The dissemination of multiple sclerosis

The Langdon-Brown Lecture 1989

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There are 60,000 people in Great Britain with multiple sclerosis, several times that number in the United States and perhaps 2 million worldwide. In each affected individual, performance is periodically interrupted in the complex network of myelinated axons and supporting glia—together constituting white matter within the central nervous system—by inflammatory mediators which penetrate the blood brain barrier. The solution to multiple sclerosis lies in understanding the epidemiological and biological factors that determine the geographical and anatomical dissemination of this difficult disease.

Some historical considerations

In 1830 Robert Carswell, a Glaswegian, later to hold the foundation chair of pathology in the University of London, attended a demonstration given by Pierre Louis in Paris where he observed morbid anatomical appearances which were subsequently included in his book illustrating the elementary forms of disease [1]. In the same city and at much the same time, Jean Cruveilhier was assembling a pathological atlas in which also was depicted patchy hardening of the brain [2,3]. In 1830, at the time Carswell and Cruveilhier were in Paris, a young English nobleman discovered, during a visit to Ramsgate, that he was impotent. Augustus D'Este was born on 13 January 1794, inconveniently soon after his parents—Lady Augusta Murray and Prince Augustus Frederick (sixth son of George III) —had met in Rome; the further details of that unhappy liaison need not here be told. Augustus had a conventional childhood for the times, suffering from green stools, gripings, St Anthony's fire and, on 26 February 1808, whilst a pupil at Harrow school, a severe attack of measles with pulmonary complications. Ill health continued to dog him and in 1822 he had an attack of bilateral optic neuritis which recurred in 1826; further episodes, affecting the brain stem, spinal cord and cerebrum, occurred over the next 20 years and by 1843 he was established on a slowly progressive course with superimposed relapses, later becoming paralysed, losing the use of his arms and eventually dying in 1848, having had symptoms attributable to multiple sclerosis for 26 years.

The details of D'Este's illness are known through the work of Douglas Firth who qualified from Cambridge in 1907 and subsequently held appointments in London. He was in charge of the Blind School Hospital at Leatherhead during the Second World War, and it was there that, 'through his interest in old papers', he rescued—and later published [4]—what remained after the attentions of 'rats and human agency' of part of a diary kept by D'Este and written by various secretaries and himself between 1822 and 1846. Later, Dr Firth returned to Cambridge as secretary of the Committee for Postgraduate Instruction for Demobilised Officers. Through their mutual interest in medical history, Douglas Firth would have known Sir Walter Langdon-Brown who had retired from the regius professorship of physic in 1935, a post to which he was deemed well suited through his grasp of modern trends in medicine and their historical background. Langdon-Brown was hesitant of speech, intensely self-effacing, sensitive to criticism, and so not critical of others —qualities that epitomise the regius professorship to this day! He died in 1946, the year in which the first multiple sclerosis society was founded.

This event brought to an end a controversy that had smouldered for nearly a century. The clinical and pathological features of 'la sclerose en plaques' were described in France by Jean Charcot and his students at the Salpetriere and by Walter Moxon, who used the term 'insular sclerosis', at Guy's Hospital. Only in Scotland, the north of England and the United States was the German name 'Multiple Sklerose' immediately adopted. English physicians preferred to call the disease 'disseminated sclerosis' until the appearance in 1954 of the classical monograph by McAlpine, Compston and Lumsden, since when the condition has universally been known as multiple sclerosis. Whilst these nosological matters were being resolved, others were establishing the methods upon which proper statistical definitions of the disease were to be based. 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 in England.

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Dissemination in time

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 1903–1954 saw a gradual evolution of methods required for accurate definition of population-based statistics. Every survey demonstrated the unpredictable clinical evolution of the disease in individuals, and the variation of its time course in populations.

During the time (1892–1902) that Richard Thomas Williamson held the post of medical registrar, the incidence of multiple sclerosis at Manchester Royal Infirmary was $43/10^5$/year [5], but it was 16 years before Russell Brain, reporting on cases seen at the Hospital for Epilepsy and Paralysis, Maida Vale, and the London Hospital [6], advocated the use of population rather than hospital denominators and reasoned that the prevalence of multiple sclerosis can be estimated by multiplying rates of incidence or mortality by duration. The first mortality figures for multiple sclerosis in the United Kingdom, published in 1927 [7], showed a national rate of $1.75/10^5$/year but with regional variations. The detailed 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 population prevalence of $13/10^5$ [8]. By 1949, 70% of his patients had died but only two survivors had deteriorated between the surveys and one deceased case had had symptoms for 43 years, providing an early demonstration of the fact that multiple sclerosis can be a benign disease [9].

Between 1984 and 1988, multiple sclerosis was restudied in Wales, but this time in the industrial south-east [10]. Serial estimates of point prevalence in 1985 and 1988 were $117/10^5$ and $120/10^5$ respectively [11]. An attempt to correct for the omission of mild or undiagnosed cases in registers based on case retrieval was made in one village—Blaenavon, Gwent—where seven cases of multiple sclerosis were registered; after reviewing the records of all 6,386 inhabitants and assessing patients with unclassified neurological symptoms, a further nine cases were identified, giving a prevalence of $250/10^5$ in this small community (unpublished observations).

The tenfold or greater increase in prevalence of multiple sclerosis in Wales over 50 years reflects a pattern which can be seen with respect to dissemination of the disease over time in practically any region where serial studies have been performed [12]. This is almost certainly not due to an increase in biological incidence; between 1947 and 1988 the number of newly diagnosed cases of disseminated/multiple sclerosis showed marked variations in South Wales, the peaks often coinciding with the appointment of a new consultant neurologist but otherwise revealing a slow increase from about 4.8 in 1947 to $8.2/10^5$/year by 1988. The temporal trends arise partly from changes in definition and classification, the availability of laboratory methods for supplementing the diagnosis, and increased clinical vigilance, but mostly depend on the steady reduction in mortality attributable to multiple sclerosis that has occurred since the Second World War. Mean duration of disease from onset of symptoms, estimated at 8 years in the early part of this century [13], has now risen to more than 25 years [14,15].

Dissemination between regions

Race

The epidemiological principles laid down by Allison have since been applied in more than 300 surveys. These show that multiple sclerosis is common in northern Europe, North America and Australia but rare in the Orient, Asia, the Indian subcontinent, Africa and South America (Fig. 1a), and it has been suggested that this latitudinal gradient reflects the involvement of an environmental factor. However, in Europe the disease is common in southern Scandinavia but not the north, in the Orkney and Shetland islands but not the Faroes or Iceland, in Italy—especially Sardinia—but not Greece or Spain, and in Sicily but not in neighbouring Malta (Fig. 1b).

It is self-evident that Europe is genetically heterogeneous even though the origins of its population are to some extent unknown. Nordic people migrated from the more northern steppes of Eurasia; the Mediterraneans, including Iberians, took a route from the southern steppes through east and north Africa; and the Alpines or Celts originated from the western plateaus of Asia and populated regions from the Hindu Kush to Brittany and parts of the British Isles. Subsequent local migrations allowed the Aryan races of Scandinavia—Vikings and Goths—to distribute their genes in northern Britain, Normandy, Sardinia, Sicily and southern Italy. The style of Norse raiders was to assimilate themselves more or less into the way of life of the local inhabitants, as a result of which the subsequent histories of the two peoples merge. The Celts moved throughout central Europe from their strongholds in Gaul and visited northern Italy and Greece as well as extensively colonising Britain, and from there the Faroes and Iceland, until they were forcibly displaced from many of these places by Norse invaders, remaining dominant within the United Kingdom only in parts of Wales, the West Country and the Fens [16].

Genetic isolates

As a consequence of these movements, genes with a high frequency in the migrating populations necessarily became concentrated in small isolates whereas others were excluded, thus creating the clines that exist for many polymorphic genetic markers in Europe [17,18], and the phenotypically more obvious distributions of language and anthropometrics. Genetic clines are particularly marked with respect to the HLA antigens B7 and DR2, alleles that increase susceptibility to

Fig. 1. *Recent (1975–1989) estimates for the prevalence (/10^5) of multiple sclerosis (a) throughout the world and (b) in Europe. Figures are taken from published sources and have been derived using methods that are not necessarily comparable.*

multiple sclerosis. The existence of small groups where ethnic and cultural mixing is incomplete and genetic disequilibria persist seems the best explanation for the unprecedented concentration of multiple sclerosis in the Orkneys and its distribution in other parts of the United Kingdom [12]—susceptibility genes being over-represented in Nordic peoples compared with Celts and Anglo-Saxons. Thus, Sutherland in 1956 mapped multiple sclerosis in Scotland, concluding that variations in frequency correlate better with the relative distribution of Nordic peoples than any putative environmental factor [19]. Contemporary studies show that the predominantly Celtic Faroe isles, Iceland and the western Hebrides [20–22] have lower rates for multiple sclerosis than Orkney and Shetland [23]. The most recent Welsh survey showed that a disproportionate number of susceptible patients had been born in England [24], and the distribution of male patients' surnames was significantly skewed in favour of English names in comparison with the census population.

The same factors have determined the distribution of multiple sclerosis in the United States. Based on his findings in 511 First World War US army recruits, Davenport explained to the second meeting of the Association for Research in Nervous and Mental Disease that multiple sclerosis is more common in Scandinavians than other groups; in discussion others suggested that multiple sclerosis had risen in frequency in the United States coinciding with the mass arrival of immigrants and that it remained a rare disease amongst descendants of the Pilgrim Fathers [25]. Detailed mapping in North America by John Kurtzke [26] shows a gradient falling from north-west to south-east, perhaps with an inappropriately high prevalence in the south-east tip of Florida, which correlates with patterns of migration from northern Europe [27] and inversely with the distribution of American blacks. The prevalence of multiple sclerosis in the Innuits of Canada is only a twentieth of that in other Canadians living in the same areas, and it is also a rare disease in the Indian tribes of North America. The relationship between frequency of multiple sclerosis and northern European migration holds up well for Canada except in one important respect. A small group of Lutherans, followers of Jacob Hutter, moved from Germany in the 19th and 20th centuries and established closed communities where social mixing and marriage outside the group are still rare [28]. Present-day Hutterites live in parts of Canada and North America which have a high prevalence of multiple sclerosis yet no cases have been observed in their communities [29]. Just as the Orcadians represent a genetic group in whom the genes conferring susceptibility to multiple sclerosis are highly concentrated, so these genes have presumably been excluded from the Hutterites in North America. The lifetime risk of developing the disease for someone growing up in the United Kingdom is approximately 1:800; this rises to 1:50 for the sibling of an affected person and to 1:2 in the special situation of identical twins one of whom already has the disease.

Histocompatibility antigens

In northern Europeans [30] multiple sclerosis is associated with the HLA haplotype A3, B7, Dw2, DR2 and DQw1, and associations with this group of antigens are also seen in northern European migrants to North America and Australasia. Even though the strength of the association weakens through southern Europe and the Mediterranean, there is a relationship between one or other of these antigens and multiple sclerosis in some unexpected populations including Greeks, Mediterranean Arabs, Iranians, coloured South Africans and black Americans. Allowing for some genetic admixture within these populations, the observations are broadly consistent with the interpretation that genes conferring susceptibility are over-represented in northern Europeans and that this accounts for the disproportionately high prevalence of multiple sclerosis in Europe and areas populated by northern Europeans [31].

But difficulties arise with this simple hypothesis. There is no association with HLA A3, B7 or DR2 in the Orkney islands, not because these antigens are any less frequent in Orcadian patients than in affected individuals elsewhere but because DR2 has a very high normal frequency in north-east Scotland and the offshore islands [32,33]. In fact, provisional estimates indicate that the distribution of multiple sclerosis in the United Kingdom correlates well with variations in the normal frequency of HLA DR2 [12]. However, DR2 cannot itself be the main genetic determinant of susceptibility; whilst it is a marker of susceptibility in the northern European population, the same phenotype is common in the indigenous people of North America, Zulus and Xhosas, and gypsies—populations that are racially protected from this disease. In some populations, multiple sclerosis does not show any HLA association or is linked to antigens other than DR2; thus in Sardinian patients, where the disease is more prevalent than in many neighbouring parts of the Mediterranean [34], and in Jordanian Arabs there is an association with DR4 [35], and no very clear pattern emerges from studies of Indians, Jewish people and Orientals irrespective of their geographical location [30].

Investigators have therefore turned to the more recently defined HLA antigens to look for a unifying hypothesis with respect to class 2 phenotypes and multiple sclerosis. In contrast to the distribution of DR2 in patients with multiple sclerosis and controls in north-east Scotland, there is a weak association with DQw1, defined serologically, suggesting that this may be a closer marker of susceptibility than DR2 [33]. Conversely, there is a stronger association between multiple sclerosis and DR2 than DQw1 in south-east Wales, New Zealand and Mediterranean Arabs [36–38], and DQw1 occurs commonly in races, eg Maoris, who do not develop multiple sclerosis. Further evidence that DQw1 is also not the elusive multiple sclerosis susceptibility gene is provided by the Sardinian study in which an association with DQw3 was observed [34].

Molecular genetics

Attention has therefore turned to molecular analysis in the expectation that a genotypic association would be identified to account for the different associations seen between and within populations. Despite using a variety of restriction enzymes and many cDNA probes hybridising with sections of the DR and DQ chains, the pattern emerges of restriction fragment length polymorphisms that are no more closely associated with susceptibility to multiple sclerosis than the class 2 phenotypes. The most recent study from Scotland has again not shown an association with DR2, but a weak association emerges with DQw1 [39]; enzyme digestion with Msp 1 identified one DQ alpha gene fragment from amongst several that are common in the normal population and which distinguished patients with multiple sclerosis from controls. This fragment occurred rarely in the presence of DR2 but was associated with DRw8 and DR7; indeed it may be allelic to DQw1, which is associated with multiple sclerosis in Scotland, raising the possibility that this DQ alpha fragment may be inherited on the other haplotype from DR2/DQw1, thus representing a second susceptibility gene for multiple sclerosis.

The associations with HLA alleles and the role played by these gene products in regulating the immune response suggests other polymorphic genes as candidates for susceptibility to multiple sclerosis. The molecules required for the development of immune response to processed antigen include class 2 histocompatibility gene products, the accessory molecules CD4 or CD8, and the T cell receptor which binds antigen only when the arrangement of accessory and class 2 molecules is appropriate. Although the presence of a particular T cell gene rearrangement independently increases the risk of developing multiple sclerosis [40,41], the products of the T cell receptor genes seem to interact with those encoded by the histocompatibility complex to confer a risk for multiple sclerosis that approaches the degree of heritability implied by classical genetics. It may be that, in addition to the histocompatibility and T cell receptor gene products, only a few other genes need to be identified in order to account for the genetic basis of susceptibility to multiple sclerosis.

The emergence of more than one genetic association in populations where prevalence is high and susceptibility factors conferring an increased biological risk are over-represented in the normal population is a prediction of the polygenic hypothesis of inheritance. Under this model, genetic and environmental risk factors are presumed to make differing contributions to the development of disease and not to be evenly distributed within the population at risk. If one factor is biologically important and common, prevalence of the disease will be relatively high since the chance of all the remaining events also occurring is correspondingly increased. However, since this risk factor is present in such a high proportion of the at-risk population, it may have a surprisingly weak association with the disease, and in these circumstances other factors which make a relatively small contribution to overall susceptibility may seemingly show stronger disease associations. Conversely, where all risk factors are infrequent, those that make the greatest contribution to susceptibility are most obviously associated with the disease, and more detailed studies will be needed to demonstrate the subsidiary risk factors. Thus, the multiple associations with genes and gene products, encoded within and outside the major histocompatibility complex and varying amongst populations and geographical regions, provide evidence in support of the polygenic hypothesis.

Place

When the movements of northern Europeans migrating west to east are traced, and notwithstanding the very considerable role that genetic factors must play in determining the geographic distribution of multiple sclerosis, it is necessary to conclude that environmental influences are also involved.

First, populations and susceptibility genes were for the most part distributed long before multiple sclerosis was first recognised. Second, with the exception of Canada, parts of the world that have been colonised from northern Europe show prevalence rates that are lower than those seen in the country of origin. The recent comprehensive study from Australia, in which four regions were surveyed simultaneously using comparable methods and working to a common prevalence date [42], showed this to be true for the white Australian population where a geographical gradient exists that cannot be explained on a genetic basis. It would be uncharitable to suggest that the factors determining migration to the penal colonies of New South Wales in the last century favoured a higher density of Celts than the free settled parts of Australia such as Tasmania, but differences in the prevalence of multiple sclerosis in New Zealand have been correlated with the higher density of Scottish descendants in the south of the South Island [43]. However, the main drop in prevalence seems to occur within the North Island where no demographic differences of this kind exist [44]. Nevertheless, the native aborigines of Australia and the Polynesian Maoris in New Zealand very rarely seem to develop multiple sclerosis.

The third point relates to the development of multiple sclerosis in populations migrating between risk zones and the consequences for their offspring. The South African studies carried out in the 1950s and the observations made in Israel and Hawaii at about the same time, showing that the risk of developing multiple sclerosis is modified in an ethnic group by place of residence in early life, are well known. In 1984 the prevalence of multiple sclerosis in Cape Town remained high in white immigrants ($58/10^5$) and was significantly lower in South African born English ($14/10^5$), Afrikaaners ($11/10^5$) and pigmented peoples ($3/10^5$), emphasising the complex interplay of race and place in determining susceptibility (B. Kies,

personal communication). Isolated reports are now appearing of multiple sclerosis developing in African blacks [45]. Because of the interest in multiple sclerosis occurring amongst Africans, vigilance has always been high and these cases may be heralding a real change in incidence in an intrinsically resistant group. More interesting is the updated prevalence for the first generation offspring of West Indian immigrants to the United Kingdom which suggests that, allowing for some unresolved diagnostic uncertainties, these descendants of African blacks, whose parents retained a low prevalence for the disease over several generations in the West Indies, have experienced a marked increase in risk through being brought up in Greater London or the West Midlands [46]; the implication is that the racial protection afforded by being black is to some extent an artefact of environment and not the result of genetic resistance.

Finally, a few epidemics of multiple sclerosis also seem to have occurred, mostly on small islands in the North Atlantic. In Iceland there has been the expected steady rise in incidence of multiple sclerosis during the 20th century, but particularly soon after the Second World War during which the peak age of incidence fell; there is some suggestion that thereafter both incidence and prevalence have fallen and age of onset has risen to the pre-war range, features that suggest a point source epidemic [21]. The most closely argued case for an epidemic of multiple sclerosis relates to the Faroe islands with a population of 30,000, where Kurtzke, working with local physicians and neurologists, concluded that symptoms due to multiple sclerosis began between the years 1943 and 1949 in 16 individuals who had never left the islands, and in a further 14 by 1973, whereas no cases were recorded before or since these dates [20]. An epidemic has been claimed for Key West, a tropical island off the coast of Florida, where 37 patients with peak onset in and around 1977–9 were identified in (1984 prevalence $140/10^5$)—an increase that could not be attributed to alterations in clinical vigilance or differential migration of symptomatic individuals to a favourable climate [47]. Conversely, in the Orkney islands, where multiple sclerosis has been scrutinised closely over many years, there has been a steady fall in annual incidence rates, a reduction in the prevalence and a shift towards a slightly older patient population since 1985 [23]. The status of these epidemics remains uncertain, and some take the view that they are artefactual, arising from sudden increases in case ascertainment.

Dissemination within families

Following the original 19th century reports of familial multiple sclerosis, cases were sporadically reported in the literature and 188 examples had been described in 85 families by 1950 [48]. Subsequent experience indicates that two individuals, generally siblings, are usually affected and larger pedigrees rarely occur; perhaps the best way of describing the risk—and one that can be applied to counselling in the clinical setting—is to assess the recurrence in individual categories of relatives rather than the overall prevalence of multiplex families (about 15%) since this allows for variations in family structure. A large population-based survey from British Columbia has shown that age-adjusted recurrence varies with gender in relatives and affected individuals, but is higher for siblings (4%) than for parents (3%) or children (2.5%) and second-degree relatives [49].

The fact that every category of relative has a recurrence risk of well under 10% more or less excludes the possibility that susceptibility arises from the effect of a single gene, whatever its mode of inheritance. Any other interpretation would require invoking a very considerable reduction in penetrance. However, the consistently higher risk of recurrence in siblings than in other relatives favours a recessive mode of inheritance for all or some of the susceptibility genes. Those who favour the view that the major aetiological factor in the development of multiple sclerosis is environmental legitimately point out that a shared environment could account for the slight increase in cases amongst siblings.

Studies of twins have been helpful in resolving the merits and demerits of the genetic case for explaining the occurrence of familial multiple sclerosis. Between 1951 and 1986, eight or more twin studies were carried out in high prevalence regions; they varied in design and not all investigators managed to avoid bias in the selection of participants. Of 195 monozygotic pairs, 23% were concordant compared with 11% of 280 dizygotic twins of which one in each pair was already known to have multiple sclerosis [31]. Undoubtedly the most careful of these studies was the Canadian survey reported in 1986 [50]: 27 monozygotic and 43 dizygotic pairs were identified from 5,463 patients attending 10 multiple sclerosis clinics, thus approximating to a population based study. The concordance rates were 26% and 2.3% respectively, compared with a rate of 1.9% in 4,582 siblings identified from two of these centres. These rates are based on clinical expression of the disease and do not take into account the extra information available from cerebrospinal fluid analysis or magnetic resonance imaging. Therefore, although there is a clear difference in concordance between the monozygotic and dizygotic pairs, even allowing for problems with ascertainment bias, the absolute differences in concordance rate and confirmation that there is a difference between the rates for dizygotic twins and all other siblings have yet to be settled.

The conclusion that race and place operate together in determining local risks for multiple sclerosis has an instructive analogy in the observation that the environment in which animals are reared radically affects the extent to which hyperglycaemia develops in inbred strains of 'non-obese diabetic' mice [51]. Some populations are protected from multiple sclerosis more or less wherever they reside but, for example, the relative protection of Africans is lost as they move into North America and northern Europe (perhaps in part owing to admixture of Caucasian genes), whereas the suscep-

tibility of northern Europeans is modified by environmental exposure in the southern Hemisphere.

Dissemination in the individual

Disability

Issues relating to the anatomical dissemination of lesions in multiple sclerosis are of considerable importance to the individual, since it is in this respect that the hopes and fears of each patient hang in the balance. Although physiologists have elegantly demonstrated the range of deficits that may arise from damage to myelinated axons within the central nervous system, disability seems to depend as much on the random but strategic placement of lesions as the dynamics of the disease process. The symptoms and signs of multiple sclerosis are in general those to be expected from any disorder in which the same parts of the nervous system are affected. Clinico-pathological correlations reveal a hierarchy in which the commonest event is damage to the blood brain barrier; a proportion of the vascular lesions result in injury to myelin or the oligodendrocyte; some of these patches may then undergo irreparable damage; although involvement of some parts of the central nervous system may not give rise to physical symptoms and signs, an alternative explanation for clinically silent disease is that many areas of focal damage represent patches of myelin injury which do not progress to demyelination.

The distribution of multiple sclerosis is skewed towards the economically most active members of the community; in all groups, the impact of bladder dysfunction, impotence, visual loss, cognitive decline and distracting sensory symptoms will vary with age, personality, occupation and social role, whereas disturbances of movement are more or less uniformly restrictive. Disability is therefore usually determined by dissemination of lesions that affect motor pathways and the clinical course that these follow. Weakness, ataxia and fatigue are amongst the most prevalent symptoms, and patients rank them higher in terms of duration and subjective persistence than other complaints; these are the burdens carried by a high proportion of patients who suffer from multiple sclerosis. Thus, almost half of a prevalent population requires help with walking and in three-quarters the gait is visibly abnormal. About 50% of patients are in a progressive phase of the disease at any one time, and most of them are aware of steady deterioration [52]. Despite these seemingly gloomy statistics, it is appropriate to remember Allison's clinical observation [9] that the clinical impact of multiple sclerosis can be mild in perhaps a quarter of cases. Some features can be identified which predict these clinical courses but they have limited value in counselling the individual. Mild forms of the disease are characterised by young onset in females with relapsing sensory or visual symptoms and complete recovery; conversely, later age of onset, usually in males with progressive spinal disease, carries a predictably poor outlook.

The blood brain barrier

The process induced by the interaction of susceptibility genes and their environmental triggers starts with inflammation. The Scottish pathologist James Dawson emphasised in 1916 that perivascular inflammation characterises the developing lesion [53]. In a series of spectacular images, the NMR group at Queen Square has demonstrated the dynamics of this process in life [54] through the use of gadolinium enhanced serial scans, showing that vascular permeability precedes parenchymal damage by several days or weeks. It has been known since the publication of Joseph Babinski's thesis in 1885 that macrophages are ultimately responsible for making contact with the myelin sheath and stripping it from the otherwise intact axons that traverse central white matter [55]. The first problem that has to be understood therefore is the nature of damage to the barrier that protects the central nervous system from immunologically active cells and macromolecules normally contained within the cerebral vasculature. The blood brain barrier is made up of endothelial cells surrounded by a basement membrane associated with pericytes; the abluminal surface is covered with a network formed from the foot processes of type 1 astrocytes which induce the endothelial cells to form tight junctions. Together this anatomical structure achieves the complex function of excluding large molecules from the circulation whilst remaining permeable to water and lipid. Specific mechanisms exist for transporting some essential nutrients and metabolically active substances across cerebral vessels. Regional variation in structure partly accounts for selective permeability but this depends more on a variety of physiological mechanisms acting in health and disease, including macromolecular vesicular transport and endocytosis.

Enumerating lymphocytes in the blood and cerebrospinal fluid and documenting their function has been used extensively as a means for understanding the immune basis of multiple sclerosis. Allowing for variations in technique, choice of reagents and expression of results, the evidence suggests that circulating CD8 cells are reduced in number, especially in patients with chronic progressive disease [56]. An alternative approach has been to study the function of lymphocyte populations without reference to their surface phenotype. Spontaneous, pokeweed mitogen and sequential concanavalin A and pokeweed stimulated IgG synthesis are significantly increased in patients with progressive multiple sclerosis compared with controls; although both findings imply a defect of suppressor activity, the functional studies correlate poorly with CD8 phenotype in the individual [57]. Nevertheless, it is an attractive hypothesis that a defect in suppressor function lowers the threshold for T cell activation, since activated T cells are selectively able to penetrate the blood brain barrier and alter immunological equilibrium within the central nervous system [58].

The passage of immune mediators also seems to take place by increased vesicular transport and partial

relaxation of endothelial tight junctions. This has led to the idea that endothelial damage is all that is required for the development of demyelination, especially since clinical signs can be induced in otherwise intact experimental animals merely by increasing T cell mediated permeability of the blood brain barrier [59]. However, animals made macrophage deficient or depleted of complement by pretreatment with cobra venom factor, which induces uncontrolled activation of C3, are resistant to the induction of experimental allergic encephalitis [60] despite the presence of blood brain barrier damage and T cell infiltration of the nervous system.

Once activated lymphocytes have disrupted the blood brain barrier, their contribution, albeit crucial, may be complete but they deliver to the abluminal surface of the cerebral vessels an assortment of potentially lethal cellular and soluble mediators. The next problem is therefore to understand which of these is responsible for damaging myelinated axons.

Mechanisms of myelin injury

Oligodendrocytes synthesise the myelin sheath that enfolds short sections of neighbouring axons within the central nervous system. The otherwise bare axonal segment found between the territory of each oligodendrocyte—the node of Ranvier—is covered by the foot processes of type 2 astrocytes. Type 2 astrocytes and oligodendrocytes are derived from a common precursor cell, the O-2A progenitor [61]. Techniques for studying oligodendrocyte development *in vitro* have shown that, in comparison with other glial types, this cell is uniquely sensitive to immunological attack but has remarkable powers of recovery.

Within a few minutes of exposing cultured oligodendrocytes to normal serum, mimicking what might happen after breakdown of the blood brain barrier *in vivo*, the cells lose their processes, the membrane leaks, the cell contents become osmotically disrupted and the oligodendrocyte is lysed [62]. This sensitivity to normal serum is not seen using type 2 astrocytes or the O-2A progenitor, and the range of insensitive cells has now been extended to include most other cellular components of the central and peripheral nervous systems [63,64]. The oligodendrocyte—essential for the synthesis and maintenance of myelin—is uniquely vulnerable to contact with normal serum.

Complement activation

The factor in serum responsible for this cytotoxicity is complement, activation occurring through the classical pathway and in the absence of antibody [65]. Normally, the classical pathway is activated only when antibody becomes membrane-bound, and this leads to fixation of C1, after which sequential activation of the complement cascade occurs with the formation of short-lived activation products that are chemotactic and activate macrophages, and of membrane attack complexes which insert themselves into the cell membrane and initially act as a calcium ionophore [66]. Oligodendrocyte lysis *in vitro* depends on the formation of membrane attack complexes and can occur in the absence of macrophages.

The evidence that complement activation is responsible for oligodendrocyte toxicity includes the demonstration that serum obtained from animals depleted of complement by treatment with cobra venom factor is inactive, as is serum specifically depleted of C1 or C9; reconstituting both restores its toxicity. Treatment with EGTA and absorption with myelin indicates that complement activation occurs through the classical pathway and in the absence of anti-myelin antibodies. The final evidence is provided by the demonstration of galactocerebroside positive cells, ie oligodendrocytes, densely stained for C9 after incubation with autologous serum [62].

Intracellular calcium

Using a chemiluminescent method in which light is emitted by contact between calcium and the photoprotein obelin (preloaded into oligodendrocytes by temperature sensitive liposomes), the addition of C9 results in an uncontrolled rise in calcium, derived mainly from extracellular sources but with some release from intracellular stores [65[. Cell lysis occurs, unless the availability of complement is reduced by dilution, whereupon intracellular calcium returns to normal and the cell remains intact. This calcium transient is associated with a remarkable change in the appearance of the oligodendrocyte seen under scanning electron microscopy. For a short while the cell retains its usual smooth configuration but, as intracellular calcium increases, the surface shows multiple vesicular extrusions on which membrane attack complexes are concentrated and which subsequently are shed. These vesicles contain a high density of these complexes, demonstrable both by transmission electron microscopy and immunological methods, and contain oligodendrocyte surface antigens [67]. Following recovery, the cell is morphologically intact and able to continue synthesising structural components appropriate for its stage of development. What the oligodendrocyte has achieved in response to intracellular signals is vesicular repair of its membrane (Fig. 2a,b), but the capacity for recovery is limited and the cell is unable to withstand repeated cycles of exposure to sub-lethal concentrations of complement.

The ability to injure the surface membrane of oligodendrocytes and induce the vesicular repair mechanisms is not unique to the membrane attack complex of complement. Other biologically active molecules act by forming ring lesions on the cell surface; both perforins, which are functionally and structurally related to the membrane attack complex of complement, and the ionophore A23817 increase intracellular calcium and, under appropriate conditions, can induce the vesicular repair mechanism (Fig. 2c,d [68]; also unpublished observations). W7, which inhibits calcium dependent activation of protein kinase mediated

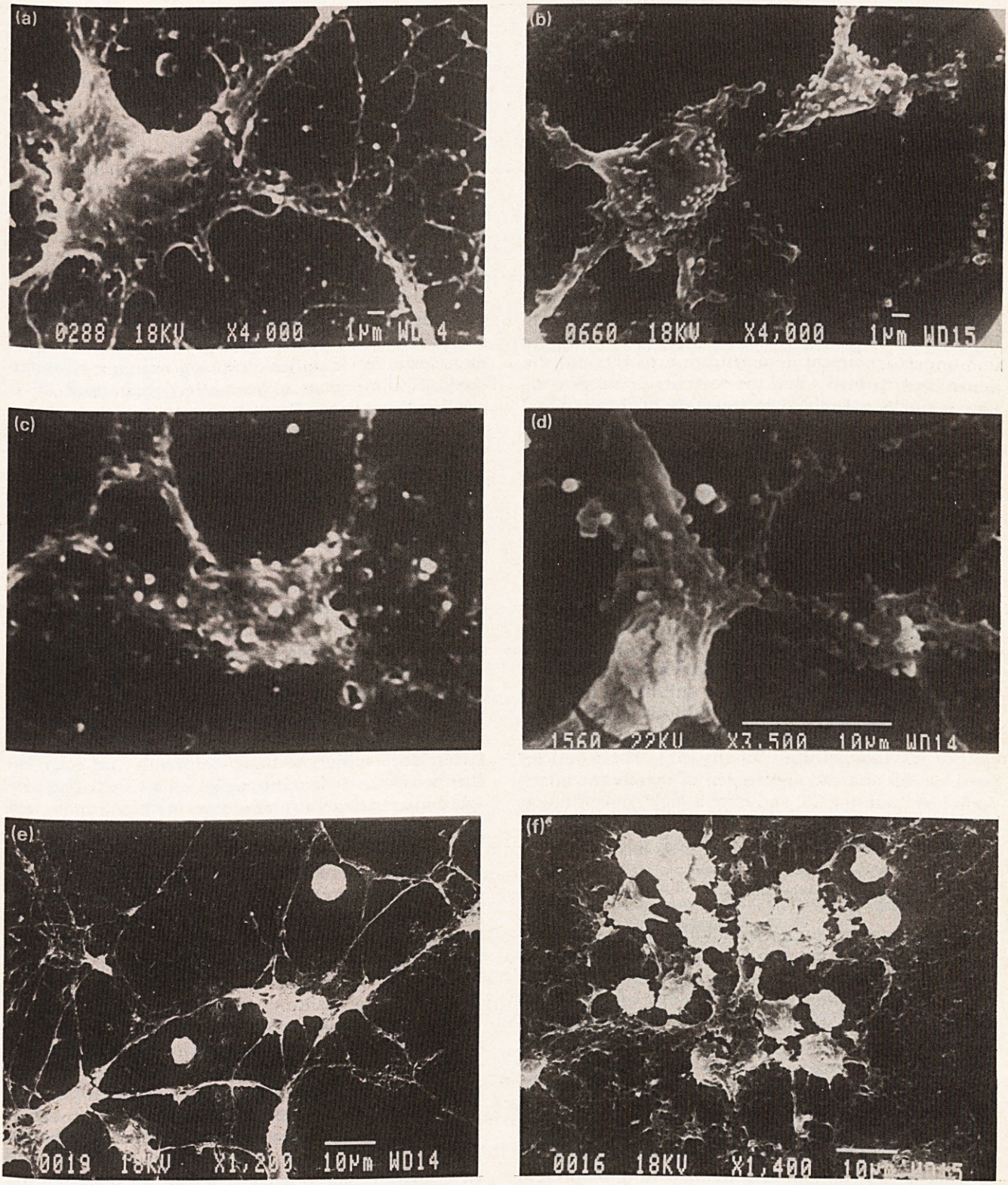

Fig. 2. *Cultured neonatal rat optic nerve oligodendrocytes shown under scanning electron microscopy (x4000).* Normal oligodendrocytes (a) are shown undergoing vesicular repair 6 minutes after exposure to sublytic concentrations of autologous serum as a source of complement (b). Oligodendrocytes and their membrane vesicles are shown after exposure to A23187 (c) and T cell derived perforins (d). An oligodendrocyte is shown in the presence of autologous peritoneal macrophages incubated with normal serum (e) and after the addition of sublytic concentrations of anti-myelin oligodendrocyte antibody (f).

by the intracellular protein calmodulin, allows concentrations of serum that would not normally be cytotoxic for oligodendrocytes to become lytic (unpublished observations). The final common pathway of oligodendrocyte damage may therefore depend upon whether or not the cell can limit the rise in intracellular calcium induced by pore-forming immunological molecules on its surface, and so achieve vesicular repair.

Occasional oligodendrocytes in areas of acute demyelination show the ultrastructural features of osmotic shock—a fragmented membrane and intracellular oedema—and the chronic lesion is usually characterised by profound oligodendrocyte depletion [69]. The contribution to the pathogenesis of multiple sclerosis made by complement mediated oligodendrocyte injury can be more directly inferred from the immunocytochemical demonstration of C9, and the neoantigen formed when the membrane attack complex is finally assembled by insertion of the terminal component, in the adventitia surrounding endothelial cells which line small blood vessels in plaques, irrespective of their histological age [70]. There is a significant reduction in the concentration of C9 [71], and the C5b–9 neoantigen is present in increased amounts [72], implying complement activation and consumption which correlates inversely with increased IgG synthesis. The most compelling evidence that intrathecal complement activation in patients with multiple sclerosis involves the formation of membrane attack complexes is provided by the presence of vesicles identical to those recovered from the supernatant of cells exposed to complement in tissue culture, in the cerebrospinal fluid of patients with multiple sclerosis but not that from those with mechanical nerve root irritation or intracranial mass lesions [67]. These vesicles bind C8, C9 and the neoantigen of membrane attack complexes but not C3, and have a high concentration of membrane pores; galactocerebroside but not myelin basic protein is present on their surface.

Role of antibody and macrophages

The inflammatory lesions of multiple sclerosis consist not only of T cells but also B lymphocytes and plasma cells which synthesise the immunoglobulin which can be detected immunocytochemically and by electrophoresis in the spinal fluid of most patients. Experimentally, it is now clear that the well established T cell mediated model of acute inflammatory encephalomyelitis, in which there is only scant loss of myelin, can be modified to produce widespread demyelination by synergistic use of myelin basic protein sensitised T cells and a monoclonal antibody directed against myelin oligodendrocyte glycoprotein [73]. In this model, demyelination seems to depend on complement activation occurring at the surface of oligodendrocytes and from non-specific phagocytosis by macrophages attracted by their receptors for the Fc portion of antibody. Incubating oligodendrocytes with serum as a source of complement and sublytic concentrations of antibody directed against several structural components of the oligodendrocyte cell surface enhances the rise in intracellular calcium seen with complement activation alone and brings this close to the threshold for cell lysis. The rise in intracellular calcium is higher using anti-myelin oligodendrocyte glycoprotein than with other myelin antibodies. This is of particular importance since myelin oligodendrocyte glycoprotein is orientated on the external surface of the oligodendrocyte cell body and its myelin sheath, whereas other antigens, such as myelin basic protein, are internalised and so not immediately available for interaction with components of the immune system. In fact, the density of myelin oligodendrocyte glycoprotein increases on the surface of developing oligodendrocytes at the same time as sensitivity to homologous serum reaches its peak [74]. Therefore, whilst complement activation is sufficient *in vitro* to injure myelinating cells, there is an additive effect when antibody is also locally available. Furthermore, even if the changes in membrane permeability are not sufficient to cause cell lysis, and despite the stimulation of vesicular repair, the rise in intracellular calcium may have physiological consequences for the oligodendrocyte and stimulate calcium activated proteases which split lamellae and disrupt the myelin sheath.

Although complement mediated injury could satisfactorily account for the injury and recovery of the oligodendrocyte and its associated myelin membrane *in vivo,* and so might underlie the appearance and resolution of new clinical symptoms, it leaves unexplained the morphological evidence that macrophages are responsible for stripping and phagocytosing the myelin sheath. During development, macrophages circulating in the cerebral vasculature enter the nervous system in response to neuronal death and establish themselves as resident microglial cells. Circulating activated macrophages can also cross the blood brain barrier and so contribute to local inflammatory processes. The implication is that the mature central nervous system contains large numbers of phagocytic cells which can secrete and respond to a wide range of inflammatory mediators, several of which—including complement and tumour necrosis factor—can directly damage myelin *in vitro,* and through oligodendrocyte injury [75]. In patients with multiple sclerosis, antibody can be demonstrated on the surface of macrophages found within plaques, and the lamellae are removed by a process that involves their attachment to coated pits after which the sheets are incorporated into macrophages as elongated vesicles [69]; the presence of coated pits indicates that this process is receptor mediated. Opsonisation of target cells by sublytic concentrations of antibody is required *in vitro* to demonstrate macrophage ingestion of oligodendrocytes (Fig. 2e,f; unpublished observations). It is perhaps relevant that any one of several antibodies will achieve both the enhanced calcium response [65] and the macrophage mediated damage of oligodendrocytes studied in tissue culture. This may give a clue to why the search for a single antigenic determinant

amongst the oligoclonal bands has been fruitless; no one antigen may be critical since several antibodies have the same effect of enhancing the intracellular consequences of complement activation and attracting macrophages on to the oligodendrocyte cell surface.

A synthesis

The hypothesis to emerge from a consideration of the human and experimental studies is that, in genetically susceptible individuals, activated T cells and macrophages, responding to environmental triggers, increase their normal surveillance of the nervous system and interact with type 1 astrocytes, further disrupting the blood brain barrier and causing a leak of immune mediators into the nervous system. Oligodendrocytes are unduly sensitive to contact with complement and other pore forming molecules, especially when antibody directed against surface components of the oligodendrocyte or its myelin processes also is present. The interaction of these soluble mediators increases membrane permeability and leads to a rise in intracellular calcium, the degree and duration of which determine whether or not reversible injury ensues. As complement activation proceeds, and if antibody also is present, macrophages are recruited and contribute to cell injury by releasing cytokines and phagocytosing the myelin lamellae. Multiple sclerosis can be regarded as a low grade vasculitis mediated by activated lymphocytes with secondary demyelination resulting from the presence of macrophages and local antibody synthesis, and brought into play by the suicidal tendency of oligodendrocytes to activate complement.

Investigators now need to tackle several problems: the nature of the process that activates T cells and induces them to express the adhesion molecules that facilitate their migration into the central nervous system; the identification of the cell surface molecules expressed on the oligodendrocyte which allow it to activate complement in the context of a leaky blood brain barrier; the identification of genes that result in a high concordance for multiple sclerosis in identical twins; and the environmental triggers that modify the expression of these susceptibility genes. Only then will this difficult disease be solved.

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