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The mystery of the origin of multiple sclerosis

WI McDONALD

From the Institute of Neurology, The National Hospital for Nervous Diseases, London

SUMMARY Our present understanding of the aetiology and pathogenesis of multiple sclerosis is discussed in relation to the views of Sir William Gowers. He perceived that both environmental and genetic factors might be implicated in the aetiology of the disease. Evidence for the former was first reported in 1903, but has become convincing only in the past 20 years; the nature of the environmental factor remains obscure. Evidence for a genetic influence on susceptibility has accumulated since the 1930s, the most compelling coming from the recent Canadian twin study. The number and mode of operation of the genetic factors is still uncertain, but there is evidence for the implication of genetically controlled cellular immune mechanisms in the pathogenesis of the disease. The precise relationship between transient changes in immunological status and the development of new lesions has yet to be defined; magnetic resonance imaging (MRI) promises to play a significant role in this analysis because of its sensitivity in detecting abnormalities in multiple sclerosis. MRI is not in itself specific; it is probable that the similar appearances in multiple sclerosis and cerebral vascular disease both derive at least in part from the influence of astrocytic gliosis on proton content and distribution. The significance of the gliosis is uncertain. Gowers believed that the primary defect in multiple sclerosis lay in the astrocyte. Recent observations on the immunological functions of this cell *in vitro* suggest that it could be involved early in the pathogenesis of the lesion.

The title of this review is a quotation from the second edition of Gowers' *Manual of Diseases of the Nervous System* published in 1893.[1] It is as apt a beginning today for a discussion of the cause and the nature of multiple sclerosis as it was then. What strikes the modern reader of the *Manual* is the precision of Gowers' observations, the elegance of the language in which he describes them, and his range. He encompassed not only clinical description and the pathology of the nervous system, but much more in medicine besides. His haemocytometer was in use until our own day and his *Manual and Atlas of Ophthalmoscopy*[2] established the role of the ophthalmoscope not only in neurology but in general medicine as well: there one reads descriptions of the retinopathies of uraemia, diabetes and leukaemia, of retinal tubercles and of what we would now recognise as acute ischaemic optic neuropathy following haemorrhage.

Gowers was a great teacher. Through his writings his influence spread far beyond those who were fortunate enough to work for him at University College Hospital and Queen Square. Weir Mitchell[3] touchingly acknowledged his indebtedness on the occasion of Gowers' knighthood at the diamond jubilee of Queen Victoria: "... Your book on nervous disease stands for us all as the best of the many great text books—It has been the rich mine from which the material for many treatises has been taken—It is the book to which I turn first when my own knowledge fails—...". Gowers' didactic tendency was pervasive and when he saw an opportunity to dispel confusion in other disciplines he took it. A good example was his concern about the difficulty of notating accurately the range over which hearing loss occurs in disease, occasioned by the muddled translation of one of his works into German. He noted the confusion in the musical literature as well and devised a rational system which he promoted in both the musical[4] and the medical press,[5] regrettably without success.

One of the topics within neurology which interested Gowers was multiple sclerosis.[6] In this review of its aetiology and pathogenesis I propose to explore the relationship between our understanding of the disease and his.

Based on the Ninth Gowers Memorial Lecture. Gowers used the term "insular" instead of "multiple" sclerosis but I have preferred to use the modern term throughout.

Address for reprint requests: Professor WI McDonald, The National Hospital for Nervous Diseases, Queen Sq, London WC1N 3BG, UK

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Aetiology

There is now abundant evidence that there are two classes of factor involved: environmental and genetic.

Environmental factors

Gower's own comments were restricted to the personal environment of the individual patient. He noted that "among the influences to which it has been immediately ascribed, the most frequent are exposure to cold....".[1] He made no comment on the geographical distribution of the disease, the first such observation coming from Byron Bramwell,[7] father of one of his former pupils, in the same volume of the *Review of Neurology and Psychiatry* which contained the medical version of Gowers' paper on musical notation.

Bramwell reviewed his own experience in private and hospital practice in Edinburgh and compared it with the recently published experience of a group of neurologists in New York. One in 58 of Bramwell's patients had multiple sclerosis compared with one in 219 of the pooled American cases. Bramwell was aware of the possible sources of error in comparisons of this kind, but concluded that the difference in frequency between the two places was real.

The next report of a possible geographical difference came from within the United States. In 1922 Davenport[8] noted that multiple sclerosis was more common as a defect of drafted men from the northern States than the southern. A new attempt to define the influence of location on risk was made[9] in 1950 when mortality data again showed a higher risk in northern than southern states.[9] This trend was soon confirmed by careful prevalence studies.[10] Unexpectedly low frequency of multiple sclerosis was also found in South Africa.[11] There was now an explosion of epidemiological studies. They led to the general conclusion that for northern European Caucasoid populations, the risk of developing multiple sclerosis increases as one goes further from the Equator in both the northern and the southern hemispheres: multiple sclerosis is more common in Scotland (where it approaches 200 per 100,000)[12-14] than in the south of England[15] and in the South Island than in the North of New Zealand.[16] As one might expect there are some variations in the relationship between latitude and reported prevalence.[17,18] Some may be due to the study in small populations of what is, after all, a rather uncommon disease; and the quality of investigations varies. However, as will become clear, some of the variations are undoubtedly real and important for our understanding of the aetiology of the disease.

A new discovery was made in the 1970s: that there are variations in risk associated with migration. In Caucasoid populations, migration between northern Europe and South Africa,[19] and in the USA, between northern states and southern,[20-22] is associated with a reduction in risk provided the move takes place in childhood. The number of patients involved in these investigations is however rather small, and as Dr ED Acheson (personal communication) has pointed out "in the study of multiple sclerosis the epidemiological method as employed up to the present has been operating at the limits of its power." Nevertheless the consistency of the observations suggests that there is something in them. The evidence that the risk of developing multiple sclerosis depends upon where an individual spends his first 15 years or so suggests that there is an environmental factor involved in the causation of multiple sclerosis.

Poskanzer *et al*[23] noted the similarity between the prevalence pattern of multiple sclerosis and that of poliomyelitis, and suggested that the environmental factor was infective. Some impetus has been given to this interpretation by the observation of clusters of cases in restricted regions. Such clusters have been recognised for many years but interpreting their significance has been difficult because clustering can occur as a statistical effect, without biological significance. A remarkable example has been reported recently from the Faroe Islands.[24] Between 1943 and 1960, 24 cases appeared and there has been only one further case since. Such clustering of cases in space and time strongly suggests that an environmental factor was operating. It was argued that it was infective, and possibly related to the advent of the British Army just before the "epidemic" began.

Two consequences of the infective hypothesis can be tested epidemiologically. The first is that *adult* migrants from a high risk area should have an even higher risk of developing multiple sclerosis after migrating to a low risk area if, as Poskanzer *et al*[23] suggested, the infectious agent is more common in the latter. Neither of two American studies provided evidence that this is so.[25,26] The second is that young migrants from a low to a high prevalence area should have an increased risk of developing the disease. There is some evidence that this may be so in Afro-Asian migrants to Israel,[27] and three cases of multiple sclerosis have been found amongst 3451 half-Vietnamese migrants to Paris, corresponding with an unexpectedly high crude prevalence rate of 89 per 100,000.[28] The total numbers in these investigations are even smaller than in the others just mentioned, and at this stage one cannot say more than that the results are consistent with the hypothesis of an infective origin for the disease. More data are needed.

In summary, the balance of evidence suggests that there is an environmental factor in the cause of multiple sclerosis. The working hypothesis is that it is infective but the epidemiological evidence is not conclusive. Neither is there direct confirmation of infection.

The question has been reviewed elsewhere.[29] Suffice it to say that a disease resembling multiple sclerosis has not been transferred from man to animals, that the same virus has not been isolated from different cases in different centres, and that the raised titre of antibodies against measles found in groups of patients with multiple sclerosis is not specific either to measles or to multiple sclerosis. Finally, the virus-like particles sometimes reported in multiple sclerosis brain can, with one possible exception, be accounted for in other ways.[30]

Genetic factors

In my account of the epidemiology of multiple sclerosis I have so far ignored an important point: for some races the risk of developing the disease is low and little influenced by latitude. Multiple sclerosis is rare or absent in the Bantu and appears to be rare in the Eskimo[17] and the Hungarian gypsy.[31] The gypsies are racially distinct from the Caucasoids in Hungary, having migrated from north India to the Balkans in the second century and then to the rest of Europe about 500 years ago.[32] In the Caucasoids the prevalence of multiple sclerosis is 37 per 100,000 whereas in the gypsies only two cases have been identified in all the neurological departments of the five Transdanubian counties serving a population of 110,000 gypsies.[31] Since the Hungarian figures are based on hospital statistics it will be important to determine whether the difference is confirmed by mortality and prevalence data based on systematic case ascertainment.

The best studied non-Caucasoid population is the Japanese. All investigations have shown that the prevalence is much lower than in Caucasoids living at comparable latitudes.[33] The prevalence in Sapporo (43° north) for example is 2:100,000 and in Boston, USA (42° north) is 41 per 100,000.[15]

A particularly interesting study has been carried out on the west coast of the United States.[34] The prevalence in Los Angeles in Caucasoids is 21·6 per 100,000; it rises to 68·7 in Washington State. In the Japanese it is only about 6 per 100,000 in both regions. A low risk (based on mortality data) is also seen in the Chinese[25] but what makes the Japanese data especially interesting is that unlike the Chinese, they have little tendency to remain in fairly closed ethnic groups in these regions, that is they more nearly share the environment of the Europeans amongst whom the risk is so much higher.[34] The evidence suggests that there is a protective genetic influence in orientals.

Gowers[1] considered the genetic component in the aetiology of multiple sclerosis in the *Manual*[1]: "direct heredity.... is quite exceptional; indirect inheritance is more common, shown by a family history of insanity, epilepsy, or some form of chronic paralysis". He does not enlarge on the nature of "indirect inheritance" but the context suggests that he believed that there exists some general kind of genetic predisposition to neurological disease. In 1908 he was one of the opening speakers at a symposium held at the Royal Society of Medicine on heredity in disease, but he did not develop his views either on the nature of indirect inheritance or on the genetic factor in the aetiology of multiple sclerosis. Indeed, he commented that multiple sclerosis is "another affection in which heredity might be expected, according to one view of its nature, but no facts have suggested it".[35] Though excited by the scientific study of heredity, he thought that at that time the study of genetics in human disease was "still at the stage of random observation".[35]

And thus it remained in relation to multiple sclerosis until the 1930s when Curtius[36] made a good case for a significant familial incidence of the disease. Pratt *et al*[37] reviewed in 1951 the world literature and added further cases of their own, recording that in a total of 310 cases the familial incidence was 6·5%. Many reports of familial multiple sclerosis followed. In Northern European Caucasoids the overall familial incidence turns out to be roughly 10%.[38,39]

Stronger evidence for a genetic factor comes from the study of twins. A number of studies have suggested that it is more common for both of a pair of twins to develop multiple sclerosis if they are monozygotic than if they are not. The data have been reviewed recently.[39] The incidence of concordance varies between different populations but overall the concordance rate does seem to be higher in the monozygotic twins (29%) than in the dizygotic (13%). However studies of concordance for disease in twins are usually subject to bias; concordant pairs are more likely to be identified than discordant.[39] The systematic study that Dr George Ebers[40] is carrying out in Canada is therefore of special interest. He and his colleagues contacted 5,000 patients with multiple sclerosis and enquired of each whether he or she had a twin. The incidence of twinning was 1/80, the expected incidence in the general population, which suggests that the risk of ascertainment bias has been minimised. They then personally examined every living twin. About 1:3 of the monozygotic pairs were concordant compared with 1:40 of the dizygotic pairs. Moreover this low concordance in the non-identical twins was similar to that for siblings, amongst whom, as we have just seen, the risk is higher than in the general population. These observations provide strong evidence for the implication of a genetic factor in the aetiology of multiple sclerosis.

The HLA system It has become clear that there is an association between multiple sclerosis and the 6th chromosome and in particular with the HLA region which is concerned with the genetic control of immune mechanisms. The strongest associations are with the

D or DR loci, which are probably equivalent. For most populations of Northern European origin, there is a strong association between multiple sclerosis and the gene products Dw2 and DR2. The association is seen in Northern Europeans wherever they live, in Northern Europe and Scandinavia itself, North America, Australia and New Zealand.[41-43] Our data for London are representative: DR2 is found in 19% of the control population and 55% of patients with multiple sclerosis.[44] It should be noted that the strength of the association in general decreases as one goes further south in Europe and that it is rather weaker in the United States than in Northern Europe itself and Australia, probably because of the greater mixture of populations in America. Such genetic mixture probably also accounts for the association of multiple sclerosis with Dw2 in the American negro; Dw2 is very rare in native black Africans.[45]

The story is however more complicated. In Arabs, we found that the association was not with DR2 but with DR4[46] and no association has been found in the Japanese[47] or the Israelis.[48] Most surprising of all is the observation that there is no significant difference in the proportion of people with multiple sclerosis who are Dw2 or DR2 positive as compared with the normal population in the Orkney and Shetland Islands,[49] and in Aberdeen (D Francis, JR Batchelor, WI McDonald, AW Downie and JEC Hern, unpublished results)—despite the very high prevalence rates. But as Compston[50] has pointed out in relation to the Orkneys and Shetlands, the incidence of Dw2 or DR2 in the multiple sclerosis group is similar to that in other Northern European groups with the disease, and the reason why no differences were found in comparison with the normal population may be the unusually high incidence of Dw2 or DR2 in the normal controls. In other words, multiple sclerosis is particularly common in this population in which Dw2 and DR2 is also common.

The question now arises whether DR2 is the critical factor which confers susceptibility to multiple sclerosis. The answer is almost certainly not, for several reasons. First, as I have just shown, the association is not universal. Secondly, in familial multiple sclerosis there is less haplotype sharing than would be expected from the population studies, although there is more than would be expected from the relationships between affected individuals.[51,52] Thirdly, if one accepts at face value the Hungarian data[30] one finds a remarkable thing. As already mentioned, the prevalence of multiple sclerosis in the Caucasoids is 37 per 100,000 and in the gypsies it appears to be only 2 per 100,000. The incidence of DR2 in the Caucasoids is of the expected order: 19·5% in the controls and 42·7% in the patients with multiple sclerosis; but in the control gypsy population the incidence of DR2 is very high indeed (56·5%) yet the prevalence of the disease is very low.[31,32] The fact that both the known cases are DR2 positive is unhelpful, because of the small numbers. Finally, in a twin study carried out in the USA there were two pairs of non-identical twins concordant for multiple sclerosis; in both pairs only one was Dw2 positive.[53]

The first conclusion that can be drawn from this mass of apparently discordant data is that the frequency with which an association *is* found between the HLA system and multiple sclerosis suggests that it has some significance. Secondly, Dw2 and DR2 are in themselves neither necessary nor sufficient to lead to the development of the disease. What then might the significance of the various associations be? One possibility is that each is conferring susceptibility on its own population and that the environmental factor is different in different regions. The Hungarian data would be hard to reconcile with this interpretation. An alternative possibility is that DR2 and DR4 are acting as markers in their respective populations for a common, hitherto unidentified single susceptibility gene in the HLA region; there are after all an enormous number of candidates. The D region is the subject of intensive investigation at present. There are now 99 specificities recognised serologically and 25 by cell typing.[54] The great majority have still to be examined in relation to multiple sclerosis. Several investigators[55,56] have argued for the view that there is a single susceptibility gene, and indeed for its being rather common and dominantly inherited,[56] the low incidence of the disease being explained by variations in "dose" of the environmental factor and the age at which it is received.

There is a third possibility: that more than one genetic factor is involved. There are now several reports suggesting that such is the case. Two loci within the HLA region concerned with the control of polymorphisms in the complement pathways have been implicated. An association with the Bf locus has been found in Australia[57] and London,[44] but not in North Rhine/Westphalia[58] or Aberdeen (D Francis, JR Batchelor, WI McDonald, AW Downie & JEC Hern, unpublished observations). An association with the C_4 locus has also been reported in a family study.[59] There are two reports of an association with a locus on the 14th chromosome coding for immunoglobulin heavy chains,[60,61] but in one of these reports the significance was reduced to borderline levels when a larger group (admittedly including less well studied cases) was included.[60] The present data are inadequate to permit firm conclusions about the role of other genetic factors to be drawn.

In summary, in most but not all populations multiple sclerosis is associated with certain genetic characteristics. The best documented are those coded for in

the HLA region of the 6th chromosome, in particular the HLA antigens themselves. Less well documented associations implicate the complement pathways, and the control of antibody structure. How these associations relate to the environmental factor is not known. Some may influence susceptibility to the disease, others severity of it. It is possible that in neither case have we yet identified the most important associations. The next step is to seek true linkages using the new techniques of DNA analysis which have proved so successful in, for example, Huntington's chorea.

Pathogenesis

I now wish to look more closely at the "origin" of multiple sclerosis referred to in the title of this review. In its context the idea included pathogenesis. The genetic associations suggest that an immune mechanism may be involved: all those so far implicated are concerned in one way or another with the immune response. Moreover, it is known that the liability to development of certain conventional autoimmune diseases such as thyrotoxicosis and chronic active hepatitis, is influenced by an individual's HLA profile.[62,63] There are four main lines of evidence that there is an abnormality of the immune mechanism in multiple sclerosis.

First, it has been known for over 20 years that there is a modest increase in the titre of antibodies against measles and related viruses in both the serum and cerebrospinal fluid of patients with multiple sclerosis.[64,65]

Secondly, it is now well established that about 90% of patients with multiple sclerosis have evidence of abnormal synthesis of gamma globulin in the central nervous system: oligoclonal bands are present at electrophoresis, and the amount of gamma globulin synthesised by the brain is increased.[66] Very recently, Compston and his colleagues have shown a highly significant reduction in the concentration of the terminal component of the complement cascade, C_9, in the cerebrospinal fluid.[67]

Thirdly, the lesions themselves contain immunologically competent cells. Dawson[68] established early this century that the plaques of demyelination are orientated around small venules which in early lesions are surrounded by mononuclear cells. Sometimes the perivascular cuff can be traced into normal-appearing adjacent white matter, suggesting that the cellular infiltration precedes extension of the myelin damage. The cuffs contain lymphocytes and plasma cells. Monoclonal antibody techniques show that the lymphocytes are mostly T cells,[69,70] probably more of the helper type than the suppressor, which corresponds with the relative proportions of these types found in the CSF of patients with multiple sclerosis.[71] In the lesions themselves, T cells are present at the active edge and extend into the adjacent normal appearing white matter.[72]

The fourth line of evidence that an immune mechanism is involved in multiple sclerosis comes from the study of the numbers of helper and suppressor cells in peripheral blood. The number of T suppressor lymphocytes falls at the time of a relapse[73] and in the early stages of acute optic neuritis,[74] a condition which has the particular advantage that the onset can be defined reasonably easily. But there has not been universal agreement either about the observations in multiple sclerosis or about their interpretation. Two main criticisms have been made. First, that the observations were wrong. Some experienced investigators simply did not find consistent changes in the helper/suppressor ratio. However, agreement is lacking about the best methods for identifying and counting T lymphocyte subsets and different approaches have been adopted in different laboratories. The sec-

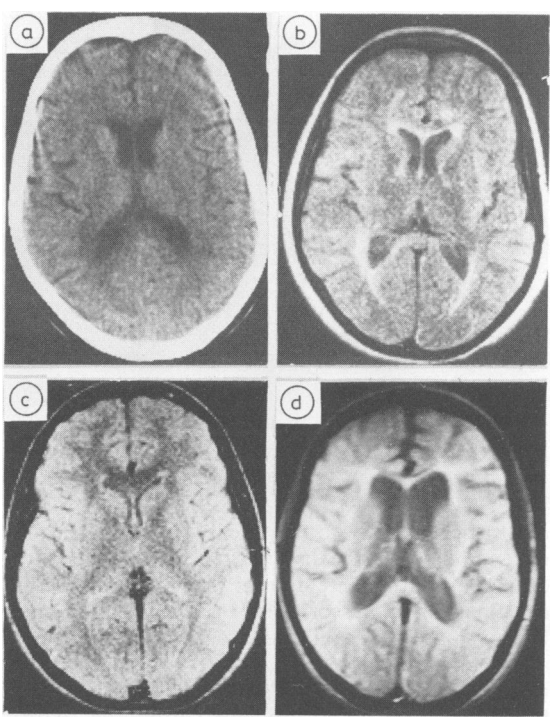

Fig 1 *(a) X-ray CT scan of the brain from a patient with multiple sclerosis. Note the low attenuation in the periventricular white matter. (b) MRI scan (spin-echo sequence) of the same patient as in (a). The periventricular abnormalities are more extensive and an additional discreet lesion is visible in the right frontal lobe. The changes are more extensive posteriorly. (c) MRI scan from a healthy control subject. (d) MRI scan from a patient aged 53 with Binswanger's disease.*

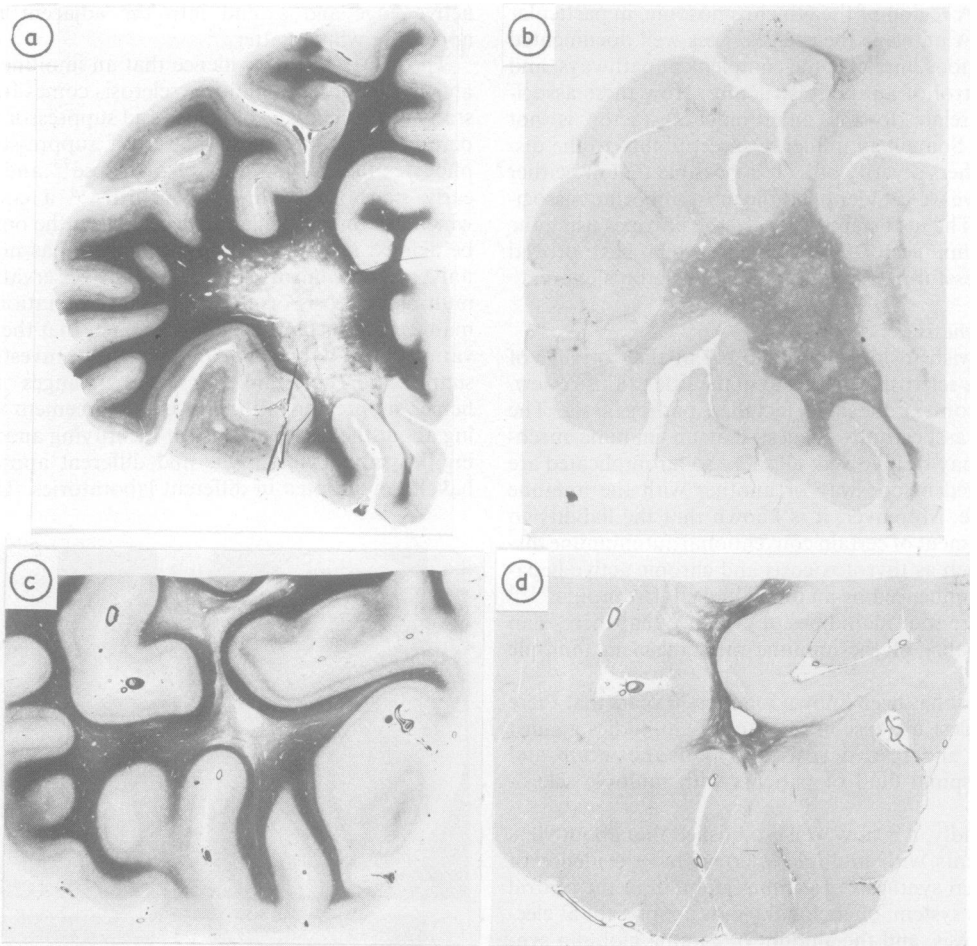

Fig 2 *(a) Multiple sclerosis: myelin preparation from the frontal lobe. (b) Section near (a) stained for fibrillary astrocyte processes. (c) Binswanger's disease: myelin preparation from the occipital lobe. (d) Section near (c) stained for fibrillary astrocyte process. (By courtesy of Dr Ivan Janota. (c) and (d) are reproduced by permission of Churchill Livingstone, publishers[98]).*

ond criticism has been that if changes did occur they were unrelated to the disease process. It is known for example that there are diurnal variations in the ratio of helper to suppressor cells,[75] and falls in the numbers of T suppressor cells can occur without symptomatic change in the patient.[74] The absence of a correlation between clinical relapse and T-suppressor cell levels does not necessarily imply that the cellular changes are unrelated to disease activity, since, as will become clear, lesions often develop without accompanying symptoms.

These are important issues which need to be resolved. Serial investigations are needed on large numbers of patients all of whom are carefully observed clinically and who are bled at the same time of day. It is noteworthy that so far positive results have been found more often in such large serial studies. A second requirement is the development of better methods for detecting new lesions in the brain.

Magnetic Resonance Imaging (MRI)

Three years ago Dr Ian Young and his colleagues at the Hammersmith Hospital made the important discovery that in multiple sclerosis many more lesions in the brain could be demonstrated by MRI scanning than by x-ray scanning.[76] Figure 1a shows an x-ray CT scan from a patient with multiple sclerosis. Regions of low attenuation are visible in the white matter around the ventricles. An MRI scan using a spin-echo sequence (fig 1b) shows that the periventricular abnormalities are more extensive. We have seen such changes in 59 of 60 consecutive patients with

clinically definitive multiple sclerosis aged 17 to 70 years (mean 38).[77] In addition there is a discreet lesion in the frontal lobe which had not been suspected from the x-ray scan. We have not seen regions of altered signal from the periventricular region in 36/37 healthy control individuals aged 19 to 62 years (mean 38) (fig 1c), although in keeping with the occasional surprise discovery of the pathological changes of multiple sclerosis at necropsy[78,79] one apparently healthy control subject showed MRI appearances indistinguishable from those of multiple sclerosis. Others have reported periventricular changes in individuals over the age of 60.[80]

Such dramatic pictures serve to remind the modern neurologist that abnormalities in the periventricular region are characteristic of multiple sclerosis. Hallervorden[81] went so far as to say that if they were not present at necropsy, the diagnosis should be in doubt. It is fascinating that Cruveilhier[82] in his description of the pathology of multiple sclerosis in the great Atlas published between 1835 and 1842 described lesions ("dégéneration grise") in the corpus callosum in one of his first cases with spinal and cerebellar symptomatology. Gowers[1] emphasised that the extent of the periventricular lesions increases posteriorly, as fig 1b shows.

The question now is whether it is possible positively to identify new lesions. Certainly multiple abnormalities may be seen in patients having their first clinical episode suggestive of multiple sclerosis. We have seen multiple cerebral lesions in 17 of 28 patients with isolated optic neuritis and in a similar proportion of patients with isolated acute brainstem symptoms. It is tempting to suggest that the presence of lesions remote from the site related to the symptoms indicates that there have been previous silent episodes of neurological damage and that the patient already has multiple sclerosis. Such a conclusion is premature. It is possible that in some of these patients the optic neuritis or the brain symptoms were the sole symptomatic expression of a more widespread but nevertheless monophasic pathological process. Our serial study of patients with isolated symptoms should help to resolve this problem.

One of the first priorities of the MRI group at Queen Square has been to look at the specificity of the changes for multiple sclerosis.[77] The diffuse periventricular changes and focal lesions seen in CT scans of patients with multiple sclerosis resemble those found in patients with evidence of diffuse cerebral vascular disease. We therefore investigated 23 patients with cerebral vascular disease aged 23 to 80 years (mean 61 years) including patients with late onset epilepsy and CT scan evidence of lesions consistent with lacune, acute stroke, transient global amnesia, and Binswanger's disease (cerebral vascular disease, hypertension and dementia). All showed focal lesions, some small and indistinguishable from the focal lesions seen in multiple sclerosis (fig 1b) others larger and corresponding with the territory of medium and large cerebral vessels. Nineteen of the 23 showed periventricular changes (fig 1) which in some patients appeared to be smoother in outline than those of multiple sclerosis, but in others were indistinguishable from them.

What do the MRI abnormalities represent? Is it oedema, which occurs in the acute lesions of both multiple sclerosis and vascular disease? Oedema alters the MRI signal, but cannot account for the changes in the chronic lesions. Is it, so to speak, myelin loss? Probably not, since it seems that myelin-bound protons contribute relatively little to the MRI signal from normal brain.[83] Is it astrocytic gliosis, which is vigorous in both multiple sclerosis and vascular disease? I would like to look at this possibility a little more closely.

Figure 2a from a patient with multiple sclerosis is a myelin preparation from the frontal lobe. An adjacent section stained for glial fibrils (fig 2b) reveals the intensity of the astrocytic gliosis. Figure 2c shows a myelin preparation from the occipital lobe in a patient with Binswanger's disease and fig 2d shows the glial preparation. The changes are similar to those in multiple sclerosis. Microscopically however there are important differences;[84] in multiple sclerosis there is a relative preservation of axons whereas in Binswanger's disease the picture is purely degenerative. The common ground between the lesions of multiple sclerosis and Binswanger's disease is the gliosis. The replacement of myelin by astrocytic processes would increase the water content per unit volume and thus alter the MRI signal. It is also conceivable that the signal may be modified by changes in the macromolecular environment provided by the glial fibrils.

There is perhaps some danger of expecting too much of MRI too soon. Specificity is one problem: quantitation of the changes in the brain is another which urgently needs to be solved before MRI can be used in one of its potentially most useful roles, that of monitoring treatment. These problems can be overcome and in other respects it is hard to underestimate its importance. Existing techniques offer the possibility of new clinico-pathological insights for example into the mechanism of the memory defects which are common even early in the course of multiple sclerosis,[85] and into the affection of the sense of smell. The distribution of the MRI changes suggests that structures mediating olfaction may be involved in multiple sclerosis. Standard texts make little reference to the possibility, but Gowers records that the olfactory "nerve" (in reality the tract) is often abnormal.[1] Dr F Scaravilli and I (unpublished) have been able to

confirm readily the presence of Cruveilhier's "dégéneration grise" in the olfactory tract where there is extensive loss of myelin histologically. Although patients rarely complain of abnormalities of the sense of smell, Pinching[86] in the course of a study undertaken for another purpose, found definite abnormalities in 15 of 22 patients with multiple sclerosis.

A third way in which MRI promises to be helpful is in elucidating the nature and sequence of events during the development of the plaque. There is some evidence that the vessels in the plaque are abnormally permeable: CT scans may show enhancement with iodine-containing agents, and there is leakage of trypan blue into plaques at necropsy.[87] In the retina too there is evidence of abnormal permeability. In a recent investigation sheathing (the ophthalmoscopic sign of perivascular cuffing) of the peripheral retinal vessels was observed in 14 of 50 consecutive patients with acute isolated optic neuritis persenting to the Moorfields Eye Hospital.[88] At fluorescein angiography, the dye leaked from the sheathed segments of the vessels. The timing of the permeability changes in relation to the evolution of the lesion is however not known. The development of contrast agents such as those recently used in the study of tumours by the Hammersmith group[89] raises the possibility of serial studies of the blood-brain barrier during life in multiple sclerosis. Looking further to the future, the newest technical advances indicate that it may be possible soon to study metabolism by NMR spectroscopy in focal regions of the individual patient's brain selected from magnetic resonance images of it.

To return to the pathogenesis of multiple sclerosis, there is, in summary, good evidence for the existence of immunological abnormalities in patients with the disease, but it is not established whether the tissue damage is actually produced immunologically or whether, as some have suggested, the immunological changes are a *consequence* of demyelination produced in some other way.[90] Demyelination can be produced by allergic means, most notably in experimental allergic encephalomyelitis. In an important recent experiment Watanabe *et al*[91] have discovered a mechanism by which experimental viral infection can lead to the secondary development, after a delay and in the absence of recoverable virus, of allergic demyelination of the central nervous system. This is a potentially important model with which to explore the pathogenesis of multiple sclerosis.

Gowers developed his ideas about pathogenesis at some length in the *Manual*,[1] and concluded that multiple sclerosis was primarily a disorder of the neuroglia. "It is" he said "essentially a process of morbid growth but may sometimes commence as an interstitial inflammation." This quotation comes from the unpublished third edition of Vol. II (sadly now missing, though the relevant page is reproduced in facsimile in Critchley's biography[6]). In this manuscript he goes further. He notes "the tendency of residual embryonal tissue to overgrow in adult life" and suggests "that the islets of sclerosis may start from points of developmental origin."

The idea of a neuroglial origin for multiple sclerosis derives originally from Rindfleisch[92] and Charcot[93] and may come as a surprise to the modern neurologist for whom research on multiple sclerosis has long focused on myelin. But as a comparison of figs 2a and b shows, glial proliferation is as striking as demyelination. It is generally assumed that the proliferation is simply a consequence of the myelin loss, but recent experiments suggest that this may be too simple a view.

Different glial cell types can now be identified using specific antibody markers combined with fluorescent dyes[94,95] and can be grown in 99% pure culture. It is thus feasible to investigate the properties of individual types of cell. Fontana *et al*[96,97] have used these techniques to explore the relationship between astrocytes and the immune system. In culture they mixed rat astrocytes with rat T-lymphocytes from a line which had been sensitised to myelin basic protein. The two cell types showed no affinity. The next step was to add myelin basic protein. If this is done to a pure culture of the sensitised T-lymphocytes, there is no reaction because the antigen must be presented by a cell (for example the macrophage) bearing on its surface the immune-associated (Ia) protein. When myelin basic protein was added to the lymphocytes in the presence of astrocytes from rats of the same strain a striking series of changes occurred. Within 24 hours the T-lymphocytes were closely adherent to the astrocytes. By 48 to 72 hours the T-cells were transformed into blast cells and were proliferating vigorously. It was possible to show that the reaction was specific to myelin basic protein by demonstrating that it did not occur when a different antigen was added to the mixed culture. It was also possible to show that the reaction would not occur unless the lymphocytes and astrocytes had the same genetic background. They showed that the astrocytes which had been in contact with the sensitised cells did indeed express the required Ia protein on their surface, by staining with an appropriate monoclonal antibody. Finally, in other experiments it was established that astrocytes release a substance closely similar to interleukin-1 which is released by the usual antigen-presenting cell in other tissues, the macrophage.

It is clear from these experiments in tissue culture that T-lymphocytes which are such a prominent feature of the plaque of multiple sclerosis can be stimulated by specific antigens which are presented to them by astrocytes. If the properties *in vivo* are similar (and

this has yet to be shown) the possibility arises that the astrocytic response in multiple sclerosis may not all be a *consequence* of damage, but an integral part of its pathogenesis. It is therefore of particular interest that cells bearing Ia proteins (which in man are the DR proteins) are present in the normal-appearing white matter beyond the active edge of the plaque in multiple sclerosis at a stage when T cells are present but there is not yet any myelin breakdown.[71] The next step will be to determine whether they are astrocytes or macrophages or a mixture of the two.

Conclusion

What can we now say about the origin of multiple sclerosis? That it is a disease produced by an environmental agent in genetically susceptible individuals in whom there is an abnormality of the immune mechanism. But many of the mysteries that perplexed Gowers remain. We do not know the nature of the environmental agent, nor do we understand the sequence of events which follows exposure to it, nor the mechanism of tissue damage. We still have no satisfactory explanation for the apparent cycles of quiescence and activity in the disease and we do not know what determines whether a patient will die within 5 years of the first symptom or be fit after 50 years. But progress should now be more rapid. Basic research is providing new insights and suggesting new kinds of observation which should be made on patients; they are becoming feasible through the application of recent remarkable technical advances such as MRI and the use of monoclonal antibodies to the study of the disease.

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