiological force than nature. The relative importance of extrinsic triggers was reviewed – surgery and pregnancy carrying a low risk, vaccination appearing to be of more importance and the situation with respect to trauma not having materially altered. The epidemiological deliberations of Acheson⁴² favoured the concept of multiple sclerosis as a disorder associated with certain locations rather than race, implying an extrinsic aetiological factor with a long latent period; but then, as now, its nature remained elusive. A number of subtle alterations were included in the account of symptoms – wild proximal upper limb tremor and feelings of swelling and tightness in posterior column sensory involvement being notable additions. The detailed assessment of spinal fluid that was to dominate research into multiple sclerosis for several years to come was hinted at by the inclusion of results on quantitative and qualitative tests for estimation of gamma globulin. And the prolonged follow-up of first cases described in the first edition of McAlpine's *Multiple Sclerosis*⁴³ was used to supplement morbidity statistics, emphasizing benign forms and suggesting that a mild course in the first 5 years carried a favourable long-term prognosis. In discussing treatment, John Walton deviated from the dogmatic line taken by Brain in six previous editions. Gone were the recommendations for arsenic, fever therapy and intrathecal tuberculin; in came prolonged courses of corticotrophin lasting

up to 10 weeks for the management of relapse, diazepam for spasticity, and propantheline for the unstable bladder.

In discussing diffuse sclerosis, Walton began to feel uneasy about the inclusion of Schilder's disease and spongy degeneration of the white matter – although sub-acute sclerosing panencephalitis and the spongiform encephalopathies had not obviously contaminated this material in earlier editions. The advent of nerve conduction studies was a further cause for concern in the classification of these diseases and metal therapy was no longer advocated.

Brain's Diseases of the Nervous System, 8th Edition, 1977

Dr Walton wrote in his preface to the eighth edition⁴⁴ that he had extensively revised the section on demyelinating diseases in 1969 (but the chapter that appeared in 1977) deviated more from the model instituted in 1933 than any previous revision. Biochemical, immunological and virological studies had started to illuminate the neurobiology of the complex unit formed by the myelin sheath and its nutrient glial cell. Walton vigorously restated Brain's view that the solution to many of these disorders lay in understanding their immunology, arguing that this would be aided by the investigation of experimental allergic encephalomyelitis which was active in the Newcastle department at that time; he felt the need to relocate more subcategories of diffuse sclerosis leaving only Schilder's disease, centrolobar sclerosis, progressive degenerative subcortical encephalopathy and Balo's disease, whilst remaining ambivalent about the status of X-linked recessive adrenoleucodystrophy,⁴⁵ which appeared for the first time.

Walton could now be more precise about the aetiology of acute disseminated encephalomyelitis, rejecting outright the long held view that the various forms arose from activation of an ubiquitous opportunistic demyelinating virus and leaning heavily on experimental studies in favour of the lymphocyte-mediated immunological hypothesis. Acute cerebellar ataxia in children received yet more prominence but Walton felt unsure whether this differed from the syndrome of opsoclonus and jerking extremities – now known to be associated with neuroblastoma in childhood and encephalitis or paraneoplasia in adults. None of the cases of neuromyelitis optica followed-up in Edinburgh from 1937, and reported by Scott after up to 30 years^{46,47} had developed recurrent demyelination, suggesting that Devic's disease was not after all a variant of multiple sclerosis; but in turning to the pathology of multiple sclerosis, the views of

Lumsden⁴² were taken as indicating that pathologically there was no distinction to be drawn between the various forms of acute monophasic and relapsing demyelination.

Walton's account of multiple sclerosis mentioned recent developments in neurovirology, including the claim that a paramyxovirus could be recovered from the brain tissue of patients with multiple sclerosis⁴⁸ – sadly, as it now turns out, no more robust than Miss Chevassut's spherulal claims – and the first experiments providing a scientific explanation for the pathophysiology of onset and recovery from symptoms.⁴⁹ In a penetrating review of the aetiology, Walton marshalled the evidence for viral infection based on population serology, analysis of cerebrospinal fluid immunoglobulin and comparative epidemiology; he drew attention to the recently described associations with alleles of the histocompatibility system,⁵⁰ and concluded that multiple sclerosis is a disorder of immune response within the nervous system, conditioned by inherited predisposition, to a variety of viral agents of which measles may be one – a formulation that had lost no impact since first stated by Brain in 1930. John Walton's account of epidemiological statistics documented a further increase in the rates for prevalence, re-affirmed the geographical trends, identified high-risk groups in all geographical areas, suggested that racial susceptibility contributed to the distribution of multiple sclerosis, and demonstrated an aetiological interplay between environmental and genetic factors.

In describing the changes in cerebrospinal fluid, Walton identified the long-neglected paper of Kabat²⁵ reporting the increase of immunoglobulin but still giving a conventional account of the colloidal gold curve. The distinction was made between quantitative and qualitative immunoglobulin abnormalities and new findings on the concentrations of immunological mediators released by inflammatory cells, capable of degrading myelin, were described. But Walton did not feel that any of these tests had influenced the ability to diagnose multiple sclerosis early in the course. Paroxysmal symptoms appeared in the clinical description of multiple sclerosis for the first time – the 1958 paper of Matthews⁵¹ having previously been ignored. The prototypic symptom complexes were classified as Charcot's triad, generalized, ocular, sensory, cerebral, spinal (progressive, unilateral and sacral), brainstem, and the acute form which was described in detail but not identified eponymously as the Marburg variant.⁵² The differential diagnosis still included meningo-vascular syphilis and tabes dorsalis – perhaps only a temporary anachronism – and for the first time included other inflammatory disorders which could mimic the spinal consequences of demyelination, notably Behcet's disease but not sarcoidosis. Good

and bad prognostic features were identified but the overall impression of a more benign disease than previously recognized emerged from scrutiny of Kurtzke's cohort of male cases in which >50% had survived >35 years.⁵³ Walton's account of the treatment of multiple sclerosis provided a much more comprehensive description of symptomatic measures than before, emphasizing the extent to which spasticity, bladder and paroxysmal symptoms could be managed. The assessment of treatment made it necessary to devise scales for comparing individual cases or groups⁵⁴ but there was no good news on the efficacy of specific immunological remedies – some of which are still being used – for influencing the long-term course of the disease, even though the short-term role of corticotrophin had been defined.⁵⁵ Barbellion had not been forgotten.

Recognition of the range of conditions in which central pontine myelinolysis might occur had altered but the association with hyponatraemia was still not explicit. Diffuse sclerosis continued to pose difficulties; even with the removal of familial sudanophilic diffuse sclerosis, Pelizaeus–Merzbacher disease, Krabbe's diffuse sclerosis and metachromatic leucodystrophy – and the diversion of Binswanger's subcortical encephalopathy which never secured a comfortable place in the chapter on demyelinating disease – Balo's concentric sclerosis and Schilder's disease still worried Walton in terms of classification and aetiology despite their stereotyped clinical descriptions. Tests for metachromatic material were advocated in differentiating these conditions but brain biopsy might be needed in a difficult case where genetic counselling, a term not previously employed, was to be arranged.

Brain's Diseases of the Nervous System, 9th Edition, 1985

The 1985 edition of Brain's textbook⁵⁶ included further major departures from the 1933 production, appearing in double column quarto format. Responding to the growing evidence for an immunological basis to the pathogenesis, Walton wrote an account of immunology and the nervous system based on a lecture given at the first congress of neuroimmunology in Stresa. Immunology had for a short while been influenced by the ability to identify and enumerate sub-populations of lymphocytes which were assigned discrete functions regulating networks of anti-idiotypic cells involved in suppressing cellular and antibody-mediated responses; and the opportunity to assign allelic phenotypes provided clear evidence for the genetic control of immune responsiveness. The detailed neuroimmunological observations relating to demyelinating disease required extensive revision

of the section on the aetiology of multiple sclerosis; not only was it necessary to document the growing list of HLA antigen associations reported in different populations of patients with multiple sclerosis, but population serology had implicated specific viral triggers operating in genetically susceptible individuals. Walton adopted the consensus view that no single agent was responsible for the interplay between genes and environment, and that exposure occurred repeatedly in early life. He did not attempt to catalogue the observations made with respect to immunological changes in the peripheral blood, but suggested that the target antigen for the immunological process might be identified through studies of cerebrospinal fluid. Several years experience with evoked potential methods had provided laboratory methods for supplementing clinical evidence for the diagnosis and the demonstration of focal areas of demyelination using computerized tomography was recommended. The suggestion that nuclear resonance imaging was likely to be even more successful was prophetic of the most significant development in the investigation of patients with multiple sclerosis since before Brain first wrote on the subject in 1930.⁵⁷ Immunological and immunogenetic characterization of patients with multiple sclerosis had not helped in assigning an accurate prognosis; and J. Gould⁵⁸ joined Barbellion in giving a personal account of the disease. Walton had hoped to provide some additional encouragement that the immunological approach to treatment might influence the long-term course of the disease, and although hints of success had at the time been reported using azathioprine with antilymphocyte globulin and thoracic duct drainage, transfer factor, copolymer I and dietary treatment, no therapy could unequivocally be recommended for the multitude of patients.

Conclusions

Taken with the 1930 *Quarterly Journal of Medicine* review, the account of disseminated sclerosis contained in the first edition of *Brain's Diseases of the Nervous System* was penetrating, ahead of its time and definitive; most of the opinions given by Russell Brain, and his predictions, were later shown to be correct and it could be argued that little of conceptual substance has since been added; nevertheless, clear shifts of emphasis and intellectual unease were always apparent in his accounts of acute disseminated encephalomyelitis, and he never felt comfortable with the nosological status of the leucodystrophies. Brain was clearly much influenced by the studies and writings of the neurological school that developed under Henry Miller in Newcastle; and his successor as head of

the department at the Newcastle General Hospital was a natural heir to authorship of the premier English textbook of neurology. Walton's re-writing of the section on demyelinating disease for the eighth edition ranks with Brain's original version in its breadth and intellectual authority; it combines the best of Brain with contemporary

knowledge and modern interpretations neatly inserted – the stitches barely being visible. Authorship for the section on demyelinating disease now passes into new hands; it is sincerely to be hoped that the newest wine will not disturb this distinguished old bottle.

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