THE PATHOGENESIS OF MULTIPLE SCLEROSIS REVISITED

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The fact that an opinion has been widely held is no evidence whatever that it is not utterly absurd; indeed in view of the silliness of the majority of mankind, a widespread belief is more likely to be foolish than sensible.

Bertrand Russell†

SUMMARY

Multiple sclerosis (MS) is a chronic disease of unknown aetiology that affects the human central nervous system (CNS). Its pathology is characterised by areas of myelin loss in a periventricular and perivenular distribution in association with conspicuous astrocytic proliferation and a variable degree of neuronal and axonal damage. Only a proportion of lesions are clinically eloquent. The principal determinant of long-term MS disability is neuronal degeneration and this may be extremely variable. The presence of mild scant lymphocytic infiltrates in the demyelinating lesions has been generally interpreted as the evidence of an inflammatory autoimmune process. Because specific T-cell mediated autoimmunity can be reproduced in animals after myelin protein sensitisation (Experimental Allergic Encephalomyelitis (EAE)) it has been assumed (but never proven) that a similar T-cell driven immune mechanism is responsible for demyelination in MS.

In this review the literature for evidence of autoimmunity in the disorder is analysed critically. In contrast to the accepted theory, the human counterpart of the experimental autoimmune demyelinating disease, EAE is not MS but a different demyelinating disorder; i.e. acute disseminated encephalomyelitis (ADEM) and acute haemorrhagic leukoencephalitis (AHLE). Extrapolation of EAE research to MS has been guided largely by faith and the bland acceptance rather than sound scientific rationale. No specific or sensitive immunological test exists that is diagnostic of MS despite the extensive application of modern technology. Critical analysis of the epidemiological data shows no association with any specific autoimmune diseases. Geographic factors and age at development suggest an early onset possibly dependant on environmental influences.

Certain neurological diseases are, however, found in association with MS, namely hypertrophic peripheral neuropathy, neurofibromatosis-I, cerebral glioma, glioblastoma multiforme and certain familial forms of narcolepsy. These share a common genetic influence mainly from genes on chromosome 17 affecting cell proliferation. Immunosuppression has failed to have any consistent effect on prognosis or disease progression. The available data on MS immunotherapy are conflicting, at times contradictory and are based on findings in animals with EAE. They show predominantly a 30% effect in relapsing/remitting MS that suggests a powerful placebo effect.

Our studies allow us to offer an alternative hypothesis of pathogenesis. We suggest that MS is a neurodegenerative and metabolic disorder with a strong polygenic influence, the predominant genes being on chromosome 17, and in conjunction with environmental factors and endogenous sex hormones. The principal cellular abnormality appears to occur in the astrocyte and this gives rise to disruption of the blood-brain barrier with secondary metabolic changes in the myelin. The process is generalised throughout the CNS, the plaques being focal areas of increased tissue damage. Our data would argue that primary progressive MS is the prototype disease and that what is needed in future research is a new approach based on the firm established facts that now exist.

INTRODUCTION

The cause of MS is unknown, as is the exact pathogenesis of the disorder.1 This point needs to be stressed as there is a common recurring statement in virtually every paper and textbook that MS is of autoimmune aetiology. Multiple sclerosis is clinically a heterogeneous condition and to date still defies both clinical and exact definition.2 Sadly, these factors may be responsible for the minimal progress that has been made towards understanding its aetiology and pathogenesis or in developing a rational mode of therapy. At present, two main theories are proffered as to its causation, namely that it may be due to a viral infection or to a viral infection which instigates autoimmune mechanisms. No firm evidence exists to support either of these contentions. Epidemiological data also suggest that exposure during childhood to some environmental agent may be the initiating event, but need not be infectious.

Certainly, the occurrence of MS is greater in first, second and third degree relatives of MS patients than in matched control populations. Similarly, the concordance rate is greater in monozygotic as opposed to dizygotic twins. Evidence thus points to it being a polygenic disorder.3

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Some studies have claimed to have found an MS susceptibility locus in the Class II region of the major histocompatibility complex (MHC); another point used in support of the autoimmune hypothesis but it should be realised that many genes also in this region have nothing to do with the immune system. The increased recurrence risk within families clearly indicates a role for genetic factors in the aetiology of MS. A number of genes may influence susceptibility to the development of MS and the subsequent course of the disease. Extensive searches across chromosomal candidate regions and whole genome screens have so far yielded few convincing candidates. In common with most other complex traits, no major susceptibility gene has been identified, although several regions of potential linkage have been associated with MS, including the chromosomal regions 1p, 6p, 10p, 17q and 19q.

As the cause of MS remains unknown, it is important to explore the possible mechanisms of disease pathogenicity that may provide clues to identifying susceptibility loci. Epidemiological studies have identified other diseases associated with MS, namely malignant glioma, neurofibromatosis and hypertrophic peripheral neuropathy. The mechanisms of these diseases are independent. It is intriguing that the gene for neurofibromatosis, a disease characterised by increased incidence of glioma, has been located on chromosome 17q, a region which has been previously associated with MS, glioblastoma multiforme, and Charcot-Marie-Tooth peripheral neuropathy.

For the past century, the major lines of research in MS have focused on an immunopathological aetiology. This has enormous implications, not only for the future and direction of research, but also in directing treatment. Despite many attempts at immunosuppression, no convincing evidence has been put forward that such therapy has any significant effect on the clinical course of the disease. Whilst there are some claims for the possible modest efficacy of β-interferon, many caveats surround this conclusion, and it should be realised that even the mechanism of how β-interferon may work is not understood, although it may have some healing effect on the blood-brain barrier. β-interferon is certainly not a cure, nor does it induce great symptomatic improvement, whilst immunosuppressive therapy has many serious side-effects and complications, including fatality. The consequence of accepting an autoimmune hypothesis may therefore have a very serious outcome in relation to therapy.

In this paper, therefore, we wish to examine critically factual information surrounding MS and to draw attention to the many fallacies that exist regarding it. Since the aim of research is to use unbiased data to direct future studies, an open-minded approach may help to direct future investigations into more fruitful paths.

**RELATIONSHIP BETWEEN MS AND EAE**

The idea that certain neurological diseases have an ‘allergic’ basis was advanced in 1927 by Glanzmann, as an explanation for the encephalomyelitis that complicates certain viral infections, such as chickenpox, smallpox and post-vaccination. Soon after the introduction of the rabies vaccine by Pasteur in 1876, it was noted that several patients developed paralysis and other neurological dysfunctions after receiving the vaccine. Critical observers also noted that often the offending dog that had bitten them was later found not to be rabid. Remlinger in 1928 analysed the clinical details of 1,164,264 patients treated with the Pasteur vaccine and found 529 cases with such neurological complications. Attention was directed later as to the possible cause of such neurological complications and at the potential for disease induction by materials in the vaccine other than the virus.

Animals would not tolerate immunisation with brain material and often developed convulsions, paralysis and weight loss. Early workers studied possible allergic reactions in the brains of animals, and these studies, coupled with the finding that whole brain extracts could induce encephalitis, gave an enormous impetus to this research. The brains of patients with such ‘neuroparalytic accidents’ were found histologically to differ from those dying of rabies. Schwentker and Rivers showed that the poorly antigenic homologous brain inoculum used to try to induce allergic encephalitis could be rendered more antigenic by autolysis or infection; the antigenicity of brain tissue paralleled its myelin content. Encephalomyelitis was capable of being induced in monkeys by repeated injections of aqueous or alcohol/ether extracts of brain, with the disease appearing after months of repeated injections. After the discovery of Freund’s adjuvant, EAE could be produced by a single immunisation in guinea pigs, rabbits and monkeys. Comparative neuropathological studies of EAE drew attention to histological similarities between this experimental model and post-rabies encephalomyelitis in humans. It is our contention that the extension of this comparison to include the prototype primary human demyelinating disease, MS, is one of the major pitfalls in MS research. Experimental allergic encephalomyelitis is totally different clinically, immunologically and histologically from MS although it does have similarities with other human demyelinating diseases. Experimental allergic encephalomyelitis is one of the best studied organ-specific experimental autoimmune diseases in animals. A voluminous literature has grown up on the immunological findings, the innovative immunological techniques and methods that have been tested or developed using this model. It has been shown that T-lymphocytes sensitised to a variety of different CNS antigens induce disease. Such antigens include myelin-basic protein and its breakdown products, i.e. encephalitogenic proteins.
and proteolipid protein (PLP) which are all part of the oligodendrocyte/myelin complex. Work on this important model is scientifically important in its own right. It is only when the data gleaned from studying the brains of mice or rats with EAE is extrapolated to humans with MS that the fallacy of such leaps of faith is demonstrable. Every time that a new observation is made on EAE, such as the traffic of lymphocytes within the brains of rats, researchers incorporate these findings into the dogma that similar findings occur in MS. However, EAE appears to be identical to post-rabies and post-infectious ADEM.

Acute disseminated encephalomyelitis and its hyperacute form, acute necrotising haemorrhagic leukoencephalopathy (variously known as acute haemorrhagic leukoencephalitis (AHLE)) are inflammatory diseases of the human CNS which occur following rabies vaccinations, other vaccinations, immunisations and after viral infections. Acute disseminated encephalomyelitis may also occur as a complication of endotoxic shock, severe burns. It may also occur where there is damage to cerebral endothelial cells. It may be a mild disorder manifest clinically by a little ataxia or can be a devastating or severe disease with death occurring within hours to days. Acute disseminated encephalomyelitis and AHLE are part of the spectrum of the same disorder. These diseases are often classified as primary demyelinating diseases but in reality they are vasculopathies of the CNS, in which only a tiny area of myelin loss occurs adjacent to the affected vessels and rarely exceeds 1–2 mm in diameter. Acute disseminated encephalomyelitis is similar to EAE and differs entirely in all aspects from MS. Comparison of AHLE and ADEM to EAE in monkeys shows that an exact analogy exists between hyperacute EAE in monkeys and between ‘ordinary’ EAE and ADEM, in all clinical, pathological and immunological aspects.

ADEM and AHLE
Abundant immunological and other evidence shows that the lesion in ADEM and AHLE in humans is at the brain/endothelial cell interface and that any demyelination which occurs is a secondary bystander reaction. These conditions should not be called primary demyelinating diseases since they are severe inflammatory disorders with little or no resemblance to the prototype primary demyelinating disease of humans, MS. Acute haemorrhagic leukoencephalitis and ADEM occur in conditions that are known to be pure endothelialopathies.

Acute disseminated encephalomyelitis has been known about for nearly 300 years since its initial description by Clifton in 1724 and has been referred to post-infectious, para-infectious, post-vaccinal, perivenous, microglial and post-rabies encephalomyelitis. Remarkably, its exact pathogenesis has not been carefully studied when one considers that this form of encephalitis accounts for one-third of all cases clinically diagnosed as encephalitis in the US. Acute disseminated encephalomyelitis is related to AHLE; indeed, the histological features of both diseases are often found in the same brain. The immunological findings that occur in ADEM, and AHLE particularly, are also found in EAE in monkeys and are absolutely different from MS. Their clinical presentation is also different being a monophasic disease. Acute disseminated encephalomyelitis and AHLE are only known to occur after predisposing causes, e.g. infection, immunisations, vaccinations or as a complication of endotoxic shock. Patients often present with fever, headache, meningism, vomiting and anorexia, rapidly followed by delirium, confusion, stupor and sometimes coma. The differential diagnosis of ADEM and AHLE is that of an acute, infectious meningoencephalitis rather than MS. In a classical case, there is no difficulty in differentiation from MS because fever, aphasia, meningism, bilateral optic neuritis, stupor and coma are decidedly rare, if they ever occur, in that disorder. Pathologically, the brain in ADEM is oedematous and swollen. Histologically, perivenous inflammation occurs with 1–2 mm in diameter of tissue destruction and fragmentation of myelin. The perivascular cellular cuff may extend for a variable distance into the white matter where there is proliferation of microglial cells and astrocytes show swelling of their cytoplasm. Microglial cells become phagocytic and lipid stains reveal that these cells are laden with fat. When the brain is examined in the recovery phase, there is perivenous fibrous gliosis. Some of these perivenous damaged areas may coalesce to form a larger lesion but these changes are entirely different from MS plaques. In the perivenous lesions of MS, the highest density of cells is at the edge while in ADEM it is at the centre of the lesion. In ADEM there may be frank fibrinoid necrosis of vessels with exudation of plasma. Occasionally glial nodules, known as Babes’ nodes, which are morphological evidence of a pre-existing viral infection may be found. Immunologically, in some cases sensitisation to myelin antigens may occur and this sensitisation may be involved in directing immunological attack at the blood vessels of the white matter. The degree of sensitisation is modest and may even be secondary. Acute disseminated encephalomyelitis is identical to EAE both clinically and histologically.

EAE
Experimental allergic encephalomyelitis has been readily induced in a wide variety of experimental animals including non-human primates. Clinically, it runs a monophasic course, usually with a dramatic onset of weakness, hind leg paralysis and incontinence of urine in lower animals but often optic neuritis, cerebellar signs and paralysis in non-human primates. The disorder clearly involves T-lymphocytes but the histological appearance varies enormously between animal species, and its clinical and histological expression depends on
such factors as the type of animal and the route and method of immunisation. Monkeys injected with a small quantity of purified myelin-basic protein in complete Freund’s adjuvant usually develop a mild monophasic clinical illness in which histologically perivenous mononuclear cell infiltrates are found in the white matter, similar to those found in ADEM in humans.\textsuperscript{22} Repeated injections using the same procedure but with the addition of pertussis bacilli in the adjuvant, or with whole brain matter as antigen, will result in an entirely different clinical and histological outcome. These animals will have multiple abnormal cerebral foci, which are frankly haemorrhagic with severe oedema, fibrinoid necrosis of blood vessels within the lesion and a cellular component varying from mononuclear lymphocyte CD4+ cell infiltrates to that of intense polymorphonuclear neutrophil exudates with extravasation of fibrin and serum.\textsuperscript{22} In our experience of inducing hyperacute EAE in baboons and monkeys, the condition is identical to AHLE in humans. Experimental allergic encephalomyelitis is an intensely aggressive inflammatory disorder in which myelin loss occurs, predominantly as a bystander reaction, in a small perivascular sleeve of tissue as opposed to MS which is characterised by large demyelinating plaques, conspicuous astrocyte proliferation with or without scant lymphocytic infiltration.\textsuperscript{34–6}

Hyperacute EAE, therefore, i.e. the disease that occurs when EAE is induced by routine methods in cats, dogs and monkeys, bears no clinical or histological resemblance to MS. This form of EAE and AHLE in humans is clinically identical with the same findings in the cerebrospinal fluid and in the brain. In EAE in monkeys and AHLE in humans, such intense cerebral oedema occurs that gross morphological displacement of brain structures often occurs along with an increase in water content of the brain of up to 20%.\textsuperscript{22} If the brain of normal animals is traumatised, it too may develop a cellular infiltrate that is composed of macrophages and T-lymphocytes.\textsuperscript{37} Concomitant with this perivenous inflammation is the breakdown of the blood-brain barrier.\textsuperscript{38} The exact mechanism of why this occurs is unknown but may be related to inflammatory mediators released from macrophages and other invading mononuclear cells. Similarly, animals with traumatic damage to the CNS will also show increased cerebral vascular endothelial permeability.\textsuperscript{39, 40} The breakdown of the blood-brain barrier is the one feature that EAE and post-traumatic lesions of the CNS have in common with AHLE, ADEM and, indeed, MS.

\textbf{Dissimilarities between EAE and MS}

The lesions in EAE are different to those in MS where the characteristic feature is the well-defined edge, clearly differentiating it from that of ADEM and hence EAE. The infiltrating cell population in EAE is composed of macrophages and T-lymphocytes.\textsuperscript{24–40} and, as pointed out by Lumsden, cannot be compared to those of ADEM.\textsuperscript{35} Mild inflammatory haematogenous infiltrates and oedema which are not consistent pathological findings in MS have been deemed by Lumsden not to be essential morphological criteria.\textsuperscript{35} He drew attention to the self-propagative character of the MS lesion which showed variable discontinuous sleeves of demyelination surrounding blood vessels which he regards as the essential distinction between the more regular and uniform perivenular lesions of ADEM and EAE.\textsuperscript{35} Experimental allergic encephalomyelitis has been used as a model for MS and it is the best studied organ-specific autoimmune disease: it is not acceptable as a model for MS for many reasons, some of which have already been alluded to. Clinically, it is a monophasic disease, the lesions in the brain and spinal cord are vasculitic and the immunological findings are not found in MS. Treatment protocols in EAE are many but those used in humans, based on the findings in animal EAE, have singularly failed in alleviating the symptoms and signs of MS. Our contention is that it is inaccurate to extrapolate the findings in this putative animal model to the pathogenesis of human MS.

Experimental allergic encephalomyelitis can be induced in a large number of susceptible animals by injection of whole brain, pure white matter, myelin-basic protein or PLP in complete Freund’s adjuvant. In susceptible and inbred animal strains, EAE can be induced by cell transfer, and this proves it to be the prototype T-cell mediated autoimmune disorder created artificially for experimental purposes. The encephalitogenic factor responsible for disease induction has also been characterised and manufactured synthetically in a number of species. Experimental allergic encephalomyelitis is under genetic influence, related to the major histocompatibility complex (MHC) Class II antigens and to other gene loci.\textsuperscript{41–42} Whilst examination of the model in strain 13 guinea pigs and in DA rats (a genetic species of rat which is similar to strain 13 guinea pigs; in both strains it is easier to induce a chronic form of EAE) suggests a chronic disorder with some remote resemblance histologically to MS, when EAE is induced in non-human primates it bears a striking resemblance to ADEM and AHLE and not to MS as already discussed. Experimental allergic encephalomyelitis in lower animals, i.e. mice and rats, classically begins in the spinal cord whilst that in monkeys generally involves the neuroaxis. The infiltrating cells are encephalitogenic, T-cells belong to the CD4 subset and are classed as T helper-1 phenotype cells which secrete a number of cytokines including IFN-\(\gamma\) and TNF-\(\alpha\) and TNF-\(\beta\). The exquisite sensitivity of these cells and their MHC restriction have all been characterised on several occasions.\textsuperscript{43} Demyelination in EAE is a highly complex phenomenon and requires not only specific mature T-cells for a variety of other factors producing co-stimulatory signals, the upregulation of adhesion molecules on both the actual
T-cells and on the endothelial cells such as ICAM-1 and VCAM-1. Suffice it to say that the immunological reactions involved in EAE, whilst of clear importance in their own right in elucidating pathogenesis, have not been shown to occur in humans. Thus therapeutic strategies based on findings in EAE have failed to succeed in humans.43,44

Extensive studies have therefore been made of this animal model since all parameters can be examined and controlled. The precise mechanisms of how lymphocytes traffic in the brain in EAE have been elucidated, as has been the role of adhesion molecules and other subcellular elements in controlling and directing cerebral lymphocyte traffic.23 This supposes that the traffic of lymphocytes in the brains of mice is similar to that of lymphocytes (when they do occur) in the brains of patients with MS. Gulcher et al. argued in examining these data: ‘This comment reflects the leap of faith that often characterises the literature on neuroimmunology of multiple sclerosis.’44 Raine accepted that it was impossible to know the dynamic movements over time of cells within the parenchyma of the brain in MS and assumed that such cellular traffic in the animal model, i.e. EAE, was similar to MS.23

Further criticisms can be made for accepting that several of the immunological reactions which occur in animals with EAE and in patients with MS are similar. One of us demonstrated many years ago that, using in vitro techniques, one could detect circulating sensitised lymphocytes in non-human primates immunised to develop EAE, and show that sensitisation occurred to myelin antigens.27,28 Detailed and repeated identical experiments on patients with MS failed to show a singular case in which clear-cut sensitisation to myelin antigens could be detected.30,33 However, sensitisation was demonstrated in patients with ADEM and in patients with AHLE.30 These results have been confirmed in different laboratories23 but there has not yet been any confirmed report that such sensitisation occurs truly and specifically in patients with MS as compared to controls and to patients with other neurological diseases.

A large number of potential MS therapies have been envisaged from experiments in animals with EAE. These include vaccination with specific encephalogenic T-cells or peptide fragments derived from similar cells, antibodies against the T-cell receptor, modification of the MHC molecule, anticytokine treatments and the intravenous, intranasal or oral administration of different encephalogenic peptides and proteins. The list is far from complete but it should be stressed that the application of these potential therapeutic techniques to humans has been consumately associated with failure.10

**MS AS A POSSIBLE AUTOIMMUNE DISEASE**

**Histological findings**

Multiple sclerosis is one of the most common neurological disorders and certainly the most common human demyelinating disease. It was first described by Carswell from Scotland and Cruveilhier from France in the 1830s, but its exact pathogenesis is still unknown. The classical lesion of MS is the plaque, an area in which there is relative preservation of axons, loss of myelin and digestion of the myelin by macrophages and microglia. Over time the lesion shows pronounced astrocytic gliosis and the final product is a gliotic scar. The plaque is centred round a blood vessel and there may or may not be a mild inflammatory infiltrate of lymphocytes. The vessel involved is usually a small vein, but may be a small artery.

Still no general agreement exists on what precisely happens in the development of this MS plaque. Earlier students such as Lumsden found that the myelin disintegrated in the absence of any infiltrating cells.45 Dawson, however, noted initial pallor of the myelin with an increase of lipid-containing macrophages.34 Most scholars are certain that in some cases there may be no inflammatory cells initially, while even in the developed plaque these are predominantly described as minimal.36 Electron microscopic analysis has shown that myelin breakdown is concomitant with the arrival of the infiltrating macrophages. Indeed, early ultrastructural studies showed changes in the myelin and in oligodendrocytes but without any infiltrating cells being present. The initial hypercellularity in the plaque is due to the presence of astrocytes and infiltrating microglia. Lumsden pointed out that gliofibrillogenesis begins simultaneously with demyelination. The histological features of MS are readily distinguished from other conditions by lack of petechial haemorrhages, accumulated haemosiderin and that of conspicuous oedema.45 It is often stated that the lesions of MS localise in a random fashion but on more careful analysis there is a distinct symmetry when small plaques and all demyelinating activity are taken into account. Lesions of MS usually tend to occur in the cervical cord before involving the cerebral hemispheres. Indeed, the symmetrical distribution of plaques was regarded by Lumsden as one of the most striking statistical findings in that disorder.45

Plaques grow slowly and it has been estimated from statistical studies of patients with long-standing MS that the rate of growth of a plaque is between 2 and 4 mm a year. The demyelinating process however can be more rapid or more severe. It is of extreme interest that Lumsden further argues ‘The basis for this predilection of the multiple sclerosis process for the optic pathways and cord is still, in the writer’s view, the major riddle in the pathology of the disease.’45 As postulated by Oppenheimer,47 these two areas are constantly being traumatised; we move our eyes conjugately in all
directions each day and we move our neck laterally and
in a flexion/extension arc constantly (whether or not we
have cervical spondylosis which would exaggerate the
movements). Such movements could predispose to
disruption of the blood-brain barrier locally. Brain and
Wilkinson noted that cervical spondylosis may be
associated with MS and they suggested that 'The effect of
cervical spondylosis upon the spinal cord may be to make
it more susceptible to the lesion of multiple sclerosis at
that level.' They found that in patients with cervical
spondylosis and MS at post-mortem there were often
widely disseminated plaques of demyelination throughout
the brain, particularly in the spinal cord at which site the
changes were most conspicuous in the cerebral cord
segments and most obvious at the levels where
spondylosis had occurred. This association of MS and
cervical spondylosis has been confirmed by Burgerman
et al.

Plaques in the spinal cord are usually longer than those
occurring elsewhere. Symmetry of plaque formation is
often seen, particularly with bilateral involvement of the
fifth nerve entry zone in the pons. In the classic early
plaque, special histological stains show preservation of
axons with myelin being the primary target. Accompanying
the damage to myelin is gliofibrillogenesis with the
development of grossly hypertrophied astrocytes.
Myelin is broken down into 'myelin balls', i.e. droplets of
fat, crystallised lipids and granules. The simultaneous
vigorou study response to the breakdown of myelin is
possibly the earliest pathological observable
abnormality. Microglia are not involved until there is
myelin breakdown whereas reactive astrocytes almost
appear simultaneously as myelin breakdown. Microglia
are activated as a normal secondary event and would be
so activated if damage to the myelin were to occur in
another way. The remarkable response of astrocytes in
MS has been commented on by many authors. Other than the response that one finds in prion disease,
the astrocytic response in MS is exceptional. Charcot
himself commented on this. Simultaneously gliofibrillae
appear and there is astrocyte swelling. Such changes in
astrocytes bear a relationship to the mechanism for
development of a glioma.

The pathological features associated with the initiation
and development of acute lesions continue to remain
controversial. Lumsden was of the view that demyelina-
tion occurred first and, simultaneously, there was
astroglifibrillogenesis and then involvement of microglia
and haematogenous cells and, subsequently, invasion by
lymphocytes. Dawson held similar views. He also, in
reviewing the earlier literature, found many examples and
cases in which on histological examination there was no
inflammation whatsoever. Serious scholars of the classical
histological lesions of MS have noted scant or even absent
'inflammatory' cellular reactions. Seitelberger stated
that the demyelination of the acute plaque occurred 'in
the absence of mononuclear immune cells. Indeed, as
exemplified by several investigators, Guseo and Jellinger
found in a detailed study of 19 cases of MS with a short
clinical course (the mean of less than one year) a significant
number of these patients had no perivascular infiltrate
in the CNS. The absence of lymphocyte cuffing in
patients with acute MS is not the exception and is said
to occur in one-third of all cases. Lymphocytes are a
normal occurrence in the perivascular spaces. Similar
infiltrates, in fact exceeding that found in MS, may occur
in a wide variety of pathological conditions including
trauma, infarcts, tumour and following infections. Most
investigators who have looked for lymphocytes in contact
with the myelin sheaths and oligodendroglia found that
'the number of lymphocytes that leave the perivascular
compartment and enter the parenchyma is very small,
both in absolute numbers and relative to the number of
macrophages present. There are multiple reports of detailed and sophisticated
immunological analysis of the inflammatory cells that are
found in the brains of patients with MS. Clearly, it is
imperative to compare their type and composition with
that found in non-specific conditions with no primary
immunological pathogenesis. Similar cells are found in a
large number of other conditions including adrenoleukodystrophy, a disorder of inborn metabolism,
and in neurodegenerative disorders such as amyotrophic
lateral sclerosis. Similar infiltrates are found up to 40
years later in the spinal cord of those with poliomyelitis.
Dawson et al. were of the opinion that the myelin sheath
was first to be affected and simultaneously changes in
the neuroglia occurred. There was then alteration in the
permeability of the blood vessels. 'The first cellular
increase is secondary to the reabsorptive processes --
and infiltration of fat granule cells: this is followed by a
proliferation in all the cell elements of the adventitae
and, at a later stage, by a modified infiltration of
lymphocyte-like cells and a few plasma cells. Since the
cause of MS is unknown the significance of the mere
finding of a scant haematogenous cellular infiltrate is
unknown. As stated, histologists have remarked on the
mildness of this infiltrate and Adams was of the view that
it was too modest to constitute 'a florid autoimmune
reaction'.

The finding of inflammatory cells in parts of the brain in
patients with MS that contain no myelin such as the
retina also the finding of cellular infiltrates away
from the plaques further raises doubt as to whether
such cells have a primary pathological function. Since
the earliest lesion in MS is not known, examination of
the brains of patients who have had the illness for some
time makes it impossible to give a precise age to the
inflammatory or demyelinating lesions found. There is
still little knowledge as to the precise pathological
processes and timing of events that occur in the genesis

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of the MS plaque. One-third of all MS plaques may not contain cellular infiltrates, and such infiltrates are often scant, lack aggressiveness and indeed may be found in parts of the brain which contain no myelin. Reliance on the presence of these inflammatory cells as the prime pathologd process in the disease therefore seems to be totally unfounded. The persistently aggressive nature of the illness classically seen in primary progressive MS but even in the relapsing/remitting type brings the disorder more in line with a neurodegenerative disease than with acquired inflammatory disorder. Indeed Confavreau and colleagues showed that patients with MS had a progressive course that was not significantly influenced in its progression by relapses and remissions.65 This finding may help to cement what is in our opinion a false separation of primary progressive MS from the other types. Our contention is that there is only one type of the disease with different rates of clinical progression. In our opinion, too, the pathological lesions are identical in both conditions and whilst it is suggested that there may be more inflammatory infiltrates in the secondary progressive disorder, this may be readily explained by the rate of tissue destruction.64 Furthermore, the finding of minor differences in the presence of oligoclonal bands in primary progressive as opposed to the remaining types do not detract from this opinion.66 The presence of oligoclonal bands is non-specific and relates to breakdown of the blood-brain barrier allowing lymphocytes to produce immunoglobulins within the parenchyma of the brain.

Recent detailed studies looking at axonal loss in MS also support our view that MS is a neurodegenerative disease.67 Generalised axonal loss correlates well with clinical deterioration compared with ‘any other measure of structural central nervous system (CNS) change investigated’.67 We will comment later on magnetic resonance spectroscopy studies on total N-acetylaspartate in the CNS white matter but here again there is good correlation with functional impairment.

Immunological findings in MS

The present hypothesis of the pathogenesis of MS is that it is an autoimmune inflammatory condition triggered by an unknown infectious agent; the basis of this hypothesis is that T-cells, specifically sensitised to an unknown antigen, invade the nervous system and cause immunological damage to myelin. A voluminous literature has grown up documenting the innumerable minimal changes found in the peripheral blood and cerebrospinal fluid of patients with MS. No one specific abnormality has ever been found and confirmed.

Attention should be given to the fact that many of these claimed findings are said to occur during the active phase of the disease, i.e. as the patient exhibits new symptoms, whilst comparative studies are done during the quiescent phase. It should be realised that for every new symptom that a patient may develop there may be at least ten demyelinating episodes occurring in the brain visible on a magnetic resonance imaging (MRI) scan, most of them clinically silent. Differentiating activity of the disease merely by documenting exacerbations or new symptoms is clearly open to misinterpretation.

In an endeavour to support a possible immunopathological basis for MS, researchers have turned to the blood and cerebrospinal fluid to identify any specific immunological abnormalities that correlate with the disease. In animals with EAE it is possible to demonstrate sensitisation of T-cells against components of myelin. Indeed, this phenomenon is also positive in humans with ADEM and AHLE, but has never been confirmed to occur in patients with MS. There are no definitive findings on conventional immunological techniques that polyclonal specific T-cell immune responses against myelin occur in patients with MS.

Using the advanced method of cloning different subsets of T-lymphocytes, it has been claimed that specific clones of T-lymphocytes sensitised to myelin-basic protein are more frequent in patients with MS than in controls. These experiments were repeated, however, and found wanting.70, 71 Further studies failed to show that there were increased numbers of specific sensitised clones of T-lymphocytes to myelin antigens in patients with MS.71-4 Notwithstanding these failures, the protagonists have put forward the idea that the T-receptor gene might be different in T-lymphocyte clones from MS patients as compared to the T-cell receptor gene usage of similar clones in patients without MS. This hypothesis also has been found wanting.73 Other claims regarding the T-lymphocyte and sensitisation to myelin or myelin-specific peptides have been made but have not stood the test of time.76

A wide variety of other immunological abnormalities have been claimed to occur in MS but are non-specific. Among these is the claim that during relapses patients have a decreased suppressor cell function77 and that these cells show a normal function when the patient is asymptomatic and decreased activity during remissions. Again the poor correlation between exacerbations, new symptoms and active demyelination should be noted. This again has been shown to be a non-specific phenomenon since suppressor cell function can vary with a number of abnormalities of the brain, including trauma and brain tumours.78, 79 Indeed, studies of the CD8 suppressor cells in MS demonstrated that they produced normal cell-mediated lysis of alloantigens and that immunoglobulin secretion might be increased.80

A variety of other abnormalities involving T-cell subsets and cell-mediated immunity has been described in MS. These have never been consistently confirmed nor proved to play a primary role in pathogenesis; similar
abnormalities have been found in patients with other neurological diseases.\textsuperscript{61} Serial analysis of T-cell activation markers and detailed analysis of cytokines failed to show any reproducible abnormality.\textsuperscript{62} No firm evidence of an abnormality of T-cell lymphocyte immunity, or of specific sensitisation to myelin antigens or other neural antigens, were confirmed.\textsuperscript{10,23} Clearly, the many claims for humoral abnormalities have not stood the test of time nor have the many studies on immunoglobulin abnormalities found in the cerebrospinal fluid.

Attempts at therapy based on experiments in rodents with EAE have so far failed. In example, it has been shown that rats given myelin antigens orally may fail on immunisation with encephalitogenic proteins to develop EAE: oral tolerance has therefore been induced in rats. In a huge trial in humans oral tolerisation to myelin antigens in patients with MS was attempted; no beneficial effect was observed. These experiments were perhaps a further cautionary tale in accepting the theory of autoimmunity in MS.\textsuperscript{33}

Association with autoimmune diseases

In the early 1960s Simpson proposed a theory of autoimmune aetiology for myasthenia gravis.\textsuperscript{84} Interestingly, this theory was developed predominantly from studying the patients with the disease and their first and second degree relatives with a demonstrably increased association of other autoimmune diseases in all three. For example, he found that 16 of 440 patients with myasthenia gravis concurrently had rheumatoid arthritis. His observations have been amply confirmed in several studies. No such association with autoimmune diseases and correlations with histocompatibility antigens and other markers were found in MS.\textsuperscript{85} This is borne out by the scant reports of single case occurrences, suggesting that there is no true association.\textsuperscript{86,87} Other workers who were keen to highlight such an association have suggested an association with diabetes mellitus\textsuperscript{88} yet studies looking specifically at this association failed to show the increased incidence of autoimmune disease and patients with MS, particularly diabetes.\textsuperscript{89} Broadley et al., by the most convoluted arguments, were unable to show any increase in autoimmune diseases in patients with MS when compared with index controls or population data;\textsuperscript{90} however, they concluded that autoimmune disease was more common in first degree relatives of patients with MS, a finding which they commented on as being consistent with previous larger groups looking especially at this relationship: ‘The finding of an increased familial rate of autoimmune disease without a corresponding increase in patients with multiple sclerosis seems counterintuitive.’\textsuperscript{90} Lumsden in a careful post-mortem study of a very large number of patients with MS was unable to show any evidence or stigmata of autoimmune disease.\textsuperscript{95} Broadley et al. found the highest association in the first degree relatives with thyroid disease but this is a difficult and misleading condition to use as a prime example of an autoimmune disease.\textsuperscript{90} Thyroid disease is extremely common, may be occult and it is difficult to determine its exact incidence. Indeed, a very detailed study from France showed an overall decrease of autoimmune disease in the first degree relatives of patients with MS, whilst reporting a high prevalence of Graves’s disease.\textsuperscript{91} Clearly no association of autoimmune disease with MS occurs and the absence of any increased incidence in such disorders in the probands leave us in no doubt that no true association exists.

Effect of immunosuppressive/immunomodulation in MS

The importance of the autoimmune hypothesis is well displayed in treatment trials with various and powerful immunosuppressive drugs. The use of these drugs adds another pitfall in the treatment of the condition. The diagnosis of MS depends on a number of different criteria combining clinical and paraclinical factors;\textsuperscript{92} the criteria which were newly introduced are helpful but still may permit a wrong diagnosis. Even if a correct diagnosis is made, patients still form a heterogeneous study group. Magnetic resonance imaging studies have shown that for each clinical symptom there may be ten silent lesions in the brain. Multiple sclerosis is a complex disease and the natural history of this disorder is not fully appreciated; the mechanisms underlying variable clinical expression are not known, but modern observations suggest that the disease is invariably progressive with a different rate of progression per patient.\textsuperscript{85,93} In a carefully conducted study Confavreux and colleagues showed that relapses in essence do not significantly influence the progression of the irreversible disability.\textsuperscript{85} Other modern observers have noted that ‘The failure of a remission to be complete may be more important than the frequency or severity of antecedent relapses in increasing neurological impairment, and in the transition to a secondary progressive phase.’\textsuperscript{93} Notwithstanding this, it should also be noted that the majority of patients with MS usually have a rather benign course; even after ten years, 75% of their patients had less than ten lesions on MRI scan of the brain and an extended disability status scale of less than three.\textsuperscript{94} It can thus be readily seen that there are many difficulties in evaluating patients on a clinical trial.

Clinical trials are, however, in abundance: a rise from 50 such papers in 1965 to more than 300 by the year 2000. This has been described by some as reflecting ‘the sense of excitement in the field of MS therapeutics’,\textsuperscript{10} but is regarded by us as a sad reflection of the gullibility of researchers in accepting an unproven hypothesis. The authors commented on this sense of excitement philosophically enough to coin the truism: ‘The road to success is paved with failures.’\textsuperscript{10} The enormous number of trials based on putative immunosuppression and immunoregulatory mechanisms has singularly failed to show a cure or to convey major benefits to MS patients in addition subjecting them to an increased morbidity.
and mortality.

Some of the trials used (listed in reference 10) were:
1. Immunosuppression: linomide, sulfasalazin, deoxyspergualine, cladribine.
3. Inducers of remyelination: IVIg (Gamimune N).
5. T-cell-receptor directed therapies: T-cell vaccination, T-cell receptor peptide vaccination.
6. Interferons: (IFNß-1a and IFNß-1b).
7. Glatiramer acetate (copolymer-1).

Claims for the powerful immunosuppressor, cyclophosphamide, led to the widespread use of this drug in MS in Europe and the US. The initial studies were not double-blinded, but double-blind, placebo-controlled studies failed to show any improvement. Similar results were found with cyclosporine and with azathioprine.

Brain and total lymphoid irradiation and plasma exchange have also been tried. The collected reports of these and other immune-mediated therapies, aimed at ‘Modifying the course of multiple sclerosis’, make for sad reading since a review of the vast number of different trials show, no definite benefit. The dramatic failure of trying to induce oral tolerance to myelin-basic protein in humans with MS has even been the subject of a best-selling book.

8-ß-interferon and glatiramer in MS
The two leading immunomodulating drugs for which beneficial claims have been made are glatiramer and INF-ß interferon. In a recent editorial data on glatiramer were said to provide reassuring information on its beneficial effects in MS. Such data as exists with both 8-interferon and glatiramer has to be looked at with extreme caution before total acceptance. Glatiramer ‘is thought to act by inducing a population of regulatory (Th-2 type) T-cells that migrate to inflammatory sites in the central nervous system (CNS), where they are activated by cross-reacting myelin antigens to exert their beneficial “bystander effect”. This process may take several months to develop. Such an explanation defies belief and lies more in the realm of science fiction.

In a study looking at the mechanisms of action of interferons and glatiramer acetate we note that ‘Over the past decade multiple sclerosis patients have benefited enormously from therapeutic research efforts’. Sadly we cannot readily accept this statement from our own clinical experience or from the data provided. Others have questioned the efficacy of such trials and in looking at the effects of copolymer 1 and 8-interferon found that the ‘copolymer 1 placebo patients fared better than the interferon treatment group’. They drew attention to the fact that ‘comparison between studies with even slightly different end-points is extremely difficult’. Of extreme importance is the caveat of Steiner and Wirguin that ‘all three studies report a very similar reduction (around 30%) in the relapse rate’. They highlight that ‘the almost identical results of clinical trials using different agents, and their inability to go beyond the 33% line, raise the possibility that the entire observed benefit is only a placebo effect, and that the significant deviation from the true placebo might be the outcome of partial unblinding of patients by the side-effects’. Similar results were found by Calabresi where improvement with ß1a-interferon was precisely 33%.

In a recent review of the possible benefits of interferon in relapsing-remitting MS, The Cochrane Review drew attention to 208 articles of which only seven met all the selection criteria and formed the subject of their conclusions. The variable quality of the trials, the inadequate methodology, the very high proportion and incomplete description of drop-outs, and the failure to adhere to the strict original intentions of the trial detract seriously from any claims that were made. These trials should be considered as single- rather than double-blind. They drew attention to the fact that if interferon-treated patients who had been removed from the study were deemed to have worsened, the significance of the reported effects was therefore lost. The efficacy of interferon on both exacerbations and on progression of the disease was modest after one to two years.

The precise action of 8-interferon is unknown but an important effect is that it reduces the permeability of the blood-brain barrier, a mechanism that may explain its modest benefit rather than immunomodulation. It is said to rapidly block the blood-brain barrier leakage, within two weeks, as seen by gadolinium-enhancement scans. Glatiramer acetate also has an effect on the blood-brain barrier but less dramatic resolution of gadolinium-enhanced MRI activity. In a recent issue of Neurology devoted to ‘Practical issues in the management of multiple sclerosis’, a number of investigators look at the action and the clinical results of treatment by glatiramer and interferons. They all begin with a statement that MS is an immunologically mediated disease and all are influenced by the comparison they make with EAE. Dr Dhib-Jalbut wrote of the amplification of immunoreactivity in the central nervous system where T-cells are further activated by antigens presented on microglia resulting in the secretion of pro-inflammatory cytokines and chemokines that attract and retain inflammatory cells in the CNS.

We have discussed in this paper the fact that there is no convincing evidence for any of these statements, indeed no antigen has ever been identified that is specific for MS. Dr Dhib-Jalbut further goes on to state that the mechanisms of action in
MS of β-interferon is by reducing T-cell activation, inhibiting interferon-gamma effects, induction of immune deviation and inhibition of the blood-brain barrier. We would humbly suggest that the data surrounding these putative mechanisms would need to be further evaluated, strengthened and confirmed before being accepted.

Glatiramer acetate (Copolymer-1) is a synthetic molecule made of four amino acids: glutamine, leucine, alanine and tyrosine. The same acids are found in myelin-basic protein and because myelin-basic protein has been suspected, but never proved to be, the antigenic component involved in MS, an intellectual jump occurs in assuming that glatiramer acetate, through its action involving immune attack on myelin-basic protein, allows one to use it in the treatment of MS. Again the original work on evaluating copolymer activity was that it blocked the induction of EAE in animals. Glatiramer has been stated to bind to human leukocyte antigen (HLA) Class II (DR) molecules as a result of this possible interaction based on data from its use in animals with EAE, and it is said to inhibit myelin-reactive T-cells by inducing anergy in such cells and bringing about anti-inflammatory TH2 cells which have 'bystander suppression in the CNS' along with 'neuroprotection'.

In the same issue of Neurology Calabresi describes the disease-modifying therapies available for relapsing-remitting MS. He reported the result of a two-year study of placebo versus β-interferon-1a. He found the beneficial effect, a reduced exacerbation rate of 34%, whilst in a further study β-interferon-1a (Avonex) he was able to demonstrate a beneficial effect of 32%. This finding was replicated in yet another study that compared placebo with interferon-beta-1a (Rebif). Examining the effects of β-interferon-1b, β-interferon-1a (Avonex) and Copolymer-1, Steiner and Wirguin noted that the 'copolymer 1 placebo patients fared better even than the interferon treated group' despite the fact that both studies were performed in the same country with patients from an identical population pool. An analysis of these three studies showed that they all had effect but the effect was all around 30% reduction of the relapse rate. These studies have a similar effect on those recently quoted in the US for both glatiramer and β-interferon.

In 1955, Beecher published his important paper on 'The powerful placebo', where he showed a placebo effect of 30%. In a trial of transfer factor in patients with MS one of us was struck by the extraordinary placebo phenomenon that was also observed in patients with MS treated by different techniques. We would therefore agree with the recent critiques on reporting clinical trials.

MS in infants
It is difficult, if not impossible, to induce EAE in neonatal animals; immunisation is only successful after a certain age. This is very important since the age at which animals become susceptible to developing EAE corresponds in humans to about the age of two years. This phenomenon of relative resistance to disease is also seen in the histology of ADEM in infants who until the age of two develop an encephalopathy rather than an encephalomyelitis after the appropriate inciting event which is characterised by the lack of infiltration of mononuclear cells.

If sensitised lymphocytes invading the brain are thought to be involved in the pathogenesis of MS, one might therefore not expect to find MS occurring below the age of two. However, there have been several reports of MS occurring in infants.

MS and HIV infection
If MS is an autoimmune disease a particularly informative setting for studying this would be in patients who have MS and are concomitantly infected with HIV infection, a situation which is known to induce a severe state of immune deficiency. Berger et al. reported seven such patients, six of whom developed an immunodeficient state after HIV infection but who continued to have relapsing/remitting MS. Some of these patients had brain biopsies, whilst another died and a full autopsy was performed; there was no doubt about the diagnosis. These data would argue strongly against any autoimmune aetiology, i.e. T-cell mediated autoimmune pathogenesis.

Effect of radiation on MS
When recipient rats involved in passive cellular transfer of EAE were previously irradiated, they were found to have more virulent disease than non-irradiated animals. Total body irradiation of these recipient animals did something to them that allowed the passively transferred sensitised cells to induce a more rapid and severe encephalitis. In other experiments, however, irradiation of the donor rat reduced the severity of EAE, but specific focal spinal cord irradiation enhanced its development. These data are consistent with the known facts that irradiation damages the blood-brain barrier. Damage to the blood-brain barrier certainly enhances EAE. Indeed, in passive cellular transfer experiments, focal damage to one area of the brain three days before transfer will render the animals exquisitely sensitive to developing EAE and they will develop it first within hours in the area of increased blood-brain barrier breakdown.

Acute radiation therapy, particularly at tumouricidal doses, may disrupt the blood-brain barrier and even cause an encephalopathy. Patients with MS who are irradiated would be expected to do badly since disruption of their blood-brain barrier would promote further demyelination. Cerebral demyelinating lesions of MS may appear as single or multiple contrast-enhancing lesions on MRJ scans, and be mistaken clinically and radiologically for primary or metastatic brain tumours. Peterson et al. reported five
such patients who received radiation therapy. Four of the patients received radiation in full tumouricidal doses and had extremely poor clinical outcomes. Magnetic resonance imaging scans of patients who have deteriorated after radiation show new lesions which have been verified pathologically as demyelinating. At autopsy in these cases there was profound demyelination. Aarli et al. reported a case of a man with MS who had a glioblastoma multiforme and was treated with radiation. He died two months later and the autopsy showed no infiltrating tumour but diffuse demyelinating disease of the white matter.

Twenty patients with MS received craniospinal radiotherapy and their cerebrospinal fluid IgG level was measured. Five patients had a transient decline in IgG synthesis which lasted three to six weeks, ten had totally inconsistent responses whilst the remaining five that were given radiation as well as ACTH and prednisolone, showed a decline in their IgG synthesis rate. What is important to note is that none of these patients was found to have experienced any improvement clinically.

Total lymphoid irradiation to induce immune suppression was also tried in MS: no clinical benefit ensued but a number of deaths occurred, these most likely being secondary to immune suppression, with an increase in the severity of the disease and the development of infections. The worsening of their demyelinating disease would appear to be the effect of radiation on blood vessels enhancing vascular permeability.

DISEASES ASSOCIATED WITH MS

Epidemiological studies in certain diseases have shown that there is an increased incidence of related disorders in the probands and first degree and second degree relatives of such patients. Studies applying similar methods to patients with MS have shown that certain diseases other than autoimmune diseases are associated with MS. Classically, these are malignant glioma, including glioblastoma multiforme, neurofibromatosis Type I and hypertrophic peripheral neuropathy.

1. Glioma

A compelling series of reports of malignant astrocytomas associated with MS have been published. Other tumours reported in association with MS have included ependymomas, meningiomas, oligodendrogliomas and odd non-gliomatous tumours but these are very rare and likely to be pure coincidental occurrences.

Multiple sclerosis always occurs first and the tumour generally tends to occur in patients with long-standing disease. In some instances the tumour appears to arise from the adjacent edge of an MS plaque but in the great majority it arises from foci far removed from the demyelinating lesions. It is interesting that there is a very high incidence of multicentric origin. In a proportion of MS cases with associated tumours it is impossible to determine whether the tumour is multifocal or not; this is a function of the extent to which the brain is sampled. A frequency of 87.5% of multicentricity for all gliomas has been found as compared to 50% when the glioma occurs with MS.

The number of reported cases almost certainly does not reflect the true incidence of this association. We have personally seen in our institutes a further case of MS, Charcot-Marie-Tooth disease and astrocytoma, and two further cases of the association with malignant astrocytoma. Neurological symptoms occurring in someone with a long-standing disease such as MS are likely to be overlooked and attributed to the original disease. Furthermore, patients with MS who die rarely come to a post-mortem examination. This is important since, in the reported cases of this unique association, several were found at post-mortem examination (that is, the association had in fact been occult).

This association highlights the role of astrocytes in both disorders. It is extraordinary that mitotic figures very rarely, if ever, occur in areas of astrocytic hyperplasia since astrocytes may divide by another mechanism which has been referred to as ‘amitosis’. Indeed astrocytes may, like melanoma and other cells, divide under certain conditions by subdivision. Glioblastomas, astrocytomas, ependymomas and oligodendrogliomas are all derived from the same progenitor glial cell.

The development of gliomas in patients with MS almost certainly does not occur by chance and is not coincidental. Most astrocytomas are sporadic with no known cause; some, however, are associated with inherited genetic disorders, e.g. neurofibromatosis Type I. This is an autosomal dominant disorder with an incidence of one in 3,000 associated with the development of tumours such as neurofibrosarcoma and optic glioma. This condition is also associated with the development of MS so that some intriguing molecular biological deficit appears to link glioma and neurofibromatosis. That common histogenesis is involved in this association is further supported in the finding of patients with MS, glioma and Charcot-Marie-Tooth disease. Furthermore, in patients with both gliomas and MS there is often multicentric origins of the neoplasm which, being a rare occurrence by itself, may suggest a common pathogenesis.

One might have expected oligodendroglia to proliferate in putative disorders associated with MS and the vast majority of neoplasms are either glioblastomas and astrocytomas (Table 1). Similarly, there is no evidence in most cases of a continuous transformation of the reactive glial cells of an MS plaque to an adjacent tumour; thus the neoplastic transformation from reactive glial cells of the MS plaque is unlikely to be the mechanism.
authors have, however, claimed that the neoplastic transformation of astrocytes has occurred from the activated cells within the MS plaque. Malmgren et al. commented on their case in which neoplastic astrocytes were found within the MS plaque suggesting the neoplastic change had arisen de novo within the plaque. Ho and Wolfe in their study of 20 cases found six astrocytomas that were multiple, which is a far greater number than is usually described as occurring in patients with glioma alone. Currie and Urich stressed that the high frequency of multiple sites of origin when glioma occurs with MS exceeded even ‘the exceptionally high estimate of 20% which Scherer, 1940 gave as the frequency of multiple tumours in all cases of glioma’.

This point is reinforced by Reagan and Freiman, who refer to the very high incidence – up to 50% – of multifocal lesions in patients who have a glioma and MS.

2. Hypertrophic peripheral neuropathies

Clinical, electrophysiological, morphological and pathological studies have shown abnormalities in the peripheral nervous system in patients with MS. Pollock et al. found peripheral nerve abnormalities in 80% or more with a reduction in myelin thickness. One difference was that the demyelinated and re-myelinated segments of the peripheral nerve did not extend laterally as occurred in MS plaques. There was no correlation with clinical findings. Earlier workers considered that these peripheral lesions were associated with malnutrition and avitaminosis. Others have attributed them to an autoimmune mechanism; in some cases molecular genetic testing revealed myelin-protein gene duplication, characteristics of Type Ia Charcot-Marie-Tooth disease.

Interestingly, the molecular abnormalities in Charcot-Marie-Tooth neuropathy are found in intrinsic Schwann cell proteins and not in the axons.

The data showing involvement of the peripheral nerve system in patients with MS are overwhelming and include altered supernormality in MS peripheral nerve, reduced myelin thickness of internodes, ultrastructural abnormalities in Schwann cells, gross onion bulb neuropathy, normal regional curare test, abnormal single fibre EMG, prolonged refractoriness of sensory nerves and abnormal slowing of motor conduction as evidenced by collision technique. In a classic case of severe onion bulb neuropathy associated with MS, both of these diseases began simultaneously: whatever caused MS was likely to be involved in the initiation of onion bulb neuropathy.

It would be reasonable to consider a promising factor that caused proliferation both of Schwann cells and glia since the rise in the CSF protein early in the course of the disease suggests root involvement at the time of developing MS. Schwann cells and glia must therefore share a common receptor. The unique finding, in this case, of Schwann cells within the plaque in the spinal cord is very remarkable. Some workers have reported that peripheral myelin can occur in MS plaques. These earlier workers suggested that there must be pluripotential stem cells within the cord so that the plaque contains in these unique cases multiplying glia and Schwann cells that arise from such pluripotential cells. The rapid proliferation, in some way, perhaps by diverting normal metabolism may cause demyelination. For such an event to occur the milieu in the spinal cord must contain such a proliferating factor(s). Whether this comes from the cord itself or from the blood is unknown. Neuregulin and the erb B receptors are likely candidates.

3. Neurofibromatosis

We were intrigued to find a young pregnant woman who presented with classical neurofibromatosis Type I and a progressive paraparesis. Investigations revealed the paraparesis to be secondary to a spinal cord MS plaque with multiple lesions throughout the white matter of the CNS. Two other cases referred to us suggested this association might be more than coincidence and a review of the literature showed neurofibromatosis and MS were reported to occur together.

Neurofibromatosis is an autosomal dominant condition with a wide intrafamilial variability in clinical manifestations. About 50% of all cases represent new mutations. There is an association with glial nodules in the brain and spinal cord and an increased incidence of glioma. The NF1 gene consists of 350 kb of genomic DNA and encodes for a protein of 2,818 amino acids, i.e. neurofibromin which is expressed in many different tissues. Its precise role is unknown but it does act as a GTPase-activating protein in the same pathway of signal transduction as ras and it may act as a tumour suppressor in controlling the proliferation and differentiation of cells. Indeed, for normal embryological development to occur the spatial and temporal expression of the NF1 gene is crucial. The gene is located on chromosome 17q11-2. Two of these genes are enclosed in an intron of this gene which includes oligodendrocyte myelin glycoprotein. This membrane glycoprotein appears in the human brain around the time of myelination. The finding of an increased association of NF1 with glioma and MS suggests this may reflect a shared pathogenesis. The finding of the gene for NF1 on chromosome 17q11-2 is of particular interest and importance.

MS, A METABOLICALLY DETERMINED NEURO-DEGENERATIVE DISORDER?

Evidence from neuroimaging

Since the earlier work of Charcot, Dejerine, Marie and Dawson, neuronal loss in MS has been recognised, and more recently, this has been confirmed by MRI, ultrastructural and magnetic resonance spectroscopy (MRS) studies. Neuronal loss in MS is an essential
### TABLE 1
Types of glioma occurring with multiple sclerosis.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Age/Sex</th>
<th>Neoplasm</th>
<th>Multicentric</th>
<th>Connected with plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>Scherer</td>
<td>29 F</td>
<td>Glioblastomatosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1949</td>
<td>Munch-Peterson</td>
<td>49 F</td>
<td>Glioblastoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1950</td>
<td>Zimmerman &amp; Netsky</td>
<td>61 M</td>
<td>Glioblastoma</td>
<td>–</td>
<td>N/A</td>
</tr>
<tr>
<td>1962</td>
<td>Matthews</td>
<td>51 F</td>
<td>Astrocytoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1963</td>
<td>Brihaye et al.</td>
<td>62 M</td>
<td>Astrocytoma</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>1967</td>
<td>Boyazis et al.</td>
<td>54 F</td>
<td>Glioblastoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1967</td>
<td>Banard &amp; Jellinek</td>
<td>44 F</td>
<td>Oligodendroglioma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1968</td>
<td>Aubert et al.</td>
<td>50 F</td>
<td>Glioblastoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1972</td>
<td>Mathews &amp; Moosy</td>
<td>44 M</td>
<td>Mixed astrocytoma and oligodendroglioma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1973</td>
<td>Reagan &amp; Freiman</td>
<td>40 F</td>
<td>Glioblastoma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1974</td>
<td>Lynch</td>
<td>44 F</td>
<td>Glioblastoma</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1974</td>
<td>Currie &amp; Urich</td>
<td>37 F</td>
<td>Glioblastoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1977</td>
<td>Russell &amp; Rubinstein</td>
<td>36 F</td>
<td>Astrocytoma (glioblastoma)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1977</td>
<td>Palo et al.</td>
<td>52 F</td>
<td>Astrocytoma</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>1978</td>
<td>Spaar &amp; Wikstrom</td>
<td>63 F</td>
<td>Semi-malignant meningioma</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>1978</td>
<td>Scully et al.</td>
<td>57 F</td>
<td>Mixed astrocytoma and ependymoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1979</td>
<td>Kalimo et al.</td>
<td>36 F</td>
<td>Astrocytoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1980</td>
<td>Lahl</td>
<td>50 M</td>
<td>Glioblastoma with cerebral gliomatosis</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1981</td>
<td>Ho &amp; Wolfe</td>
<td>63 F</td>
<td>Protoplasmic astrocytoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1984</td>
<td>Vieregge et al.</td>
<td>43 F</td>
<td>Astrocytoma grade II</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1984</td>
<td>Malmgren et al.</td>
<td>54 M</td>
<td>Glioma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1986</td>
<td>Nahser et al.</td>
<td>42 F</td>
<td>Astrocytoma grade II</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1987</td>
<td>Barnard &amp; Geddes</td>
<td>43 F</td>
<td>Malignant oligodendroglioma</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>1989</td>
<td>Aarli et al.</td>
<td>63 M</td>
<td>Glioblastoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1989</td>
<td>Shankar et al.</td>
<td>34 F</td>
<td>Oligodendroglioma</td>
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<td>2000</td>
<td>De Caso et al.</td>
<td>63 F</td>
<td>Ependymoma</td>
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*In this case, the neoplastic astrocytic cells resembled the astrocytes within the demyelinated plaques.*
part of the disease since demyelination alone does not adequately explain the functional impairment and long-term disability. It is also important to stress here that there is significant heterogeneity in the pathological pattern of MS demyelination and myelin loss in MS is likely to be the final pathway of multiple pathogenetic mechanisms.

Data from MRS clearly point to early metabolic changes in evolving MS lesions. Based on new magnetic resonance technology, it is now clear that metabolic changes appear first, often weeks before (e.g. three months in one study) the appearance of gadolinium (Gd) enhancement in MS. Total brain (rather than regional) N-acetyl aspartate (NAA), a marker of functional neuronal mass, correlates well with relapses. Reduction of total brain NAA is an excellent predictor of focal relapses in MS, suggesting that relapses (and their biological marker, demyelination) are related to global reduction of brain metabolic function (reduced NAA), reversible in some cases. Since white matter has a limited metabolic repertoire, compromised areas of white matter will retain water and swell. Increased water content in the metabolically compromised white matter will appear as an increased signal in the T2-weighted images in MRI. Focal breakdown of blood-brain barrier (lesion enhancement) probably occurs in response to the metabolic changes, allowing macrophages to be drawn into the lesion. These cells will phagocytose the swollen myelin, representing the initial ‘inflammatory’ infiltrate well documented in Dawson’s original observations. That global metabolic compromise is an integral component of developing MS lesions is indicated by the fact that grey matter lesions are always present, notably in the basal ganglia and at the grey-white junctional areas of the cortex. This is distinct from primary oligodendrogial disease, as seen in progressive multifocal leukoencephalopathy (PML) that spares grey matter and (unlike MS) involves the subcortical ‘U’ fibres. Unlike conventional MRI, magnetic resonance spectroscopy studies in MS have shown very significant axonal damage, even in the normal appearing white matter (NAWMM), early in the disease. Magnetic resonance spectroscopy measures of NAA correlate with clinical changes in MS disability. Multiple sclerosis patients with progressive cerebellar deficit and low cerebellar functional scores have lower cerebellar NAA compared to MS patients with fewer cerebellar symptoms and the reduction in their NAA. N-acetyl aspartate measures of corpus callosum in MS showed a progressive decline in the NAA resonance in serial study. This is also true for the spinal cord where reduced NAA levels correlated with reduced axonal areas in the spinal cord cross-sections in an autopsy study. In contrast, post-mortem tissue sampling by using MRI has confirmed low specificity of T2-weighted imaging. Using in vivo quantitative magnetic resonance studies, T1-weighted images were found to be more relevant than T2-weighted images in identifying lesions that cause disability. T1 hypointensity (‘black holes’), on the other hand, strongly correlated with axonal loss.

Metabolic changes were observed well before the appearance of magnetic resonance lesions in serial MR studies that included proton MR spectroscopic imaging (MRSI), contrast-enhanced MRI imaging and volumetric lesion studies of 25 patients with mild to moderate clinical deficits over a period of two years. Regional metabolite changes were both dynamic and reversible. In four patients strong lipid peaks in the absence of Gd-enhancement and magnetic resonance-defined lesions were observed, clearly indicating that demyelination can occur independent of ‘inflammatory’ changes. It should be remembered that, when examined at autopsy, one-third of all plaques contain no inflammatory infiltrates. While focal reductions in NAA levels did not always imply axonal loss, reduction in whole brain NAA was a putative marker of the MS disease burden. As compared to healthy controls, reduction in whole brain NAA in this study was found to be greater in older rather than younger patients consistent with the clinical experience that older MS patients usually have worse outcomes. The age-dependent decrease of whole brain NAA in MRS suggests that progressive neuronal cell loss is a cardinal feature of the disease, very similar to other neurodegenerative diseases. The similarity of cerebellar MRS changes in MS patients with cerebellar symptoms and autosomal dominant cerebellar ataxia attest to this view.

Direct pathological studies of the NAWM have revealed axonal loss and the degree of volume loss was greater than that from the anticipated loss from MS lesions alone. Recently, it was shown with T1-weighted magnetic resonance follow-up studies that the degree of ‘inflammatory activity’ is a poor predictor of not only T1- but also T2-lesion load at long-term follow-up, indicating that the T2-lesion load is not an accurate measure of the MS pathology. Consistent with the previous observations, the authors of the latter study found that the baseline T1-lesion load was the single most important factor in the subsequent increases in hypointense T1-lesion load. Taken together, these findings clearly confirm that the so-called inflammatory-demystinating indices in conventional MRI (abnormal increased signals in T2-weighted MRI and Gd-enhancement) do not predict long-term MS disability and are poor outcome measures for treatment trials designed to prevent progression to disability. It also appears that long-term MS disability is largely predetermined by the axonal loss already present at the symptom onset, a feature characteristic of neurometabolic and degenerative diseases. Imaging and pathological studies in chronic demyelinated cervical spinal cord plaques clearly indicate that slow axonal degeneration rather than acute change is responsible for chronic disability in MS. A predominance of widespread NAWM changes over focal lesions appears to be the hallmark of primary progressive
of normal myelinated white matter can be measured by diffusion tensor MRI. In this form of neuroimaging, magnitude and translational motion of the water molecules (‘anisotropy’) with respect to the white matter fibre tracts can be defined. Myelin and cell membranes provide natural barriers to diffusion across the white matter fibres.\(^\text{183}\) As a result, the water molecules can diffuse only along these fibres. Therefore, a high degree of anisotropy is expected in normal myelinated white matter fibres and this has been confirmed in histologic and imaging studies.\(^\text{183-5}\) On the other hand, decreases in diffusion anisotropy have been shown to occur in diseases that affect myelin or axonal integrity, such as MS, neurodegenerative diseases, cerebral ischaemia and leukodystrophies.\(^\text{185-9}\)

In MS, reduction in the functional anisotropy in diffusion tensor MRI precedes any other change in the conventional MRI. This applies to patients with clinically definite MS and normal T2-weighted magnetic resonance scans\(^\text{190}\) and patients with clinically isolated syndromes suggestive of MS.\(^\text{191}\) The anisotropy measurements also correlate well with evidence from histologic and MRS studies.\(^\text{192}\) It is thus clear that the disease process in MS extends well beyond the borders of the plaque identified in the T2-weighted images. There is a progressive gradient in the decline of anisotropy observed in MS from the NAWM to the peri-plaque and intra-plaque white matter with the latter showing the most extensive changes. A progressive decrease of magnetisation transfer ratio is also seen to extend from the remote NAWM towards the plaque.\(^\text{192}\) In contrast, the white matter abnormalities in ADEM do not extend beyond the focal areas of injury and the magnetisation transfer ratios of the uninvolved brain and spinal cord in ADEM are practically identical to the values observed in the healthy control subjects.\(^\text{193}\) The anisotropic changes in the normal appearing brain tissue is always present in all clinical phenotypes of MS irrespective of their presentations.\(^\text{195, 191, 194}\)

The basis of the anisotropic gradient that extends from the NAWM to the fully formed MS plaque in MS is important in the understanding of its pathogenesis. Irrespective of the clinical phenotype, two consistent abnormalities are revealed in the MS brain by the newer imaging technologies. Firstly, there is reduced brain metabolism and secondly, the water diffusibility is reduced along the white matter fibre tract, and the plaque is centred round the area where the anisotropy is lowest. Such findings are unique to MS, being absent in ADEM, Devic’s neuromyelitis and in patients with other systemic immunological diseases associated with multiple T2-weighted signal abnormalities in the MRI.\(^\text{195}\) Changes in MRS and diffusion tensor imaging appear to occur before other magnetic resonance changes and correlate with functional impairment in MS.\(^\text{191}\) Results of a follow-up study showed that 80% of the newly formed MS lesions are hypointense on unenhanced T1-weighted scans associated with the highest anisotropy changes.\(^\text{196}\)

However, more than half (44%) of these new lesions returned to isointensity spontaneously during the course of the follow-up.\(^\text{196}\) This spontaneous reversibility is very characteristic of metabolic disease. Data from the MRS and diffusion tensor imaging do, therefore, suggest that MS is a neurodegenerative disease in which the rate of myelin loss is metabolically determined. In this paradigm, plaque formation is a subacute process that follows a failure of metabolic reversibility and characteristically occurs in an area farthest from the NAWM. This is comparable to the zonal architecture proposed in the functional anatomy of the hepatic lobule where the metabolic changes tend to be maximum towards the periphery of the lobule.

It may not be out of place to consider possible explanations for reduced anisotropy in MS. As already noted, anisotropic changes in the MS brain are extensive, being abnormal in virtually all white matter regions and always extending well beyond the focal areas of myelin loss.\(^\text{192}\) In the developing brain, increased permeability and anisotropic diffusion across myelin has been shown to occur before the onset of myelination. Premyelination anisotropy may be due to a number of changes, including an increase in fibre diameter and axonal membrane changes.\(^\text{197}\) This may explain why demyelination may occur in infancy or in the structural disorders of axons and myelin (leukodystrophies). It has also been postulated that as a result of change in energy metabolism, oligodendrocytes may fail to meet its required energy demand in mitochondrial encephalopathies leading to demyelination. However, anisotropy may also be reduced by glial proliferation.\(^\text{198}\)

Because glial cells are fairly amorphous and glial proliferation is not a structurally organised process, anisotropy will be reduced in areas where glial proliferation occurs.\(^\text{197}\) It is our contention that the reduced anisotropy in the MS brain is a direct function of glial proliferation and consequent metabolic changes in the myelin lead to plaque formation by way of increased permeability. It is the generalised glial proliferation in MS that accounts for the globally reduced anisotropy; the metabolic changes contribute to the formation of plaque in the areas of maximum compromise.

A final comment has to be made about the so-called ‘inflammatory’ magnetic resonance lesions. The conventional MRI data (T2-weighted and Gd-enhancement) in MS merely show that some MS plaques
are swollen (oedematous) with a breakdown of the blood-brain barrier. These changes would certainly be expected if myelin and cell membrane permeabilities are altered. However, to suggest that these magnetic resonance changes in the MS plaques reflect specific T-cell mediated autoimmune inflammatory process has not yet been substantiated. As previously stated, at least one-third of MS plaques in pathological studies show no evidence of inflammatory infiltrate, and the mononuclear infiltrate in the other plaques is either mild or inconsistent. Comparable infiltrates are encountered, as described, in diseased brain due to stroke, tumour or indeed, even in Alzheimer's or motor neurone disease. Logic therefore dictates that cellular infiltrates are unlikely to be responsible for oedema in the MS plaques or focal breakdown in the blood-brain barrier. This is certainly supported by the data from the magnetisation transfer and diffusion tensor MRI in MS.

Pregnancy and MS

The effect of pregnancy on MS provides an important clue to the nature of this yet unknown factor stimulating glial proliferation and reducing myelin metabolism. Pregnancy has an apparent stabilising effect on the clinical course of MS. Indeed, Confavreux has commented that the effect of pregnancy on MS is better than the treatment effects of β-interferon or glatiramer.200 However, the three-month, post-partum period shows an increasing relapse rate. The effect of pregnancy on MS contrasts sharply with systemic lupus erythematosus (SLE), a classical autoimmune disease, where a flare-up of disease is common during pregnancy.

Comparative epidemiology of MS and neurodegenerative diseases

In this review, we have suggested that MS is not an autoimmune disease due to its intrinsic clinical, immunological, radiological and histological differences with ADEM and its experimental model, EAE. In our opinion, MS has the characteristics of a metabolically determined neurodegenerative disorder with strong genetic influence. There is now evidence from epidemiological studies that other neurodegenerative diseases (Parkinson's disease and motor neurone disease), once thought to be evenly spread and to occur at a uniform rate throughout the world, are influenced by geographic factors similar to MS.201 This analogy can be extended further in that we, and others, have shown that MS may be precipitated, but not caused, by specific trauma to the CNS.50, 202 Trauma has also been implicated in the precipitation both of Parkinson's disease and of motor neurone disease.203, 204 Of great interest is the finding that electrical injuries are statistically significant in a prospective trial of looking at the role of trauma in MS,205 and both motor neurone disease and Parkinson's disease have been described as occurring following electrical injuries.206, 207 Further data indicating that MS is a progressive neurodegenerative disorder is found in a recent study looking at clinical analysis of 250 families in which a cohort of 262 pairs of co-affected siblings were studied.208 The authors of this report found that once the disease was established, concordance was more related to the ultimate clinical course than to the number of attacks or presentation and the end result of disability and handicap scores was similar.

The proposition that MS is a prototype autoimmune disease is weak and open to question: MS is not a model of EAE or, indeed, of any known autoimmune disease. Its histology compares more favourably with other forms of demyelination known to be metabolic in aetiology, such as leukoencephalopathies due to mitochondrial encephalopathy, central pontine myelinolysis and Marchiafava-Bignami disease. Many scholars of MS in the past have argued strongly that the disease is toxic/metabolic in origin.209 The suggested association of a HLA in MS is neither strong nor persuasive. Such data for a claimed association with DR2 would argue against any link with diabetes, since the presence of DR2 protects against this disorder. Whatever immunologic finding that has been claimed to be specific for MS is soon found wanting. There is never a shortage of candidates such as the heat-shock protein or β-crystalline that is found in brains with other neurological diseases as well as normals.210 It genuinely is time to seek a paradigm shift in the pathogenesis of MS and look anew at the known facts.

CONCLUSION

Multiple sclerosis remains a disease of unknown aetiology. In recent years, most researchers have uncritically accepted the hypothesis that it is an autoimmune disorder. An in-depth review of the literature failed to support this concept, and the immunological claims for this disease are tenuous and fragile. There is no one specific immunological abnormality found in MS that does not occur in patients with other diseases or in normal controls. The acceptance of EAE as a model for MS is an unfortunate error that has its basis on faith rather than science. Whilst EAE is a good example of an experimental organ-specific autoimmune disorder in animals, it cannot be accepted as a model for MS for a wide variety of reasons. This is particularly important in relation to the development of MS pharmacotherapy. We have analysed the literature on immune-modifying therapy in MS and it is clear that none of these agents can qualify as a candidate therapy under scrutiny.

A clear association of MS exists with other glial disorders of proliferation and differentiation. Based on comparative neuropathology and neuroimaging data, it is proposed that the initial lesion in MS is one of astrocytic proliferation and plaque formation and is a consequence of metabolic abnormality affecting myelin permeability. We believe these pathogenic changes in MS are influenced by a
combination of genetic and environmental factors. One of the genes most likely to be involved in MS pathogenesis may be located on chromosome 17. The gene expression in MS is influenced by external factors, and whilst such factors have not been identified with certainty, one of these is likely to be the influence of sunlight, perhaps mediated through vitamin D metabolism.\(^3\)\(^1\)

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