Seminar

Multiple sclerosis

Alastair Compston, Alasdair Coles

Multiple sclerosis is the prototype inflammatory autoimmune disorder of the central nervous system and, with a lifetime risk of one in 400, potentially the most common cause of neurological disability in young adults. As with all complex traits, the disorder results from an interplay between as yet unidentified environmental factors and susceptibility genes. Together, these factors trigger a cascade of events, involving engagement of the immune system, acute inflammatory injury of axons and glia, recovery of function and structural repair, post-inflammatory gliosis, and neurodegeneration. The sequential involvement of these processes underlies the clinical course characterised by episodes with recovery, episodes leaving persistent deficits, and secondary progression. The aim of treatment is to reduce the frequency, and limit the lasting effects, of relapses, relieve symptoms, prevent disability arising from disease progression, and promote tissue repair. Despite limited success in each of these categories, everyone touched by multiple sclerosis looks for a better dividend from applying an improved understanding of the pathogenesis to clinical management.

Previously unrecognised, multiple sclerosis makes a fleeting appearance in the early 19th century before taking centre stage as clinical neurology began to flourish in the 1860s. By the beginning of the 20th century, a disease only a few years earlier meriting individual case reports had become one of the most common reasons for admission to a neurological ward. Now, multiple sclerosis is recognised throughout the world, with around 2·5 million affected individuals, accounting for an estimated £1·2 billion expenditure per annum in the UK.[1] These crude statistics conceal the harsh reality of a frightening and potentially disabling disease for young adults. In writing, through music, or via images on canvas, talented individuals have portrayed their personal experiences of multiple sclerosis; they speak for the many denied these cultural conduits for expressing the hopes and fears of young adults facing an uncertain neurological future.

For the pathologist, multiple sclerosis is a disorder of the central nervous system, manifesting as acute focal inflammatory demyelination and axonal loss with limited remyelination, culminating in the chronic multifocal sclerotic plaques from which the disease gets its name. For the patient, multiple sclerosis threatens an apparently infinite variety of symptoms but with certain recurring themes and an unpredictable course. For the neurologist, multiple sclerosis is a disorder of young adults diagnosed on the basis of clinical and paraclinical evidence for at least two demyelinating lesions, affecting different sites within the brain or spinal cord, separated in time. For the clinical scientist, multiple sclerosis is the prototype inflammatory autoimmune disease of the central nervous system in which knowledge gained across a range of basic and clinical neuroscience disciplines has already allowed rational strategies for treatment. For all these groups, multiple sclerosis remains a difficult disease for which solutions seem attainable yet remain elusive.

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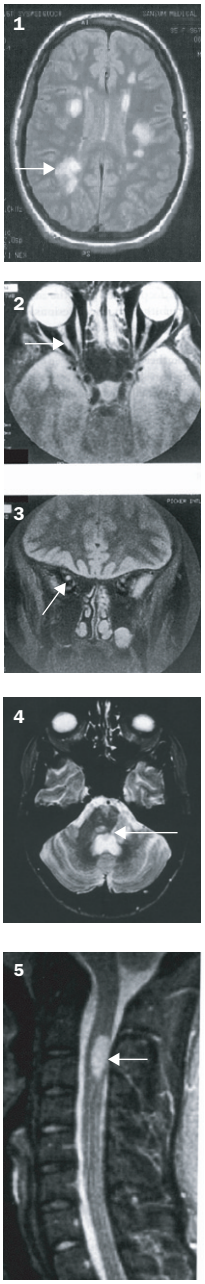
Pathological physiology and anatomy

The oligodendrocyte, a principal target of immune attack in multiple sclerosis, synthesises and maintains the myelin sheath of up to 40 neighbouring nerve axons in the central nervous system. Compact myelin consists of a condensed membrane, spiralled around axons to form the insulating segmented sheath needed for saltatory axonal conduction: voltage-gated sodium channels cluster at the unmyelinated nodes of Ranvier, between myelin segments, from where the action potential is propagated and spreads passively down the myelinated nerve segment to trigger another action potential at the next node.

The consequences of demyelination for saltatory conduction explain many clinical and laboratory features of multiple sclerosis. Partially demyelinated axons conduct impulses at reduced velocity—explaining the characteristic delays in conduction of evoked potentials. Demyelinated axons can discharge spontaneously and show increased mechanical sensitivity—accounting for the flashes of light on eye movement (phosphenes) and electrical sensation running down the spine or limbs on neck flexion (Lhermitte's symptom and sign). Partially demyelinated axons, whose safety factor for conduction is compromised, cannot sustain the fall in membrane capacitance induced by a rise in temperature, and conduction fails—leading to the characteristic appearance of symptoms and signs after exercise or a hot bath (Uhthoff's phenomenon). Ephaptic transmission (cross-talk) can arise between neighbouring demyelinated axons, resulting in paroxysmal symptoms—trigeminal neuralgia, ataxia, and dysarthria, or painful tetanic posturing of the limbs, lasting one or two minutes and often triggered by touch or movement. Individuals with multiple sclerosis characteristically tire during physical and cognitive tasks, and take longer to recover: although poorly

Search strategy

We did a computer-aided search of PubMed to March, 2002, for aspects of multiple sclerosis pertinent to this review, to supplement our existing awareness of the primary literature. Because of limitations on the number of citations, we made selections from the 11 648 reports published on multiple sclerosis in the past decade to support our interpretations with criteria for assessing experimental studies and evidence-based medicine.



Site	Symptoms	Signs	Treatment: Established efficacy	Equivocal efficacy	Speculative
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)	–	–	–
	Hemi-sensory and motor	Upper motor neuron signs	–	–	–
	Affective (mainly depression)		Antidepressants	–	–
	Epilepsy (rare)		Anticonvulsants	–	–
	Focal cortical deficits (rare)		–	–	–
Optic nerve	Unitateral painful loss of vision	Scotoma, reduced visual acuity, colour vision, and relative afferent pupillary defect	Low vision aids	–	–
Cerebellum and cerebellar pathways	Tremor	Postural and action tremor, dysarthria	–	–	Wrist weights, carbamazepine, isoniazid, beta-blockers, clonazepam, thalamotomy, and thalamic stimulation
	Clumsiness and poor balance	Limb incoordination and gait ataxia	–	–	–
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear, and other complex ophthalmolplegias	–	–	Baclofen, gabapentin, isoniazid
	Vertigo		–	Prochloropher-azine, cinnarizine	–
	Impaired speech and swallowing	Dysarthia and pseudo-bullbar palsy	Tricyclic anti-depressants	–	Speech therapy
	Paroxysmal symptoms		Carbamazepine, gabapentin	–	–
Spinal cord	Weakness	Upper motor neuron signs	–	–	–
	Stiffness and painful spasms	Spasticity	Tizanidine, baclofen, dantrolene, benzodiazepines, intrathecal baclofen	Botulinum toxin, IV corticosteroids	Cannabinoids
	Bladder dysfunction		Anticholinergics and intermittent self-catheterisation, suprapubic catheterisation	Desmopressin, intravescial capsaicin	Abdominal vibration, cranberry juice
	Erectile impotence		Sildenafil	–	–
	Constipation		Bulk laxatives, enemas	–	–
Other	Pain		Carbamazepine, gabapentin	Tricyclic anti-depressants, TENS	–
	Fatigue		Amantadine	Modafanil	4-aminopyridine, pemoline fluoxetine
	Temperature sensitivity and exercise intolerance		–	–	Cooling suit, 4-aminopyridine

Figure 1: **Lesion sites, syndromes, and symptomatic treatments in multiple sclerosis**
TENS=Transcutaneous electric nerve stimulation. T2-weighted magnetic-resonance imaging (MRI) abnormalities in the cerebrum (panel 1), right optic nerve (longitudinal section, panel 2, and transverse section, panel 3), brainstem and cerebellar peduncle (panel 4), and cervical spinal cord (panel 5).

understood, and probably multifactorial, fatigue in multiple sclerosis can be very disabling, even in isolation.

The symptoms and signs of multiple sclerosis merely reflect the functional anatomy of impaired saltatory conduction at affected sites (figure 1). The cerebrum is almost always involved when assessed with magnetic resonance imaging (MRI), but most white matter abnormalities cannot be linked to specific events or clinical symptoms. Involvement of the anterior visual pathway is the rule. Lesions of the brain stem and cerebellar pathways produce precise clinicopathological correlations; typically, coordinated movement of the eyes, limbs, bulbar musculature, and axial muscles is disrupted. The spinal cord is frequently affected, leading to alterations in motor, sensory, and autonomic functions.

How is the disease diagnosed?

Revised diagnostic criteria classify individuals in the categories of multiple sclerosis, not multiple sclerosis, or possible multiple sclerosis, and incorporate evidence from MRI.[2] As with the previous diagnostic criteria, individuals must have a minimum of two attacks, affecting more than one anatomical site, but, assuming an initial presentation suggestive of multiple sclerosis, the second lesion need not necessarily be clinically expressed (figure 2).

Investigations are done for four main reasons in patients with multiple sclerosis: they allow doctors to see the anatomical dissemination of lesions in time and space (imaging); they permit the assessment of intrathecal inflammation (spinal fluid analysis); they show that conduction has altered in a pattern consistent with

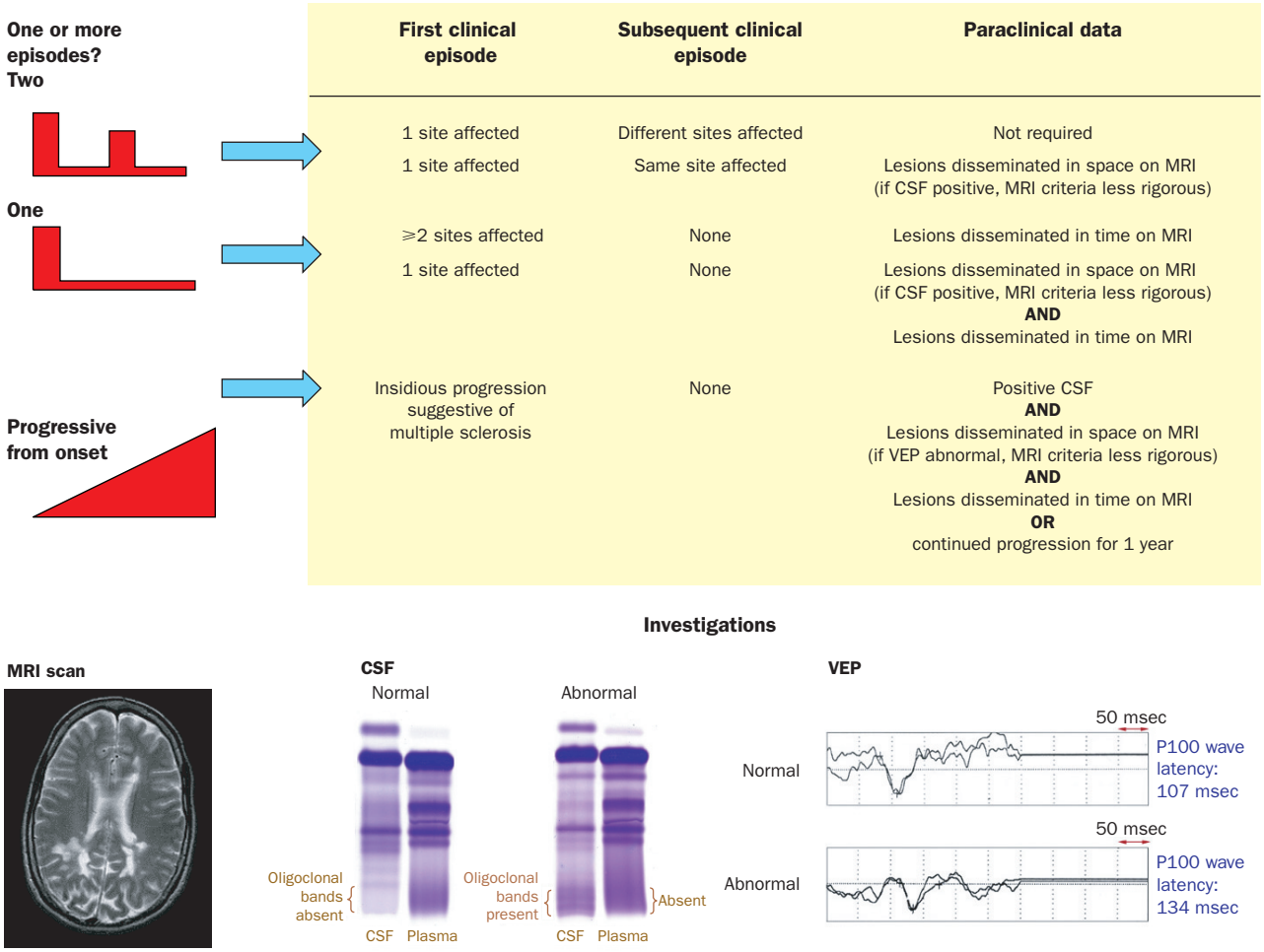


Figure 2: **Criteria for diagnosis of multiple sclerosis**
MRI=magnetic resonance imaging; CSF=cerebrospinal fluid; VEP=visually evoked potential test. The principle is to establish that two or more episodes affecting separate sites within the central nervous system have occurred at different times, using clinical analysis or laboratory investigations. Dissemination in space based on magnetic resonance imaging (MRI) requires: any three features from (1) one gadolinium (Gd) positive or nine T_2 MRI lesions; (2) ⩾1 infratentorial lesion; (3) ⩾1 juxtacortical lesion; or (4) ⩾3 periventricular lesions. If VEPs or CSF are positive, ⩾2 MRI lesions consistent with multiple sclerosis are sufficient. Dissemination in time of magnetic resonance lesions requires: one Gd positive lesion at >3 months after the onset of the clinical event; or a Gd positive or new T_2 lesion on a second scan repeated 3 months after the first. Patients having an appropriate clinical presentation, but who do not meet all of the diagnostic criteria, can be classified as having possible multiple sclerosis.

demyelination (evoked potentials); and they allow the exclusion of conditions that mimic the disease. The most frequent error is to allow the diagnosis of multiple sclerosis in patients with progressive disease at a single site (usually spinal) where a structural lesion has not been excluded. Other traps include making the diagnosis when several related individuals are apparently affected (see below); diagnoses other than familial multiple sclerosis include the hereditary spastic paraplegias and ataxias, and (much rarer) adult onset leucodystrophies and vasculopathies (CADASIL). The clinical and laboratory features of multiple sclerosis are mimicked by granulomatous and vasculitic diseases of the brain, each of which can arise in the absence of systemic manifestations or informative serology.

More than 95% of patients with multiple sclerosis have T_2-weighted white matter abnormalities, but these are not diagnostic. They occur about 15 times more frequently than new clinical events. Imaging is not necessary for diagnostic purposes in patients with a history of relapsing disease, affecting multiple sites within the central nervous system. The major practical use is in the investigation of individuals with clinically isolated lesions or progressive disease at a single site. For instance, in a study of 71 patients with a clinically isolated lesion followed-up prospectively for 14 years,[3] 44 of 50 with abnormal MRI scans at presentation subsequently developed multiple sclerosis, compared with four of 21 who had normal imaging results. Furthermore, the number and volume of abnormal MRI lesions at presentation and at 5 years was predictive of disability at 14 years, albeit with relatively low correlation coefficients of 0·5 and 0·6, respectively. There is less cerebral involvement in patients with primary progressive multiple sclerosis than in those who have comparable disability from secondary progression. Variations in imaging protocols are beginning to distinguish separate components of the underlying pathological process—inflammation (gadolinium DTPA enhancement of T_1-weighted lesions, indicating that the lesion is of recent origin), demyelination (magnetisation transfer ratio), astrocytosis (T_2-weighted lesions, the signal arising from increased water content), and axonal damage (reduction in diffusion tensor imaging anisotrophy and N-acetyl-aspartate spectra with chemical shift imaging, or the presence of focal atrophy and T_1-weighted black holes).[4]

Cerebrospinal fluid protein electrophoresis shows oligoclonal IgG bands in more than 90% of cases. Their

role in the pathogenesis of multiple sclerosis is unresolved. Screening spinal fluid against cDNA expression, phage display, or random peptide libraries has not distinguished common antigen specificities; some antibodies are directed against components of the oligodendrocyte or its myelin membranes, and others recognise extrinsic antigens including viruses, but collectively these specificities only account for a minority of the bands. Diagnostically, spinal fluid oligoclonal bands confirm that the underlying pathology is inflammatory, which can be useful in excluding alternative explanations, especially in the context of progressive spinal cord syndromes and in elderly patients in whom imaging abnormalities are not discriminatory.

Demyelination characteristically delays the latencies of visual, auditory, and somatosensory evoked potentials, as well as central motor conduction times, leaving the amplitude of responses unchanged. Before the advent of MRI, these abnormalities provided evidence for clinically silent lesions; now, their role is confined to the provision of circumstantial evidence for demyelination in diagnostically difficult situations, such as syndromes that progress from onset.

The natural history of multiple sclerosis

Multiple sclerosis affects twice as many women as it does men; this unexplained bias mimics that seen in other putative autoimmune diseases. The disease has an incidence of about seven per 100 000 every year, prevalence of around 120 per 100 000, and lifetime risk of one in 400. 80% of patients present with relapsing/remitting disease and, typically, the illness passes through phases of relapse with full recovery, relapse with persistent deficit, and secondary progression. In about a quarter of patients, multiple sclerosis never affects activities of daily living; conversely, up to 15% become severely disabled within a short time. Episodes happen at random intervals, but initially average about one per year, decreasing steadily thereafter. In 20% of patients, the disease is progressive from onset, hence termed primary progressive—affecting the spinal cord and, less frequently, the optic nerve, cerebrum, or cerebellum. Disease onset is usually in the third or fourth decade, but 2% of patients with multiple sclerosis present before age 10 years, and 5% before age 16 years. In children, the distinction from acute disseminated encephalomyelitis can often only be established by observing the subsequent natural history. Overall, life expectancy is at least 25 years from disease onset with most patients dying from unrelated causes.

The prognosis is relatively good when sensory or visual symptoms dominate the course of multiple sclerosis in adults, and there is complete recovery from individual episodes. This pattern is most common in young women. Conversely, motor involvement, especially when coordination or balance are disturbed, has a less positive prognosis. The outlook is also poor in older men who develop the disease. Frequent and prolonged relapses with incomplete recovery at onset and a short interval between the initial episode and first relapse are adverse prognostic features,[5] but the main determinant of disability is onset of the progressive phase.[6]

Fixed disability in multiple sclerosis is acquired through two distinct mechanisms: incomplete recovery from relapse and disease progression. Patients with relapsing-remitting multiple sclerosis accumulate disability from disease onset more slowly than those with primary progressive multiple sclerosis. However, beyond a degree of disability sufficient to limit walking to less than 500 m without aid or rest (Kurtzke expanded disability status scale [EDSS] of 4·0), subsequent accumulation no longer correlates with mode of presentation, suggesting that the pathological substrate for progression determines disability at this stage of the disease.[7]

Prospective studies show that around 10% of upper respiratory (adenovirus) and gastrointestinal infections, arising in patients with multiple sclerosis, are followed by relapse, and about 30% of new episodes relate to infection. The emerging evidence suggests that disease activity is neither increased nor initiated by vaccination.[8,9] There is a reduction in relapse rate for each trimester of pregnancy, but with about a three-fold higher risk in the puerperium,[10] and no net effect of pregnancy on relapse rate. There is no evidence that trauma causes multiple sclerosis, triggers latent disease in someone who has the underlying disease process, or alters the course in individuals who have already experienced symptoms. People with multiple sclerosis cope less well with symptoms while exposed to stress, but psychological factors do not directly affect disease activity.

What causes multiple sclerosis?

Multiple sclerosis is caused by an interplay between genes and the environment. The disease predominantly affects northern Europeans. There is a familial recurrence rate of about 15%. The age-adjusted risk is higher for siblings (3%), parents (2%), and children (2%) than for second-degree and third-degree relatives. Recurrence in monozygotic twins is around 35%. The risk for half-siblings is less than for full siblings. Recurrence is higher in the children of conjugal pairs with multiple sclerosis (20%) than in the offspring of single affecteds (2%). Conversely, the risk is not increased either for individuals adopted into a family with an affected individual or in the non-biological relatives of adoptees who themselves develop multiple sclerosis (figure 3). Unlike some other complex traits, large Mendelian pedigrees do not seem to contaminate series and bias the evidence for heritability; multiple sclerosis seems to be genuinely polygenic.[11]

The genes responsible for complex traits are not mutations coding for aberrant gene products but normal polymorphisms. They act independently or through epistasis, and each polymorphism can exert a small contributory effect on some as yet undefined structure or physiological function. Susceptibility genes can be identified by association or linkage, or both, targeted either at candidate regions or applied systematically across the entire genome.

Extensive searches have yielded few secure candidate regions. Results of population studies suggest an association between the class II MHC alleles DR15 and DQ6 (DRB1*1501 and DQB2*0602) and the gene for TNF-α encoded within the same linkage group. A specifically different association (with DR4 and its DRB1*0405-DQA1*0301-DQB1*0302 genotype) is seen in Mediterranean populations. The list of candidate genes that have been screened includes many adhesion molecules, immune receptors or accessory molecules, cytokines and their receptors or antagonists, chemokines, growth promoting molecules, and structural genes of the myelin-oligodendrocyte unit. Disappointingly, the low yield from this trawl is not definitively advanced by eight whole genome linkage screens done in USA, Canada, UK,[12] Finland, Sardinia, Italy, Scandinavia, and Turkey. Each cohort involved between 21 and 225 families, together involving in excess of 1500 individuals, for each of between 257 and 443 microsatellite markers. In common with most other complex traits, no major susceptibility gene has yet been identified, although

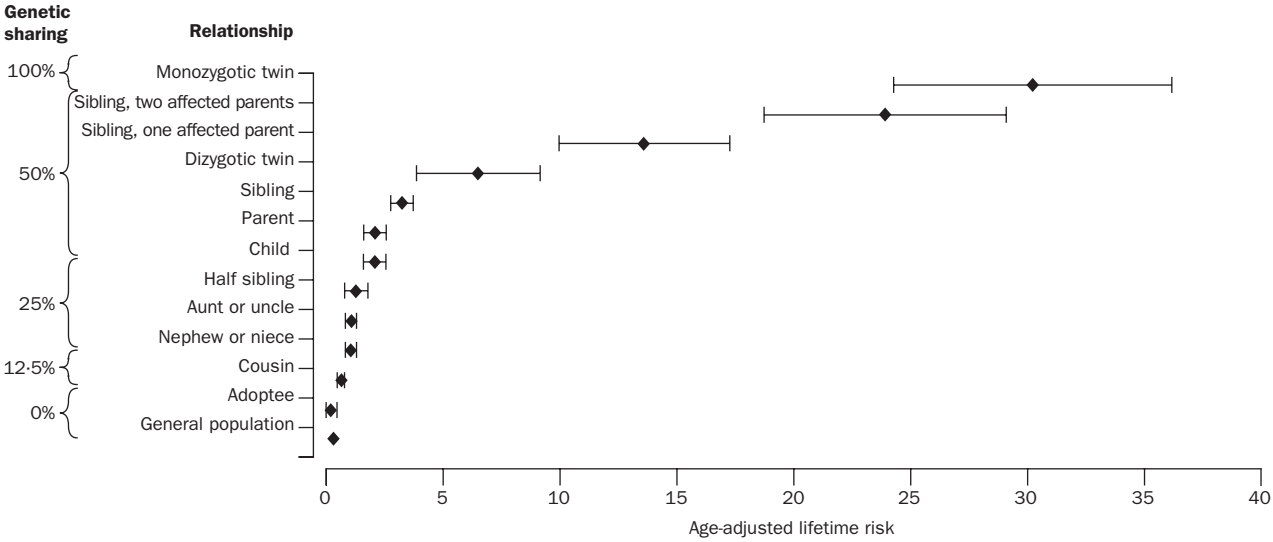


Figure 3: **Recurrence risks for multiple sclerosis in families**
Age adjusted recurrence risks for different relatives of probands with multiple sclerosis. Pooled data from population based surveys. Estimated 95% CIs are shown (kindly prepared by Simon Broadley).

several promising chromosomal linkages are provisionally linked and associated with multiple sclerosis—at 1p, 6p, 10p, 17q, and 19q.[13]

The distribution of multiple sclerosis cannot be explained on the basis of population genetics alone. Outside Europe, prevalence rates among white people are half those documented for many parts of northern Europe. In Australia and New Zealand, there are gradients in frequency that do not follow genetic clines. The risk is higher for English-speaking white people who migrate into South Africa as adults than as children. The low frequency of multiple sclerosis in Africans increases substantially for first-generation descendants raised in the UK. Results of surveys of multiple sclerosis have prompted speculation on the occurrence of epidemics in Iceland, the Orkney and Shetland Islands, and the Faroes although others prefer the interpretation that these merely indicate improved case recognition. There is age-linked susceptibility to viral exposure in those who are constitutionally at risk of developing the disease. Attempts to reliably implicate specific environmental agents are frustrating. Recent, yet unsubstantiated candidates, include *Chlamydia pneumoniae*[14,15] and human herpes virus 6.[16]

Evolution of the plaque

Maturation of the individual lesion involves several stages:

- immune engagement
- acute inflammatory injury of axons and glia
- recovery of function and structural repair
- post-inflammatory gliosis and neurodegeneration.

Healthy individuals harbour autoreactive myelin T cells, normally kept in check by regulatory T cells. One hypothesis to explain the breakdown of immune regulation in autoimmune diseases is molecular mimicry, which suggests that peptide (the environmental factor), presented in the groove of specific class II molecules (one component of inherited risk), is immunologically indistinguishable from self-antigen and, hence, an appropriate response to infection generates inappropriate inflammation against some component of the oligodendrocyte-myelin unit. In common with all organ-specific autoimmune diseases, this systemic defect results not in a sustained autoimmune attack on the entire target organ but, rather, in inflammatory lesions that are temporally and spatially segregated.

Failure of regulation leads to proliferation, activation, and entry into the circulation of autoreactive T cells; they express adhesion molecules and induce reciprocal changes in endothelia, allowing access across the blood-brain barrier into the central nervous system. There, activated T cells re-encounter antigen and activate microglia (the CNS macrophage); they, in turn, express class II molecules, re-present antigen to T cells, and set up a proinflammatory loop, which provides an infiltrate rich in activated T cells and microglia with some neutrophils (figure 4).

Toxic inflammatory mediators are released, sustaining breakdown of the blood-brain barrier and leading to injury of axons and glia. Nitric oxide might act directly on normal or hypomyelinated axons, transiently blocking conduction[17] and reversibly increasing deficits arising from already compromised pathways. As acute inflammation resolves, pathways are released from nitric oxide-induced physiological conduction block. Symptoms also improve as surviving functional pathways are reorganised at the cellular[18] and systems[19] level. Together, these mechanisms account for remission early in the disease. But tissue vulnerability is easily exposed. When compounded by high axonal firing frequency, nitric oxide causes structural (and hence irreversible) changes to axons.[20] Axonal transection in acute inflammatory plaques is shown histologically[21] and radiologically through reduction in the neuronal spectroscopic marker, N-acetyl aspartate (NAA).[22] These transected axons undergo Wallerian degeneration during the subsequent 18 months,[23,24] but this action does not seem to extend the lesion or shape the clinical deficit.

Cytokines and growth-promoting factors released by reactive astrocytes and microglia as part of the acute inflammatory process promote endogenous remyelination. But, over time, astrocyte reactivity seals the lesion and gliosis causes a physical barrier to further remyelination, reducing the capacity to accommodate cumulative deficits, and marking transition to the stage of persistent deficit.

Most axonal loss is seen in secondary progressive multiple sclerosis.[25] We propose that chronic axonopathy is not due directly to inflammation, but results from loss of trophic support normally provided to axons by myelin or glia, acting directly or through the maintenance of electrical activity, or both.[26,27] As such, chronic axonal degeneration might slowly increase the clinical deficit, decaying a compromised but functioning pathway and leading to disease progression.

Treatment of multiple sclerosis

Against this background, our analysis of treatments follows a mechanistic approach rather than clinical pragmatism. The aims of treatment are to:

- reduce relapse rates
- prevent fixed disability directly attributable to relapse
- provide symptomatic management of fixed neurological deficits
- prevent disability acquired through progression
- treat established progression.

Reducing relapse rates in multiple sclerosis

Since permanent disability can be caused by incomplete recovery from episodes, relapse frequency is bound to correlate with accumulation of disability during the relapsing-remitting phase of multiple sclerosis. The dividend from reducing the relapse rate is best shown by use of the beta interferons: interferon beta-1a (Avonex, Biogen, and Rebif, Ares-Serono), and interferon beta-1b (Betaferon and Betaseron, Schering), which has one aminoacid substitution and is non-glycosylated. These type-1 interferons were first used in multiple sclerosis for their anti-viral action, in view of the propensity of viral infections to trigger relapses. In fact, their mechanism of action is immunological and complex: we prefer the evidence for functional antagonism of proinflammatory cytokines and downregulation of class II MHC antigen expression;[28] but other modes of action[29]—including effects on the blood brain barrier[30]—can be equally well argued. The three beta interferons have been studied in separate placebo-controlled trials[31–33] of between 301 and 560 patients with relapsing-remitting multiple sclerosis initially over 2 years, but some extension studies have also been done.[34,35] In all, the annual relapse rate for individuals treated with interferon beta was significantly reduced by 30–37% (placebo group rates ranging from 0·9 to 1·2, and treated patients from 0·61 to 0·78 relapses per year). Only in trials of the two interferon beta-1a preparations, not interferon beta-1b, was this change in relapse rate also accompanied by reduction in the accumulation of disability. But this reduction could be accounted for by a fall in the accumulation of relapse-related deficits, rather than an effect on secondary progression.

Three other agents reduce relapse frequency, and the accumulation of disability, in relapsing-remitting multiple sclerosis; each has similar efficacy to the beta-interferons and acceptable adverse effects profiles.

Glatiramer acetate (Copaxone, Teva), a mixture of synthetic polypeptides composed of four aminoacids, was noted serendipitously to suppress experimental allergic encephalomyelitis, perhaps by inhibiting the binding of myelin basic protein (MBP) to the T-cell receptor or by altering the phenotype of myelin-autoreactive T cells.[36] The drug is licensed for the treatment of relapsing-remitting multiple sclerosis in the USA and in Europe on the basis of results from a trial of 251 patients,[37] in which the annualised relapse rate was reduced by 25% in the treated group.

Azathioprine inhibits lymphocyte proliferation by inhibiting purine synthesis, and probably has similar efficacy to the beta interferons, although the trial data were obtained in a less rigorous manner and reported more candidly.[38,39]

Mitoxantrone inhibits DNA repair and synthesis in dividing and non-dividing cells through inhibition of DNA topoisomerase II; it is potentially much more toxic than the beta interferons, but has a US licence for the treatment of aggressive relapsing disease, including patients with high relapse frequency in the progressive phase.[40,41]

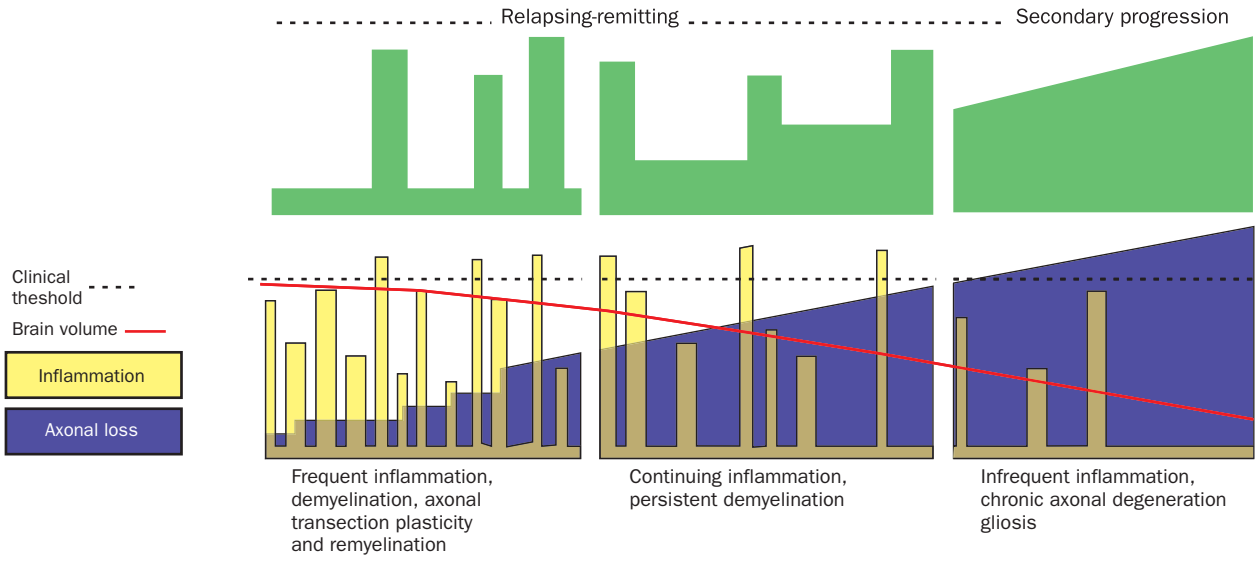
Prevention of disability attributable to relapse

Corticosteroids, bound to their cytoplasmic receptors, enter the cell nucleus and inhibit transcription of proinflammatory cytokines, such as interleukin 1, interleukin 2, tumour necrosis factor-α (TNF-α) and proinflammatory enzymes, including collagenase, elastase, and plasminogen activator. These anti-inflammatory effects have long been used for acute treatment of multiple sclerosis relapses—conventionally given as intravenous methylprednisolone over 1–5 days,[42] although oral steroids might be just as effective.[43] All trials to date indicate that corticosteroids reduce the duration of relapses and hence their short-term morbidity, but not the ensuing permanent deficits. Interpretation of the most comprehensive study—the Optic Neuritis Treatment Trial (ONTT)[44]—has been controversial. 427 patients were randomly assigned placebo or corticosteroids to be given intravenously or orally. At 1 year, there was no difference in visual function of the affected eye between treatment groups. At 2 years, there was a significant increase in recurrent optic neuritis in the oral corticosteroid group; and a significant reduction in the proportion of patients with a second demyelinating episode in the intravenous steroid group.[44] Intuitively, these post-hoc results seemed implausible, and they were no longer apparent at 5 years.[45]

Our position is that corticosteroids might fail to reduce disability acquired through relapses because their administration is delayed. Peripheral mononuclear cell production of nitric oxide ex vivo reaches a peak within 72 h of symptom onset during relapses of multiple sclerosis;[46] corticosteroid administration after that time—at 6 days in ONTT—is unlikely to protect or rescue axons from acute inflammatory transection. Support for this interpretation comes from a trial in which 90 people with relapsing-remitting multiple sclerosis were randomised to receive best medical care with the option for steroids only during relapses, or regular pulsed corticosteroids: 5 g methylprednisolone over 5 days every 4 months for 3 years, then every 6 months for the next 2 years. At 0·6, the annual relapse rate was equivalent for both groups. But the regular pulsed group had significantly less disability, lower probability of accumulating sustained disability, lower T1 lesion volume, and less brain atrophy at the end of 5 years. The implication is that regular pulsed corticosteroids do not alter the mechanisms that initiate relapses in multiple sclerosis; rather, they reduce the consequences of each relapse for axons.[47]

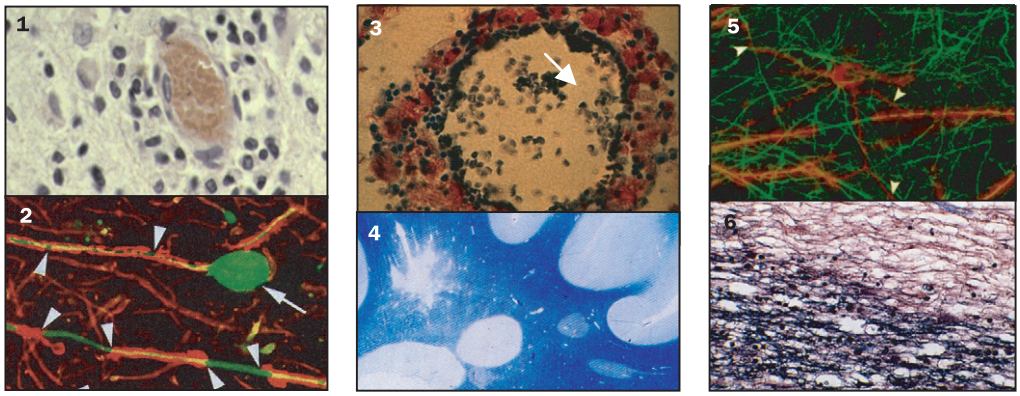
Symptomatic management of fixed neurological deficits

Fixed neurological deficits in multiple sclerosis are best managed by a multidisciplinary team, attending to physical therapies, psychological, and social interventions supplemented by medical treatments. The benefits of intense inpatient rehabilitation outlast the duration of therapy by up to 9 months.[48] The symptoms that are most amenable to treatment are spasticity and sphincter dysfunction (figure 1). Spasticity causes discomfort and

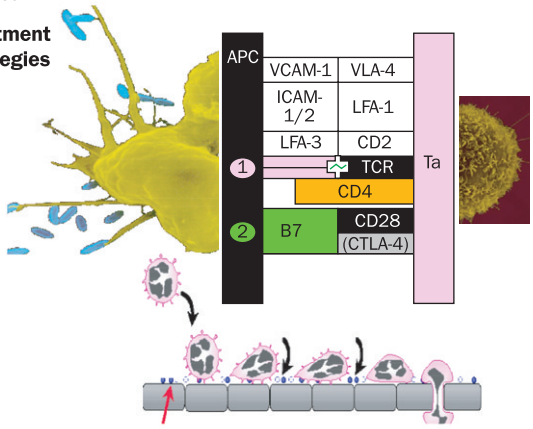


Pathology

Perivascular inflammation (panel 1) causes acute axonal transection (panel2),[21] and microglimedicated removal of myelin (panel 3) with persistent demyelination despite some remyelination (panel 4); chronic lesions show further axonal loss (panel 5)[72] and gliosis (panel 6).
This scheme does not depict primary progressive multiple sclerosis in which there is pronoused axonal degeneration with or without a preceding inflammatory phase.

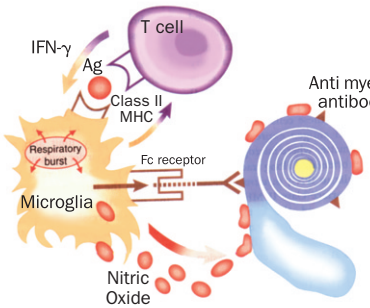


Treatment strategies



Action on peripheral autoreactive T-cell activation or migration, or both

Mitoxantrone
Azathioprine
Methotrexate
Cyclophosphamide
Paclitaxel
Bone marrow transplantation
Teriflunomide
Aletuzamab (Campath-1H)
Natalzumab (anti-VLA4)
Altered peptide ligand
T-cell vaccination
Mucosal tolerance

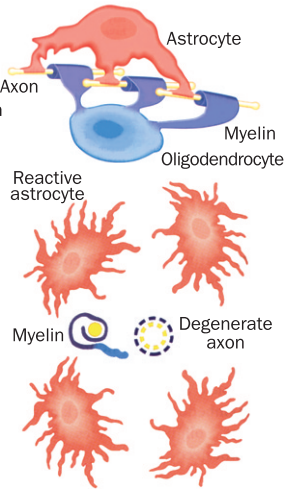


Action on T-cell-microglial interaction in the central nervous system

IFN-β
Glatiramer acetate
Gene therapy
Cytokine therapies
Metalloproteinase inhibitors
Macrophage inhibitors
IFN-α

Axon protection

IV methylprednisolone
Riluzole



Action to promote repair

Growth factors
IV immunoglobulin
Cell implantation

Figure 4: **The course, pathogenesis, and treatment of multiple sclerosis**

hinders care. It is usefully treated by baclofen, which acts on spinal cord GABA-$_B$ receptors to suppress reflex arcs that have been released from higher inhibitory control; or tizanidine, which acts through spinal cord α_2 receptors to modulate presynaptic release of excitatory aminoacids. Bladder symptoms are most easily categorised by measuring the postmicturition bladder volume. If greater than 100 mL, there is primarily failure to empty and the treatment is ideally intermittent self-catheterisation; if the bladder empties fully but stores poorly, the detrusor might be inhibited by anti-cholinergics such as oxybutynin.[49] In fact, most patients have a combination and experience the urge frequently to empty a partially filled bladder against a closed sphincter. Erectile impotence is successfully treated with sildenafil citrate, a phosphodiesterase inhibitor that acts predominantly on nitric oxide within the penile vasculature. Paroxysmal attacks respond well to membrane-stabilising drugs—typically carbamazepine. No pharmacological treatment has shown a useful effect on the tremor of multiple sclerosis. There are advocates for thalamotomy and thalamic stimulation in highly selected patients. Fatigue cannot be satisfactorily treated; lowering body temperature might help and small trials report some benefit from amantadine[50] and modafanil.[51]

Prospects for improved treatment of disease activity

In view of the fact that the ability to suppress relapses and limit their consequences is partial, no informed analyst could reasonably conclude that (despite their achievements) the beta-interferons are a definitive therapy in multiple sclerosis. The pharmaceutical industry has responded by sponsoring studies with combinations of established drugs (such as beta interferon and cyclophosphamide) without compelling evidence for synergistic benefit to date, together with a significant investment in novel immunotherapeutic strategies.

There are two approaches to reduce the activation and proliferation of autoreactive T cells. One is to search for new agents that suppress immune activity non-specifically and have acceptable safety profiles. Past attempts (with cyclophosphamide, ciclosporin, lymphoid irradiation, cladribine) have shown evidence for efficacy but with major side-effects; examples of this legacy are paclitaxel, teriflunomide, and autologous bone marrow transplantation, in which the limited efficacy seen to date must be weighed against the procedural mortality of around 5%.[52] The second strategy is to assume that the specific interaction between MBP, T cells, and antigen-presenting cells is the pivotal event driving multiple sclerosis. Several drugs have been designed to manipulate this interaction—for instance, vaccination with T-cell receptor subtypes,[53] myelin-basic protein-specific T-cell clones,[54] or disrupted MBP peptides. Although the results are disappointing, it would be premature to judge whether the strategy is wrong or the reagents insufficiently active. The two trials of altered MBP-peptide ligand therapy in multiple sclerosis are instructive. The hope was that, by minor changes in the presumed immunodominant peptide, autoaggressive MBP-reactive T cells might be tolerised. In fact, one drug promoted MBP Th1 cells that caused relapses of multiple sclerosis[55] and another induced Th2 MBP reactivity, which might have reduced multiple sclerosis disease activity, but caused intolerable allergic adverse effects.[56] A trial of oral myelin therapy, designed to exploit the innate capacity of mucosal cells to induce tolerance to gut proteins, also failed to show any efficacy.[57]

Alternatively, there are treatment strategies to reduce the effect of activated T cells; by blocking their entry into the brain (with an antibody against the α4 integrin, Antegren, in phase III trials)[58] or by neutralising putative toxic products. For instance, there have been two studies of agents that antagonise TNF-α, a cytokine believed to drive inflammation in multiple sclerosis. Unexpectedly, clinical relapses and MRI lesion formation each increased.[59,60] This result indicates our limited understanding of the pathogenesis of multiple sclerosis and the usefulness of therapies as experimental probes.

Prevention of disability acquired through progression

There have been three trials of interferon beta in secondary progressive multiple sclerosis. One, involving 718 patients treated with Betaferon, was stopped early because a significant effect on disability was achieved; treated patients took 9–12 months longer to reach a sustained increase in disability (by one Kurtzke point) than did controls.[61] This study led to extension of the European licence for Betaferon for patients with secondary progressive multiple sclerosis. However, a larger study[62] with the same agent given to 939 patients with secondary progressive multiple sclerosis from the USA, showed no benefit on disability. Patients in the US trial had longer disease duration and fewer relapses, in the 2 years before the study and during the trial, than did those in the other study.[61] Similarly, treatment with Rebif for 3 years had no effect on disability in 618 patients with secondary progressive multiple sclerosis.[63] These patients were older, had longer disease duration, and had fewer relapses than seen in those in the European Betaferon study. The implication is that positive results of the European Betaferon study could have arisen through reduction in accumulation of disability dependent on relapse rather than an effect on disability due to disease progression. This view is supported by the finding of equal rates of cerebral atrophy between the placebo and treated groups,[64] although an apparent delayed effect of interferon beta on cerebral atrophy had been seen in an earlier study.[65]

The relation between progression and relapse is emphasised by a small, uncontrolled study of patients with secondary progressive disease treated with a short pulse of Campath-1H (a monoclonal antibody that depletes T cells and modulates their activity). New MRI lesion formation and relapses were almost completely abolished for 18 months.[66] However, half of the patients continued to have progression of disability; these patients showed continued cerebral atrophy, and loss of spectroscopic markers of axons, despite the absence of cerebral inflammatory activity. Patients who progressed also had the greatest MRI inflammatory activity before treatment, suggesting that the progressive phase of multiple sclerosis indicates chronic axonal loss triggered by inflammation but maintained through non-inflammatory mechanisms. A similar dissociation between effective suppression of new lesions and continued cerebral atrophy in progressive patients was seen in a trial of the lymphocytoxic drug cladribine, a purine nucleoside analogue resistant to the action of adenosine deaminase.[67]

Our conclusion is that immunomodulatory drugs are of little use once axonal degeneration has reached a critical threshold and clinical progression is established. It follows that there might be an opportunity, early in the disease course, to suppress those components of the inflammatory process that initiate the cascade leading to delayed progression. Thus, the aim of immunotherapies is not only to reduce relapse frequency, but also to prevent transition to the secondary progressive phase of the illness. There have been two placebo-controlled studies[68,69] of interferon beta-1a in the earliest identifiable form of the

disease: 241–383 patients with a single clinical demyelinating event and multiple lesions on MRI, a poor prognostic sign for a subsequent diagnosis of multiple sclerosis. The known effect of interferon beta-1a on relapse rate was replicated; treatment reduced the chance of developing a second episode over 2–3 years by 25–44%. However, there was no difference in disability between the groups and, with such a short observation period, no likelihood of detecting an effect on rate of transition to secondary progressive disease. Thus, the essential issues in the therapy of multiple sclerosis—does early effective anti-inflammatory therapy reduce the proportion of patients who ever enter the secondary progressive phase, or usefully affect the slope of that progression?—are only now being addressed in trial design. Time has been lost, and several years will pass before an answer is available. But, since the result cannot be prejudged, parallel strategies for limiting the effect of progression are needed.

Can surviving axons be remyelinated?

The informed patient often expresses disappointment that management aims merely to limit further damage without seeking to restore the neurological past. Endogenous remyelination is limited to the acute inflammatory phase, and this timing raises the issue of whether, paradoxically, anti-inflammatory treatment might contribute to the failure of repair. For those axons that degenerate early as a direct result of the inflammatory process, efforts at remyelination might have little to offer; conversely, if the naked axon is resistant to the inflammatory milieu but has poor survival properties, remyelination might be neuroprotective and its timing important.

The therapeutic challenge is whether to enhance endogenous remyelination or develop exogenous cell-based therapies. Experimentally, endogenous remyelination restores conduction and function in young and adult nervous systems.[70,71] The lesions of multiple sclerosis do contain oligodendrocyte progenitors, but these seem unable to usefully engage naked axons.[72–74] Manipulation of mechanisms involved in receptor-ligand growth factor interactions during the inflammatory phase of tissue injury might energise these indolent progenitors and improve remyelination. Thus, one option is to wait until a therapy is available that can be given systemically and delivered simultaneously to all affected parts of the central nervous system. The alternative is first to prove that structure and function can usefully be restored in a single informative lesion before tackling the secondary task of making this intervention diffusely available in the central nervous system. The initial proof of principle will almost certainly involve cell implantation; at present, the most promising candidates are autologous peripheral nerve Schwann cells[75] or olfactory bulb ensheathing cells.[76] How best to plan the difficult transition from experimental to clinical science in the context of a multifocal and multiphasic disease has been much discussed. The ideal lesion would be accessible, responsible for clinically significant and stable deficits, resulting from persistent demyelination, and at a site where the risks of failure would be acceptable (perhaps through the presence of an intact paired structure or pathway) and where tissue was shown to be undergoing progressive axonal degeneration in the absence of active inflammation. The optic nerve is perhaps the best candidate, because the symptoms are clinically eloquent, physiological assessment and imaging are well developed, and serial atrophy is seen after unilateral optic neuritis despite recovery of vision;[77] this combination suggests postinflammatory axonal degeneration consistent with loss of trophic support from myelin.[27]

Is multiple sclerosis more than one disease?

A major part of future studies will be to resolve the question of disease heterogeneity.[78] Because primary progressive multiple sclerosis affects an older (predominantly male) population, has a less favourable prognosis, and is associated with fewer radiological and histological inflammatory lesions—such that these patients are disenfranchised with respect to clinical trials of immunomodulatory drugs—this type of multiple sclerosis is considered by many to be a separate disorder.[79] Harding's disease is diagnosed in patients who meet the clinical criteria for definite multiple sclerosis, with typical magnetic resonance imaging abnormalities and cerebrospinal fluid oligoclonal bands, but disproportionate involvement of the anterior visual pathway.[80] These patients have mutations of mitochondrial DNA not generally seen in multiple sclerosis. In Oriental patients, involvement of visual and spinal cord pathways dominates the clinical features of multiple sclerosis. The phenotype of demyelinating disease in individuals from Africa also typically combines these anatomical features of Devic's disease with a relapsing remitting course and severe disability. Genetic analyses suggest specifically different MHC associations in northern Europeans and the Mediterranean (especially Sardinians), and (perhaps) between primary progressive and relapsing-remitting multiple sclerosis; stratifying the provisionally identified regions of interest from whole genome linkage screens suggests clusters of genes that group to confer susceptibility through epistasis.

The notion of heterogeneity is further developed in pathological studies with biopsy and necropsy material, in which four distinct but overlapping histological types are described. Type 1 constitutes perivenous inflammation with a sharp definition to the edge of the lesion and pronounced remyelination. Type 2 consists of perivenous demyelination with local deposition of immunoglobulin and terminal complement components within sharply defined lesions also having remyelination. Type 3 lesions are badly defined and, although also inflammatory, mainly show evidence for oligodendrocyte apoptosis. Type 4 consists of perivenous inflammation with sharply defined lesions but oligodendrocyte loss in the normal appearing white matter. The histopathological appearances are generally similar between lesions from each patient, but the nature of necropsy or biopsy material makes it more difficult to show subtype consistency over time.[81]

The past and future of multiple sclerosis

Within 40 years of its first depiction, the clinical and pathological details of multiple sclerosis had been adequately characterised. Over the past 120 years, ideas have consolidated on the cause and mechanisms of inflammatory demyelination and axonopathy. In the past 10 years, therapies have emerged that modestly affect the course of the illness. Current research is increasingly seen as coherent and focused on the hot topics that need to be solved to limit, repair, and prevent the damage caused by multiple sclerosis.

Conflict of interest statement

Both authors have participated in meetings sponsored by, and received travel grants and honoraria from, pharmaceutical companies marketing treatments for multiple sclerosis; we are principal investigators in a trial of aletuzumab (Campath-1H) sponsored by Ilex oncology; our department has received financial support for participation in randomised controlled trials of interferon beta-1a in multiple sclerosis (Biogen and Serono); DASC was formerly chairman of the European Medical Advisory Board of Biogen, and he receives honoraria for acting in an ad hoc capacity as advisor to various pharmaceutical companies who have drug development programmes for multiple sclerosis.

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