

The story of multiple sclerosis

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Multiple sclerosis was first depicted 160 years ago. The unnamed patient was French, the illustrator a Scotsman. In the six decades which followed, French and German physicians gave a coherent clinico-pathological account of the disease. In the early part of the 20th century, ideas began to formulate on the cause of the disease. Research over the last 50 years has begun to illuminate the mechanisms of tissue injury and the therapeutic era, which will surely culminate in the application of successful strategies both for limiting and repairing the damage, has now begun. What follows is not a conventional history of achievements in the field of multiple sclerosis but is intended as background to the chapters which follow; it is the story of multiple sclerosis.

NAMING AND CLASSIFYING THE DISEASE: 1849–1983

Few would disagree that the serious study of human demyelinating disease began with the studies of Jean Martin Charcot at the Salpêtrière in the last three decades of the 19th century. Charcot was aware of at least three patients with *sclerose en plaques* in whom symptoms had begun in 1855 (see Ordenstein 1868 [*observations* III and VII]; Babinski 1885a [*observation* VIII]), and was particularly struck by the clinical appearance of a maid employed in his house whom, initially, he thought had Parkinson's disease (cited by Bourneville and Guérard 1869). Three cases were presented to the *Société Médicale des Hôpitaux* on 9th May 1866; Alfred Vulpian (1866) was the sole author of the report which appeared in parts but the third of these makes clear that the paper was read by Charcot and in the first sentence Vulpian reminds his readers that it was Charcot who had described sclerosis of the lateral columns to the society in the previous January (actually it was on 8th March 1865; Charcot 1865).

Within a few years, Charcot had gathered together the early descriptions so effectively, adding his own clinical and pathological observations (Charcot 1868a; 1868b; 1877), that the condition was named eponymously after him by Julius Althaus in 1877. However, Charcot was evidently a poor historian, and it is a shame that in his attempt to emphasize his own contributions and those of fellow Frenchmen, the published versions of his lectures are disingenuous with respect to the contributions of non-Francophones. These irritations apart, where others had merely depicted and described aspects of the pathology or made clinical observations, Charcot recognized that multiple sclerosis was a distinct entity; he gave it nosological status, made accurate clinico-pathological correlations, emphasized its frequency, speculated on the pathophysiology, and despaired of effective treatment.

Charcot's contributions are in making the story coherent, but on either side of his publications from the late 1860s are important pathological depictions (Carswell 1838; Cruveilhier c1841 – who also gave clinical details of the patients he illustrated) and case reports in German (Frerichs 1849; Valentiner 1856) and in English from the United Kingdom (anon [Moxon] 1873), Australia (Newman 1875; Jamieson 1886), the United States (Hammond 1871; Seguin *et al* 1878) and Canada (Osler 1880).

It has been remarked that despite his emphasis on the disease, Charcot only collected 34 cases throughout his professional career (Sherwin 1957). To us, this seems no mean achievement and it is a mark of Charcot's international influence that a disease which merited individual case reports in the 1870s had become one of the commonest reasons for admission to a neurological ward by the turn of the century – this almost certainly represents an epidemic of recognition rather than the effect of altered biological factors, and is a phenomenon which

seems to have repeated itself down the years (see chapter 3).

Charcot referred variously to his disease as *la sclerose en plaques disseminées*, *la sclerose multiloculaire* or *la sclerose généralisée*; these names were translated in the New Sydenham Society edition of his lectures (which spread his influence amongst the English-speaking world) as *disseminated (cerebrospinal) sclerosis*. This name was preferred to *insular sclerosis* or *lobular and diffuse sclerosis* under which the first cases had been reported in England, Australia and the New World. It was in Germany that the term *multiple Sklerose* was used from the outset (with variations including *multiple inselformige Sklerose*, *multiple Hirnsklerose* and *multiple Sklerose des Nervensystems*). This term was occasionally used elsewhere but *disseminated sclerosis* soon became the accepted term amongst English-speaking physicians, even though *sclerose en plaques* persisted in France (and translated in Italian as *sclerosi in plache*); according to Pierre Marie (1895), *polynesian sclerosis* was preferred by some authorities. Consistency of nomenclature was only achieved in the 1950s with the formation of lay patient support groups.

On 1st May 1945, there appeared a classified advertisement in the *New York Times* which read:

"Multiple Sclerosis. Will anyone recovered from it please communicate with the patient. T272 Times."

The responses indicated the need to organize and finance research into the cause, specific treatment and cure and spurred Miss Sylvia Lawry, who had placed the advertisement on behalf of her brother, to form The Association for the Advancement of Research into Multiple Sclerosis; on 30th July the name was changed to the Multiple Sclerosis Society in recognition of the fact that services to persons with the disease and their families were needed. Tracy Putnam established the first medical advisory board. One of

the initial scientific awards was to Dr Charles Lumsden. In 1952, at the invitation of Lord Howard, Miss Lawry met (Sir) Richard Cave in the United Kingdom. Having ascertained from the Medical Research Council that they would have been sympathetic to the receipt of grant applications in the field of multiple sclerosis but none had been received, the Multiple Sclerosis Society of Great Britain and Northern Ireland was formed with the dual purposes of promoting (and funding) research and providing a welfare and support service for affected individuals and their families. The medical advisory board was organized by Douglas McAlpine. These aims were eventually realized through the tireless endeavours of Mr John Walford who joined the society in February 1954; when he retired in 1994, £30 million had been committed to research and a further £55 million to welfare. The inaugural meeting was held at the Chenil Galleries in Chelsea, London on 2nd December 1953 and the guest speaker was the minister of health, Mr Iain McLeod. Two consultant neurologists, present to answer questions, preferred to remain anonymous and are identified in the minutes only as Mr A and Mr B. They were Dr Douglas McAlpine and Dr Arnold Carmichael. The International Federation of Multiple Sclerosis Societies was established by Miss Lawry, Sir Richard Cave and others in 1966.

The process of renaming the disease, which gathered momentum with the formation of these societies, was consolidated in 1955 with publication of the monograph *Multiple Sclerosis* written by Douglas McAlpine, Nigel Compston and Charles Lumsden (Fig. 1.1A–C) (McAlpine *et al* 1955), since when the condition has universally been known as *multiple sclerosis*. Douglas McAlpine died in 1981 aged 91 years. He came from a prominent industrialist family in Great Britain. McAlpine had a distinguished military career in both world wars, serving as a neurologist in the Middle East and India, and was appointed to the con-

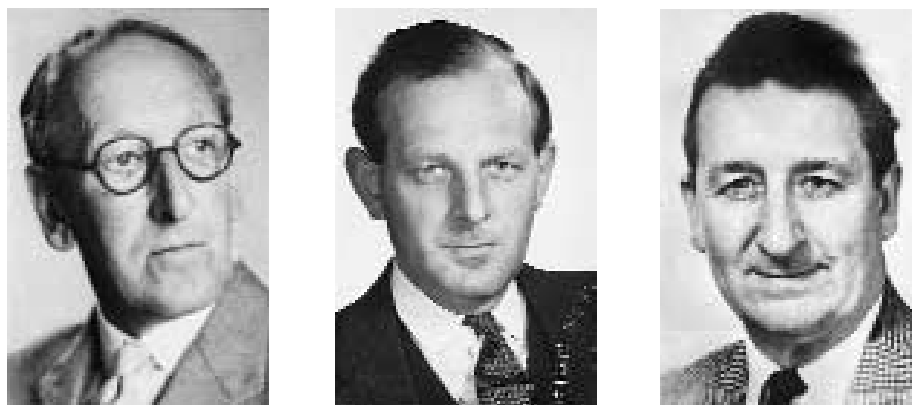


Fig. 1.1 (A) Douglas McAlpine (1890–1981); (B) Nigel Compston (1918–1986); (C) Charles Lumsden (1913–1974).

sultant staff of the Middlesex Hospital in 1924 where one of the neurology wards is named after him. After receiving the International Federation of Multiple Sclerosis Society's first Charcot award, McAlpine wrote to one of his co-authors:

"... the Charcot Award has come my way. Special praise was given in N.Y. to our first book. Without your constant help it would never have seen the light of day;"

and later that year, he added:

"your letter shall be kept as a memento of our happy time together. You made me see light in matters that were then (and still some are) beyond my ken..."

Nigel Compston died in 1986 aged 68 years. Educated in Cambridge, he also qualified from the Middlesex Hospital in 1942 and served in the Royal Army Medical Corps. Despite the close association with Douglas McAlpine which culminated in the publication of *Multiple Sclerosis*, his subsequent career was as a general physician at the Royal Free Hospital where the clinical haematology ward is named after him. He was for many years treasurer of the Royal College of Physicians of London; his memorial in the College garden (after Wren) is "*Si monumentam requiris, circumspice*" (if you need a monument [to the man] look around you).

Charles Lumsden died in 1974 aged 61 years. Educated at Aberdeen University, he learned the techniques of tissue culture and immunocytochemistry (with EA Kabat [see below]) in the United States during the late 1940s (after serving, amongst other places, in the Faroe Islands with the Royal Army Medical Corps), and applied these to the study of demyelinating disease, publishing the first papers on experimental allergic encephalomyelitis (EAE) from the United Kingdom. As Professor of Pathology at the University of Leeds, Lumsden was vigorous in his defence of pathology as the prime discipline of medicine. A shrewd but shy man, who painted and played the violin with distinction, he seldom changed his opinion since his position was not often wrong.

John Kurtzke (1988) has reviewed the history of the naming of multiple sclerosis and the classifications which were introduced for epidemiological purposes in order to weight the diagnosis in the absence of pathological proof. Allison and Millar (1954) classified cases as *early* (few physical signs but a recent history of remitting symptoms), *probable* (soon changed to early probable or latent: no reasonable doubt about the diagnosis), *possible* (findings suggesting the diagnosis and no other cause found but the history static or progressive and with insufficient evidence for scattered lesions) and *discarded* disseminated sclerosis. Until the mid-1980s, all surveys of multiple sclerosis

used the Allison and Millar criteria with some modifications within categories, including introduction of the term (clinically) *definite* (Bauer *et al* 1965; Broman *et al* 1965). The principles developed by John Kurtzke in classifying United States army veterans, on which consensus was later reached by a panel of examining neurologists, was formalized by Schumacher *et al* (1965) who categorized definite cases as those showing objective evidence for disease affecting two or more white matter parts of the central nervous system (CNS), occurring in episodes separated by >24 hours or with progression over 6 months, in a person aged between 10 and 50 years at onset and in whom a competent observer can find no better explanation.

Further modifications adapted by Rose *et al* (1976) were definitions for *probable* multiple sclerosis (two episodes but signs at a single site *or* a single episode with signs of widespread disease) and *possible* disease (two episodes with no or few signs). The McDonald and Halliday (1977) criteria added a definition for *proven* multiple sclerosis (evidence from autopsy or biopsy), refined the early probable or latent cases (two episodes and a single affected site *or* a single episode and two affected sites), and tackled the difficult issues of *progressive probable* (progressive history with multiple sites affected), *progressive possible* disease (progressive history affecting a single site), and *suspected* multiple sclerosis (one episode at a single site unless the optic nerves are affected). Most recently, the Poser committee criteria incorporated information available from laboratory investigations within the categories of clinically definite and probable multiple sclerosis and these have gained widespread acceptance (see Table 5.1) (Poser *et al* 1983). The Poser criteria do not deal with suspected cases and investigators have therefore assumed these to be all patients thought to have demyelinating disease but without clinical symptoms, signs or laboratory evidence for more than one lesion. Adapting from the Allison and Millar classification to the Poser criteria does not materially affect estimates for the total number of identified cases but differences do arise when surveys are restricted to the categories of definite and probable (Poser) and probable and early (Allison and Millar) cases, since the proportion in the suspected and possible categories needing exclusion differs significantly between the two classifications. Some surveys have used the Poser criteria but ignore features such as age at presentation (normally between 10 and 59 years) and particular investigations. Laboratory methods are now available which show the anatomical distribution of lesions, provide evidence for the nature of the disease process, and exclude conditions which mimic multiple sclerosis (see chapter 8).

DEPICTIONS OF MULTIPLE SCLEROSIS: 1838–1981

Physicians seeking to document and understand disorders that arise from disease of the nervous system, working in the early part of the 19th century, inherited a doctrine developed in classical times, which had remained largely unchallenged for almost 11 centuries. With the publication of *de Fabrica*, Andreas Vesalius (1543) gave the first accurate description and depiction of the human brain. Others borrowed, refined or distorted the details of his neuroanatomy but the next milestone was the clinical descriptions of Thomas Willis in the mid-17th century; Willis (1684) referred to his doctrine of the nerves as *neurology*. In the 18th century, anatomical methods and clinical description were combined in the emerging discipline of pathological anatomy and the first atlases of brain disease appeared. Matthew Baillie devoted fascicle 10 of his series of *Engravings Accompanied with Explanations Intended to Illustrate the Morbid Anatomy of some of the Most Important Parts of the Human Body* (1802) to the cranium, brain and its membranes. There is nothing to suggest that he saw the lesions of multiple sclerosis but Baillie concludes with a note of thanks for the specimen provided by Robert Hooper. Hooper's own work entitled *Illustrations of the Morbid Anatomy of the Human Brain and its Membranes* appeared in 1826; in 1828, the plates were reissued under a different title, the author offering those who purchased the (1826) loose sheets the privilege of exchanging them without expense. In his otherwise excellent history of neurology, Lawrence McHenry (1969) initiates a serious gaffe in claiming that Hooper's plate 4 illustrates the appearances of multiple sclerosis; in fact, this is a reference to plate 4 of Carswell's atlas (1838; see below) an error which has been extensively copied, notably by Dr JD (Jerry) Spillane in his magnificent *The Doctrine of the Nerves* (1981), and McHenry reproduces a plate showing an intracerebral haemorrhage, a pontine haemorrhage and a subdural haematoma that is a later plate from Carswell. However, not all Hooper's plates were published. The originals together with proof copies of the published versions were purchased at auction by Professor Greenfield of Edinburgh and eventually found their way into the collection of Sir William Osler (1929). They were bequeathed to the Medical Faculty of McGill University, Montreal but the archive does not contain any illustration suggestive of the lesions of multiple sclerosis.

It is against this background that the first depiction of the lesions of multiple sclerosis can be considered. Nowadays, Jean Cruveilhier's *Anatomie*

pathologique du corps humain; descriptions avec figures lithographiées et coloriées; des diverses alterations morbides dont le corps humain est susceptible is usually found in two volumes bearing the title dates 1835 and 1842, respectively; however, the separate livraisons had started to appear from 1829 which accounts for variation in the date given for publication of Cruveilhier's illustrations of multiple sclerosis. Volume I contains livraisons 1–20, and volume 2 numbers 21–40. Livraison 32 plate 2 and livraison 38 plate 5, both in volume 2, depict the lesions of multiple sclerosis; their publication date cannot have been 1835, as cited by Charcot and faithfully reproduced by others, and is obviously much later (Putnam 1938; Compston 1988). The rival claim for priority is Carswell's *Pathological Anatomy; Illustrations of the Elementary Forms of Disease* (1838) in which plate 4 figure 1 shows a *peculiar diseased state of the cord and pons varolii*, which modern commentators have interpreted as representing the macroscopical appearances of the plaques seen in multiple sclerosis (Fig. 1.2). Charcot wrote (in the English translation by George Sigerson):

"disseminated sclerosis is mentioned for the first time in Cruveilhier's Atlas d'anatomie pathologique, 1835–42 ... in parts 22 and 23 you will observe representation of the lesions found in disseminated sclerosis and side by side

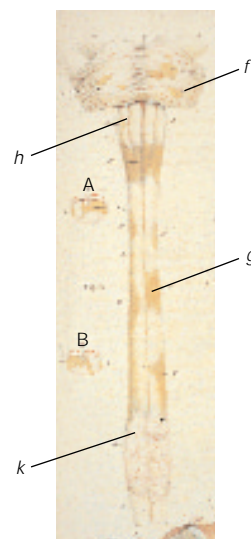


Fig. 1.2 Isolated points of the pons varolii of a yellowish-brown colour; *g* patches of the same kind on the spinal cord, all of them occupying the medullary substance which was very hard, semi-transparent and atrophied. The atrophy was more conspicuous in some points than in others and is particularly well seen in the figure at *h* where it affects the right olivary body; *k* softening of a portion of the cord. A and B represent transverse sections of the cord to show that the discolouration commences on the surface of the white and extends inwards to the grey substance. From Carswell (1838).

you can read the clinical observations which relate to them... Previous to this epoch, so far as I am aware, there is no trace of disseminated sclerosis to be discovered anywhere. After Cruveilhier, Carswell in the article on atrophy contained in his atlas, 1838, has had lesions depicted which pertain to multiple sclerosis."

Charcot's citations do not follow the collation of Cruveilhier's atlas in any of the copies to which we have access.

Robert Carswell studied medicine at the University of Glasgow and was later commissioned by Dr John Thompson of Edinburgh to make a collection of drawings illustrating morbid anatomy in connection with which he spent 1822–3 at hospitals in Lyon and Paris. He returned to Paris after graduating as an MD in 1826 and remained there until 1831 by which time he had been appointed to the inaugural chair of pathology at London University; for a while he studied with Pierre Louis in France in order to complete the 2000 water colours of pathological specimens which he later personally engraved on stone in preparation of his pathological atlas. We do not know the names of the patients with multiple sclerosis depicted by Carswell and he never saw them in life; one was under the care of M^r Louis in the hospital of La Pitie and the other under M^r Chomel at La Charite. In the preface to the atlas, dated 15th December 1837, Carswell indicates that he intended 12 fascicles to be included and implied that these had been produced serially; instructions to the binders show that the order of production was the reverse of that in which the fascicles would appear in book form so that the section on *atrophy*, which appears fourth and contains the depictions of multiple sclerosis, was evidently one of the last to be prepared. However, Putnam (1938) has pointed out that this plate has at the foot "*R Carswell ad nat del: Day and Haghe Lith^{rs} to the King*", and, unlike illustrations from some of the later fascicles which are signed "*Drawn on stone by Dr Carswell. A Ducotes. Lithog^r 10 St Martins Lane*", it must have been prepared before June 1837 – since that was the month in which King William IVth died and was succeeded by Queen Victoria. Haghe failed to reverse the disposition of the lesions on the surface of the medulla but was otherwise faithful to Carswell.

Plate 4, figure 4 and the corresponding legend depicts and describes a brownish patchy external discolouration of the midbrain, pons, cerebellum and spinal cord. In the accompanying text Carswell wrote:

"I have met with two cases of a remarkable lesion of the spinal cord accompanied with atrophy. One of the patients was under the care of Mr Chomel in the hospital of La Charite; both of them affected with paralysis. I did not see

either of the patients but I could not ascertain that there was anything in the character of the paralysis or the history of the cases to throw any light on the nature of the lesion found in the region of the spinal cord. I have represented the appearances observed in one case in plate 4 (figure 4)."

The cases illustrated by Carswell were therefore observed by him not later than 1831, may have first appeared in a separate fascicle produced in 1837 and were published in book form in 1838.

Jean Cruveilhier, born in Limoges in 1791, elected to study medicine under Dupuytren in Paris soon after entering the priesthood; he graduated in 1811. Twice he failed to secure appointments as surgeon to the City Hospital in Limoges, despite meanwhile having taken the chair of operative surgery in Montpellier. He was appointed in 1825 to the professorship of anatomy in Paris. Subsequently he held the first chair of pathology in the Faculty of Medicine, provision for which had been made in Dupuytren's will. He remained in Paris, benefiting from material at the Salpetrière and the Musée Dupuytren until the siege of Paris when he moved to his country estate at Succac near Limoges, dying there in 1874 aged 83 years.

The many surviving copies of Cruveilhier's atlas exist either with the livraisons bound sequentially by number, each containing an heterogenous collection of plates and clinical descriptions, or rearranged by subject with the plates interleaved in varying order presumably at the whim of individual collators. The case illustrated in livraison 32, plate 2, figure 1 (Fig. 1.3A) had died in the Salpetriere but the name, dates and details are not given; the same is true for another unnamed female patient with the same condition illustrated in figure 2. In the accompanying text, Cruveilhier uses, for the first time, the term *grise masses disseminées*. Figure 3 shows the case of Madame Gruyer, a 43-year-old embroiderer who had a severe movement disorder, likened to chorea. She spent 2 years as a patient at the Hôpital Necker under the care of Laennec and 10 years at the Salpetriere. Figure 4 depicts the brain and spinal cord of Darges (aged 37) whose clinical condition was that of a pseudobulbar palsy. In seeking to establish the date of publication of this livraison, some importance should be attached to the case of femme Cherpin (in whom the lesions illustrated do not resemble those of multiple sclerosis; figure 6); she occupied bed number 8 in St Gabriel ward up until at least 15th September 1838. The text of livraison 32 also mentions another patient alive on 30th November 1838 and cites a publication dated 1839. This dates the appearance of livraison 32 as not earlier than 1839. Livraison 38,

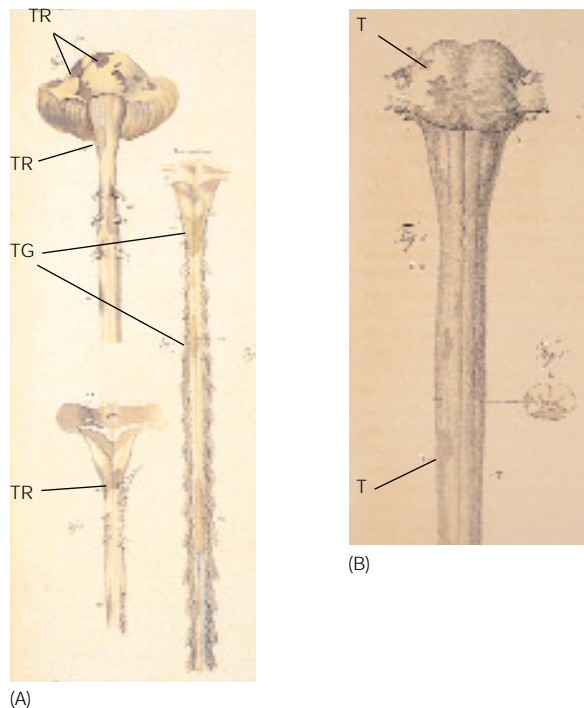


Fig. 1.3 (A) Reddish grey islets TR on the protuberantia and cerebellar peduncles. Other reddish-grey islets TR, TR, TR on the anterior and lateral aspects of the medulla. Other reddish islets TR, TR are visible on the posterior aspects of the medulla: the roots rising at the level of these islets are atrophied. Fig. 2 shows the posterior aspect of a medulla belonging to another subject; it shows exactly the same change, that is to say a grey transformation by disseminated masses TG, TG. (B) Figs 1 and 1' show us a new example of this lesion of the medulla which I have described (see livraison xxxii) under the name grey degeneration or transformation of this organ. From Cruveilhier (c1841).

plate 5 (Fig. 1.3B), illustrates the case of Josephine Paget who was blind, paraplegic and had severe proprioceptive sensory loss mimicking locomotor ataxia. She was in bed 16 of St Joseph ward at the Charite on 4th May 1840 and died on 20th March 1841. Another patient described in this livraison was alive in August 1841, and Marshall Hall's *Diseases and Derangements of the Nervous System* (published in 1841) is cited in the text. Based on the clinical details provided, alternative diagnoses could be suggested for the cases described in livraison 32; the evidence for multiple sclerosis is more compelling for Josephine Paget but her case history, and hence livraison 38 itself, cannot have appeared until 1841.

It is likely that Carswell and Cruveilhier met at some stage in Paris between 1826 and 1831 when the former returned to London. It seems coincidental that two pathologists working from the same pool of material in the same city at the same time should independently have described a new disease. Although there is a striking similarity in the distribution of lesions affecting the pons illustrated by Carswell and by Cruveilhier in livraison 38 plate 5, Josephine Paget

was alive at the time of publication of Carswell's atlas, so it cannot be the same case illustrated in each pathological work.

Until 1850, the main methods available for printing anatomical illustrations were woodcuts in which a relief of the image was carved on pear or boxwood; alternatively, metal plates were engraved with line drawings and produced separately from the printed text. Lithography, invented in 1798, produces the image with water repellent grease on stone or metal and inks the contrasting dampened and greased surfaces. Coloured medical illustrations were first used (in Gaspare Aselli's *De lactibus, sive lacteis venis*, which appeared posthumously) in 1627. Photography, developed by Niepce, Daguerre and Fox Talbot in 1839 and 1840, respectively, was used sporadically in medical texts in the 1850s, and later by Duchenne and Luys who published the first photographic atlas dedicated to neuroanatomy in 1873. Charcot placed great emphasis on medical illustration and was responsible for much of the material which appeared in the *Nouvelle Photographique de la Salpêtrière* (Bourneville and Regnard 1876–1880) and the *Nouvelle Iconographie de la Salpêtrière* (various authors; 1884–1912). Photographs of Charcot's cases appear in the later writings of Pierre Marie and other students during the early 1890s. By this time, others (for example, Bramwell) were occasionally photographing clinical and histological features of neurological disease, although prior to the discovery of X-rays there was a surprising reluctance to illustrate the nervous system with photographs. We believe that the first photographs dealing with multiple sclerosis were the series of photomicrographs of spinal cord pathology illustrated in volume three of the *Nouvelle Iconographie* (Blocq and Londe 1890) and showing the gross and microscopic appearance of extensive symmetrical demyelination in the dorsal root entry zone of the cervical cord (Fig. 1.4). Not until 1905 was a clinical photograph published of an individual with multiple sclerosis (Scherb 1905); this patient developed an isolated cerebellar syndrome in 1898 with disturbances of posture whilst walking and sitting which, despite formidable alcohol intake, the authors considered to be a *formes fruste* of *sclerose en plaques* (see Fig. 1.21).

Radiological techniques were not used routinely to identify the lesions of multiple sclerosis even following the introduction of computerized tomography (CT), but this situation changed dramatically with the application of magnetic resonance imaging (MRI) to multiple sclerosis (Fig. 1.5) (Young *et al* 1981); this technique has subsequently been routinely applied to the diagnosis of multiple sclerosis, the understanding of its pathogenesis, and the assessment of treatment (see chapter 8).

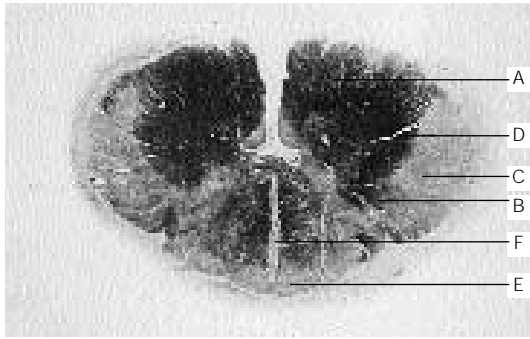


Fig. 1.4 Multiple sclerosis. Area of great change. A: healthy part; B: marginal area with little sclerosis; C: lateral fascicles showing considerable change; D: sclerotic area of Turck's fascicule; E: posterior part of Goll's cord in very changed state; F: significantly thickened posterior septum. From Blocq and Londe (1890).

CASE REPORTS AND PERSONAL ACCOUNTS OF MULTIPLE SCLEROSIS: 1824–1991

Although the diagnosis of demyelinating disease can perhaps retrospectively be made from a clinical description given by CP D'Angiers Ollivier in his monograph on diseases of the spinal cord (1824), it is difficult to substantiate the claims made on behalf of Gabriel Andral (Hammond 1871) or Marshall Hall and John Abercrombie (Wilson 1940). We also remain to be convinced that the case of St Lidwina of Schiedam represents an early description of multiple sclerosis (Medaer 1979). However, it is an indisputable fact that the manuscript diary kept by Augustus D'Este, grandson of George III, between 1822 and 1848, together with his almanac for 1847–1848, contain a personal account of the disease (see below; Firth 1948).

After Cruveilhier, it is generally held that Frerichs (1849), writing in German, first described pathological features of multiple sclerosis in patients whom he had observed in life; subsequently, his student Valentiner (1856) described two cases in which relapse and remission were first emphasized as cardinal features of the disease and the presence of cognitive symptoms was also noted. The first patient was a 21-year-old man who presented in 1853; the next year he developed a hemiplegia followed soon after by mental symptoms with a stuporous loss of interest. He died within 2 years of onset and the autopsy showed numerous different sized greyish-red patches with jagged contours. The second case was a woman aged 20 who, in 1850, developed weakness of the right leg which progressed to a paraparesis. She improved but 2 years later developed dysarthria and altered sensation. She died within 3 years of onset and similar pathological features were noted from which Valentiner concluded:

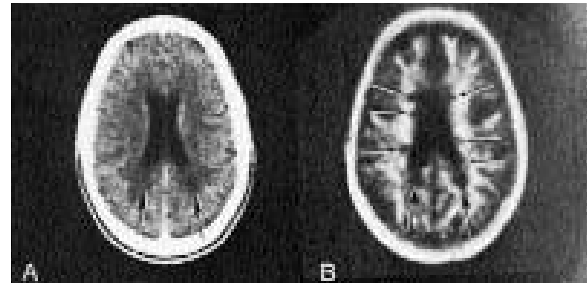


Fig. 1.5 Comparable (A) CT and (B) MRI scans (in patient 10) at mid-ventricular level. The two posterior periventricular lesions seen on the CT scan are also seen on the MRI scan (large arrows). In addition 6 smaller lesions are seen on the MRI scan at the lateral margin of the lateral ventricles (small arrows). The sharply defined area on the medial margin of the left posterior horn is a circular artefact. Reproduced with permission from Young *et al* (1981).

“to what extent the relative remissions of single symptoms represent a recovery of diseased brain regions cannot be stated as our lack of understanding of the localization of certain central functions as well as of the nature of the disease process forbid any reflection on this.”

Demyelination was first depicted by Froman (1864) (Fig. 1.6).

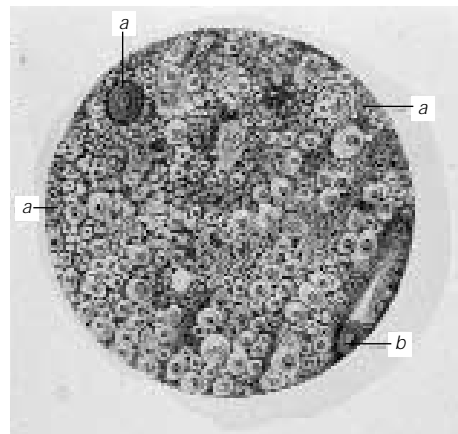


Fig. 1.6 Cross-section through the fibrillary degenerated tissue in the vicinity of normal (areas). The original septae are still visible and surround part myelinated and part naked axons. Sometimes they surround empty holes or rare cross-sectioned fibrils. The septae are in the majority – and in particular at their crossing points – enlarged and contain rows of dense granules which can be identified as cross-sectioned fibrils. The fibrils which are densely packed in the inner spaces of the septae, as well as those which are derived from the granules and grow into the holes of the meshwork, are missing. The eight large distinctly outlined cells appear as homogenous and shiny masses; also their processes were – as far as they could be delineated – shiny, and only in the periphery of the cells were there fine ill-defined processes in continuity with the surrounding granulated fibrils. A number of nuclei were freely located in the tissue which was surrounded by a small rim of protoplasm held together by fine granulated septae. The discernible nuclear fibres originated in part from the nuclei or sometimes were just found adjacent to them. At the upper edge of the graph there was an elongated fibril which originated from the adjacent nucleus. *b*: Blood vessel with thickened vascular wall; *a*: a similar vessel is seen at the left upper edge of the figure. From Fromann (1864).

By 1877, when physicians started to refer to Charcot's disease, the disorder was well known to neurologists working in the United Kingdom and case reports had appeared under the name of *insular sclerosis* in issues of the *Lancet* for 15th February 1873, 3rd and 17th April and May 1st 1875 (Anon 1873; 1875a; 1875b; 1875c). All but one of these patients was under the care of Dr William Moxon at Guy's Hospital (the other was communicated to a meeting of the Clinical Society of London by Dr Thomas Buzzard) and presumably Moxon wrote the case reports. In Ireland, a patient of Sir Christopher Nixon was shown at autopsy to have lesions of disseminated sclerosis (Nixon and McSweeney 1893), and Tweedy (1894) diagnosed in life a confirmed case of insular sclerosis with extensive lesions in the spinal cord and brainstem; as in the cases described by Moxon, sexual habits and domestic activities were blamed for precipitating the neurological disease.

On 4th December 1867, Dr JC Morris presented the case of the late Dr CW Pennock (who developed progressive disturbances of sensation and motor function in the limbs with sphincter involvement from 1843) to a meeting of the College of Physicians of Philadelphia at which Weir Mitchell provided the pathological description of multiple grey lesions (Morris 1868). A number of cases also appeared in Hammond's *Treatise on Diseases of the Nervous System* (1871). Hammond's account precedes by a number of years the two case reports of Seguin *et al* (1878) and his subsequent description of patients having the combination of severe bilateral optic nerve (or chiasmal) and spinal cord demyelination (Seguin 1880); Seguin is usually credited with describing the first cases from North America and this may be because Hammond allowed confusion to contaminate his otherwise precise clinical observations.

Multiple sclerosis was demonstrated at autopsy in Canada by William Osler (1880) and he also diagnosed a number of cases in life; one of us (GCE) has scrutinized the 786 autopsy records made by Osler at the Montreal General Hospital and found one definite and two possible cases, providing an estimate for disease frequency (c1:800) which suggests that multiple sclerosis may not have increased in incidence over the last 100 years (Ebers 1985b).

The existence of insular sclerosis was first brought to the attention of Australian neurologists by Dr AK Newman (1875) who described the differential clinical diagnosis and despaired of identifying effective treatments. Retrobulbar neuritis had been described by MacLaurin (1873), and the first local case was reported by Jamieson (1886), one of whose patients with multiple neuritis had features which led Frith (1988) to concur with Jamieson that this was an exam-

ple of multiple sclerosis. After a flurry of further case reports, Flashman and Latham (1915) published a detailed clinico-pathological description of multiple sclerosis which set the scene for the experimental and investigative work which has since appeared from Australia.

Down the years artists, poets, authors and ordinary people have left personal accounts of what it is like to have multiple sclerosis. In 1830, at the time Carswell and Cruveilhier were studying in Paris, a young English nobleman discovered, on a visit to the seaside resort of Ramsgate in southern England, that he was impotent. Augustus D'Este was born on January 13th 1794, inconveniently soon after his parents – Lady Augusta Murray and Prince Augustus Frederick, Duke of Sussex (sixth son of King George III of the House of Hanover) – had met in Rome; the further details of that unhappy liaison need not be told here other than to report that the King, acting on the grounds that the union of descendants is invalid without the Royal Consent, caused the marriage (conducted in Rome and re-enacted in England during December 1793) to be annulled at the Court of Arches in August 1794, thus making the issue illegitimate. Augustus had a conventional childhood for the times; he was inoculated with Lady Mary Wortley Montagu's small pox, and suffered green stools, gripings and St Anthony's fire. His mother with whom he lived indulged Augustus's every whim and he seems to have behaved in a manner, during adolescence and as a young man, which gave the English aristocracy of the time a deservedly bad name. After studying at Harrow school, where he contracted measles on 26th February 1808, D'Este joined the VIIth Royal Fusiliers in 1812 and eventually reached the rank of Lieutenant Colonel.

The surviving part of his diary begins with a description of bilateral optic neuritis which developed in 1822 and recurred in 1826 (Fig. 1.7); he had episodes of diplopia and weakness in the legs with perineal numbness in 1827, after which he was never able to run fast or dance. During 1828 he had unpleasant sensory symptoms and fatigue but continued with his military career until developing urinary retention; he became constipated, had a single episode of faecal incontinence, and found himself to be impotent whilst attempting the aforementioned commercial encounter. Thereafter, the diary contains accounts of visits to European spas, opinions given and treatments suggested. Presumably missing parts document other events for by 1843 D'Este was ataxic, numb below the waist and had spasms at night; in that year he had an episode consistent with brainstem demyelination which partially recovered but before long he was well established on a chronic progressive

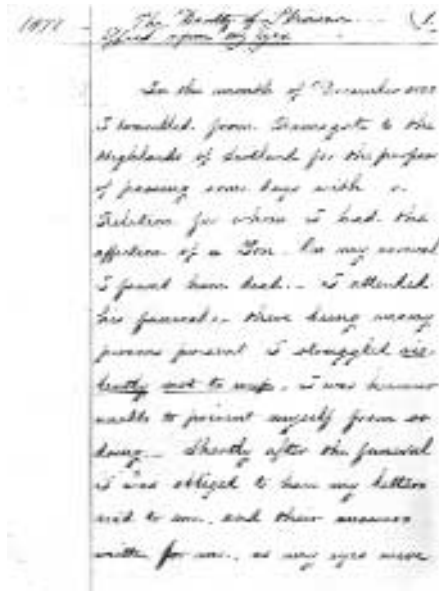


Fig. 1.7 First page of *The Case of Augustus D'Este*. Reproduced with permission from Firth (1948).

course with superimposed relapses and later became paralysed, losing the use of his arms and eventually dying in December 1848, after having had symptoms intermittently for 26 years.

The details of D'Este's illness are known through the work of Douglas Firth. He was in charge of the Blind School Hospital at Leatherhead (England) during the second world war and it was there in 1942 that:

"through [his] interest in old papers he rescued and later published the 72 pages which remained after pilfering and the attentions of rats and human agencies of the diary and almanac written by various secretaries and himself between 1822 and 1846." (Firth 1948)

Both documents may be consulted in the library of the Royal College of Physicians of London.

It is significant that historians disagree on the nature of the neurological illness from which Heinrich Heine died in 1856, aged 59 years. Macdonald Critchley (1969) diagnosed neurosyphilis; Schachter (1933) and Ernest Jellinek (1990) consider that Heine had multiple sclerosis. Traditionally, these are the conditions that are the great mimickers of most other neurological diseases. Heine was a poet whose work was much used by composers of *lieder* (Schubert), major operas (Wagner and Strauss) and ballets (Adam and Egk). His early promise does not seem to have been sustained and, like D'Este, good family connections and a comfortable living enabled him to lead a somewhat erratic social and matrimonial

life which, when his medical symptoms began, caused him to conclude that they were due to:

"one of those illnesses which Germans suffer who privatize abroad."

From the age of 35, he had intermittent neurological symptoms which can be interpreted as recurrent demyelination affecting the optic nerves and brainstem followed 10 years later by bulbar symptoms and hemisensory and motor disorders with impaired sphincter function; he was bed bound for the last 8 years of his life due to progressive tetraplegia with spasms from which he took solace with increasing doses of opium. He was attended amongst others by Julius Sichel, who had earlier (1837) linked amaurosis with disorders of the spinal cord, and provided a colour illustration of optic atrophy at around the time of Heine's death.

Until the publication of Augustus D'Este's diary, the best known personal account of multiple sclerosis was *The Journal of a Disappointed Man* published on 31st March 1919 by Bruce Frederick Cummings who wrote under the pseudonym WNP Barbellion, a name he took from a sweet shop in Bond Street, London. 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. The final entries of Barbellion's diary read:

"October 12th ... I am only twenty eight, but I have telescoped into those few years a tolerably long life: I have loved and married, and have a family; I have wept and enjoyed, struggled and overcome, and when the hour comes I shall be content to die. October 14th to 29th: miserable. October 21st: self disgust. Finis. [Barbellion died on December 31st (1917)]."

In fact he was far from dead on new year's day in 1918. Barbellion aped Mark Twain in ensuring that news of his death was announced prematurely so that he might enjoy reading posthumous notices of his book. However, his diary was declared:

"an acerbic bid for immortality, written by a smart alec rotter"

and he only enjoyed his literary fantasy for 18 months, dying aged 30 on 22nd October 1919 at Gerrards Cross. Others have suggested that he accelerated his illness by following contemporary advice to take arsenic and strychnine on a weekly basis. HG 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 justifying the statement that, through illness, biological science lost one of its most promising recruits. On 26th April 1913, aged 24, Barbellion first records in his diary that his speech and right side are impaired and believes that he must have locomotor ataxy; he saw a well-known nerve specialist (Dr H[eadl]) who seems to have had similar suspicions. Barbellion had what we would easily recognize as symptoms of demyelination but over the next 2 years, despite seeing several neurologists, he remained without a diagnosis until, on attempting to enlist in November 1917, he read on the certificate in the sealed envelope issued by his doctor that multiple sclerosis had been diagnosed at presentation and communicated to his family. He looked up Risien Russell's chapter on the disease in Clifford Allbutt's *System of Medicine* (see below). For Barbellion, learning the true nature of his illness placed him in a posthumous and rather relaxed state, released (or so he claimed) from his former self-obsession and ambition. Temporarily restored to health, he began again to contemplate a number of zoological projects but he had to run from the library, after coming across "*an enormous quarto memoir in the Trans. Roy. Soc. Edinburgh on The Histology of — — [Disseminated Sclerosis]*" – Dawson's great work (see below). Increasingly troubled by alternating hemipareses and disturbed sensation in the hands, Barbellion showed good neuroanatomical sense but a less critical approach to the writings of Pierre Marie in telling his diary (January 1917) about:

"the millions of bacteria gnawing away [his] precious spinal cord".

Whatever its nature, the process of demyelination did continue and the latter part of Barbellion's diary contains a mixture of nostalgia for his past excursions (literary and field) into natural history, some critical self-analysis, and comparisons between his own condition and that of ordinary healthy people, rehearsing internal and bitter dialogues from which he gained some strength:

"I do not envy you your absorption in the petty cares of a commonplace existence."

The doctor as patient promises special insights into the subjective experience of multiple sclerosis. In her early 20s, Dr Janette Gould sequentially lost vision in both eyes, remembered an episode of weakness in one arm attributed at the time to neurasthenia, and lost her balance (Gould 1982); the effect of these undiagnosed complaints caused domestic strain and her mar-

riage soon ended in divorce. When her vision again deteriorated, and it was suggested that she might see a neurologist, she remembered the illness, eventually diagnosed as multiple sclerosis, which had affected her late father. She describes the clumsy way in which her own diagnosis was established and eventually communicated, relief only being provided by a sympathetic general practitioner who allowed time for detailed discussion. Six years later, and with many impairments affecting aspects of daily living, she describes displacing the reality of the illness with professional and social events; trips and holidays planned around facilities for the disabled lack challenge and yet certain sanitary arrangements are unarguably beneficial, allowing Dr Gould periodically to do new things. The tone is positive, the catalogue of impairments considerable, and the personal dividend from a few practical adjustments and kindnesses plain to see.

Sandy (Alexander) Burnfield qualified in medicine in 1968 from the London Hospital; however, as he describes in *Multiple Sclerosis: a Personal Exploration*, he had by that time already graduated as a patient having developed optic neuritis 3 years earlier and read the full implications of this diagnosis in the medical school library. As a newly qualified house officer he was confronted by the disease in the neurosurgical and neurological departments, and symptoms soon returned with the development of a useless dominant hand. Burnfield is critical of his initial management and the evasive tone of the neurologist with whom he first dealt, but praises Dr Stanley Graveson (at that time senior neurologist to the Wessex Neurological Centre in Southampton). During the early years of his training as a specialist in psychiatry, he experienced further relapses and developed persistent disabilities, although happily he remains fully independent 30 years after presentation. His is a beautifully crafted book in which he makes the transition from an initial position of fear and uncertainty to acceptance, adjustment and confidence, describing the cathartic process with dignity. Much of the book is a readable account of the disease for lay persons but Sandy Burnfield orientates his journey with a personal philosophy established in part during psychoanalysis but based mainly on personal qualities, as those who have met him will attest. In chapters on coming to terms with multiple sclerosis, marriage under stress, fulfilment and self respect, Dr Burnfield has left a personal account which is nonetheless valuable as a general manual for anyone having or dealing with multiple sclerosis.

Records also tend to be left of the lives of individuals whose contributions to cultural or literary life are curtailed by illness. One such was the British cel-

list Jacqueline Du Pre. Menuhin (1996) has described the early recognition of her talent for the instrument which she wanted to play from the age of 4, her precocious success leading to a first solo recital aged 16 at London's Wigmore Hall, and the initial public performance of Sir Edward Elgar's cello concerto – the work with which she was most closely associated and which has, as a result, acquired special symbolism for the plight of the individual with multiple sclerosis. Jacqueline Du Pre's meteoric rise was not associated with unqualified self-confidence but this returned after a period of study with Mstislav Rostropovich and led to a brilliant 4-year period of performance with her husband, Daniel Barenboim. At the age of 28, she developed symptoms due to multiple sclerosis and the condition soon interfered with her ability to perform; the illness was aggressive, resulting early in the need for a wheelchair and she died in 1987, aged 42. Jacqueline Du Pre is one of many ordinary people in whom multiple sclerosis abbreviated an extraordinary career; her memory and example provide a poignancy which has subtly altered public awareness of the illness in the United Kingdom to the advantage of the Multiple Sclerosis Society. The International Federation of Multiple Sclerosis Societies periodically awards a Jacqueline du Pre fellowship to a young and talented investigator from an underprivileged country.

In a different medium, Peter MacKarell (1990) left a record of what it is to have multiple sclerosis. As an artist and illustrator, who held academic appointments at Goldsmith's College in south London, his reaction to the development of visual symptoms in 1980 (aged 47) was quickly to embark on a personal, and necessarily lonely, journey externalized in the form of a series of paintings which, in a surreal way (he calls it *Joycean*), simultaneously depict the painter and his visualized world (Fig. 1.8). After a moderately long first remission during which he found difficulty in describing and recording some aspects of the visual experience of optic nerve demyelination, more obvious disabilities accumulated and, by their nature, these inhibited but did not prevent the execution of his works. The rapid evolution of unilateral visual loss over 3 days, and its subsequent recovery, are depicted. Next, in the Avalon series (named after the boat he took to convalesce in Ireland), he applied neuroanatomy by painting circles, the normal left-sided hemifield juxtaposed with his amblyopic right-sided view in order to emphasize the paleness, blurring, bleached reds, impression of a blue filter, and perversions of normal visual illusions familiar to artists. His dominant (left) hand became paralysed early in 1987 and he spent the next several months in hospitals and at a home for the chronic young sick

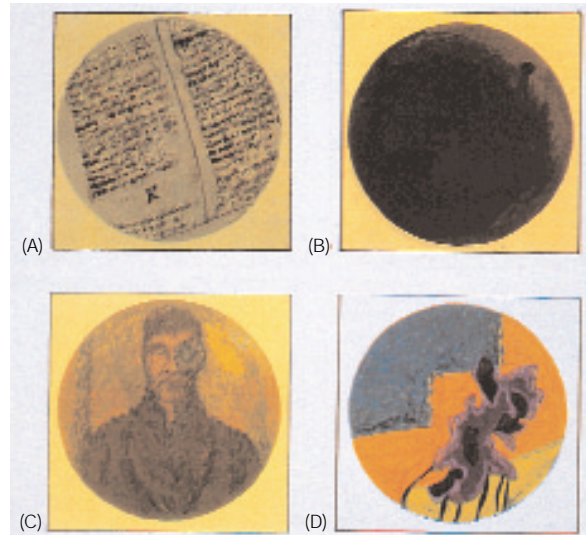


Fig. 1.8 (A) Pageswim; (B) Look at my voice; (C) Portrait of the artist in a maroon dressing gown; (D) Flag iris 2. Reproduced with permission from MacKarell (1990).

before his own home was adapted to allow domestic care. This is where – blind, paralysed and unable to paint – he died towards the end of 1988. That summer, he had dictated a final account of his illness in which he began by summarizing the experience of deteriorating eyesight as “*I saw this*” or, in Spanish (for it is taken from Goya), “*Yo Lo Vi*”. His attitude is one of adjustment and compensation as the gift of a set of coloured crayons brings home the truth that he can no longer distinguish the reds and greens. As conduction slowed in his optic nerves, so his verbal and other mental processes seemed to quicken; neatly, MacKarell elided his disappearing powers of vision with ideas on the sophistication of languages which sought to distinguish the 11 colours of Burlin and Gray. In the paintings which he executed after recovering from the first episode of optic neuritis, he recalled deliberately emphasizing those hues, especially red, which he knew from medical consultations and experience selectively to be affected; later, it proved necessary to modify his techniques still further as cervical cord demyelination forced a sinistral to dextral change in manual activity. However, his final statement, entitled *The Odyssey*, remains optimistic, with plans for an active confrontation of deteriorating vision and motor control.

The professional writer as patient offers a special opportunity to describe for others the personal experience of multiple sclerosis. In November 1982, soon after recovering from a phase of low personal confidence, Brigid Brophy (at the age of 53) tripped on leaving a restaurant and was briefly concussed;

several months later, she again noticed difficulty in raising her foot to cross a pavement and realized that the episode could not be dismissed as *hapax legomenon* (one-off); it was now a symptom which increasingly interrupted her walking. Encounters with the medical profession proved unrewarding and confrontational with undue emphasis on diet (insufficient protein and too much alcohol), iatrogenic anaemia, irrelevant replacement of thyroid hormone and long waits in clinics. Brophy (1987) tells one side of a story cataloguing administrative and clinical frustrations with which doctors are familiar and, with her vulnerable self-esteem, she contrived a fictional version in which a figure in authority whose trade is scientific exactitude and for whom veracity is therefore never questioned, undermines an otherwise stable domestic relationship by sowing the seeds of mistrust. Eventually, transfer to a tertiary centre led to evoked potentials, brain imaging and spinal fluid analysis and she learned the diagnosis of multiple sclerosis. Resolutely opposed to research involving animal tissue, Brophy speculates on the cause of multiple sclerosis (her daughter was tested for the *genetic trait* at the Naomi Branson Trust in Newcastle [for reference to this work, see Field 1989] and found to be normal). She declares that the solution will emerge from computer modelling of the replies to case-control epidemiological questionnaires; her hunch is that an emotional shock in the 5 years before onset will be shown to be crucial. Soon requiring a wheelchair and other aids to daily living, Brophy deplores the dependence on others which this sporadically *disgusting* disease imposes, and the slowing of functions which contaminates even those activities which do remain possible for an intellectual who writes; but, in the end, she settles for the Proustian nostalgia of re-running remembrances of times past.

Ben Sonnenberg, born in New York in 1936, warns us in the subtitle of his autobiography that nothing had prepared him for the development of multiple sclerosis at the age of 34, although he too had a prolonged prodrome of diagnostic uncertainty despite medical attention (Sonnenberg 1991). On diagnosis, he immediately read the classical and more recent medical literature. The conversion from relapsing-remitting disease to secondary progression and the need for two malacca canes did nothing to slacken the pace (or performance) of Ben Sonnenberg's serial approach to relationships with women. By 1978, he preferred ground-floor accommodation and soon was using an electric wheelchair affectionately known as an *Amigo*. He also read other personal accounts of what it is like to have multiple sclerosis; he was largely dismissive of these efforts but did single out Brigid Brophy's *Baroque-n'-Roll* and Barbellion's

Diary of a Disappointed Man and *Last Diary*. All three developed metaphors for the poorly understood process affecting their nervous systems; Sonnenberg listened for:

"the silent Virus or the still-as-a-stone Autoimmunity which being long past [genetically predetermined] can be read like Linear B only by cryptoanalysts."

PATHOGENESIS OF MULTIPLE SCLEROSIS: 1849–1972

The German school

Frerichs (1849) had to wait for pathological validation of his case material by Valentiner, his pupil, who described the abnormal firmness or leathery consistency in irregularly circumscribed parts of the white matter, rarely involving the grey matter of the cord, with a poverty of blood vessels. The patches were almost normal in colour or milky white, dull and occasionally greyish-red. There was a loss of nerve elements. Frerichs' cases had shown exacerbations and remissions, alternately affecting each side of the body with selective involvement of the lower limbs, disturbance of mobility outweighing that of sensibility, with major manifestations in the spino-medullary junction, and psychiatric symptoms; they were young persons otherwise in good general health.

At that time, Rokitansky (1857) described connective tissue proliferations in the cord, pons and medulla producing progressive paraplegia and, 7 years later, Rindfleisch (1863) first emphasized the change around blood vessels which has so dominated ideas on the pathogenesis of multiple sclerosis from that time:

"If one looks carefully at freshly altered parts of the white matter in the brain, one perceives already with the naked eye a red point or line in the middle of each individual focus, the transversely or obliquely cut lumen of a small vessel engorged with blood. In the spinal cord the ... grey foci (in a transverse section) intervene in a wedge-shaped manner in the substance of the anterior columns from the periphery... The shape and position of these correspond exactly to the supply territory of each blood vessel. All this leads us to search for the primary cause of the disease in an alteration of individual vessels and their ramifications; an assumption which is completely confirmed by microscopic examination. All vessels running inside the foci, but also that traverse, the immediately surrounding but still intact parenchyma are in a state characteristic of chronic inflammation... Their walls are enormously thickened by the accumulation of nuclei and cells in the adventitia."

Frommann (1864) illustrated the occurrence of demyelination (Fig. 1.6) and astrocytosis, and collective wisdom was summarized by Leyden (1863) who recommended that multiple sclerosis and chronic myelitis should be considered as the same disorder; he emphasized that women are affected more often than men with age of onset usually in the third decade, almost always without a family history and with exposure to dampness or psychic events as major provocative factors. For Leyden, the prognosis was generally poor with occasional pleasant surprises.

Otto Marburg (1906) presented an extensive description of acute multiple sclerosis and his is the first detailed clinical and pathological account of fulminating cases leading to death within 1 year. Marburg emphasized that the disease process in these patients mimics, in all essential respects, components of the more chronic case, but he also identified distinguishing features. He depicts a convincing example of concentric sclerosis, later described by Balo (1928) as *encephalitis periaxialis concentrica*, and showed that the disease process is not confined to the brain and spinal cord, drawing attention to demyelination of the peripheral nervous system in all three of his cases. Following the writings of Eduard Rindfleisch (1863), Marburg stressed the vascular orientation of lesions, considering the *Kornchenzelle* to be small perivascular round cells which take up myelin debris. Multiple sclerosis was therefore a primary inflammatory demyelinating disease possibly mediated by a soluble myelinotoxic factor and with relative sparing of axons. He recognized the abundance of nerve fibres with very thin myelin sheaths and discussed whether these are areas of incomplete demyelination or remyelination. Marburg also recognized an acute axonal pathology with reactive change and the presence of thin atrophic nerve fibres. In these and many other respects, his ideas were ahead of their time and Marburg anticipated the contemporary formulation of the pathogenesis of multiple sclerosis which we describe throughout this book.

The French school

Charcot made many contributions to the clinical neurology of *sclerose en plaques*. He left a brilliant account of the clinical symptomatology delineated the cerebral, spinal and mixed cerebrospinal forms (Fig. 1.9), and formulated views on the pathogenesis. Apart from these fundamental clinico-anatomical correlations, he developed many ideas concerning mechanisms and pathophysiology, provided the first attempts at measurement, and threw down a therapeutic gauntlet to his successors. Charcot took the

view that overgrowth of glia strangles the myelin sheath, sometimes leading to degeneration of the axis cylinders and with secondary blood vessel changes (Fig. 1.10). He suggested that the naked axis cylinders might again clothe themselves with myelin and thus effect a *restituto ad integrum* (to quote from Dawson [1916]; see below).

Amongst the manifestations of cerebral involvement was amblyopia on which he wrote (quotations in English are from the New Sydenham Society translations of Charcot's lectures, 1877):

"Amblyopia is a persistent and frequent symptom of cerebro-spinal disseminated sclerosis but it rarely issues in complete blindness. This is worthy of notice since patches of sclerosis have been found after death occupying the whole thickness of the nerve trunk, in the optic nerve, in cases where during life an enfeeblement of sight simply had been noted. This discrepancy between symptom and lesion constitutes one of the most powerful arguments to show that the functional continuity of the nerve tubes is not absolutely interrupted although these, in their course through the sclerosed patches, have been despoiled of their medullary sheaths and reduced to axis cylinders."

Charcot also wrote on the cognitive manifestations of multiple sclerosis:

"Most of the patients affected by multilocular sclerosis, whom I have had occasion to observe, have presented at a certain stage of the disease a truly peculiar facies. The look is vague and uncertain; the lips are hanging and half open; the features have a stolid expression, sometimes even an appearance of stupor. This dominant expression of the physiognomy is almost always accompanied by a corresponding mental state which deserves notice. There is marked enfeeblement of the memory; conceptions are formed slowly; the intellectual and emotional faculties are blunted in their totality. The dominant feeling in the patients appears to be an almost stupid indifference in reference to all things. It is not rare to see them give way to foolish laughter for no cause, and sometimes, on the contrary, melt into tears without reason. Nor is it rare, amid this state of mental depression, to find psychic disorders arise which assume one or other of the classic forms of mental alienation."

Charcot described the triad of nystagmus, dysarthria and ataxia resulting from involvement of brainstem-cerebellar connections although his functional anatomy of this region was not sophisticated:

"One symptom which doubtless struck you all from the first on seeing the patient enter ... was certainly the very special rhythmical tremor by which her head and limbs were violently agitated whilst she was walking. You have likewise noticed that when the patient sat upon a chair, the tremor

disappeared ... from her upper and lower limbs, but only partially from the head and trunk ... In complete repose ... you will be able to assure yourself of the utter absence of all trace of tremor in the different parts ... To cause the rhythmical agitation again to appear throughout the body, it will suffice to make the patient rise from her seat ... You can see that, in the several acts prescribed by the will, the

tremor increases in direct ratio with the extent of the movement executed. Thus, when the patient wishes to lift a glass full of water to her lips, the rhythmical agitation of the hand and forearm is scarcely noticeable when taking hold of the object; ... but ... at the moment when the goal is being attained, the glass is ... dashed with violence against the teeth, and the water is flung out to a distance."

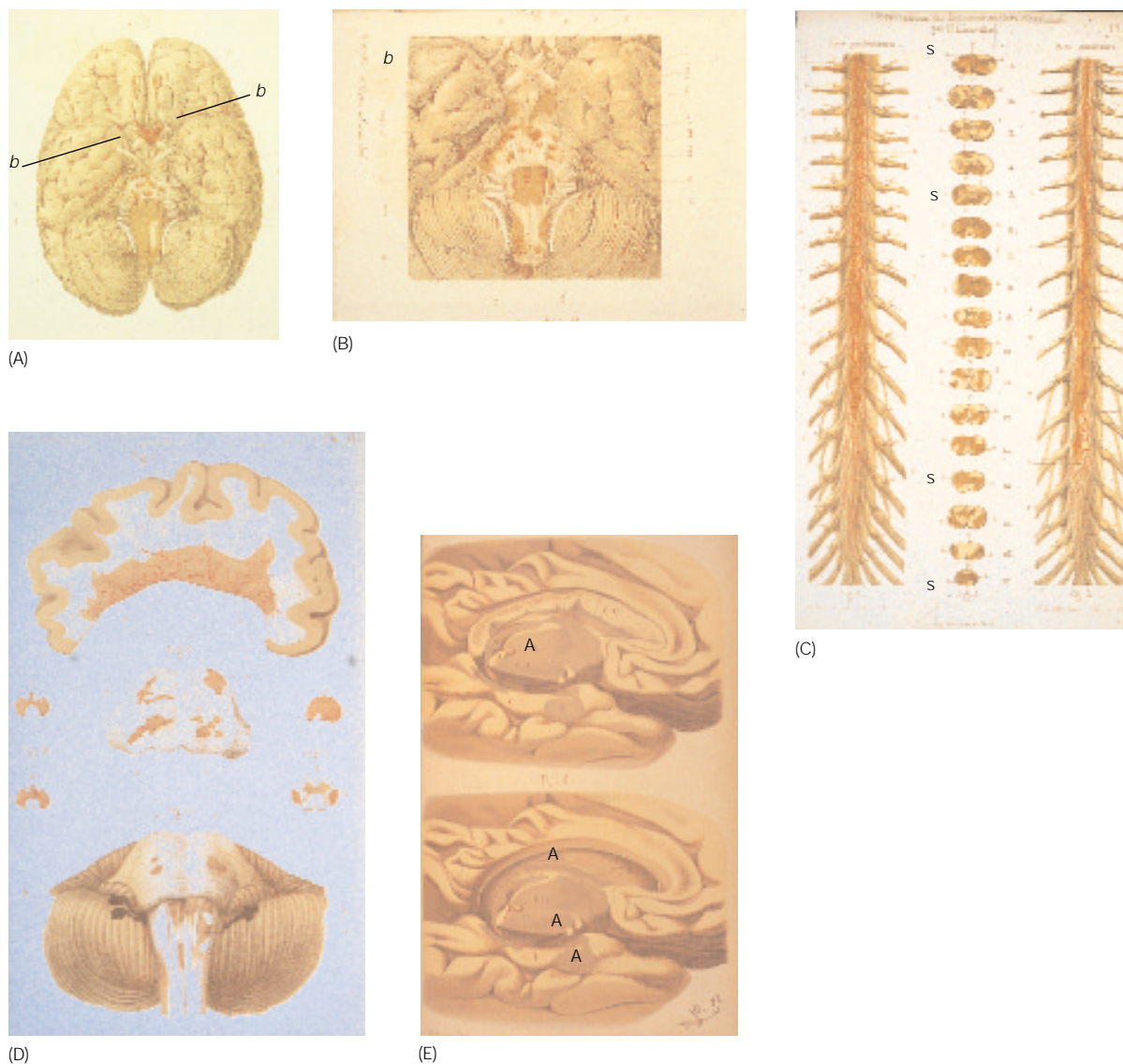


Fig. 1.9 (A) and (B) Base of the brain. *b*: Islets of sclerosis along the optic nerves; *b'*: healthy portion of one of the optic nerves. Patches of sclerosis, disseminated over different parts of the protuberantia, some superficial, others deep seated. Surface slightly depressed at these points. The nerves emerging from the pons appear healthy. (C) Anterior and posterior aspects of the spinal cord (the dura mater is divided and thrown back at either side). *s*: Patches and islets of sclerosis, irregularly disseminated, various in form and dimensions, irregular, isolated or partially united by connections visible on the surface. They predominate here especially in the dorsal region. No 1 from the superior portion of the cervical region immediately beneath the bulbus rachidicus to ... No 5 ... superior dorsal region ... No 14 superior portion of the dorso-lumbar enlargement and No 17 ... terminal cone. From Charcot (1872). (D) Fig. 1. *a.a.*: patch of sclerosis arising on the lateral ventricular wall. Superior wall. Fig. 2. Section of the protuberantia, the superior half seen from the inferior aspect. *a.a.a.*: nuclei of the sclerosis. Fig. 3. *a.a.a.*: Patches of sclerosis; one of them cuts the left olivary body into two parts. *b.b.*: Black colouration of the epidemia by silver nitrate. Fig. 4. A.B.B'C: sections of the medulla. (*d.d.* anterior part) A. Above the brachial enlargement. B.B'. The middle of the medulla. C. Three centimetres above the termination of the medulla. Observation 1: multiple sclerosis. From Ordenstein (1868). (E) Multiple sclerosis. Upper figure: Inner aspect of the left hemisphere, A, sclerotic patches occupying the corpus callosum, CC; the optic tract, CO; the convolution of the hippocampus, CH. Lower figure: In this figure, the corpus callosum was lifted up to show the ventricular wall. CS: corpus striatum. The other letters have the same significance as in the upper figure. From Charcot (1892).

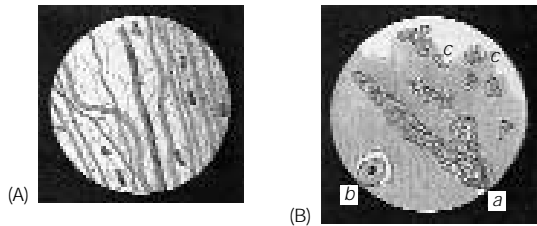


Fig. 1.10 (A) Fresh preparation, taken from the centre of a patch of sclerosis, coloured with carmine, and dilacerated. In the centre is seen a capillary vessel, supporting several nuclei. To the right and left of this are axis cylinders, some voluminous, others of very small diameter, and all deprived of their medullary sheaths. The capillary vessel and the axis-cylinders were vividly coloured by the carmine; the axis cylinders present perfectly smooth borders, without ramification. Between them are seen slender fibrillae of recent formation, which form on the left and in the centre a sort of network resulting from the entanglement or anastomosis of the fibrils. These are distinguished from the axis cylinders, 1° by their diameter, which is much smaller; 2° by the ramifications which they present in their course; 3° by taking no colouration from carmine. Nuclei are scattered about; some of them appear to be in connection with the connective fibrils; others have assumed an irregular form, owing to the action of the ammoniacal solution of carmine. (B) Patch of sclerosis in the fresh state: *a*, lymphatic sheath of a vessel distended by voluminous fatty globules; *b*, a vessel divided transversely. The adventitious coat is separated from the lymphatic sheath by a free space, the fatty globules which distended the sheath having disappeared; *cc*, fatty globules, gathered into small groups, dispersed here and there over the preparation. From Charcot (1868b [parts 2 and 3]).

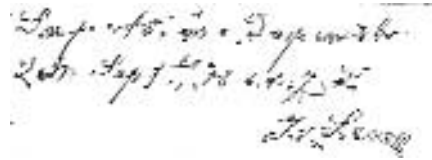
On spinal disease, Charcot described the characteristic weakness, spasticity, ankle clonus (spinal epilepsy) and loss of sensibility, referring to the case of Josephine Paget originally described by Cruveilhier:

"We should not, however, forget that some of the symptoms of ataxia are found ... when the sclerosed islets in certain regions of the cord spread over a certain height of the posterior columns. A case, the history of which may be found recorded at length in Cruveilhier's Atlas of Pathological Anatomy may be cited as an example of this class. It is the case of the patient Paget. In order to grasp and use a pin she required to have her eyes open, otherwise the pin dropped from her fingers. On a postmortem examination, it was found that one of the sclerosed patches occupied a considerable extent of the posterior columns in the cervical enlargement of the cord."

We can admire Charcot for two other aspects of his contribution to *sclerose en plaques* – the attempt to measure deficits and to give them a pathophysiological explanation (Fig. 1.11A and B). He documented the amplitude and range of tremor, distinguishing this from the effects of mercury and Parkinson's disease, and used handwriting to document these clinical features. On pathophysiology he wrote:



(A)



(B)



(C)

Fig. 1.11 (A) Tremor. AB: In all the schemes, periods of rest are illustrated. BC shows the period which accompanies a voluntary movement (writing, carrying a glass to the mouth, etc.). (B) Example of handwriting in a patient with *sclerose en plaques*. From Charcot (1880; 1872). (C) Bilateral unsteady gait. Figs 18 and 19: unsteady gait; multiple sclerosis. Fig. 20: unsteady gait; experimental drunkenness. Fig. 21: unsteady gait being cured from Meniere's giddiness treated with quinine sulphate. From de la Tourette (1886).

"I have expressed the opinion that the axis cylinders deprived of medullary sheathing in the midst of the foci of sclerosis plays an important part. The transmission of voluntary impulses would still proceed by means of the denuded axis cylinder but it would be carried on irregularly in a broken or jerky manner and would thus produce the oscillations which disturb the due execution of voluntary movements."

Here is a sophisticated prediction of the pathophysiology of impulse conduction in demyelinated axons, which was eventually elucidated both in the peripheral and central nervous systems (NS) in the 1960s (McDonald 1963; McDonald and Sears 1970; see chapter 11), but it is an analysis which lacks the anatomical precision of circuitry in the motor system.

Charcot's first student, Ordenstein, was put to work on the clinical distinction between *scleroses en plaques* and Parkinson's disease (Ordenstein 1868). Part two of his thesis concerns the history, pathological anatomy, symptomatology, aetiology, prognosis and therapeutics of the disease and documents four cases. These identify 1855 as the year in which Charcot probably first started to recognize the clinical manifestations of multiple sclerosis; *Alexandrine C.* became aware during pregnancy of difficulty in using her legs but may have had symptoms for the previous 2 years and the diagnosis was established clinically at the Salpêtrière in 1863. Ordenstein also identifies *femme B*, a patient of Charcot's who died in 1867, as the seventh case described in the entire literature; she had autopsy-proven *sclerose en plaques* with extensive demyelination in the cerebrum and spinal cord and had also presented in 1855 with weakness in the legs followed in 1857 by sensory symptoms and loss of vision. Figure 2 from Ordenstein's thesis is the first depiction of the lesions of *sclerose en plaques* from Charcot's laboratory (see Fig. 1.9D).

Bourneville and Guerard (1869) completed the clinical description and provided additional illustrations; later, it was Bourneville who collated and saw through to publication Charcot's lectures on neurological and general medical disease. Joseph Babinski's medical thesis, entitled *Étude anatomique et clinique sur la sclerose en plaques*, appeared in 1885. Babinski emphasizes hemiplegia as a manifestation of multiple sclerosis; the work also contains an elaborate description of early multiple sclerosis lesions, showing the interaction of macrophages with demyelinated nerve fibres. Babinski is the young physician catching the swooning Blanche Wittmann in the much reproduced painting by Pierre Brouillet of Charcot demonstrating hysteria at the Salpêtrière during one of his Tuesday lectures. Gilles de la Tourette (1886) described the gait in neurological disease and depicted the footprints of ataxic patients with *sclerose en plaques* (Fig. 1.11C).

The last of Charcot's pupils to write at length on multiple sclerosis was Pierre Marie (1895) who gave four lectures on the subject to the Faculty of Medicine in 1891. More than his predecessors, Marie sought to classify and record the gait disturbance distinguishing spastic from cerebellar components; on hemiplegia, he was lavish in his praise for the thesis of Ms Blanche Edwards (we have been unable to trace this work), preferring her account to that of Joseph Babinski (1885). The same analytical approach pervades his description of upper limb tremor. He was no less thorough in his discussion of sensation, dealing at length with the special senses, hearing and vision, and distinguishing disorders of acuity and

colour vision (largely borrowed from Uhthoff [1889]) from eye movements; he referred both to external and internal ophthalmoplegias. Marie had been awarded the Civrieux prize of the Academy of Medicine in 1885 for his account of disordered bladder, bowel and sexual function in multiple sclerosis, although he considered these to be rare manifestations. He was strong on the bulbar and visceral manifestations, predated Kinnier Wilson (see below) by several decades on the description of impulsive laughter (which Charcot had himself mentioned), and allowed glycosuria as a sign of demyelination in the floor of the 4th ventricle. More than others writing at that time, Marie recognized the variable symptoms at onset, delineating a number of stereotyped presentational syndromes and documenting the subsequent clinical course, including the category of benign multiple sclerosis, and making the distinction between progression from onset and its development during the course of the illness. In fact, his account of primary progressive multiple sclerosis is faultless, noting the later age of onset, the worse prognosis, the relative absence of histological (or clinical) involvement of the cerebrum, and the more frequent axon degeneration (see chapter 10).

The English school

Although descriptions of the pathology and clinical symptomatology of multiple sclerosis were available in continental Europe, it is a mark of the contribution which Charcot and his school made in bringing this disorder to general attention that there is no mention of diseases recognizable as multiple sclerosis in standard textbooks prior to 1868. In that year, *A System of Medicine*, edited by Russell Reynolds (1868), physician to the National Hospital in London was published – almost one entire volume of which is devoted to diseases of the nervous system. Although there are descriptions of chronic sclerosis of the cord, these cases are not suggestive of multiple sclerosis; at best, the series may have included some examples of primary progressive disease. Sir Clifford Allbutt (1871) in *On the Use of the Ophthalmoscope in Diseases of the Nervous System and of the Kidneys* describes RB (case 103; referred by Mr Sedgwick of Boroughbridge in Yorkshire) as having chronic disease of the spinal cord manifesting as paralysis, altered sensation and impaired bladder control with reduced central vision and pale optic discs, but he offers no diagnosis.

This situation changed when Moxon (1875) described 8 patients, some of whom had already featured in the *Lancet*, and provided the first detailed description of multiple sclerosis in the English language (Fig. 1.12). In his definitive account, Moxon



Fig. 1.12 Section of the brain showing insular sclerosis. The whole brain is shrunken looking, as will be seen by observing the very uneven elevation of the convolutions and their narrowness, and the depth and width of the sulci between them. The centrum ovale majus, which the section reveals, shows many patches of the colour of the grey matter of the brain, or paler or mottled. These patches are insulated and are scattered very irregularly. From Moxon (1875).

combined clinical and autopsy observations in 2 patients and described at length the intention tremor of the head and upper extremities, the weakness which may precipitate pressure sores, paraplegia in flexion or extension, nystagmus with dysarthria, impaired control of the sphincters, exaggerated reflex activity, pathological laughter and crying as a manifestation of incipient dementia, and death from pulmonary or bladder infection. His accounts of these patients remind us of the intimacy of the medical encounter and the trusting way in which *Emily B* confided in one of the attendant nurses her assumption that the shock of finding her husband in bed with another woman had precipitated the episode of ataxic quadriplegia with which she presented in August 1872 and which Dr Moxon had no difficulty in distinguishing from paralysis agitans; however, for poor Emily, there was to be no relief and she died after accumulating many other deficits in January 1873, having been ill for <6 months.

At autopsy, there were 40 white matter plaques, some the size of *hemp-seed*, affecting the cerebrum, pons and medulla – appearances which had on earlier occasions been confused with *heterotopia cerebri*; histology showed destruction of the medullary fibres, replacement by fine connective fibrils and granular corpuscles. The case of Emily B was described again in detail in the *Lancet* of 3rd April 1875. Edward M featured on 1st May; he was ataxic and paralysed but also showed visual failure and prominent sensory symptoms.

The historian George Trevelyan has remarked that:

“the poetry of history lies in the quasi-miraculous fact that once on ... this familiar spot of ground walked other men and women ... thinking their own thoughts but now all gone, one generation vanishing after another, gone as utterly as we ourselves shall shortly be gone like ghosts at cock-crow.”

Emily B (aged 25), Matilda P (aged 23), James P (a veterinary surgeon aged 33), Sarah H (a servant aged 37), George N (a clerk aged 35), Albert F (a splint cutter for matches aged 24), Harriet B (also described in the 3rd April 1875 issue of the *Lancet*, a servant aged 38) and Edward M (a footman aged 32) were all admitted to Guy’s Hospital over a 2-year period from January 1873; they described distortions of movement and sensation, suffered the alternating anxieties and hopes of the neurologically ill, died or became disabled, and are now remembered only for their clinical histories and lesions in the cerebrum, pons medulla and spinal cord. Although Guy’s Hospital and William Moxon can take credit for priority in the description of multiple sclerosis in the English language, not all its physicians were uncontaminated by Charcot’s other disease – historical revisionism. Sir Samuel Wilks, writing in 1878, was at pains to point out that:

“I myself had observed years ago scattered patches of deposit in the cerebrospinal centres, but had failed to associate them with any special form of malady; subsequently Charcot described this sclerosis, disseminated throughout the cord, with the prevailing symptoms which accompany it.”

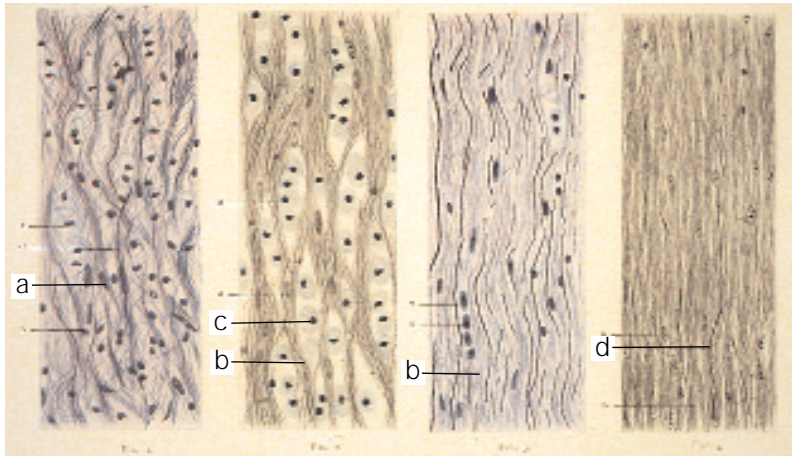
James Dawson (1916) summarized everything of significance prior to his time and left the greatest pathological account of multiple sclerosis in the English language. He assigned priority (wrongly) to Cruveilhier (c1841) for the first depiction, Ferriehs (1849) for the initial clinical description, Rindfleisch (1863) for formulating ideas on the aetiology, and Vulpian (and Charcot) (1866) for pulling the whole story together. He summarized controversies on the causation and epitomized these as the *exogenous* or *endogenous* schools but substituted the terms *inflammatory* and *developmental*, respectively. He assembled teams of inflammationists, developmentalists and on-lookers (mainly contemporary) whose views he considered to be undecided or uninterpretable. Within the framework of inflammation, he considered unproven the question of whether the process was targeted against neuroglia, parenchyma, blood vessels or the lymph circulation; and, in turn, developmental disorders might represent deficiency of the nerve elements (*anlage*) or multiple gliosis.

Charcot and his school were classified by Dawson as subscribing to the view that multiple sclerosis results from an inflammatory affection of neuroglia which delineates zones within each plaque and surrounds the central blood vessel. Redlich (1896) and Huber (1895) had broadly similar ideas but saw the insult as a toxin- or microorganism-induced primary degeneration of the myelin sheath with secondary inflammation and blood vessel changes. Dawson himself favoured the hypothesis of Rindfleisch (1863) who assigned priority to the blood vessels, proposing a sequence in which a chronic irritative condition of the vessel wall alters the nutrition of nerve elements, leading to atrophy with metamorphosis of the connective tissue producing monster glia (Deiter or Rindfleisch cells). In reviewing the history of ideas on the pathology of multiple sclerosis, Dawson indicated that the vascular view was shared by Dejerine (1894), Williamson (1894; 1908) and Marie (1884; 1895); the latter suggested that infections initiate the changes in blood vessels but also emphasized the contribution of axon degeneration. The developmental school was headed by Strumpell (1896) who drew analogies with disorders in which congenital abnormalities were invariably associated with secondary gliosis and considered that exogenous insults act upon an intrinsically weakened system. Bramwell (1904) also saw multiple sclerosis as a developmental disturbance. Dawson's team of "don't knows" included practically everyone who wrote on the pathology of multiple sclerosis between 1903 and 1916 when he himself laid his thesis before the Royal Society of Edinburgh. Amongst this contemporary group was Bielschowsky (1903) who discussed preservation of axis cylinders (nerve fibres) and suggested that the vascular process is directed at nerve fibres more uniformly than glia; he also speculated upon the possibility of regeneration. Curiously, Dawson neglected Marburg's (1906) important monograph identifying shadow plaques but did refer to *Markschattenherde*, which he considered to be evolving lesions, and he mentioned three hyperacute cases with an accelerated clinical pattern of relapses, rapid accumulation of deficits and characteristic histological features.

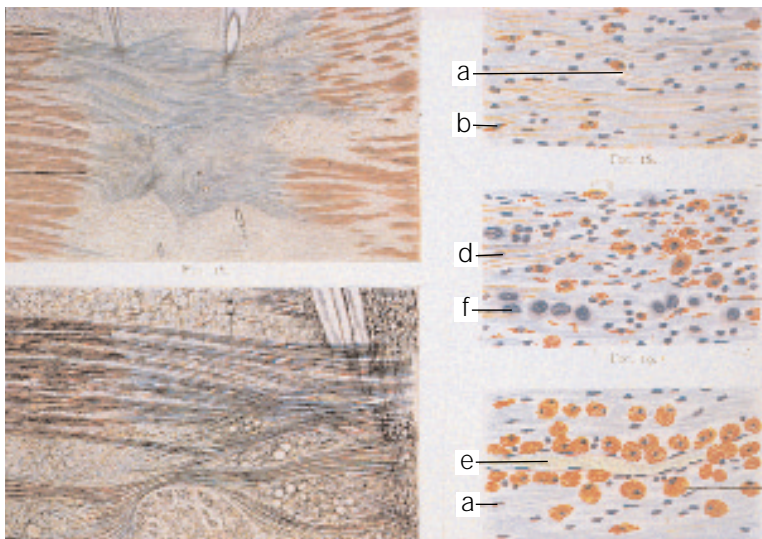
Reviewing the histology of 9 personal cases (LW, a kitchenmaid aged 28; CS aged 22; Mrs G aged 30; JW; SS, a nurse aged 44; CG, a baker's shopwoman aged 24; J McN, a cabinet maker aged 42; MR, a typist aged 33; and LH aged 30), Dawson devoted the majority of his text to LW, admitted under Dr Alexander Bruce on 4th April 1910 with a 2-year history of weakness and tremor in all four limbs, dysarthria and sphincter disturbance. In hospital (29th May) she had an episode of brainstem demyelination (deafness and tinnitus, right facial palsy, numb left arm, right lateral rectus

weakness, tongue deviation to left and dysphagia). In August, she lost vision in both eyes, developing increasing bulbar failure and dying from septicaemia on 5th September 1910. Dawson described the features of early and established lesions in the spinal cord and cerebrum and offered an analysis of their evolution through stages of fat granule cell myelitis (in the cord) to glial hyperplasia (Fig. 1.13). He devoted text to the unusual lesions, including *Markschattenherde*, and those appearing in grey matter and around the ventricles, optic nerve, peripheral nerves and roots. Next, he turned to an analysis of the changes to be observed in each cellular element of the CNS – nerve cells and their axons, neuroglia, blood vessels and lymphatics. Form, symmetry and the distribution of lesions were all addressed. After listing the tragic accumulation of lesions throughout the CNS of poor LW, Dawson attempted a clinico-pathophysiological correlation; weakness in the legs was consistent with the extensive spinal cord gliosis, intention tremor with lesions in the superior cerebellar peduncles and red nuclei, disordered eye movements with the peri-aqueductal plaques, and extensive cranial nerve palsies with involvement of the pons and medulla.

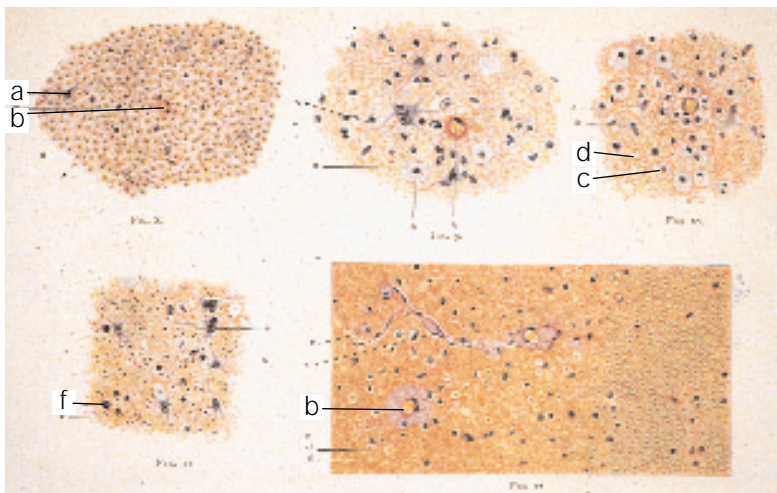
Dawson's own studies showed that old (sclerotic lesions) were characterized by complete absence of myelin (Weigert stain), dense fibrillary tissue (glial stain), persistence of axis cylinders (silver stain), numerous blood vessels (diffuse stains), no active myelin degeneration (Marchi stain) and an abrupt transition to normal tissue. In acute lesions, the differences were infiltrated blood vessels, active demyelination with fat granule cells, and transitional zones shading into normal tissue. He illustrated the text with 22 colour and 434 black and white figures in 28 plates (Fig. 1.13). In concluding his magisterial account, Dawson returned to the inflammatory *versus* developmental divide; he noted that Muller (1910), the most articulate teacher from the developmental school, proposed that the participation of the blood vessels within the lesion is secondary and that the glial proliferation is more than reparatory, but he had difficulty with the notion of *multiple gliosis* (reminiscent of Charcot) as the essential process. He extended his ideas on brain inflammation to include a sequence of events which, although not disease-specific, produces recognizable clinical characteristics when directed at glia leading to degeneration of the myelin sheath with fat granule cell formation, and a reactive change in glia involving cell proliferation with fibril formation culminating in sclerosis – the whole picture is triggered and modified by exogenous factors whose influences fluctuate, causing the characteristic relapses (remissions depending more on re-routing of synaptic connections than remyelination).



(A)



(B)



(C)

Fig. 1.13 (A) [Figures 1–4] Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical spinal cord. Sections cut in longitudinal direction of the nerve fibres show increasing glia fibril formation. a: Glia nuclei; b: glia fibrils; c: fat granule cells; d: persistent axis cylinders. Figs 1 and 3 Ford-Robertson's methyl violet stain. Figs 2 and 4 palladium methyl violet. (B) [Figures 16–17] Persistence of axis cylinders across a demyelinated area in the pons ... [Figures 18–20] Stages in the demyelination of an area and in the evolution of the fat granule cell. a: Small glial nuclei; b: transition forms between a and b; c: fat granule cell; d: nerve fibre; e: blood vessel; f: proliferated glia nuclei. (C) [Figures 8–12] Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical cord. a: Glia nuclei; b: blood vessel; c: fat granule cell; d: myelinated nerve fibre; e: finely granular glia tissue; f: naked axis cylinder; g: transition to normal tissue. Fig. 8: Alterations in the glia cell and myelin. Fig. 9: Gitter cells. Fig. 10: Fat granule cells accumulated in blood vessels. Fig. 11: Glial fibrils increasing and axons intact. Fig. 12: Gliosis with few cells and preserved axons. From Dawson (1916).

No work has so influenced neurologists in the English-speaking world as Russell Brain's *Diseases of the Nervous System* which first appeared (1933) 3 years after he wrote, on the grand scale, a masterly review for the *Quarterly Journal of Medicine* on clinical and pathological aspects of multiple sclerosis (Brain 1930); we can usefully trace the evolution of prevailing views on the pathogenesis (and other aspects, see below) of the disease through the many editions of this textbook. Drawing heavily on the observations of Dawson (1916), 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 indicate 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. Dr Brain restated the doctrine of neurobiology inherited from Ramon y Cajal and his students Del Rio Hortega and Penfield (see below), 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 (CSF) could as easily gain access to the brain parenchyma through the Virchow-Robin spaces, as could material crossing the vessel walls.

By 1940 (2nd edition), Brain's reading of the pathological papers of Dawson (1916), Putnam (1936; Putnam and Adler 1937) and Greenfield and King (1936) presented a much clearer view of the sequence of perivascular lymphocytic infiltration, lipid 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 (1933; see below). 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. Russell Brain had reconsidered his views on demyelinating disease when he returned to the topic in 1951; 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 model first mentioned in his 2nd edition (Brain 1940). 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.

The section on the pathology of multiple sclerosis and related demyelinating processes which appeared in the 1st edition of *McAlpine's Multiple Sclerosis* was written by Charles Lumsden (1955). Lumsden immediately struck a gloomy note in his account by concluding that demyelination might be arrested but never reversed; he went on to emphasize the error rate in autopsy series of patients diagnosed as having multiple sclerosis during life, the symmetry and confluence of plaques, the invariable involvement of the cerebrum irrespective of clinical phenotype, the sparing of peripheral nerves and absence of pathological change outside the CNS, the nature of shadow plaques which he considered to be areas of partial demyelination, and the frequency of secondary Wallerian (axonal) degeneration. Lumsden characterized acute plaques as those with preserved myelin sheaths albeit with interspersed fat-laden microglial cells and with some degree of axonopathy; chronic plaques featured a rim of active myelin removal by microglia, an intermediate zone of gliosis and an acellular core with parallel arrays of astrocytic fibrils and preserved axons. Lumsden speculated on the possibility of intact axons undergoing remyelination with consequential restoration of function. However, he also emphasized the absence of oligodendrocytes both from the rim of acute lesions and in chronic plaques, and he considered it unlikely that surviving oligodendroglia might proliferate. Lumsden subscribed to Rindfleisch's (1863) view on the pivotal role of the vascular lesion but he denied that the vasculopathy is thrombotic; he had no explanation for the periventricular distribution of plaques. Lumsden had his own way of revising books and he entirely replaced the 1955 version in 1965 and again in 1972 where he set out his conception of multiple sclerosis as an autoimmune disease in which exposure of myelin following various biological accidents induces anti-myelin antibody formation leading to plaque formation. The 1972 version contains, in addition to its revision of the pathological anatomy, a definitive account of the chemical pathology of multiple sclerosis; it is said that hard work on this edition took its

toll and Lumsden had several periods of illness prior to his early death in 1974.

Charcot (and Dawson) had both emphasized the preservation of axons in demyelinated lesions but Charcot had already hinted at a connection between the slow development of paresis in patients with spinal multiple sclerosis and the health of axons:

“Generally one of the lower limbs is first and solely affected. The other limb is seized, sooner or later, in its turn; the paresis advances with extreme slowness ... but at last the day comes when ... they may be confined to bed ... This resistance of the axis cylinders ... may account for the slowness with which the paretic symptoms advance in disseminated sclerosis and for the long space of time which elapses before they give place to complete paralysis and permanent contracture.”

Charcot had described axon loss in some lesions of *sclerose en plaques* (1868b) but Lumsden identified Putnam (1936) as the originator of the concept that there is substantial axon degeneration in the pathology of multiple sclerosis – a position modified by Greenfield and King (1936), who also put pay to the notion that axons might regenerate in multiple sclerosis.

DISCOVERY OF GLIA AND REMYELINATION: 1858-1988

Rudolph Virchow (1858) first described neuroglia (*nerve glue*) and assigned them two functions – mechanical support of nerve cells and tissue repair. Three further activities were proposed before the end of the 19th century – nutritional support of neurones (Golgi 1883), engulfment of cellular debris (Bevan Lewis 1897) and isolation of nervous conduction (originally suggested by Santiago Ramon y Cajal’s brother Pedro [Robertson 1897; Cajal 1913]).

Oligodendrocytes were not recognized as a distinct macroglial sub-population until many years after Virchow’s original description, due to the lack of specific histological stains. Robertson (1899) reported the presence of small, process-bearing cells throughout both grey and white matter which stained selectively using a platinum impregnation technique. Believing them to be derived from mesoderm, he named them mesoglia but, in retrospect, this was the first description of the oligodendrocyte (Fig. 1.14) (Penfield 1924). Cajal (1913) described a *third element* of the nervous system (in addition to neurones and neuroglia), which he considered to be analogous to peripheral nerve Schwann cells. Hortege (1921) distinguished two cell types within Cajal’s third element, which he named microglia and oligo-

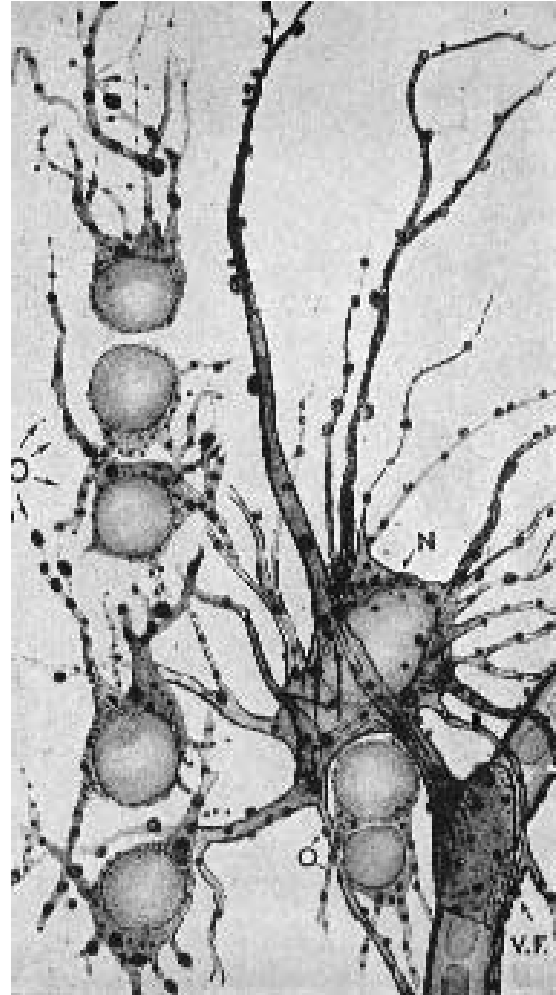


Fig. 1.14 Oligodendrocytes (O) are seen in contact with the processes of a neuron (N); an astrocyte is shown with processes extending towards oligodendrocytes and contacting a blood vessel (at VF). From Penfield (1924).

dendrocytes; he also proposed a mesodermal derivation for microglia, which form a resident macrophage-related population within the CNS, but even now their origin remains controversial. Hortege (1921) classified oligodendrocyte subtypes as perineuronal or interfascicular, with four further types based on variations in cell morphology. Although the biological significance of these differences remains obscure, his contribution included the recognition that oligodendrocytes make the myelin sheath which surrounds axons in white matter of the CNS.

In fact, the role of neuroglia in myelin synthesis had been appreciated before Hortege’s discovery of the oligodendrocyte, Virchow (1858) having introduced the term myelin and described sheaths around nerve fibres; apart from Cajal’s (1913) suggestion that his third element was the CNS equivalent of Schwann

cells, Hardesty (1904) depicted neuroglia as directly involved in myelin synthesis and, with the illustration of spiral projections from oligodendrocytes extending towards developing myelin sheaths in white matter from young animals (Hortega 1928), Penfield (1932) was able to conclude that oligodendrocytes:

“have to do with the elaboration and maintenance of myelin.”

Despite Hortega's contribution, the technical difficulty of demonstrating cytoplasmic connections between oligodendrocytes and myelin maintained uncertainty concerning the nature of myelinogenesis. Hypotheses included the suggestions that CNS myelin is produced by astrocytes, by axons, or by fusion of multiple vesicles within oligodendrocytes. Eventually, Bunge *et al* (1961) provided electron micrographs of developing white matter showing oligodendrocytes which extend processes continuous with the outer aspect of the myelin sheath (Fig. 1.15), in a manner similar to the way in which Geren (1954) had shown a few years earlier that the Schwann cell ensheathes the peripheral nerve axon. Subsequent ultrastructural studies have established that a single oligodendrocyte can myelinate internodal segments of 30–50 axons.

Asking whether structural repair occurs in demyelinated lesions is not a new question. In his medical thesis, Joseph Babinski (1885a) posed the question in chapter 3 of the section on pathological anatomy: “*Les tubes nerveux de la moelle peuvent-ils se régénérer après d’avoir été détruits?*”. In fact, his account deals more with contemporary concepts on regeneration of nerve fibres than remyelination but the answer was staring him in the face since one of the lithographic illustrations to his thesis shows thin layers of myelin surrounding axons which are closely associated with fat granule cells removing myelin debris (Fig. 1.16). For Babinski, this was a demyelinating lesion; for us, it is a remyelinating acute inflammatory plaque. Despite their careful depictions and thoughtful analyses, neuropathologists were also slow to realize the significance of the shadow plaques or *Markschattenherde* which Marburg (1906) and Dawson (1916) each considered to be evolving lesions (although Marburg did consider the possibility of remyelination).

Against this background, the topic of remyelination makes no serious progress until the demonstration by Richard and Mary Bunge (Bunge *et al* 1961) of myelin repair occurring in cats following demyelination induced by CSF barbotage. After removal of myelin by macrophages, new compact myelin lamellae formed around axons. They commented upon,

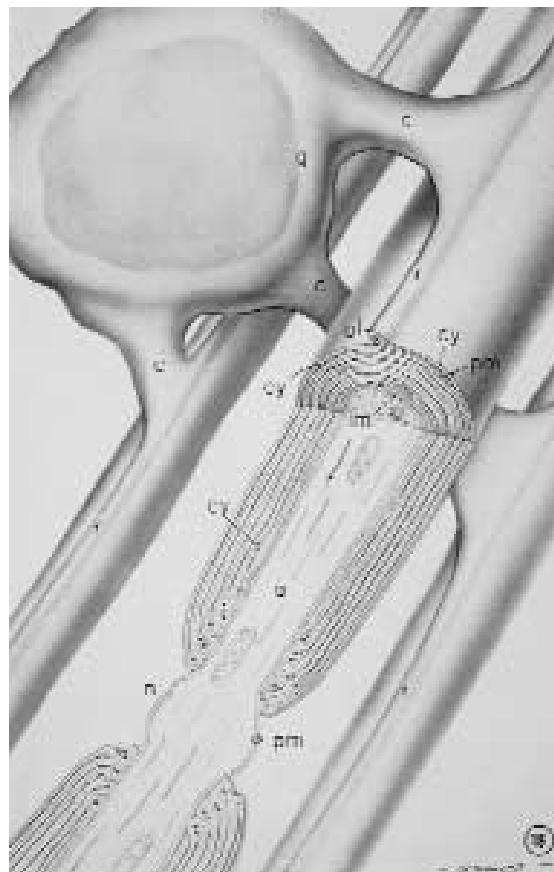


Fig. 1.15 Illustration of both known and hypothetical aspects of the mature myelin sheath and its relationship to a glial cell. The unit or plasma membrane (pm) is designated as two lines separated by a space except in the mitochondria where it is represented by a single line. The inner mesaxon (im), formed as a glial process completes the initial turn around an axon (a) and starts a second, is retained after myelin formation is completed. Some cytoplasm of the glial process is present here. Cytoplasm is trapped occasionally at cy. On the fully formed sheath exterior, a bit of glial cytoplasm is also retained. In transverse section, this cytoplasm is confined to a loop (ol) of plasma membrane (pm) but, along the internode length, it forms a ridge (r) which may be continuous with a glial cell body (g) at c. When viewed transversely, the sheath components are oriented in a spiral, only the inter- and outer-most layers ending in loops; in the longitudinal plane, every myelin unit terminates in a separate loop at both ends of the internode. Within these loops, glial cytoplasm is also retained. We believe that this cytoplasm, contained within the expanded lateral edges of the spiralled glial process, is a continuous cord helically wound around the axon, like cable about a spool. The outer loop, inner mesaxon and sheath endings at a node (n) are illustrated and evidence for a spiral arrangement of myelin lamellae is presented. The connection (c) between a glial cell body and a mature sheath has not been demonstrated. Reproduced with permission from Bunge *et al* (1961).

but did not draw particular attention to, the fact that the myelin lamellae were inappropriately thin for the axon diameter. The Bunges concluded, on the basis of electron microscopy, that the remyelinating cell was an oligodendrocyte and produced the now classical cartoon of one oligodendrocyte synthesizing myelin along short segments of several neighbouring axons. Furthermore, they demonstrated ultrastruc-

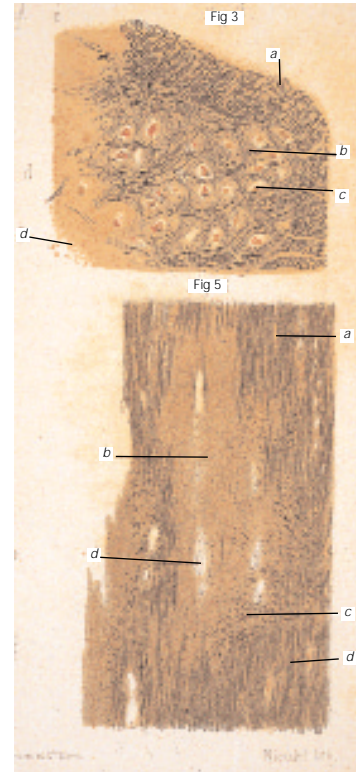
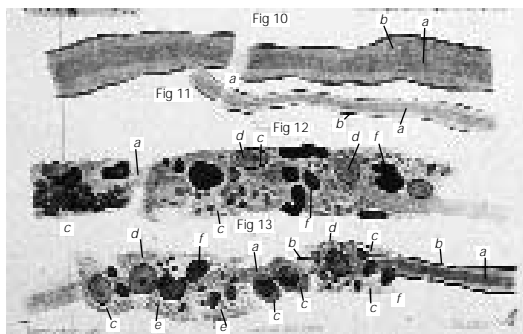


Fig. 1.16 (A) Figs 10 and 11. Normal myelin tubes of the medulla seen in longitudinal section. *a*: Axis cylinder; *b*: myelin sheath; *a*: axis cylinder stripped by a break in the myelin sheath – enlargement $\times 1000$ diameters. Fig. 12. Multiple sclerosis. Distorted myelin tube seen in longitudinal section. *a*: Axis cylinder; *c*: cells surrounding the axis cylinder; *d*: nuclei of these cells; *e*: protoplasm of these cells; *f*: myelin balls – enlarged $\times 1000$ diameters. Figure 13. Multiple sclerosis. Myelin tube, whilst normal on one side, is in the process of modification on the other side. *a*, *c*, *d*, *e*, *f*: As in the preceding figure; *b*: myelin sheath; *c*: migratory cells whose protoplasm does not contain myelin debris – enlargement $\times 1000$ diameters. (B) Fig. 3. This figure represents point *b* of Fig. 2 [not shown] enlarged. *a*: Nerve tubes of the white matter; *b*: network of nerve fibres of the grey matter; *c*: nerve cells; *d*: sclerotic tissue – enlarged $\times 30$ diameters. Fig. 5 – Multiple sclerosis. Longitudinal section of the dorsal region at the level of the pyramidal decussation. *a*: Normal myelin tubes; *b*: multiple sclerosis; *c*: granulations demonstrating tubes in the process of disintegration. *d*: Vessels – enlarged $\times 6$ diameters. From Babinski (1885a, b).

tural features of the remyelinating cell which distinguished this from a mature oligodendrocyte and, on morphological grounds alone, suggested the involvement of a precursor cell which was bipotential and able to differentiate either into the reactive astrocyte or myelinating oligodendrocyte; this reactive macroglia was thought equivalent to the spongioblast and so the concept was advanced both of biopotentiality and the need for a remyelinating cell to have stem cell properties. Finally, the Bunge proposed that the reactive macroglial cell is derived from a mature oligodendrocyte and so they started the debate on de-differentiation in the oligodendrocyte lineage as the basis for remyelination and repair.

Perier and Gregoire (1965) published the first electron microscopic studies of multiple sclerosis plaques, demonstrating axons partially or completely sur-

rounded by thin myelin lamellae which they considered to be evidence for remyelination (Fig. 1.17). Confirmation that their observations did indeed represent spontaneous remyelination had to await experimental studies. With Richard Gledhill and Barry Harrison, Ian McDonald showed that compression of the cat spinal cord produced lesions in the posterior columns which repair with terminal cytoplasm-filled loops, attached to the axolemma by transverse bands, having short (67–85 μm) internodes and uniformly thin myelin (Fig. 1.18) (Gledhill *et al* 1973). These are the morphological criteria which have since reliably been used as evidence for remyelination – myelin which is embedded in a satellite cell with a continuous membrane from the surface of the cell around the axon, back to the surface again and compacted but inappropriately thin for the corresponding axon and with a short internode.

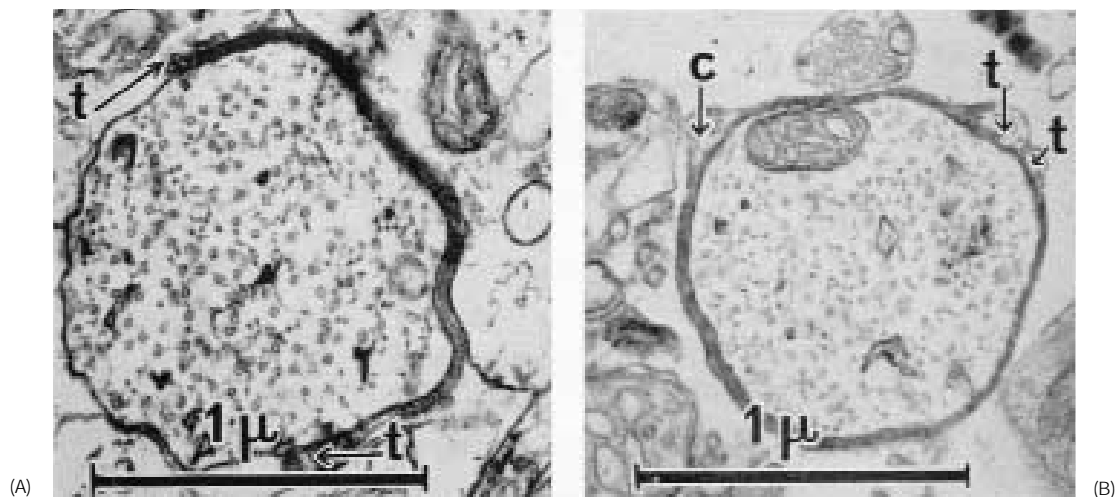


Fig. 1.17 (A) An axon containing numerous tubules is half surrounded by a flattened glial cell process from which cytoplasm has been expelled except at the level of the two terminal tongues (t). (B) Another axon completely encircled by a flattened glial cell process from which the cytoplasm has been expelled except in one place (c) and at the level of the two terminal tongues (t) whose apposition constitutes the precursor of the future mesaxon. These pictures suggest abortive remyelination. Reproduced with permission from Perier and Gregoire (1965).

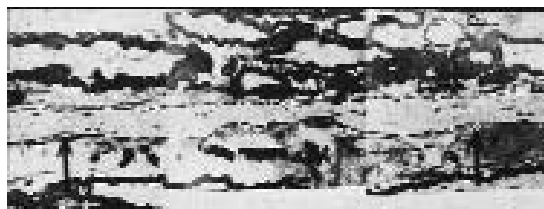


Fig. 1.18 One-month lesion. An axon approximately 5 μm in diameter is covered by an inappropriately thin myelin sheath. The arrows mark nodes. The internodal distance is 76 μm . Reproduced with permission from Gledhill *et al* (1973).

Experimental proof that remyelination restores conduction, and neurophysiological correlations with the histological features, were provided by Ken Smith, Bill Blakemore and Ian McDonald (Smith *et al* 1979; 1981; see chapter 11 for further details and additional historical perspectives). At 1 month, areas of the spinal cord demyelinated with lysophosphatidyl choline were remyelinated by oligodendrocytes and conduction through the lesion was restored but with a reduced safety factor (Fig. 1.19). By the late 1970s, it was clear therefore that spontaneous remyelination can follow demyelination in the CNS, both experimentally and in the context of multiple sclerosis, and that remyelination restores secure saltatory conduction. The stage was then set for an era of experimental studies aimed at exploring the neurobiology of remyelination and the implications for restoration of structure and function in demyelinated lesions. These pre-clinical attempts at repair also needed the development of accurate ideas concerning the anatomical location of defined clinical syndromes and the ability to assess functional deficits.

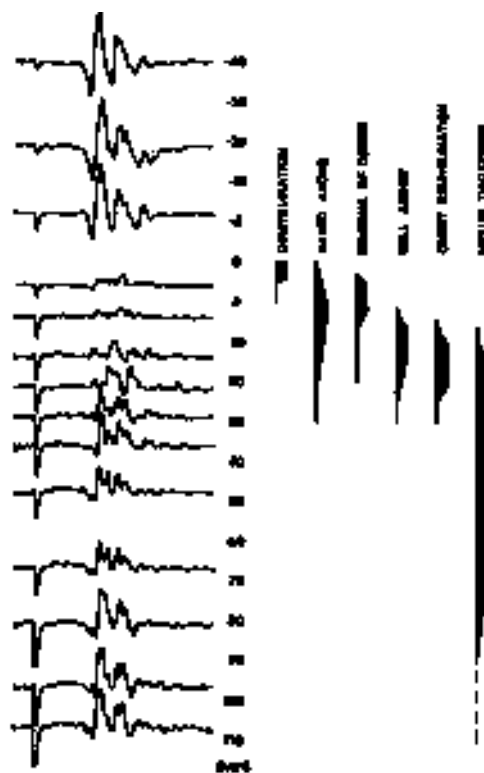


Fig. 1.19 Temporal relationship between the compound action potentials recorded through the lesion and the sequence of histological events at the lesion. The block and subsequent restoration of conduction correlate with the periods of demyelination and remyelination, respectively. Reproduced with permission from Smith *et al* (1981).

Charcot measured clinical deficits and speculated on their physiological basis but he lacked clear ideas on their neuroanatomical basis. Joseph Babinski first added the concept of *adiadochokinesis* (1902; 1913) to the terms *action* and *intention tremor* introduced by Sir David Ferrier who had earlier demonstrated the cerebellar basis for inco-ordination. In his magisterial work on the histology of the CNS published (in Spanish) between 1897 and 1904 (English translation of the French edition [1909–11] published in 1995), Cajal applied the neurone doctrine to circuitry underlying motor control and showed the connectivity of Purkinje cells in the dentate nucleus of the cerebellum with input from contralateral corticopontine fibres and output to the opposite cortex via the red nucleus through the superior cerebellar peduncle. Neurophysiological techniques, developed over a number of years, culminated in the introduction of evoked potentials for measuring conduction, initially in the human optic nerve but subsequently in other central sensory and motor pathways (see chapter 11 for further details and additional historical perspectives). The group of Martin Halliday and Ian McDonald showed the sequence of reduced amplitude followed by delayed conduction in the evolution of acute optic neuritis (Fig. 1.20) (Halliday *et al* 1972). Subsequently, the prevalence of abnormal visual evoked potentials was described in multiple sclerosis (Halliday *et al* 1973a); distinctions were made between the reduced amplitude with preserved latency which characterizes compression of the anterior visual pathway (Halliday *et al* 1976); and the important observation was made that, with time, there may be a reduction towards normal in the latency of the evoked potential; this is seen much

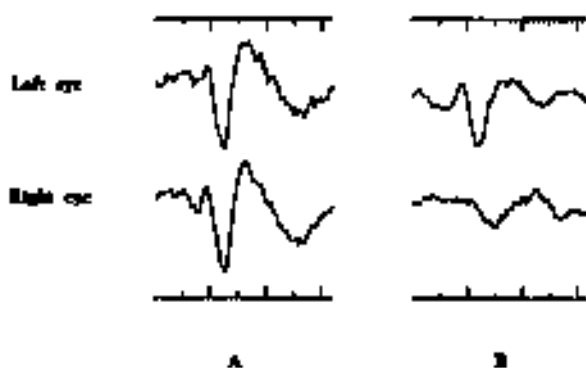


Fig. 1.20 (A) Pattern evoked responses, recorded from a midline occipital electrode from the left and right eye of a healthy subject. Two patients who were recovering from acute attacks of optic neuritis in the right eye with onset, (B) 4 weeks and (C) 3 weeks previously. Time scale: 10, 50, and 100 ms. Note the delayed peak of the response from the affected eye and its smaller peak-to-peak amplitude. Reproduced with permission from Halliday *et al* (1972).

more frequently in childhood than in adult optic neuritis, suggesting that there is an enhanced potential for remyelination and restoration of normal conduction velocity in the juvenile demyelinated optic nerve (Kriss *et al* 1988).

The discovery by Tom Sears and Hugh Bostock in the 1970s (Bostock and Sears 1976; 1978) that conduction can be restored in persistently demyelinated axons opened the way to an understanding of the early, rapid recovery that may be seen after individual episodes of demyelination; it also provided a basis for understanding the mechanism of the long delays in visual evoked potentials (see chapter 11). Thus, by the 1970s, sufficient lines of evidence were in place from clinical, pathological and experimental studies to show that adult nervous systems have the capacity for endogenous remyelination and work could begin on the development of strategies for enhancing and supplementing this repair (see chapters 9 and 14).

REVIEWS OF MULTIPLE SCLEROSIS: 1871–1955

The impact of knowledge on the nature of multiple sclerosis and its clinical manifestations for the common reader can best be charted by scrutinizing reviews which appeared from the time of the earliest clinical and pathological descriptions and depictions (Fig. 1.21). We have already referred to Hammond's (1871) textbook. This was written very soon after Charcot's lectures were first published and, in noting its astonishing mixture of perception and confusion, we should remember its transitional timing with respect to the evolution of ideas on multiple sclerosis. Following the French school, Hammond started with the difficulty that typically arises in distinguishing the tremor of paralysis agitans from emotional agitation and multiple (cerebral) sclerosis. He had observed onset of a clinical condition which he designated as cerebral sclerosis with epileptic paroxysms but did not describe these in sufficient detail for us to decide whether these episodes were the paroxysmal tonic seizures of demyelination or more typical epileptic attacks (see chapter 5). He classified the sensory features as anaesthetic or hyperaesthetic, distinguished impaired awareness of position sense, mentioned a vibratory sensation felt in the arm on lying down (which may have been Lhermitte's symptom) and observed facial myokymia. Conversely, his description of the gait is wrong, and he appears to confuse not only the festination, propulsion and retropulsion of Parkinson's disease but also some other clinical features of striatal neurology, including the characteristic posture.



Fig. 1.21 Crude multiple sclerosis or Babinski's cerebellar syndrome. Reproduced with permission from Scherb (1905).

Hammond's thesis was that some examples of paralysis agitans are in fact cases of multiple sclerosis and that other authors (including Parkinson himself – a copy of whose 1817 essay he had been unable to locate in New York [it is of legendary rarity in the original]) were confused. Hammond also emphasized a cerebral form of multiple sclerosis in which headache and apoplectiform onset were followed by generalized tremor; he would not make the diagnosis of cerebral sclerosis if the weakness or paralysis preceded tremor, except in the face. He looked after 9 cases (mostly with the cerebral form, rather older than would now be usual and mostly males) and studied the pathology, in one instance noticing that the lesions were confined to white matter where connective tissue had hypertrophied at the expense of nerve elements. At autopsy, 18 separate hard lesions were present in the hemispheres but there were

none in the brainstem or spinal cord. In these 9 patients, the course was progressive with incontinence and dementia as inevitable late consequences. On the aetiology, Hammond mainly favoured precipitation by infection.

When the London edition of his book appeared in 1876, Hammond had acquired a much broader view of multiple sclerosis, paying less attention to the cerebral manifestations, which he continued to confuse with striatal neurodegeneration, but adopting a much more spinal position and noting the difference between rest and intention tremor. He remained critical of others for their inability to distinguish the clinical features of the disease, and took Vulpian (and Charcot [1866]) to task for confusing the whole subject by bringing together cases which had no affinity except as regards the general character of the lesion – not actually such a bad position. Perhaps the problem was that in not 1 of the 31 cases then under his care had it proved possible to obtain pathological confirmation of the diagnosis and he still considered multiple sclerosis unlikely in any patient with multiple episodes affecting different parts of the nervous system if tremor preceded paralysis. Although the stimulus for research at the Salpêtrière on *sclerose en plaques* had been the wish to distinguish paralysis agitans from multiple sclerosis, Hammond accused Parkinson, Charcot and Ordenstein amongst others of failing to make proper distinction between these and related conditions; he insisted that:

"the affection which Parkinson described and called the shaking palsy is not a single disease."

Sir William Osler's account of the disease in his *Principles and Practice of Medicine* (1892) is uninspiring but he refers to 10 cases described in his important monograph on *The Cerebral Palsies of Children* (1889); the cases were from a series collected by Drs Kerlin and Wilmarth at the Pennsylvania Institution for Feeble-Minded Children at Elwyn. It does not seem that Osler had a good grasp of what was then meant by *sclerose en plaques*; although a case of idiocy with right hemiplegia and epilepsy had at autopsy several macroscopically hard patches in the cerebral hemispheres which to Osler corresponded to the *sclerose tubereuse* of Bourneville, this and the other 9 cases are now suggestive neither clinically nor pathologically (with two possible exceptions) of multiple sclerosis.

We have already paid tribute to the pivotal contributions to knowledge on multiple sclerosis which appeared in the German literature after Carswell and before Charcot. The great textbook of Moritz Romberg (1846) is entirely silent on the topic. Two works dominate the German neurological school from the latter part of the 19th century. Adolf Strumpell (1896), who

was firmly wedded to the aetiological theory of glial overgrowth in multiple sclerosis, allowed the possibility of precipitating events; these might be toxic or infectious and, although he had no time for the more general theories of Oppenheim (see below) and Marie (1895), he was convinced by the role of antecedent physical trauma – and for the first time, admitted the medico-legal consequences of this opinion. In discussing inflammation, he first mentions plasma cells but emerges with an uncompromising verdict on the endogenous aetiology of multiple gliosis. In later editions (translated into English; Strumpell 1931), he considered that the rigid clinical definitions of Charcot had restricted awareness of the disease; he advanced the concept of the *spastic-ataxic* patient, and made much of headache as a common symptom. Hermann Oppenheim (English edition; 1911) wrote in a style which reminds us of Kinnier Wilson

“I may be permitted to add that my treatises, ... [and] the earlier editions of this textbook, contain all that is essential”.

Tin, carbonic oxide and mercury but not zinc or manganese were considered to be the toxic causes of multiple sclerosis, but perhaps Oppenheim’s real contribution (time will tell) was to articulate the idea that the aetiology is heterogenous. With Wilson, Oppenheim disliked the term intention, preferring motor tremor – a name he credited to Schultze; but he erroneously suggested that it was he, Oppenheim (1889), who had first described uncontrollable laughter, and he offered a case of his own as an example of what seems to be bilateral internuclear ophthalmoplegia. Oppenheim recognized that hot baths are harmful to patients with multiple sclerosis. Generously, he credited Strumpell with first recognizing changes in the abdominal and other cutaneous responses but omitted reference to his compatriot in pointing out that familial cases of multiple sclerosis can be confused with hereditary spastic paraplegia (after whom the disorder is named) and essential hereditary tremor. Oppenheim was much exercised in his discussion of the differential diagnosis on the issue of diffuse sclerosis and conditions which are now segregated as the leucodystrophies.

Althaus (1877), dedicating his book on diseases of the nervous system to Moritz Romberg with whom he had studied in Berlin, proposed the term Charcot’s disease and had clearly himself encountered patients with multiple sclerosis. He gave rather a stereotyped description of the illness that begins with motor symptoms which are sufficiently vague often not to attract medical attention and which might remit, followed by persistent and progressive paraplegia in flexion or extension with disturbances of co-ordination and cerebation heralding the final agonal phase.

For Althaus, this was a disease which rarely lasted beyond the age of 40, although he noted a better prognosis for life in purely spinal forms; his understandable insistence on the presence of intention tremor (following Charcot) may explain why recognition of the disease increased, with a consequent rise in prevalence, as variations in the presentation and clinical manifestations came to be accepted towards the close of the 19th century.

Sir William Gowers (1888) described disseminated or insular sclerosis under the heading of degenerations of the brain. He had seen an autopsy-proven case in a 7-year-old child and was aware of presentation in the 7th decade. He recorded familial disease in siblings and noted the higher than expected frequency of a preceding exanthematous illness. He offered no new insights into the pathology but emphasized the disappearance of axis cylinders (axons) late in the disease. He did not arbitrate on the contrary views of Charcot and Erb on whether the tremor was due to erratic conduction through any motor pathway or dependent on involvement of strategically placed lesions in the pons and cerebellum. Gowers said more about the optic nerve than earlier commentators, describing unilateral and bilateral optic neuritis, with or without disc swelling, and noted both the pupillary changes and sequence of optic disc appearances present on ophthalmoscopy. In other respects, his account is merely a rehearsal of contemporary opinions on the nature and manifestations of the disease.

Sir Thomas Clifford Allbutt was in the habit of inserting scraps of paper and other jottings in personal copies of his books, but volume VII of his *System of Medicine* presented by Lady Allbutt to the University of Cambridge after his death in 1935, contains few clues to the evolution of his thinking on multiple sclerosis. The chapter is written by Dr James Samuel Risien Russell (1899). We find only a half page torn from an article by Byrom Bramwell in which Allbutt has underscored sections dealing with the differential diagnosis and the distinction from hereditary ataxias. In the main text, Allbutt has pencilled alongside the clinical descriptions:

“case seen by TCA. M aet 35 nystagmus, excessive k.j ankle clonus on one side R only. O. discs normal. Speech doubtful. No intention tremor (says he had it but it is gone) Both legs “weak” and spastic but R much worse.”

Allbutt opted for the term insular sclerosis and pencilled in the index:

“even docked of a syllable, Disseminate sclerosis is too long – Ed”.

Risien Russell accepted the authenticity of the 34 paediatric cases described by Totzke in his inaugural

dissertation to the University of Berlin (1893; which we have been unable to trace) in whom 2 had symptoms at birth and no fewer than 31 presented before the age of 14 years – autopsy cases described by others proved to Risien Russell that the illness may affect young children. He began with an account of the *formes frustes* of multiple sclerosis usually manifesting such elusive symptoms as to be declared hysterical:

“but the astute physician can remain confident that his interpretation of organic disease will in time be proved correct and that the period of triumph for those who regard the cases as functional will be brief”.

His description of the symptomatology is generally more comprehensive than any other contemporary version, especially with respect to the ophthalmic and ocular manifestations, but he added no new insights. The differential diagnosis is comprehensive and introduces conditions not mentioned by other writers of the time, including primary lateral sclerosis, Westphal’s pseudo-sclerosis and other leucodystrophies.

In his review and 1st edition of his textbook, Russell Brain (1930; 1933) 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. He recognized that the geographical distribution of multiple sclerosis was uneven and delineated regional trends that have subsequently been confirmed, including the susceptibility and resistance of northern Europeans and Blacks, respectively. He accepted that the disease occasionally occurs in sibling pairs but, in line with his views on the cause, was adamant that familial disseminated sclerosis arose from common environmental exposure and not the influence of genetic factors. 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 involvement of the *conus medullaris* (see chapter 5); he observed the high frequency of disseminated sclerosis after an episode of optic neuritis. 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. Never before had this amount of information

been so cogently reviewed and Brain’s grasp of an increasingly difficult subject was magisterial. In the 2nd edition, Brain (1940) offered a classification of demyelinating disease that has survived all subsequent editions with little modification. He noted the first description of EAE in monkeys (Rivers and Schwentker 1935) and so shifted abruptly to the view that demyelinating disorders are due to an allergic reaction in the brain and not the result of direct viral infection.

In several editions, Brain overlooked the important announcement by Kabat *et al* (1942) on the quantification of immunoglobulin in the CSF of patients with disseminated sclerosis (Fig. 1.22). The 4th edition (1955; barely keeping up with Dr Brain’s progress in announcing that Sir Russell had been made a baronet in 1954) emphasized important new work on acute disseminated encephalomyelitis from Newcastle (Miller 1953) and McAlpine’s (1931) recommendations for distinguishing 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 (see chapter 7).

Samuel Alexander Kinnier Wilson, who rather liked the term *polysclerosis*, provided an authoritative account of disseminated sclerosis in the first edition of his textbook (1940). He proposed that a case described by Marshall Hall was an early description of multiple sclerosis:

“M aged 28 years is affected by weakness and agitation of the right arm and leg, augmented on any occasion of agitation and moving. It is observed as he walks or when he passes his cane from one hand to the other. There is besides a peculiar lateral rocking motion of the eyes and a degree of stammering and defective articulation.”

Wilson’s version of the disease is structured along the lines of aetiology, symptomatology, pathology, nature and pathogenesis, differential diagnosis and treatment; the text is rich in references to the primary literature, numerically cognate and pleasingly literate. Dismissive of anecdotes provided by patients on the role of precipitating factors, Kinnier Wilson illustrated his own belief that trauma and shock might be instrumental in precipitating the disease: an RAF pilot with much uncomplicated experience of air combat was subsequently thrice shot down and soon developed manifestations of disseminated sclerosis; a heavy mirror fell on a young woman’s arm injuring the ulnar nerve and she soon showed features of (spinal) polysclerosis – precipitated but not directly induced at a site remote from that traumatized. Wilson was one for the subtleties of symptomatology in early diagnosis – an abdominal reflex that can be tired, a few kicks of

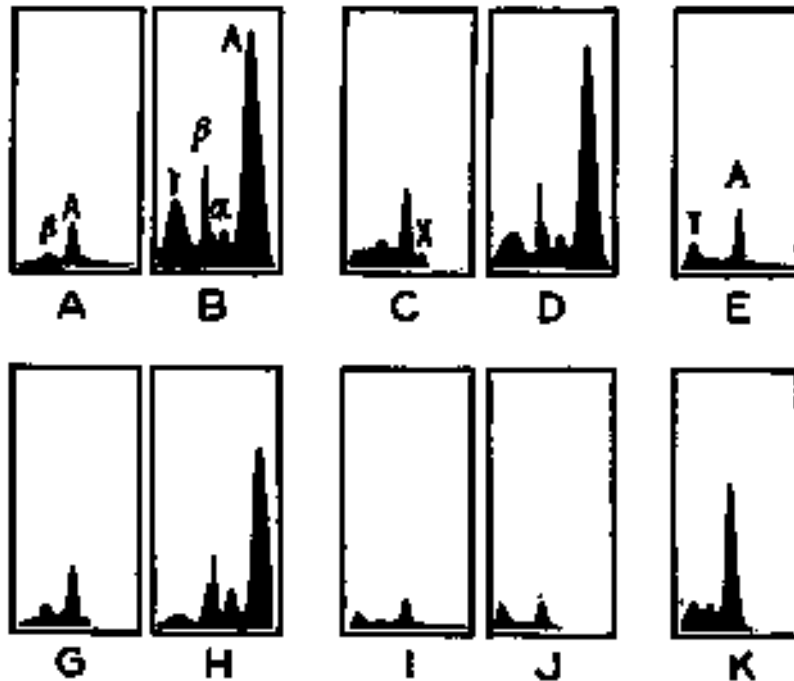


Fig. 1.22 Electrophoretic patterns. (A) and (B) Idiopathic grand mal (normal), spinal fluid and serum. (C) and (D) Anxiety state (normal), spinal fluid and serum. (E) and (F) Lymphopathia venereum, spinal fluid and serum. (G) and (H) Multiple myeloma, spinal fluid and serum. (I) Multiple sclerosis, spinal fluid. (J) Neurosyphilis, spinal fluid. (K) Diabetic neuritis, spinal fluid. (L) Left frontal cystic astrocytoma, cyst fluid. From Kabat *et al* (1942).

nystagmus, and smiling cheerfulness on the patient's face: he emphasized the lumbo-sacral presentation with perineal numbness and sphincter disturbance but surprisingly, since he had himself described bilateral internuclear ophthalmoplegia (1906), was somewhat reticent on disturbances of eye movement; he was doubtful about trigeminal neuralgia or facial palsy as manifestations of multiple sclerosis, and had never seen deafness. Wilson (who allowed a typographical error in referring to *effective* reaction) had himself re-defined the syndrome of pathological laughter and crying in multiple sclerosis and other forms of pseudo-bulbar palsy (1924), recalling a patient who convulsed the ward with a Rabelasian peal of laughter and reference to the condition of his trousers in answer to a question on bladder control (Wilson's penchant for music-hall humour was well known to his colleagues); he described the *spes euphoria* and *eutonia scleroticans* and listed aspects of cognitive decline which feature so much in contemporary analyses of symptomatology in multiple sclerosis (see chapter 5). Histologically, the disease was to Wilson an encephalo-myelitis periaxialis scleroticans and he had no doubts on its toxic nature; he allowed the possibility of spirochaetal infection as the cause but considered the work of Miss Chevassut and his consultant colleague Sir James Purves Stewart as fully

discredited (see below); he was equally dismissive of the glial overgrowth doctrine.

Douglas McAlpine accumulated clinical records on 1072 cases of multiple sclerosis of whom a proportion were consecutive examples seen at onset and these formed the basis for his clinical descriptions and classification of the disease (Fig. 1.23) (McAlpine *et al* 1955). In conversation, Nigel Compston was never in doubt that he carried the main burden of collating this information and writing the first manuscript version. In summarizing features of the clinical course, McAlpine and Compston emphasized a number of special features – the symmetry of bilateral lesions, paroxysmal manifestations of demyelination, the predictable evolution of individual lesions according to anatomical principles, the variety of words used by patients to describe motor and sensory symptoms, early disappearance of the abdominal reflexes, the frequency of pupillary hippus (as distinct from the Marcus Gunn pupil – which curiously is not mentioned despite having been described in 1904), occasional upper limb wasting (illustrated by Oppenheim in his textbook) with absent tendon reflexes (also with Horner's syndrome in the case of WJ). Throughout, McAlpine and Compston relate their analyses to the lives and experiences of individual patients, placed in social context and identifiable to

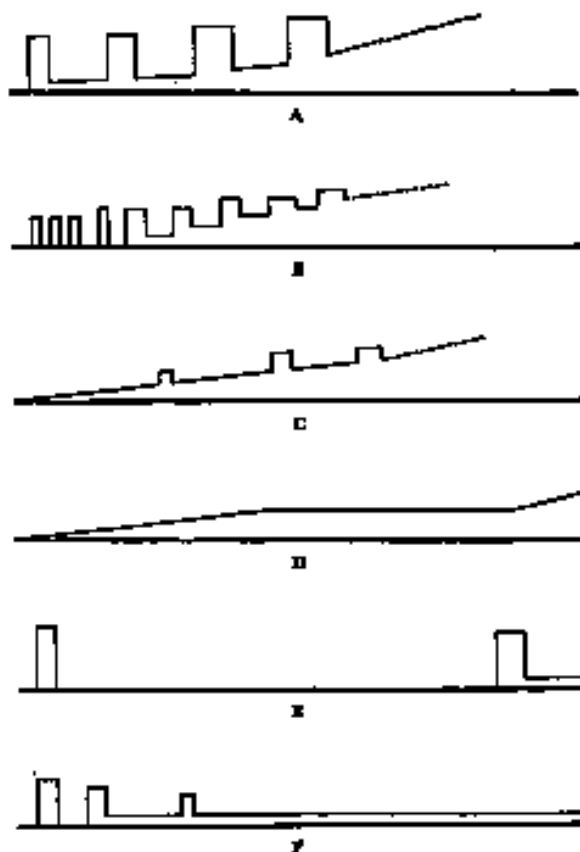


Fig. 1.23 (A) Relapses with early and increasing disability. (B) Many short attacks, tending to increase in duration and severity. (C) Slow progression from onset, superimposed relapse, and increasing disability. (D) Slow progression from onset without relapses. (E) Abrupt onset with good remission followed by long latent phase. (F) Relapses of diminishing frequency and severity; slight residual disability only. Reproduced with permission from McAlpine *et al* (1955).

any archival scout by their initials and case numbers. McAlpine and Compston used classical neuroanatomical principles of fibre organization within the spinothalamic tract and dorsal columns to explain the march of sensory symptoms as inflammation (and demyelination) spread laterally through the laminae and vertically to involve neighbouring segments. The authors dealt at length with features of the natural history which had not previously been described in such detail, pointing out the systematic reduction in relapse rate with time, the interval between the presenting and first subsequent attack depending on mode of presentation, the relationship between age at onset and the progressive course from onset, and aspects of prognosis – observations which were summarized in one of the most reproduced cartoon depictions of the course of multiple sclerosis. Their differential diagnoses, organized by syndrome, addressed the complex relationship between cervical

spondylosis and spinal cord demyelination, the nosological status of Devic's disease and acute disseminated encephalomyelitis (each distinct from but easily confused with multiple sclerosis) and emphasized the need for diagnostic caution in the context of a family history, especially when this involved a stereotyped phenotype amongst affecteds.

EPIDEMIOLOGY OF MULTIPLE SCLEROSIS: 1883–1976

The earliest systematic studies of multiple sclerosis in populations, defined demographically, were made in the first two decades of the 20th century, in continental Europe, the United Kingdom and the United States. By the beginning of the 20th century a disease that had merited individual case reports 25 years previously was one of the commonest reasons for admission to a neurological ward. The efforts of 19th century investigators were directed at describing variations in the clinical presentation of multiple sclerosis; their work highlighted the need for an epidemiological approach to the disease and the period 1900–1950 saw a gradual evolution of the methods required for accurate definition of population-based statistics (see chapter 2). Every survey demonstrated the unpredictable clinical evolution of the disease in individuals and the variability of its time course in populations.

Distribution of multiple sclerosis and environmental factors

The incidence of multiple sclerosis at Manchester Royal Infirmary was $43/10^5$ /year during the time (1892–1902) that Richard Williamson held the post of medical registrar (Williamson 1908), but it was not for 16 years that Russell Brain, reporting on cases seen at the Hospital for Epilepsy and Paralysis, Maida Vale and the London Hospital advocated the use of population- rather than hospital-based denominators and reasoned that the prevalence of multiple sclerosis can be estimated by multiplying rates for incidence or mortality by duration (Brain 1930). In 1940, Brain revised his figure for prevalence to $20/10^5$, noting that urban cases were more common than rural, that the disease rarely occurs in childhood and that only 7% of patients develop multiple sclerosis after the age of 50 years; incorrectly, Brain reversed the 3:2 sex ratio in favour of men. By 1955, he had updated his figures for prevalence to 1:2400 ($42/10^5$) for England and Wales and 1:1570 for Scotland ($64/10^5$) – establishing the latitudinal differential for the United Kingdom that remains unexplained to this day. Meanwhile, at the National

Hospital in London, during the 17-year period to 1925, 1398 of the 15 923 admissions had multiple sclerosis (Wilson 1940). The first mortality figures for multiple sclerosis published from the United Kingdom in 1927 showed a national rate of 1.75/10⁵/year (Wilson 1927). Isabel Wilson studied 688 persons who died with multiple sclerosis in the United Kingdom during 1925, noting regional variations from a high in Peterborough to a low in Buckinghamshire, but her main concern (picking up on an idea proposed by Dr JD Dawson) was to show, on the basis of differential mortality rates amongst farm workers, that the disease was caused by leptospiral infection. She preferred as vector for the distribution of multiple sclerosis, not *Homo Scandinavicus* (see below) but *Rattus Norvegicus*. Wilson carried out the first case-control study and showed a higher frequency of presumed exposure to water (on the basis of occupation) amongst 72 patients compared with individuals having other neurological diseases.

In 1883, Marie described 13 children with multiple sclerosis (he does not provide a reference) but later (1895) he indicated that he considered other diagnoses more likely in a number of these paediatric sclerotics. The following year saw the publication of his paper on *Insular Sclerosis and the Infectious Diseases* (1884). Noting the freedom needed when interpreting clinical as opposed to experimental results, he considered the anecdotal association of acute infectious disease (typhoid, pneumonia, malaria and the childhood exanthemata) and the onset of multiple sclerosis as sufficient to establish their causal relationship; in fact, he thought it more likely that several organisms were involved, alone or in combination:

“the fact, thank God, has been well established viz that the cause of insular sclerosis is intimately connected with infectious disease”.

Marie was prepared to accept that recovery was easily explained on the basis that the essential element needed for nerve conduction, the nerve cylinder, was preserved, and he joined Charcot in concluding that remyelination was responsible for restoring both structure and function but, for him, the disease was triggered by infection, depended on changes in the blood vessels, and resulted in an inflammatory interstitial reaction of the glia.

Section five of Brain's review dealing with *experimental transmission and bacteriology* analysed a controversial episode. In 1913, the Englishman Bullock (who changed his name to Gye), claimed to have transmitted the disease from man to rabbits. Khun and Steiner (1917) reproduced this finding using CSF from patients with multiple sclerosis injected into guinea pigs or rabbits. These apparent successes were

matched by as many failures (Marinesco 1919), but it was about this time that general interest in the spirochaete as a potent cause of neurological disease led to the description of this micro-organism in tissue removed from patients during life who had multiple sclerosis. These claims culminated in the report by Chevassut (1930) that the organism *Spherula insularis*, designated as viral, could be cultured from the CSF of >90% of patients with disseminated sclerosis but not controls. In his review, Brain quickly disposed of the spirochaetal theory of disseminated sclerosis but took a more reserved position with respect to Miss Chevassut's findings, suggesting that technical factors may have made it difficult for her directly to visualize the organism in 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 (1930); 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 episode at the Royal Society of Medicine in 1931; Dr Denis Brinton told us that when Carmichael (1931) reported his inability to confirm the findings, Miss Chevassut left the meeting in tears and was not subsequently encountered in neurological circles.

The subsequent history of infectious agents in multiple sclerosis has remained undistinguished. Squeamishness should not prevent us from mentioning the Schaltenbrand experiment (for a detailed review, see Shevell and Bradley 1994). Georg Schaltenbrand, who died in 1979, trained with Harvey Cushing and Pearce Bailey in the United States and established the University Clinic in Wurzburg in 1950. He took forward his claim to have transferred multiple sclerosis to monkeys using human spinal fluid by, in turn, infecting *verblodete Menschen* with material from these and other primates; one recipient, who had a glioblastoma multiforme, died after the second injection of monkey spinal fluid and was shown to have demyelinating lesions in the conus and peripheral nerves. Later, Schaltenbrand claimed to have produced autopsy-proven demyelination in an individual by injecting spinal fluid from a patient with active multiple sclerosis. It seems that Schaltenbrand (1943) performed this procedure on up to 45 human subjects, including children with psychiatric disease or idiocy from an institute in Werneck. Inevitably, there has been both exposure (Anon 1950; Shevell and Bradley 1994) and defence (Bailey 1950) of Schaltenbrand's work and we do not offer judgement but merely document a dark episode in the story of multiple sclerosis.

Scientifically, no more glorious was the claim in 1972 that an agent present in tissue extracted from patients with multiple sclerosis transfers a cytopathic effect to mice (Carp *et al* 1972; Koldovsky *et al* 1975), but the *Carp agent*, serenaded by the *Lancet* as a “*milestone in multiple sclerosis*”, disappeared from scientific attention when the results could not be reproduced (Carp *et al* 1977). The same fate awaited the human T-cell lymphotropic retrovirus (Koprowski *et al* 1985) and paramyxovirus SV5 (Goswami *et al* 1987). Innes and Kurland (1952), writing in the proceedings of the first symposium organized by the National Multiple Sclerosis Society (of the United States of America), summarized all attempts to transmit multiple sclerosis down to 1952. They considered the evidence to be inconclusive: whilst some of the experiments had produced neuropathological changes, these did not illuminate the problem of multiple sclerosis other than by showing that demyelination has many causes; the donor might or might not have multiple sclerosis; the causative agent might or might not be present; the studies had not involved many recipients and the sampling was sparse; coincidental events could have been responsible for the reported neuropathological changes. In chapter 3, we update the list of putative but unproven viral triggers for multiple sclerosis based on population serology and viral isolates.

The initial epidemiological studies only provide snapshots of the frequency of multiple sclerosis but they do document the evolution of improved methods for accurate case ascertainment. Byrom Bramwell (1917) first provided evidence on the natural history of the disease, although the patients which formed the basis for his survey had already received various medications, and he headed the section on disease duration as the *results of treatment* in 200 cases of disseminated sclerosis. One hundred and six were known to have died; 64 were alive, but the majority of these were deteriorating, and the clinical status of 30 was unknown. The duration of disease (including living cases) was just over 12 years; 14/170 had lived longer than 25 years after diagnosis (the longest was 37 years) and 3/170 had died within a year. In the fatal cases, life expectancy was <5 years in 21%, <10 years in 51% and <20 years in 87%.

The systematic study of multiple sclerosis in populations within the United Kingdom began in 1929 when Sydney Allison personally studied 40 cases in north Wales and derived a point prevalence of 13/10⁵ (Allison 1931). By 1949, 70% of his patients had died but only 2 survivors had deteriorated between the surveys and 1 deceased case had had symptoms for 43 years, providing an early example of benign multiple sclerosis (Allison 1950).

The second publication from the Association for Research in Nervous and Mental Diseases (ARNMD) contained a summary of recent publications dealing with epidemiological (and other) aspects of multiple sclerosis, recorded verbatim the discussion of these papers, and presented a summary of the ARNMD Commission under the presidency of Henry Alsop Riley. The contributions of Charles Davenport, Pearce Bailey, Llewellyn Barker, Israel Weschler and Charles Dana were at that time influential in shaping contemporary thoughts on the aetiology of multiple sclerosis and in stimulating surveys of the disease. Davenport (1921; 1922) mapped the frequency of defects found in men drafted into the United States army and showed that the maximum rate for multiple sclerosis was in the states of Michigan and Minnesota (each 18/10⁵), followed by Wisconsin, and he noted that these high rates were in adjacent states bordering the great lakes. Case material was recruited from three military camps and, although the number of affected individuals remained small (only 15 for the whole of Michigan), he rejected idiosyncratic neurological diagnostic habits as the explanation. Davenport identified a number of other disorders clustered in these geographical areas and suggested the link between goitre, chorea, varicose veins, varicocele and various heart defects with Scandinavian ancestry. He presented his results in an interesting chart which showed a gradient in frequency of multiple sclerosis (/10⁵) from 1 in Indians, to 2 in mountain regions, 6 in coloured agricultural communities from the south, 10 in German and Austrian districts, 16 in the Scandinavian section, and 29 in Finns. Davenport had already drawn attention to the noticeable differences between racial groups at a meeting of the New York Neurological Society in 1902.

At that time, distinction from ataxic paraplegias, diffuse degenerations and spastic paraplegias was imprecise and, by 1921, Davenport already suspected that many of these patients did in fact have multiple sclerosis. He obviously held some of his neurological colleagues in scant regard and dismissed, on the grounds of diagnostic idiosyncrasy, the claims of Van Wart who, in 1905 (not referenced), claimed a rate for multiple sclerosis of 44/10⁵ neurological cases in Louisiana. Davenport recognized that many confounding factors were being introduced and that the main variation between the studies related to selection of the denominator rather than variations in numerator. In particular, he noted a racial predilection for the use of certain clinics. However, he was impressed by the survey carried out by Miss Louise Nelson who took statements concerning the birthplace of 70 foreign-born patients with multiple sclerosis from the records of the Montefiori Home and

related the absolute number of cases to at-risk individuals from different racial groups. She (and Davenport) saw at once the lower than expected rates for Russians and Italians, the slight increase for Irish and the even higher rates for English, Germans, Swedes and Norwegians. Since Davenport could not see any reason why Scandinavians should have preferentially decided to use the Montefiori Home, and taking his subsequent analysis of the distribution of multiple sclerosis in the United States by racial origin, he concluded that Scandinavians are at especially high risk of multiple sclerosis (Fig. 1.24). Davenport then took the trouble to visit the Swedish hospital in Brooklyn but found no cases of multiple sclerosis resident or listed in the records – although he did note that the hospital had a very low frequency of neurological case material in general. He recognized that the African race is not completely protected from the disease even though the rates are low; and he pointed out that the disease is infrequent in Japanese.

The volume of ARNMD devoted to multiple sclerosis ended with the conclusions of the learned commission which included the comment that:

“In the United States it seems to occur more in the region of the great lakes – at least among young males, while in Europe it prevails more in northern parts than in Italy and about the Mediterranean sea. It is not a familial disease and it is not inherited, there being rare and doubtful exceptions; but in the ancestry, there is often evidence of a neuropathic stock. Acute infections may immediately precede the disease in a small percentage (10 or 12%) and it occurs no more frequently in persons who have had the usual children’s infections and fevers than those who have not had them. Further laboratory studies of the use of prolonged and intensive field work including some of the

methods suggested by ecology are necessary to give us a knowledge of the real cause of multiple sclerosis. Which cause we do not now know.”

Although carefully conducted regional surveys were performed during and after the late 1920s, information on the epidemiology of multiple sclerosis did not materially increase until the 1950s. Bing and Reese (1926) had documented the frequency of the disease in the Swiss cantons, providing rates between 1918 and 1922 of around $36/10^5$ but with variation from 3 to $74/10^5$. Sallstom (1942) collected morbidity statistics for multiple sclerosis in Swedish hospitals between 1925 and 1934 and reported a (period) prevalence of $34/10^5$. The steady rise in hospital cases was rightly attributed to relaxation in admission criteria and there did not seem to have been a change in annual incidence rates, although these were not directly assessed. This generation of epidemiologists was not content to document numbers of cases but used their surveys to explore aetiological hypotheses relating to the impact of environmental factors such as domicile, climate and soil conditions. Periodically, examples (or anecdotes) relating to specific infections were once again highlighted, such as the suggestion that multiple sclerosis might be related to swayback in sheep (Campbell *et al* 1947); the first of the clusters (6 cases) was reported from a Berkshire village (Campbell *et al* 1950). Cross-cultural studies continued to illustrate differences in geographical (or racial) frequency of the disease; in addition to the work of Davenport, it was known that multiple sclerosis was uncommon in Japan (Miura 1911), China (Woods 1929) and India (Sprawson 1927), and the influential studies of Geoffrey Dean (1949) on the effect of migration on the frequency of multiple sclerosis in South Africa were beginning to appear at that time with the demonstration of 36 cases in the Union (see chapter 3).

The next milestone in the epidemiology of multiple sclerosis was publication of the second ARNMD volume devoted to the disease in which Limburg (1950) used mortality statistics to document the distinct geographical distribution of the disease. Mortality rates were greater in temperate zones than the tropics or sub-tropics and showed higher figures in northern parts of the United States and Italy than in southern regions. A more extensive survey of mortality for 31 countries between 1951 and 1958, adjusted to the 1950 population of the United States, again showed regional variations but with a trend towards lower rates, reflecting the impact of improved health care following the introduction of antibiotics and other treatments for complications of multiple sclerosis in the early 1950s (Goldberg and

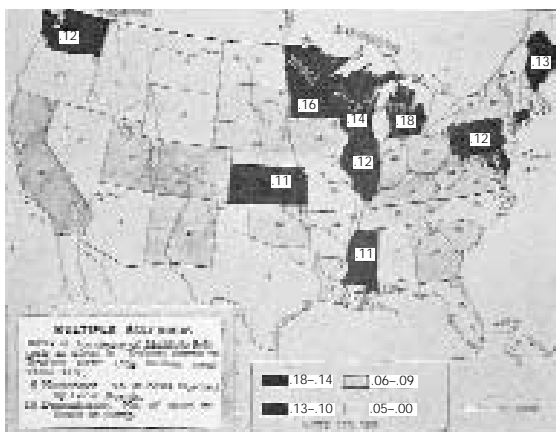


Fig. 1.24 Distribution of multiple sclerosis in North America by state. ‘Dodge’, ‘Grant’, and ‘Custer’ in the Great Lakes region are the names of camps at which the drafted men from those localities were mobilized. From Davenport (1921).

Kurlund 1962). The ranking of high-frequency countries in these analyses maintained the primacy of Northern Ireland and Scotland, with high rates also in southern Scandinavia and the northern Mediterranean countries, Canada, Australia, New Zealand and the northern United States. As Davenport (1922) had noted, non-whites from the United States had half the rate of caucasians, and low frequencies were reported for Asia, Africa and the Caribbean.

In 1954 the *Report to the Northern Ireland Hospitals Authority on the Results of a Three Year Survey on the Prevalence and Familial Incidence of Disseminated Sclerosis* appeared (Allison and Millar 1954). This publication provided the first detailed account of epidemiological methodology, reproduced the charts used to record information, featured the population against which all subsequent standardized prevalence ratios have been compared, and suggested a classification for multiple sclerosis which has since been extensively used. Regional rates provided the first substantial increase in estimates for incidence ($2.74/10^5/\text{year}$) and prevalence ($79/10^5$) which heralded the modern era (see chapter 3). The distribution of the disease was commented upon with no firm conclusion being reached on the urban-rural divide.

The epidemiological principles laid down by Davenport and Allison and Millar have since been applied in many hundreds of surveys, most carried out since 1950, and coinciding with research on paralytic poliomyelitis which culminated in the development of a suitable vaccine; analogies with the epidemiology of poliomyelitis served to strengthen the idea that the geographic distribution, age specificity and socio-economic predilections of multiple sclerosis could be explained on the basis of age-dependent consequences of infection by an ubiquitous agent. These ideas were sustained by the emerging concepts of slow virus infection in the 1950s. The individual who has worked hardest to make sense of epidemiological information relating to multiple sclerosis gathered since the first appearance of this book in 1955 until the present day is John Kurtzke; his contributions are of lasting importance (Fig. 1.25) and are described in detail in chapter 3. Kurtzke classified the published surveys of prevalence depending upon whether the diagnosis of multiple sclerosis was confirmed by individual investigators (*type A*) or assumed from information available in existing medical records (*type B*). Within these limits, he accepted further variations in methodology and made the influential suggestion that the distribution of the disease fits bands of high, medium and low prevalence. High risk ($>30/10^5$) was



Fig. 1.25 Point prevalences for multiple sclerosis in Europe to show regional differences in the frequency and the definition of high-, intermediate- and low-risk areas. Reproduced with permission from Kurtzke (1975a).

found in northern Europe, the northern United States, Canada, southern Australia, and New Zealand; medium risk ($5\text{--}29/10^5$) characterized southern Europe, the southern United States and northern Australia; and low risk ($<5/10^5$) areas included Asia, South America and many uncharted regions (1975a; 1975b; 1977).

Genetics

In analysing the evidence for familial clustering, Davenport had shown that familial cases tend to occur amongst sibships but may also affect first-degree relatives in more than one generation, each pedigree rarely containing more than three affected individuals. Davenport closed with a much quoted summary:

"In conclusion, may I be permitted the suggestion that whatever may eventually prove to be the endogenous cause of multiple sclerosis, the factor of heredity cannot be left out of account ... there are probably internal conditions that inhibit and others that facilitate the development of this disease or the endogenous factors upon which it depends and so it comes about that the manifestations or symptoms of the disease differ in different persons; and that they are sometimes very similar in closely related individuals because the hereditary factors of the constitution in which they operate are similar. It seems most probable that such geographical, ethnological and familial distribution as multiple sclerosis shows depends in part upon one or more hereditary factors".

John Sutherland carried out an epidemiological survey of multiple sclerosis in Scotland for his med-

ical thesis submitted to the University of Glasgow in 1950. He showed a difference in the distribution which correlated with the location of Nordic peoples, being higher in the Orkney and Shetland islands and in Sutherland (his family name derives from this region) by comparison with the more Celtic fringe of the western isles and mainland (Fig. 1.26). Although superficially latitudinal, the gradient therefore appeared to be influenced more by genetic than environmental factors.

The concept of a role for genetic factors in the aetiology of multiple sclerosis, explicit in the writings of Davenport and Sutherland, had earlier been suggested by Charcot on the basis of the occasional family history. Direct information on familial clustering was provided by Eichorst (1896) who described a mother-son pair with multifocal demyelination in the spinal cord demonstrated at autopsy, and Cestan and Guillain (1900) made clear the distinction between familial multiple sclerosis and the hereditary spastic paraplegias. Curtius (1933) accepted 84 reports in the literature of familial multiple sclerosis and he performed the first systematic study of recurrence risks in 3129 relatives of 106 probands living in Bonn or Heidelberg. Ten additional cases were identified and the relative risk for multiple sclerosis through having an affected relative was estimated at 40; there were no

examples of multiple sclerosis in a control population. In his monograph, Curtius sought to identify aspects of the natural history of multiple sclerosis which might be influenced by genetic background, and he was clearly aware of the apparent association with von Recklinghausen disease (see chapter 4). Curtius' study was criticized for lack of evidence of multiple sclerosis in many of the relatives on which his conclusions were based, but Curtius and Speer (1937) confined their subsequent study to near relatives and, on the basis of 4 cases amongst 444 relatives, also concluded that siblings had 40-fold the population-risk of developing multiple sclerosis (Fig. 1.27).

McKay (1950) accepted as familial 177 cases occurring in 79 pedigrees to which he added 11 cases of his own amongst 5 families. He emphasized that the commonest relationship between affecteds was sibship with parental and more distant kinship accounting for 14% and 16%, respectively. Reports of multiple sclerosis occurring in both of a pair of twins were accepted by McKay in five instances. Pratt *et al* (1951) collated 184 familial cases of multiple sclerosis, providing familial recurrence rates of between 0 and 9.4%, and reported a familial incidence in their own material of 6.5%, siblings being the main group at risk (0.5%). Müller (1953) took Pratt to task for methodological inadequacies but came up with a

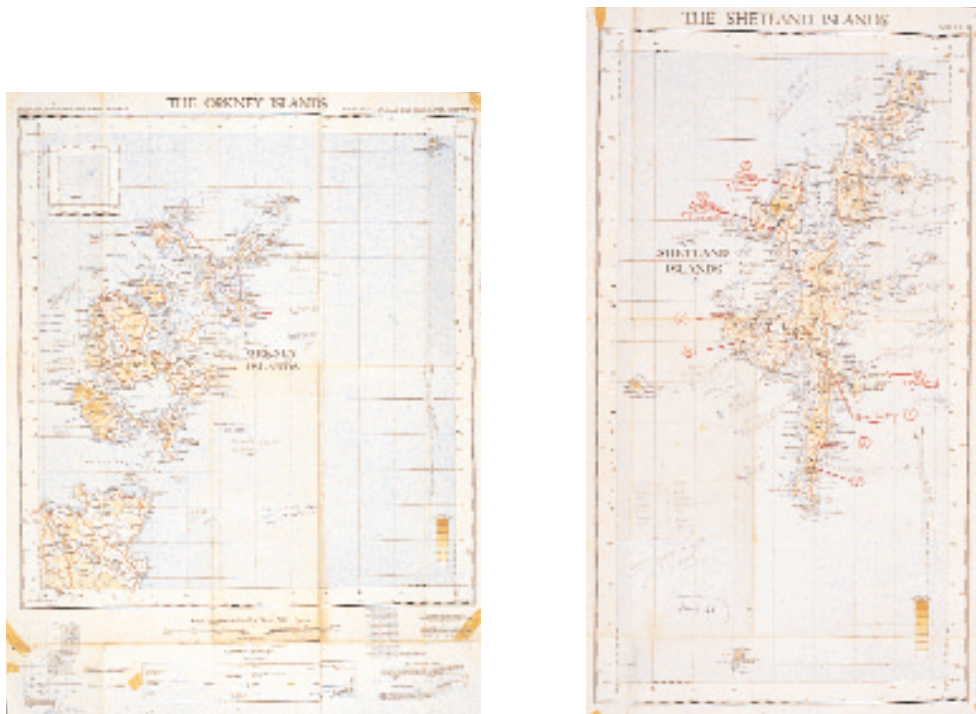


Fig. 1.26 Ordinance survey maps of (A) Orkney and (B) Shetland islands used by John Sutherland to show the names and distribution of cases in the first survey of multiple sclerosis from Scotland and the offshore islands. Kindly provided by Mrs Patricia Sutherland and Professor Mervyn Eadie.



Fig. 1.27 Hereditary aplasia of the fourth and sixth cranial nerves in a daughter (left) and mother (right); the latter in addition presents with multiple sclerosis (family 53).

more or less identical figure in his own survey. Schapira *et al* (1963) found a positive family history in 24/607 (4%) consecutively presenting patients, noticing that females had nearly 3-fold the prevalence of male siblings and that relatives were affected in the order: sisters, mothers, brothers and fathers.

Case reports provided the suspicion that hereditary factors are involved in the development of multiple sclerosis but it was necessary to carry out epidemiological studies to establish whether this finding was due to chance. Allison and Millar (1954) reported population-based figures for familial multiple sclerosis, identifying 44/668 families with 2 or more individuals affected by the disease. Sibships dominated the series (recurrence 1.15%, giving a relative risk of between 5 and 15).

Douglas McAlpine gave a paper on hereditary factors in multiple sclerosis to the 6th International Congress of Neurology, held in Brussels in July 1957 (McAlpine 1957). Reviewing the literature, he reprimanded the authors of many textbooks for ignoring this feature of the disease. In his thoughtful review, McAlpine addressed for the first time many of the issues which have since preoccupied genetic research in multiple sclerosis, and not all of which have been solved. He collated published reports on familial disease and found the rates to be reasonably uniform at 5–10%, although with some variations attributable to methodology, for example a lower figure (2.6%) in the national survey of Denmark conducted by Hyllested (1956). He noticed that the recurrence rate was higher for siblings (1%) than offspring (c0.3%). He considered seriously the impact of consanguinity and produced supporting evidence from the surveys of Northern Ireland (Millar and Allison 1954) and Scotland (Sutherland 1956). He noted that Curtius (1933), Garcin (1936) and Pratt *et al* (1951) had each described sibling pairs affected with multiple sclerosis who were reared apart. McAlpine had encountered 4 examples of conjugal multiple sclerosis and knew of 4 others; he predicted the importance of

studying the recurrence risks in their offspring (see chapter 4). He summarized the evidence as implicating a genetic factor and considered this to be consistent with either the infective or allergic theories of the aetiology which were prevalent at the time; furthermore, McAlpine speculated that the mechanism might involve a genetically determined alteration in the structure of myelin, rendering individuals vulnerable to as yet unidentified factors needed to precipitate demyelination.

The first laboratory studies aimed at identifying the basis for genetic susceptibility were necessarily limited by the few polymorphic systems which could then be studied. Alexander *et al* (1950) and Beebe *et al* (1967) failed to show a distortion in the normal distribution of blood groups amongst patients from New England, whereas McAlpine *et al* (1965) reported a slight excess of group O in a study of patients from six English cities. In an admirably comprehensive survey which combined statistical power with ethnic and regional homogeneity of the participants, Simpson *et al* (1965) compared blood groups in 507 patients and 94 419 controls, also demonstrating a slight increase in group O which was not significant; a further study from Newcastle in northern England (MacDonald *et al* 1976) confirmed this relationship (and also drew attention to the association between multiple sclerosis and homozygosity for *cde* together with some other minor blood groups); the authors considered that McAlpine's earlier criticism of this work was harsh but in re-appraising the 1965 edition, McAlpine backed off from his position with respect to blood groups and susceptibility to multiple sclerosis (McAlpine 1972); significantly, MacDonald drew attention to the high frequency of blood group O in populations having a high frequency of multiple sclerosis.

In 1972 an association was described between multiple sclerosis and HL-A3 (now HLA-A3: Naito *et al* 1972; Bertrams *et al* 1972). In the same year Jersild *et al* (1972) reported an association with the linked allele

HLA-B7 but (incorrectly) concluded that this was the weaker (and biologically less significant) association. Jersild *et al* (1973) then looked at the relationship between multiple sclerosis and the HLA-D types which were defined by mixed lymphocyte cultures. An association was shown with the antigen Ld-7a (later renamed Dw2), present in 70% of Danish patients compared with 16% of controls. In the late 1970s, the availability of HLA typing led to the first family studies (Alter *et al* 1976; Olsson *et al* 1976), including sibling-pair analyses (Zander *et al* 1976), cross-cultural studies (which hinted at specifically different associations in certain populations; Brautbar *et al* 1976; Saito *et al* 1976), correlations with clinical course and severity (Jersild *et al* 1973), and the assessment of risk in isolated demyelinating syndromes (Platz *et al* 1975; Stendahl *et al* 1976). In 1975, Winchester and colleagues reported an association between multiple sclerosis and an antigen expressed only on B lymphocytes, designated Ag-7a, and more detailed reports were published in the following year of the relationship with the class II allele HLA-DR2 (Terasaki *et al* 1976; Compston *et al* 1976), which remains the best characterized candidate susceptibility gene for multiple sclerosis (Fig. 1.28).

Douglas McAlpine wrote in January 1977 on receiving a reprint describing the HLA-DR2 association with multiple sclerosis:

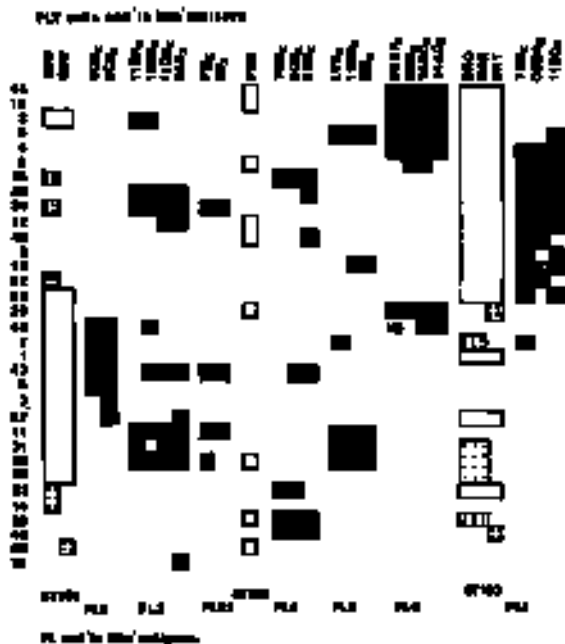


Fig. 1.28 Correlations between typing reagents identifying the first serologically-defined human class II major histocompatibility complex antigens (here designated BT antigens) and those defined by (primed) lymphocyte typing. The multiple sclerosis-associated antigens are BT101 (see Compston *et al* 1976) and PL2.

"The intricacies of modern immunology are beyond my comprehension but from your results it is clear that this is proving a field of the greatest importance in MS ... You are right in thinking that your approach is likely to show positive results in some members of MS families. Yes, for long, I have suspected a genetic influence. See The Problem of Disseminated Sclerosis (Brain 1946; 69: 233). I reported 8 examples of familial MS in a series of 142 cases and concluded that the familial incidence was significant but Curtius (1933) was the first to recognize the genetic factor. In our first book (1955) ... we referred to these facts."

ATTITUDES TO THE TREATMENT OF MULTIPLE SCLEROSIS: 1841–1983

From the first descriptions of multiple sclerosis and the early clinico-pathological correlations, individuals and their physicians lamented the difficulty of altering the natural history or, when honesty prevailed, even of masking symptoms. In chapter 14 we identify as landmarks in the history of multiple sclerosis, the demonstration that corticotrophin alters the rate of recovery from an individual episode and the meta-analysis of azathioprine. However, even though real progress was not made for over 100 years after the first depictions of multiple sclerosis, this did nothing to limit speculation or contain therapeutic experimentation; in fact, multiple sclerosis soon acquired a regrettable reputation for maverick medicine based on shameless exploitation of its capricious natural history which favoured the uncritical and those devoted to extrapolation from anecdotal experience.

Within a few years of recovering from his first episode of optic neuritis, Augustus D'Este was in the hands of the quacks: he experienced steel-water in Driburg (on the advice of Dr Sprangenberg); beef-steaks, fortified wines and linament brushes (Dr Kent); astringent plasters and tepid baths (a Milanese doctor); urethral dilatation and 15 baths a day (Dr Sprangenberg, again); galvanism ("if anything be clear to me ... it is ... that electricity is the most powerful Agent to my injury instead of to my recovery – the air of Brighton I should place in a similar category"); repeated versions of bathing in tepid, hot, sea or medicinal waters in many specifically different locations together with shampooing (Drs Brown, Granville, Barlow, Daniell); ingestion of strychnine, metallic salts (especially silver), tonics and aperients (various, including Richard Bright and Dr JR Farre); hydropathy at Grafenburg (Dr Praesnitz); cantharides (Sir Benjamin Brodie); and a mere 30 substances ingested in various combinations of tinctures, tonics, soothing drafts, powders and potions (Dr Seymour who visited D'Este on 49 occasions).

On treatment, Charcot came straight to the point:

"After what precedes, need I detain you long over the question of treatment? The time has not yet come when such a subject can be seriously considered. I can only tell you of some experiments which have been tried the results of which have, unfortunately, not been very encouraging."

By comparison, his pupil Pierre Marie was much more positive, presumably because he was wedded to the aetiological role of infection and so saw an opportunity for prevention and cure:

"I have little doubt that ... by the employment of ... the vaccine matter of Pasteur or lymph of Koch the evolution of insular sclerosis will some day be rendered absolutely impossible."

Although one senses some uncertainty in Hammond's mind on the diagnostic status of the cases he classified as having multiple sclerosis, he was not in doubt that their condition could be improved with hyoscyamus and barium chloride, supplemented with lavish doses of electricity, cod-liver oil, iron, strychnine, two glasses of wine daily, and a moderate amount of exercise (Hammond 1871). Althaus (1877) says not a word on treatment; Gowers (1888) uses silver nitrate, quinine, hypodermic arsenic (recommended by Eulenberg), notes that Germans prefer hydrophathy and electricity (which he approves for associated peripheral nerve palsies), and advises against pregnancy. Risien Russell (1899) considers the therapeutic prospects in disseminate(d) sclerosis to be gloomy in the extreme – no medicinal agent having the slightest effect in arresting the disease or retarding its progress. Reluctantly, he uses silver nitrate or chloride, and arsenic, each to be administered subcutaneously, concluding that solanine only works in the symptomatic control of tremor when an erroneous diagnosis of hysteria has been made; massage, hydrotherapy and electrical treatment might help spasticity; adjustments to lifestyle are likely to be more useful, including relocation from cool to sunny climates, elimination of depression, ensured rest, fresh air (in an open carriage or wheel chair) and a diet rich in cod-liver oil; infections are so clearly implicated in the causation as to demand prolonged rest from an individual attack and the possibility of metallic poisoning offers an obvious means of prevention. In time honoured fashion, Risien Russell concludes with the rousing hope that:

"a not very distant future may bring us face to face with a rational and more hopeful means of dealing with so intractable a disease".

In line with contemporary fashion, Bramwell (1917; and other sources) gave his patients silver

nitrate and arsenic to influence the course; he used hydrobromic acid or bromide of potassium for spasticity and strychnine and iodide of potassium or nuxvomica for paralysis, but in no case did it appear to be of the slightest use. Massage, electricity, hydrophathy and suspension were of equally doubtful efficacy. Richard Williamson (1908) tried many drugs and found none to be helpful with the possible exception of quinine which he favoured whilst recognizing that this apparent therapeutic effect could not necessarily be dissociated from the natural history of the disease. In Germany, Strumpell (1931) considered rest in hospital to be essential and there he would administer galvanism, carbonic acid baths, friction, iodide of potassium, ergotin, silver nitrate or salvarsan (because of the spirochaetal aetiology), aspirin, arsenic and injections of fibrolysin – all supplemented by gymnastic exercises. Conversely, Oppenheim (1911) insisted that hot baths and electrical stimulation should be avoided: mercury never worked and caused optic neuritis; silver nitrate and iodide of potassium or Crede's silver ointment were useful treatments; and symptoms could be managed with Veronal for tremor and antiphlogistic-diaphoretic treatment during acute attacks of myelitis or encephalitis; blood letting could be remarkable in its effects.

No one had very coherent ideas on the mechanisms of action of these agents and few even thought it necessary to speculate. As McDonald (1983) has pointed out, the rationale for using arsenic was as mysterious to eminent pharmacologists as it was to neurologists of the day; silver had been known to the Arabs who considered that nervous diseases were influenced by the phases of the moon which, in turn, were associated with silver in their system. Gowers (1888) reasoned that since the demyelinating component was more amenable to treatment than the astrocytosis, this was a specific indication for arsenic and silver salts but he offered no explanation for this didactic view.

It has been suggested that WNP Barbellion hastened his own demise through injudicious use of nerve stimulants. He always attributed variations in the natural history of his disease to the mixture of arsenic, morphine and strychnine, which he took regularly from mid-1916. However he knew this to be merely palliative, at best, and after telling his wife, who knew all along, of the diagnosis in November 1916, entertained the hope that:

"a physician from London will gallop up hotspur, tether his horse and dash in waiving a reprieve – the discovery of a cure;"

instead, he tried homeopathy and electrotherapy.

We are fortunate in having available the encyclopaedic collation of treatments which Brickner (1936) identified as having been used prior to 1935; it is a sorry catalogue of thwarted hopes and dashed lives. He rightly identified many of the factors which compromise the scientific evaluation of any new treatment in multiple sclerosis, and the need to time the intervention so as to coincide with a phase of the disease which is actually amenable to treatment. His table, running to 29 pages, lists in alphabetical order substances and methods from antimony to X-ray, almost all of which were somewhere in contemporary use. Trial methodology is conspicuously absent and many studies involved only a trivial number of cases observed for a short period. Brickner welcomed the American Neurological Association's initiative in 1934 to standardize at least some aspects of the protocol for a clinical trial. Surveying what was then therapeutically active, Brickner was particularly attracted to the study of malaria therapy reported by Grosz (1924) who segregated cases depending on clinical course (relapsing and progressive), and used a meaningful functional outcome such as ability to walk. Fever therapy was then very popular and Brickner identified 11 different methods for inducing pyrexia; there were 24 trials of salvarsan, reflecting contemporary interest in the spirochaete and multiple sclerosis. Dreyfus and Mayer (1929) also used malaria in a large number of cases and stratified their analysis according to severity and duration; mild cases of recent onset responded best to treatment, as expected from the natural history. Brickner also singled out the studies of antimosan and stibenyl by Creelius (1928), which involved 27 and 6 patients, respectively, studied for up to 5 years; the published results seem to us unimpressive and Brickner himself concluded that any therapeutic effect was short lived. Surgery (including sympathectomy, root section and laminectomy) was in use as a treatment for multiple sclerosis. Parenteral treatments included fibrolysin, haemolytic sero-therapy, auto-transfusion and implantation of spleen, thymus, thyroid, liver or brain (sadly, no reference is given for this first brain transplant in multiple sclerosis). The Purves Stewart vaccine had been given to 550 patients in 7 trials. Brickner (1935) himself had used quinine hydrochloride; and very distinguished neurologists were using sodium salicylate or sulphate, tetraphan and X-rays. Putnam (1939) used Brickner's table of treatments to perform an armchair meta-analysis, claiming that a mean of 47% of 1407 treated patients (usually receiving fever therapy, arsenicals or quinine) improved compared with 69% of 133 untreated patients, but he advised caution in drawing the cynical conclusion that medi-

cal treatment is useless in multiple sclerosis or that the placebo effect is superior.

Fever therapy induced by malaria, typhoid vaccine and other organic or microbial pyrogens, also featured prominently in Brain's account of treatment; there was no hint of adverse effects. The study in which Purves Stewart (1930) treated a large number of patients 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 CSF, was cited with the conclusion that removal of the organism from <10% 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 recommended, and agents such as sodium salicylate or X-irradiation mentioned; Brain concluded that:

"the multiplication of remedies is eloquent of their inefficacy".

Sadly, in the first edition of his textbook, he could offer nothing other than tact, judgement, metals and fevers by way of treatment and even the use of liver had disappointed him. Kinnier Wilson considered:

"the pharmacopeia to have been ransacked for nerve tonics which might influence the course of multiple sclerosis"

but he recommended arsenic in the form of Fowler's solution, injections of sodium cacodylate, Crede's silver ointment, other germicidal colloidal metals, including selenium, and aspirin, quinine and mercury. With others, he had used lecithin and fibrolysin but 18 months' treatment terminated in the final rebellion of his hitherto compliant patient. Wilson induced pyrexia with anti-typhoid or paratyphoid vaccines and he used malaria or electrical methods; surprisingly, these pyrogens did not appear to exacerbate the disease. He was unimpressed by the use of whole liver in comparison with its effect in subacute combined degeneration of the cord.

By 1955, Douglas McAlpine and Nigel Compston at last had something to say about treatment with which we would still agree. They distinguished the needs of the patient early in the illness from problems that arise later. Initially, the requirement is for rest with rehabilitation, taking 3–6 months (ideally) in a sanatorium. For the first time, the authors discuss the need for open discussion of the diagnosis, except in the unmarried young adult and those judged to be of 'low moral fibre', and they warn patients not to accept uncritically general accounts of the illness that they may read. Discussions on marriage and child-

bearing should be advisory and not proscriptive, but they consider that it makes sense to delay pregnancy until the illness has been quiescent for about 2 years. Interest in fever therapy had not waned and we know that Nigel Compston visited Professor Cloake in Birmingham to assess a protocol for its induction with intravenous TAB vaccine; Cloake noticed a temporary increase in symptoms during the peak of the fever (101°F), which McAlpine and Compston attributed to vasodilatation since they had seen a similar phenomenon with the use of nicotine acid and NAB (arsenic). Cloake was an advocate of arsenic which he gave four times annually for the first 5 years and three times thereafter. This work was described in his (the first) Humphry Davy Rolleston lecture to the Royal College of Physicians in 1947 on *the treatment of disseminated sclerosis by artificial pyrexia and the prolonged administration of arsenic*. The lecture remained unpublished and the then Harveian Librarian, Sir Charles Dodds, and his successor wrote serially to Professor Cloake between 1953 and 1966 trying to extract a written version of the lectures but (despite promises of imminent dispatch) had no success; the correspondence closes with an unanswered note of condolences to Philip Cloake's widow, dated April 1969, adding that the College still hoped to acquire the 1947 manuscript should this be found amongst Cloake's papers, but it never arrived. McAlpine had himself used arsenic for many years but, in a small uncontrolled trial, Compston (1953) was unable to provide any scientific evidence in support of this approach to treatment. Histamine-induced vasodilatation had been used by Horton and Wagener (1948) in patients with optic neuritis, more of whom appeared to regain normal vision compared with the effects of typhoid vaccine which many had previously received. McAlpine and Compston were unimpressed by the effect of histamine on relapse rate in patients with established multiple sclerosis (Horton *et al* 1944), and they were no more enthusiastic about liver and vitamin B12 or the dietary regimen of Swank (1953) – assembling powerful arguments against the simultaneous use of more than one therapeutic agent, and highlighting the lack of controls and failure to allow for the natural history of the disease in qualifying the putative use of this treatment for multiple sclerosis.

The bladder could be managed by altering habits, through the use of atropine and phenobarbitone, and with early use of M and B (sulphonamide) or mandelic acid and hexamine as urinary antiseptics. McAlpine and Compston recommended the systems for rehabilitation of traumatic injuries of the nervous system that had recently been introduced by (Sir) Ludwig Guttmann (1952). They could not envisage any cir-

cumstance in which it would be valid to terminate a healthy pregnancy in the context of multiple sclerosis but they advised against elective surgery for trivial complaints. It was against this largely historical therapeutic background that McAlpine and Compston were able to introduce their readers to the original results of Glaser and Merritt (1952), Fog (1951) and Miller and Gibbons (1953) who reported on the role of corticotrophin in accelerating recovery from relapse in multiple sclerosis, although they found this to be profoundly disappointing by comparison with cases of acute disseminated encephalomyelitis. The combined experience of McAlpine and Compston in 1955 was 2 treated patients, including 1 with optic neuritis. A very few cases had been treated with antibiotics (chloramphenicol and penicillin) to control secondary infections. McAlpine and Compston could not reach any conclusions concerning the role of specific disease-modifying agents but they ended their account of treatment with a summary of guidelines adapted from (Sir) Austin Bradford Hill's writings on controls, power, confounding and matching in clinical trials (Hill 1952). Wrongly, in our view, they considered that the main aim of any treatment should be to reduce the frequency of relapse, ideally demonstrated by comparison between cases or controls but exceptionally through serial observation of individual cases. They felt that influencing disability was a secondary aim in treatment trials, mainly because this was thought to depend absolutely on relapse rate. They advocated the use of follow-up clinics, believing that so long as these were not advertised as being for people with *multiple sclerosis*, the example of the disabled would not unduly affect the morale of milder cases. They were at pains to point out the need to attend to social aspects of the patient's illness and to involve the family in discussions and decisions.

During the 1960s and 1970s, coherent ideas began to form on the pathogenesis of multiple sclerosis and, with added impetus from the results of using corticosteroids in multiple sclerosis and other conditions which were then accepted as immune or inflammatory in nature, these led to the use of various immune suppressants as they became available. Ian McDonald (1983) charted the transition from theories on the spirochaetal, spherulitic, bacterial and vasculitic causes of multiple sclerosis into specific therapies since the time of D'Este, and with characteristic breadth of view provided present-day partners, based on no less flimsy a logic, for many of these apparently absurd treatments. Clinical charisma and the exploitation of frightened vulnerable patients and their relatives litter the historical highways and byways of therapeutic endeavour in multiple sclerosis. It has not been a golden road.