Multiple sclerosis

Alastair Compston, Alasdair Coles

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Department of Clinical Neurosciences, University of Cambridge Clinical School, Addenbrooke's Hospital, Cambridge, UK
(A Compston FRCP, A Coles FRCP)

Correspondence to:
Dr Alasdair Coles, University of Cambridge Clinical School, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK
ajc1020@medschl.cam.ac.uk

Multiple sclerosis is primarily an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons. Initially, inflammation is transient and remyelination occurs but is not durable. Hence, the early course of disease is characterised by episodes of neurological dysfunction that usually recover. However, over time the pathological changes become dominated by widespread microglial activation associated with extensive and chronic neurodegeneration, the clinical correlate of which is progressive accumulation of disability. Paraclinical investigations show abnormalities that indicate the distribution of inflammatory lesions and axonal loss (MRI); interference of conduction in previously myelinated pathways (evoked electrophysiological potentials); and intrathecal synthesis of oligoclonal antibody (examination by lumbar puncture of the cerebrospinal fluid). Multiple sclerosis is triggered by environmental factors in individuals with complex genetic-risk profiles. Licensed disease modifying agents reduce the frequency of new episodes but do not reverse fixed deficits and have questionable effects on the long-term accumulation of disability and disease progression. We anticipate that future studies in multiple sclerosis will provide a new taxonomy on the basis of mechanisms rather than clinical empiricism, and so inform strategies for improved treatment at all stages of the disease.

Introduction

> "…the chief curse of the illness…I must ask constant services of people I love most closely…it is an illness accompanied by frustration…it is an illness that inflicts awareness of loss…sporadically it is, in its manifestations, a disgusting disease"
>
> *Brigid Brophy, 1929–95*[2]

The depiction of "a remarkable lesion of the spinal cord accompanied with atrophy" by Robert Carswell in 1838[3] anticipated a more or less complete description of the pathological anatomy and clinical features of multiple sclerosis (named thus in 1955) by the last decades of the 19th century. Over the next 100 years, ideas developed for the cause and pathogenesis of this disease on the basis of studies of the epidemiology, genetics, pathology, immunology, and neurobiology. The era of treatments that modify the disease gathered momentum in the 1990s. Research has moved the study of multiple sclerosis from a system based on exploratory approaches into a productive discipline grounded in first-class clinical science. As a result, new questions relating to definition, nosology, cause, mechanisms, and management now challenge several existing concepts. Meanwhile, affected people wait for a solution to this unpredictable and frightening disease of the CNS; their hopes and fears are poignantly expressed, from time to time, in writing, music, drama, and the visual arts.[1]

Phenotype of multiple sclerosis

> "April 30, 1913: went with M- to see a well known nerve specialist—Dr H-. He could find no symptoms of a definite disease, tho' he asked me suspiciously if I had ever been with women. H- chased me around his consulting room with a drum stick, tapping my nerves and cunningly working my reflexes. Then he tickled the soles of my feet and pricked me with a pin—all of which I stood like a man."
>
> *W N P Barbellion, 1889–1919*[4]

The principle of diagnosis is to establish from clinical evidence, supplemented by laboratory investigations, that disease activity which is consistent with focal demyelination has affected more than one part of the CNS and on more than one occasion.

Diagnosis

In most patients, clinical manifestations indicate the involvement of motor, sensory, visual, and autonomic systems but many other symptoms and signs can occur (table). Few of the clinical features are disease-specific, but particularly characteristic are Lhermitte's symptom (an electrical sensation running down the spine or limbs on neck flexion) and the Uhthoff phenomenon (transient worsening of symptoms and signs when core body temperature increases, such as after exercise or a hot bath).

New criteria allow for safe and early diagnosis, which avoids incorrect attribution of symptoms and signs in young adults to multiple sclerosis, and allows timely discussion about management before tissue injury has compromised the ability to undertake activities of daily living (figure 1).[5,6] In many situations, clinical evidence is sufficient for establishment of the diagnosis and laboratory studies are superfluous; but, when the diagnosis is ambiguous, paraclinical features can decide the matter. MRI shows focal or confluent abnormalities in white matter in more than 95% of patients. Their presence alone, however, does not make the diagnosis of multiple sclerosis; characteristic radiological lesions can appear in people without clinical signs of disease and

Search strategy and selection criteria

We reviewed *McAlpine's Multiple Sclerosis* (4th edition)[1] and supplemented this summary of the published work with a PubMed search from October, 2005, to June, 2008, with the search term "multiple sclerosis", without restriction of language.

	Symptoms	Signs	Treatment		
			Established efficacy	Equivocal efficacy	Speculative
Cerebrum	Cognitive impairment	Deficits in attention, reasoning, and executive function (early); dementia (late)			Cognitive training
	Hemisensory and motor	Upper motor neuron signs			
	Affective (mainly depression)		Antidepressant drugs		
	Epilepsy (rare)		Anticonvulsant drugs		
	Focal cortical deficits (rare)				
Optic nerve	Unilateral 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, β blockers, clonazepam, thalamotomy, and thalamic stimulation
	Clumsiness and poor balance	Limb incoordination and gait ataxia			
Brainstem	Diplopia, oscillopsia	Nystagmus, internuclear and other complex ophthalmoplegias			Baclofen, gabapentin
	Vertigo			Prochlorperazine, cinnarizine	
	Impaired swallowing	Dysarthria	Anticholinergic drugs		Speech therapy
	Impaired speech and emotional lability	Pseudobulbar palsy	Tricyclic antidepressant drugs		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	Cannaboids
	Bladder dysfunction		Anticholinergic drugs and/or intermittent self-catheterisation, suprapubic catherisation	Desmopressin, intravesical botulinum toxin	Abdominal vibration, cranberry juice
	Erectile impotence		Sildenafil		
	Constipation		Bulk laxatives, enemas		
Other	Pain		Carbamazepine, gabapentin	Tricyclic antidepressant drugs, TENS	
	Fatigue		Amantadine	Modafanil	Pemoline, fluoxetine
	Temperature sensitivity and exercise intolerance				Cooling suit, 4-aminopyridine

TENS=transcutaneous electrical nerve stimulation.

Table: **Symptoms and signs of multiple sclerosis by site**

many individuals older than 50 years have non-specific white matter cerebral lesions, which should not be interpreted over-enthusiastically. Not only is MRI an indicator of the anatomical dissemination of lesions, when used serially it can also show new plaques appearing over time and so substitute, under new diagnostic criteria, for a subsequent clinical episode (figure 1). At any age, lesions detected in the spinal cord are invariably abnormal. The unique contribution of evoked potentials to the diagnosis of multiple sclerosis is that a prolonged latency reflects the specific effect of demyelination on saltatory conduction. The presence of oligoclonal bands after protein electrophoresis of the cerebrospinal fluid, which is seen in about 90% of patients, suggests intrathecal immunoglobulin synthesis. Inevitably, diagnostic criteria do not confer absolute protection against error, and confusion can arise (panel 1).

Clinical course

80% of patients present with an acute episode affecting one (or occasionally several) sites, which is known as the clinically isolated syndrome. If accompanied by white-matter abnormalities detected by MRI at clinically unaffected sites, the chance of a second attack of demyelination subsequently occurring, and so fulfilling the diagnostic criteria for relapsing-remitting multiple sclerosis, increases from 50% at 2 years to 82% at 20 years.[7] New episodes occur erratically but the rate seldom exceeds 1·5 per year. With time, recovery from each episode is incomplete and persistent symptoms accumulate. Eventually, around 65% of patients enter the secondary progressive phase; in 20%, the illness is progressive from onset. In both these situations, progression starts at around 40 years of age.[8] Primary and secondary progressive multiple sclerosis often manifest as spinal disease, but

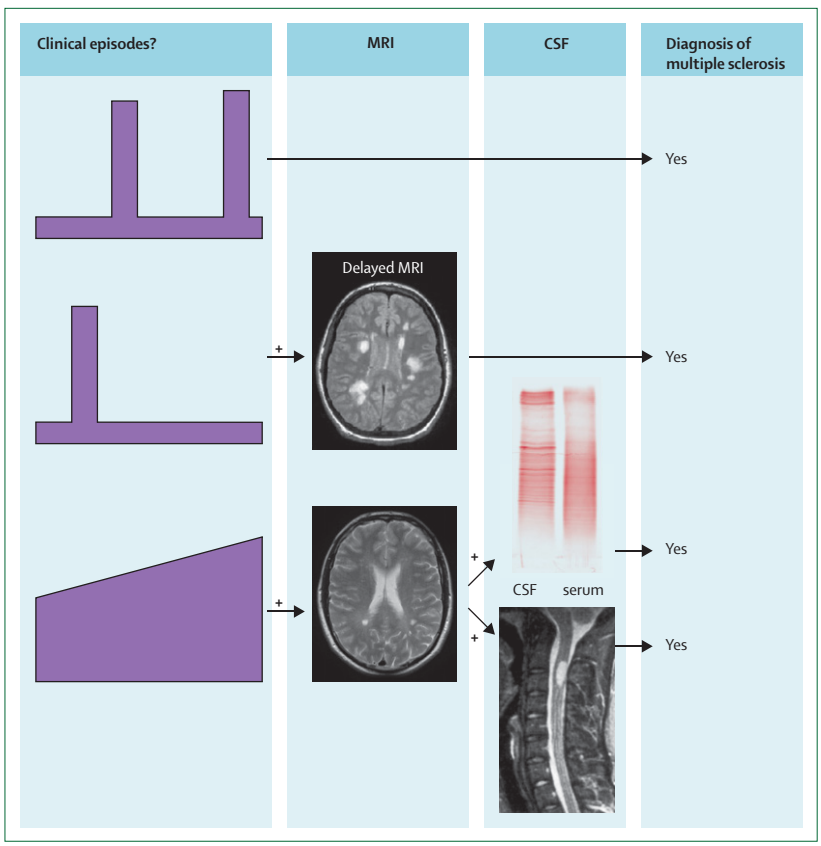


Figure 1: **Criteria for the diagnosis of multiple sclerosis**
Modified from the McDonald criteria.[6] The principle is to establish dissemination in time and place of lesions—ie, that episodes affecting separate sites within the CNS have occurred at least 30 days apart. MRI can substitute for one of these clinical episodes. Dissemination in time of magnetic resonance lesions requires:
one gadolinium-enhancing lesion at least 3 months after the onset of the clinical event; or a new T2 lesion compared with a reference scan done at least 30 days after onset of the clinical event. In the case of recurrent stereotyped clinical episodes at the same neurological site, criteria for MRI definition of dissemination in space are three features from: (1) one gadolinium-enhancing lesion or nine T2 MRI lesions; (2) one or more infratentorial lesions; (3) one or more juxtacortical lesions; or (4) three or more periventricular lesions; (a spinal cord lesion can replace some of these brain lesions). Primary progressive multiple sclerosis can be diagnosed after 1 year of a progressive deficit and two of: (1) a positive brain MRI; (2) a positive spinal cord MRI; and (3) positive oligoclonal bands. Patients having an appropriate clinical presentation, but who do not meet all of the diagnostic criteria can be classified as having possible multiple sclerosis. CSF=cerebrospinal fluid.

Panel 1: **Differential diagnosis of multiple sclerosis**

- Systemic diseases complicated by CNS involvement that follow a relapsing-remitting course (eg, systemic vasculitis)
- Diseases of the brain and spinal cord confined to selected physiological systems and usually following a progressive course (eg, the hereditary cerebellar ataxias)
- Disorders affecting one anatomical site and with either a relapsing-remitting or progressive course (especially, tumours and other structural lesions)
- Monophasic disorders affecting many neuroantaomical sites (eg, acute disseminated encephalomyelitis)
- Non-organic symptoms that, intentionally or otherwise, mimic the clinical features of multiple sclerosis (so-called functional or somatisation disorders)

syndromes that are attributable to dysfunction of optic nerves, cerebrum, or brain stem can also occur. Children with multiple sclerosis are usually girls and presentation is commonly with encephalopathy. They take longer from onset to reach the secondary progressive stage than adults, but nevertheless do so at a younger age.[9] In all cases, the clinical course usually evolves over several decades. Death is attributable to multiple sclerosis in two-thirds of cases and to the increased risk and complications of infections—particularly of skin, chest, and bladder—in people with advanced neurological disability. The median time to death is around 30 years from disease onset, representing a reduction in life expectancy of 5–10 years.[10] People with multiple sclerosis also have a greater risk of suicide, reflecting an increased lifetime frequency of depression of up to 50%, in some studies,[11] which is either a manifestation of cerebral inflammation or, more probably, a response to the uncertainties and restrictions that are imposed by a progressive disabling illness.

The relapse rate decreases during each trimester of pregnancy but with about a three-fold increase in the puerperium, especially in women with disease activity in the year before pregnancy and those who have new episodes while pregnant.[12] The clinical course is unaffected by breast feeding or epidural anaesthesia. The risk of a relapse is doubled after viral exposure (95% CI 1·4–3·0),[13] especially upper respiratory (adenovirus) and gastrointestinal infections.[14] Conversely, persistent parasitic infection seems to protect from disease activity, perhaps by promotion of T-regulatory-cell activity.[15] Vaccinations do not affect disease activity in multiple sclerosis.[16]

What causes multiple sclerosis?

> "As I sit and write, millions of bacteria are gnawing away my precious spinal cord, and if you put your ear to my back the sound of the gnawing I dare say could be heard"
>
> *W N P Barbellion, 1889–1919*[4]

The cause of multiple sclerosis involves environmental exposure and genetic susceptibility. Arguing the merits of one faction versus the other is unproductive. Each is clearly implicated, together with the cultural condition of age at which the interplay between genes and the environment occurs.

The environmental factor

The global distribution of multiple sclerosis can be generalised as increasing with distance north or south of the equator, but that summary conceals many places with disproportionately high or low frequencies (figure 2).[17,18] Multiple sclerosis is common in regions populated by northern Europeans but this distribution is modified by where individuals who are at risk of disease live early in life. Several studies have also reported increasing incidence of multiple sclerosis over time, although these data can be confounded by heightened awareness of the disease and new diagnostic techniques. Orton and

colleagues[19] report a significant increase in incidence of multiple sclerosis in Canadian women, but not men, over the past 30 years, causing a change in the female to male ratio to more than 3:1. What environmental factor this finding shows, however, is not so clear.

Migrations involving large numbers of people affect the distribution of multiple sclerosis. Studies from South Africa,[20] Israel,[21] Hawaii,[22] and of immigrants to the UK[23] correlate the risk of multiple sclerosis with place of residence in childhood (figure 2). Migration from high-risk to low-risk regions in childhood is associated with a reduced risk, and from low to high prevalence parts of the world with an increased risk of developing multiple sclerosis by comparison with the population of origin. However, analysis based on a homogeneous Australian population shows no effect of age-at-migration, with 15 years as the point of stratification, suggesting that the risk of exposure spans a wider age range than was originally suggested.[24]

Patients with multiple sclerosis report being infected with measles, mumps, rubella, and Epstein-Barr virus at later ages than do HLA-DR2 matched controls.[25] In particular, on the basis of a population of 3 million, infection with Epstein-Barr virus as a young adult increases the risk of subsequently developing multiple sclerosis (relative risk 3·0 [95% CI 1·3–6·5]).[26] These data lend support to the so-called hygiene hypothesis whereby individuals not exposed to infections early in life, because of a clean environment, make aberrant responses to infections when encountering these challenges as young adults. Lang and colleagues[27] describe a basis for molecular mimicry between Epstein-Barr virus and a self protein, so that an immune response to the virus inadvertently cross-reacts with myelin and induces demyelination; four DRB1* restricted T-cell receptor peptide contacts are identical for myelin basic protein and Epstein-Barr virus. Studies investigating pathological changes suggest that a high proportion of B cells, accumulating in lesions of chronic multiple sclerosis, are infected by Epstein-Barr virus.[28] Frustrated by the low dividend from systematic searches for candidate infectious agents with sophisticated methods for virus detection, some commentators have suggested other environmental triggers such as low sunlight, vitamin D deficiency, diet, geomagnetism, air pollutants, radioactive rocks, cigarettes, and toxins.[29–31]

The genetics

Multiple sclerosis has a familial recurrence rate of about 20%. Overall, the reduction in risk changes from 3% in first-degree relatives (siblings, 5%; parents, 2%; and children, 2%), to 1% in second-degree and third-degree relatives (figure 3). These confer relative risks of 9·2, 3·4, and 2·9, respectively, compared with a background age-adjusted risk in white northern Europeans of 0·3%.[32–35] Population-based series of multiple sclerosis in twins from Canada and the UK show higher clinical concordance rates in monozygotic than in dizygotic pairs (25% *vs* 5%).[36,37] Conversely, studies from France and Italy provide equivalent rates irrespective of zygosity.[38,39] Individuals with multiple sclerosis who were adopted soon after birth

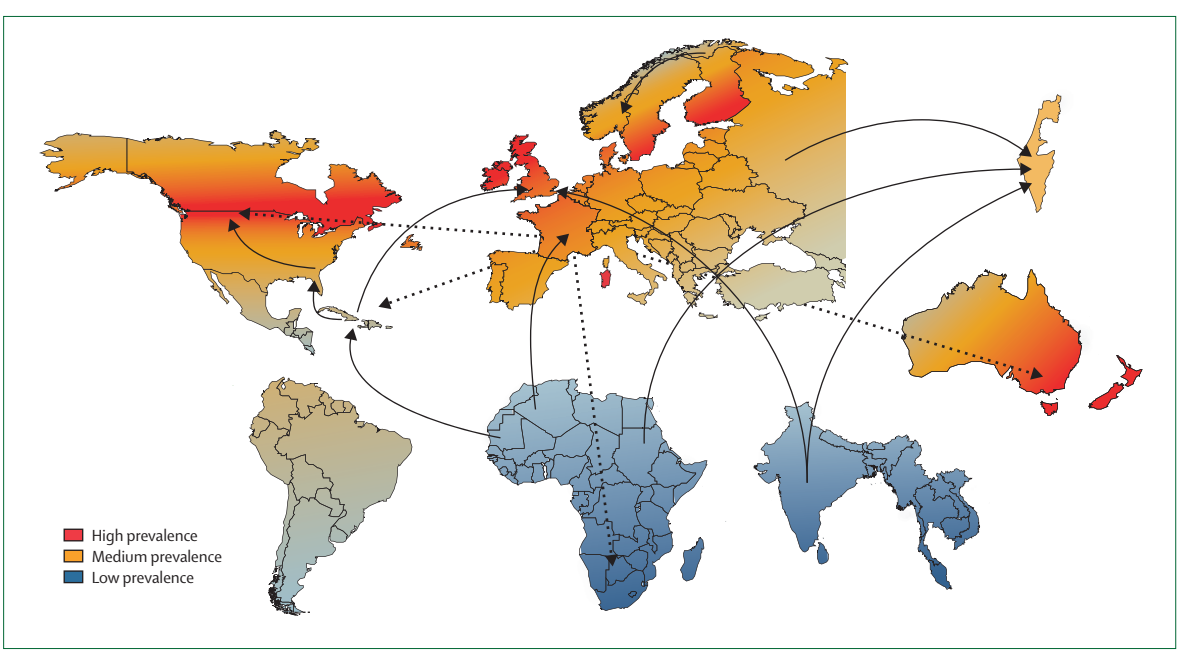


Figure 2: **Geography of multiple sclerosis and migrations**
The five continents are depicted to show medium prevalence of multiple sclerosis (orange), areas of exceptionally high frequency (red), and those with low rates (grey-blue). Some regions are fairly uncharted and these colours are only intended to provide an impression of the geographical trends. Major routes of migration from the high-risk zone of northern Europe, especially including small but informative studies, are shown as dotted arrows. Studies involving migrants from low-risk to high-risk zones are shown as solid arrows.

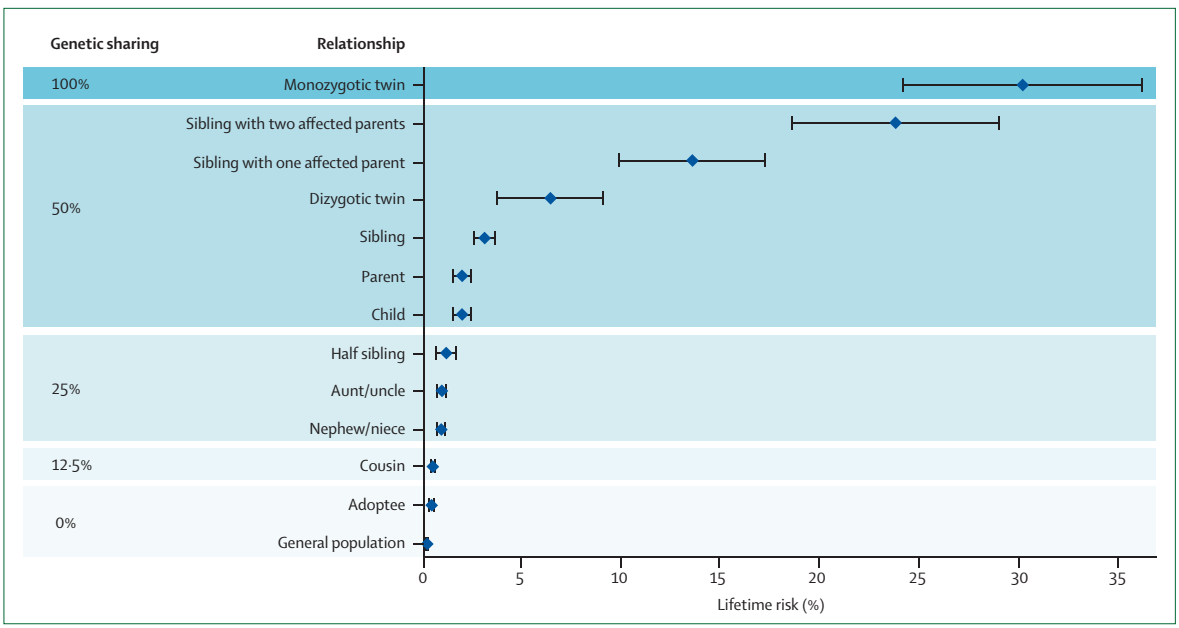


Figure 3: **Recurrence risks for multiple sclerosis in families**
Age-adjusted recurrence risks for different relatives of probands with multiple sclerosis, and degree of genetic sharing between relative and proband. Pooled data from population-based surveys. Error bars indicate the estimated 95% CIs.

and those having affected members of their adoptive family, have the same risk as does the general population and, therefore, a substantially lower frequency than that observed in the biological relatives of index cases.[40] The same is true for step-siblings of index cases.[41] The age-adjusted risk for half-siblings is lower than that for full siblings and with no difference in risk for half-siblings reared together or apart.[40] The recurrence risk is higher for the children of conjugal than single-affected parents.[42,43] Together, these studies implicate genetic factors in determining familial clustering and individual susceptibility to multiple sclerosis.

Published work on the association of multiple sclerosis with other autoimmune diseases is conflicting. The most consistent findings are of increased autoimmune thyroid disease in patients, or their first-degree relatives,[44] but these results have not been supported by a large population-based study.[45]

The association between multiple sclerosis and alleles of the MHC was identified in the early 1970s.[46,47] These markers have been refined as DR15 and DQ6 and the corresponding genotypes DRB1*1501, DRB5*0101, DQA1*0102, and DQB2*0602.[48] The association is strongest in northern Europeans but is seen in all populations apart from Sardinians and some other Mediterranean groups in whom multiple sclerosis is associated with DR4 (DRB1*0405–DQA1*0301–DQB1*0302).[49] Following this early success, three approaches were used unproductively over the next 30 years to identify other genetic risk factors. First, linkage or association with candidate genes chosen from a-priori knowledge of the pathogenesis or some other selection process.[1] Second, non-prejudicial whole genome screening for a link between a chromosomal region of interest[50] or association between markers and susceptibility genes resulting from linkage disequilibrium.[51] Third, the use of genetic isolates and other informative populations having implications for understanding the disease more generally.[52,53]

With adequately powered studies and the availability of reagents that allow high-density screens of the genome or regions of interest, new additions to the list of susceptibility loci include a protective effect conferred by HLA-C5[54] and of HLA-DRB1*11,[55,56] and increased susceptibility associated with single nucleotide polymorphic markers for the interleukin-2 and interleukin-7 receptor α chains.[57–60]

Disease mechanisms

> "Yesterday, the wind was taken out of my sails…my eye caught the title of an enormous quarto memoir in the Trans Roy Soc, Edinburgh: The Histology of ------ --------- . I almost ran away to my room"
>
> *W N P Barbellion, 1889–1919,[4] referring to James Dawson's monograph[61]*

The hallmark of demyelinating disease is formation of the sclerotic plaque, which represents the end stage of a process involving inflammation, demyelination and remyelination, oligodendrocyte depletion and astrocytosis, and neuronal and axon degeneration (figure 4). Despite no shortage of opinion, the order and relation of these separate components remain fully to be resolved.

Myelin is synthesised by mature oligodendrocytes, each of which contacts short segments of 20–40 juxtaposed axons in white-matter tracts of the CNS. Developmental

processes are regulated by defined growth factors that orchestrate proliferation, migration, differentiation, and survival of oligodendrocyte precursors into myelinating cells.[65,66] The elongated oligodendrocyte processes make contact with nearby axons and form a cup at the point of contact that encircles the axon, thereafter extending along the nerve fibre to form an internodal myelinated segment. With maturation, $Na_v1.2$ (sodium) channels are retained along the myelinated axon but replaced by $Na_v1.6$ channels at the intervening nodes of Ranvier where electrical resistance is low, thereby facilitating depolarisation, generating electrical current and, in turn, triggering saltatory conduction.[1]

Pathogenesis

We believe that the disease process starts with increased migration of autoreactive lymphocytes across the blood–brain barrier. The transition from physiological surveillance to a pathological cascade arises from regulatory defects that allow these cells to set up an immune response within the brain. Regulatory lymphocytes from people with multiple sclerosis fail to suppress effector cells.[67] These autoreactive cells do not effectively apoptose on stimulation, because of overexpression of β-arrestin 1, which is a key promoter of naive and activated CD4+ T-cell survival.[68] Presumably, failure of local regulatory mechanisms within the brain accounts for the particular sites of inflammation, dominated by perivascular CD8+ cell infiltrates, causing so-called plaques that cluster around the lateral ventricles and corpus callosum, in the cortex and subcortical white matter, the optic nerves and brainstem, and throughout the spinal cord. Investigators have recently discovered that the key role assigned historically to T-helper 1 (Th1) (interferon-γ secreting) cells in experimental allergic encephalomyelitis was misplaced. Rather, inflammation is driven by a newly-designated T-lymphocyte subtype that secretes interleukin-17 under interleukin-23 control.[69] Interleukins 17 and 22 disrupt the human blood–brain barrier, allowing efficient penetration of Th17 cells into the brain where they can kill human neurons.[70,71]

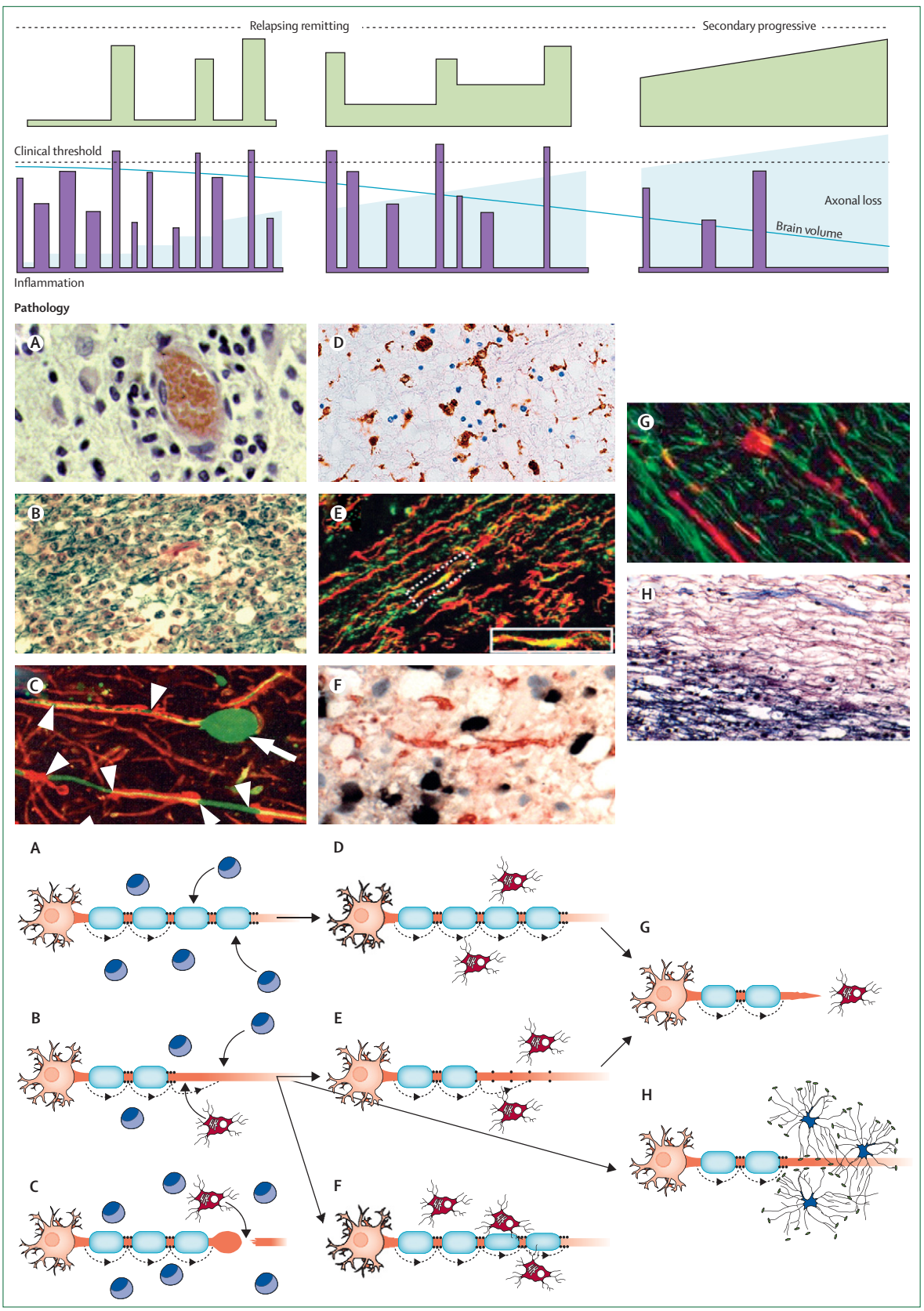
The antigen specificity of these immune responses is unresolved, not least because many autoreactive lymphocytes can be detected in healthy individuals. Originally, myelin proteins were favoured as candidates for initiation of the disease process in multiple sclerosis, but other specificities are now also implicated. For example, it is suggested that an autoimmune response against αB crystalline prevents physiological suppression of inflammation;[72] and that antibodies against neurofascin might mediate axonal injury in multiple sclerosis.[73] As T and B lymphocytes, plasma cells, and macrophages accumulate, pro-inflammatory cytokines amplify the immune response through recruitment of naive microglia. Contact is established between activated microglia and components of the oligodendrocyte-myelin unit that is opsonised with ligands for microglial Fc and complement receptors. A lethal signal is then delivered through cell surface bound tumour necrosis factor α (TNFα).[74] Acute demyelinating lesions also show extensive axonal injury with transection[62,75] (figure 4C) that correlates with T-cell and microglial infiltration.[76] With onset of the secondary progressive stage, areas of demyelination coexist with diffuse axonal and neuronal degeneration, associated with the accumulation of hyperphosphorylated and insoluble tau.[77] Lesions seem to grow slowly by radial expansion as focal brain inflammation fades into diffuse parenchymal microglial activation resulting in extensive abnormalities of the normal appearing white matter,[78] in which a delicate balance exists between anti-inflammatory genes upregulated in oligodendrocytes and pro-inflammatory pathways activated in microglia.[79] B-lymphoid follicles accumulate in the meninges sustaining a compartmentalised humoral immune response that can drive intrathecal antibody production and damage nearby cortex;[80] these are the cells that harbour Epstein-Barr virus.[28] Pathological changes of primary progressive multiple sclerosis are characterised by reduced plaque load, less evidence for inflammation, and the absence of lymphoid follicles.

Remyelination (figure 4) accounts for the appearance of shadow plaques. It is most active during the acute inflammatory process coinciding with phagocytic removal of myelin debris, but also occurs in the progressive phase. The mature nervous system maintains a pool of oligodendrocyte precursors that can migrate in response to semaphorin 3A and 3F.[81] Undifferentiated oligodendrocyte precursors surround the lesions of multiple sclerosis[82,83] and presumably act as the source of cells having the potential to remyelinate naked axons.[84] In 20% of people with multiple sclerosis, plaques are eventually remyelinated.[85] Clearly, remyelination is less successful in other instances, with cycles of demyelination and remyelination apparently exhausting the capacity for tissue repair.

To some extent, every pathological component can be detected in life with MRI: to distinguish inflammation (Gadolinium-diethylenetriaminepenta-acetic acid [Gd-DTPA] enhancement), axonal loss,[86] demyelination and remyelination (magnetisation transfer ratio), astrocytosis (T_2-weighted lesions), and alterations in normal appearing white matter.[87] Provisional reports suggesting that the presence of serum antibodies against myelin proteins predict early conversion from clinically isolated syndromes to definite multiple sclerosis have not been confirmed.[88] However, antibodies to specifically cleaved products of myelin-basic protein do seem to be associated with multiple sclerosis.[89] Concentrations of neurofilament light chain and glial fibrillary acidic protein in cerebrospinal fluid indicate tissue damage and therefore correlate loosely with disability.[90]

Pathophysiology

Although compensation can arise from redundancy in individual systems or tracts, pathways that are strategically


Relapsing remitting
Secondary progressive
Clinical threshold
Axonal loss
Brain volume
Inflammation
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placed eventually lose the safety factor for conduction, altering in ways that are characteristic and account for particular manifestations of multiple sclerosis. Partially demyelinated axons cannot transmit fast trains of impulse, explaining symptoms resulting from physiological fatigue. Depolarisation might traverse the lesion but at reduced velocity, accounting for the characteristic delay of evoked potentials (figure 4B). Partially demyelinated axons can discharge spontaneously, producing unpleasant distortions of sensation. Increased mechanical sensitivity results in symptoms induced by movement including flashes of light provoked by eye movement, and the electric sensation felt in the spine or limbs on neck flexion (Lhermitte's symptom). Spontaneous discharge in facial nerve neurons in the brain stem accounts for myokymia. The failure of conduction in partially demyelinated pathways associated with a rise in temperature is an indicator of reduced capacitance of the thinning myelin sheath, accounting for the temporary increase in severity of pre-existing symptoms with exercise and a hot bath (Uhthoff symptom). Ephaptic transmission between neighbouring and partially demyelinated axons causes brief and usually unpleasant paroxysmal attacks that are often triggered by touch or movement.

Symptom recovery might suggest resolution of conduction block in structurally intact nerve fibres as the episode of inflammation wanes.[91] When structural damage has occurred, sodium channels are redistributed across the demyelinated axonal membrane[92] (figure 4E). Electrical activity is restored, but alterations in sodium and calcium exchange can prove hazardous until normal nodal arrangements are re-established by remyelination.[93] Experimentally, remyelinated axons can again conduct the nerve impulse and restore function.[94] We can assume that remyelination in multiple sclerosis also contributes to recovery.

Figure 4: **The course and pathogenesis of multiple sclerosis**
This scheme illustrates how the pathological processes of inflammation, demyelination, and axon degeneration explain the clinical course of multiple sclerosis. (Arrows indicate the progression of pathology). Course: CNS inflammatory activity might precede clinical symptoms by many years, and MRI has shown that for every clinical episode there are roughly ten new plaques; this tenet is illustrated as a notional clinical threshold, below which the effects of individual inflammatory lesions can be compensated for and above which they cause symptoms. Pathology: the first event is lymphocyte-driven inflammation (A: lymphocytes are seen around a blood vessel, haematoxylin and eosin stain). This inflammation might impede the saltatory propagation of the action potential (arrowheads) in three ways: soluble inflammatory mediators might cause conduction block in structurally intact axons (A), or there may be demyelination (B: luxol fast blue myelin stain showing very early lesion with several macrophages laden with myelin and some intact myelinated nerves)[1] or axonal transection (C: non-phosphorylated neurofilaments [SMI32 staining] marks terminal axon spheroids).[62] Microglia are activated, and contribute to inflammation and to repair by removal of myelin debris and promotion of remyelination (F: oligodendrocyte with proteolipid protein mRNA [black] connected to remyelinated axon with proteolipid protein immunoreactivity [red]).[1] If this fails, persistently demyelinated axons adapt by redistributing ion channels (E: sodium-channel redistribution along denuded axons, antipan Nav channel antibody [green], antineurofilament [red]),[63] which might prove maladaptive and promote chronic neurodegeneration (G: confocal of a shadow plaque, with a remyelinating oligodendrocyte [red-proteolipid protein antibodies], and degenerating unmyelinated axons [green-neurofilament antibodies]).[64] Microglia can become chronically activated, in the absence of lymphocytic inflammation, in areas of normal appearing white matter and also lead to neuronal loss in later stages of the disease (D: CD68+ microglia).[1] In response to chronic tissue injury, astrocytes cause gliosis, which can act as a mechanical barrier for repair (H: haematoxylin and eosin stain). Not depicted is primary progressive multiple sclerosis in which there is significant axonal degeneration with or without a preceding inflammatory phase.

Are the inflammatory and degenerative processes independent?

Disease progression in multiple sclerosis depends on accumulated axon degeneration. Therefore, attitudes have shifted in the past decade from the focus on multiple sclerosis as a demyelinating disease to a broader perspective in which the relative contributions of acute and chronic axonal loss, and their dependence on inflammation, also have to be understood in reaching a coherent account of the pathogenesis. Four formulations can be proposed. First, inflammation is the exclusive pathogenic event from which all else follows. Second, neurodegeneration occurs first and inflammation is merely a secondary response. Third, inflammation and neurodegeneration both contribute to the clinical course, but are fully independent processes. Finally, inflammation exposes an intrinsic neurodegenerative susceptibility that renders axons vulnerable to cumulative injury.

Aspects of the natural history can serve as a surrogate for the axonal contribution to tissue injury. Hensiek and colleagues[95] assessed 1083 families with two or more first-degree relatives having multiple sclerosis and showed concordance for age at onset and clinical course, but not severity. These findings suggest a familial effect both on episodic and progressive phases of the disease. In turn, axon degeneration is thought to be affected by factors, over and above those that establish inflammation. With use of natural history data, Kremenchutzky and co-workers[96] conclude that the progressive phase of multiple sclerosis is an age-dependent degenerative process, and that chronic axonal loss specific to the corticospinal tract is the pathological substrate for progression, beginning early in the disease course and before clinical symptoms manifest. Confavreux and Vukusic[8] also consider that times to reach disability milestones, and the ages at which these landmarks are reached, follow a predefined schedule that is not obviously affected by episodes or by the initial disease course. According to this analysis, relapsing-remitting disease can be regarded as multiple sclerosis in which insufficient time has elapsed for conversion to secondary progression; secondary progressive multiple sclerosis is relapsing-remitting disease that has grown older; and primary progressive disease is multiple sclerosis that has been amputated from its usual preceding relapsing-remitting phase. Panel 2 outlines the three mechanisms of axonal injury.

Our position is that progression in multiple sclerosis is due to cumulative loss of axons, initiated and maintained by complex inflammatory responses acting in individuals who are inherently susceptible to neurodegeneration, and changing as tissue damage increases. At any one time, the extent of that injury indicates the interplay of active

Panel 2: Three mechanisms of axonal injury

1. Brief exposure of the (rat) spinal cord to nitric-oxide donors produces reversible conduction block in normal axons[97] (figure 4A)
2. A separate and destructive sequence follows more prolonged exposure to inflammatory mediators:[98] nitric oxide acts directly and indirectly via NMDA receptors on more mature neurons,[99] and soluble factors released by activated microglia impair mitochondrial (cytochrome oxidase) activity of neurons[100] resulting in energy failure and altered ion exchange mechanisms across the axonal cell membrane.[1] This effect is exacerbated by the spread of sodium channels away from the node of Ranvier across the exposed demyelinated axon membrane; extrusion of the consequent increased sodium influx makes yet greater metabolic demands on the axon and neuron[63,101] (figure 4E)
3. Loss of trophic support by oligodendrocytes and myelin contributes to neuronal and axonal loss: in vitro, cells of the oligodendrocyte lineage support neuronal survival by release of insulin-like growth factor (IGF)-1,[102] whereas neurofilament phosphorylation and axonal length are increased by glial cell derived nerve growth factor (GDNF);[103] IGF-1 and GDNF modulate the direct effects of nitric oxide on survival of neurons and axonal injury mediated by exposure to nitric oxide in vitro[104] (figure 4G)

inflammation, existing neurodegeneration, and the dynamic vulnerability of intact axons. Although the absolute amount of inflammation can reduce, its effect is never altogether lost in view of the increasing susceptibility of injured axons to residual inflammatory insult.

Complexity and heterogeneity in demyelinating disease

Genetic analyses are predicated on the assumption that multiple sclerosis is one disease, but some evidence for genetic heterogeneity exists. For example, although mitochondrial genes do not contribute generally to susceptibility in multiple sclerosis,[105] mutations of mitochondrial DNA are responsible for a rare illness similar to multiple sclerosis that is characterised by disproportionate involvement of the anterior visual pathway.[106,107]

Specifically different mechanisms are thought to be involved in the pathogenesis of tissue injury in multiple sclerosis:[108,109] T-cell infiltrates and macrophage associated tissue injury (pattern 1); antibody and complement-mediated immune reactions against cells of the oligodendrocyte lineage and myelin (pattern 2); hypoxia-like injury, resulting either from inflammation-induced vascular damage or macrophage toxins that impair mitochondrial function[110] (pattern 3); and a genetic defect or polymorphism resulting in primary susceptibility of the oligodendrocytes to immune injury (pattern 4). The original proposal was that each individual with multiple sclerosis had only one type of pathological lesion; however, a recent study suggests that acute plaques show pattern 2 pathology in all individuals, and the other patterns are seen rarely.[111]

These separate mechanisms can explain differences in the extent of demyelination, oligodendrocyte injury, remyelination, and axonal damage that are seen across the spectrum of multiple sclerosis[85] and related disorders—ie, neuromyelitis optica[112] and Balo's concentric sclerosis (pattern 3).[113] But an alternative interpretation is that the core process of T-cell mediated brain inflammation is merely modified by different immunological effector mechanisms, thus creating a state of mechanistic complexity rather than true disease heterogeneity (figure 5).

Neuromyelitis optica

> "In December 1822, I ... was obliged to have my letters read to me, and their answers written as my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence"
>
> *Augustus d'Este, 1794–1848*[114]

Until recently, the typical form of demyelinating disease seen in Africa, Asia, east Asia, and Aboriginal populations was neuromyelitis optica or optic-spinal multiple sclerosis. The relapsing-remitting phenotype, affecting many sites within the brain and spinal cord, was uncommon.[1] With the identification of anti-aquaporin (AQP) 4 antibodies as biomarkers of neuromyelitis optica,[115,116] awareness of neuromyelitis optica in northern European people has increased. Diagnostic criteria for neuromyelitis optica are optic neuritis and myelitis with two or more of three supporting criteria; a contiguous spinal-cord lesion of three or more segments in length; brain MRI at onset that is not diagnostic for multiple sclerosis; and neuromyelitis optica-IgG seropositivity.[117,118]

Neuromyelitis optica is characterised by demyelination and necrosis of white and grey matter of the spinal cord, acute axonal injury, antibody deposition, and perivascular complement activation.[112] AQP4 is not detectable in the optic nerve and spinal cord lesions.[119,120] Conversely, AQP4 expression is increased in active and recently remyelinated lesions of multiple sclerosis but lost in the chronic plaques. The gratifying response to plasma exchange in some patients with neuromyelitis optica (and those with the pattern 2 neuropathology of multiple sclerosis) suggests a primary pathogenic role for antibody and complement.[121]

In Japan, not all patients who are positive for AQP4 antibodies show the typical phenotype of optic-spinal multiple sclerosis. Up to a third of seropositive patients and some with relapsing-remitting multiple sclerosis also show the long thoracic spinal lesions, and the same cord appearance can be seen in those who are AQP4 negative.[122] This overlap suggests that patients can be intermediate between seropositive neuromyelitis optica and seronegative relapsing-remitting multiple sclerosis. Perhaps the most telling link is the switch in clinical phenotype from optic-spinal to conventional multiple sclerosis that has

been observed over a short period in Japan[123] to coincide with changes in industrialisation, and in the French West Indies with patterns of migration.[124] One interpretation is that cultural changes expose the intrinsic vulnerability of individuals who are at risk of demyelinating disease encountering infections later in childhood and at a crucially altered phase of maturation in their immune repertoire.

Together, these observations suggest that neuromyelits optica is a prototypic demyelinating disorder from which, through genetic stratification and selection in response to epidemic microbial challenge, changes occur in the immunopathogenesis, histological complexity, and distribution of lesions converting to the phenotype of relapsing-remitting multiple sclerosis.[125]

Management and treatment of demyelinating disease

> "A physician from London will gallop up hotspur, tether his horse and dash in waiving a reprieve—the discovery of a cure"
>
> *W N P Barbellion, 1889–1919*[4]

Temporary improvement can be achieved at times of symptomatic deterioration with high-dose methyl prednisolone.[126] Plasma exchange given up to 1 month after onset can usefully reduce persistent deficits although not subsequent disease activity.[127,128] In many situations, the priority is to improve the quality of everyday life by masking individual symptoms. The most amenable are the unstable bladder, erectile dysfunction, spasticity (whereas the treatment of other motor disabilities is less rewarding), pain, and paroxysmal episodes (table). For patients who develop serious disabilities and impairments, comprehensive care includes access to physical and occupational therapists, neuropsychologists, social workers, and other health-care professionals providing expertise in the management of chronic neurological illness. Increasingly, the available services and management of disability are coordinated by specialist nurse practitioners.

The pivotal studies of present licensed therapies of multiple sclerosis were fairly small (involving only a few hundred patients) and of short duration (2–3 years).[129–133] Therefore, long-term efficacy is not established to the satisfaction of all analysts. The available treatments are expensive and do not always meet standards for cost-effectiveness. As a result, use remains uneven, and treatment of multiple sclerosis is a topic much debated and besieged by the issues of health economics.

The efficacy of present treatments varies with the stage reached in the course of the disease. In retrospect, the negative results from trials of conventional immunotherapies—such as cyclophosphamide and ciclosporin—recorded in the 1980s and early 1990s, reflect selection of patient cohorts with progressive disease, which we now understand is largely driven by non-inflammatory mechanisms. The type I interferons were first used in the 1970s on the grounds that their antiviral activity might

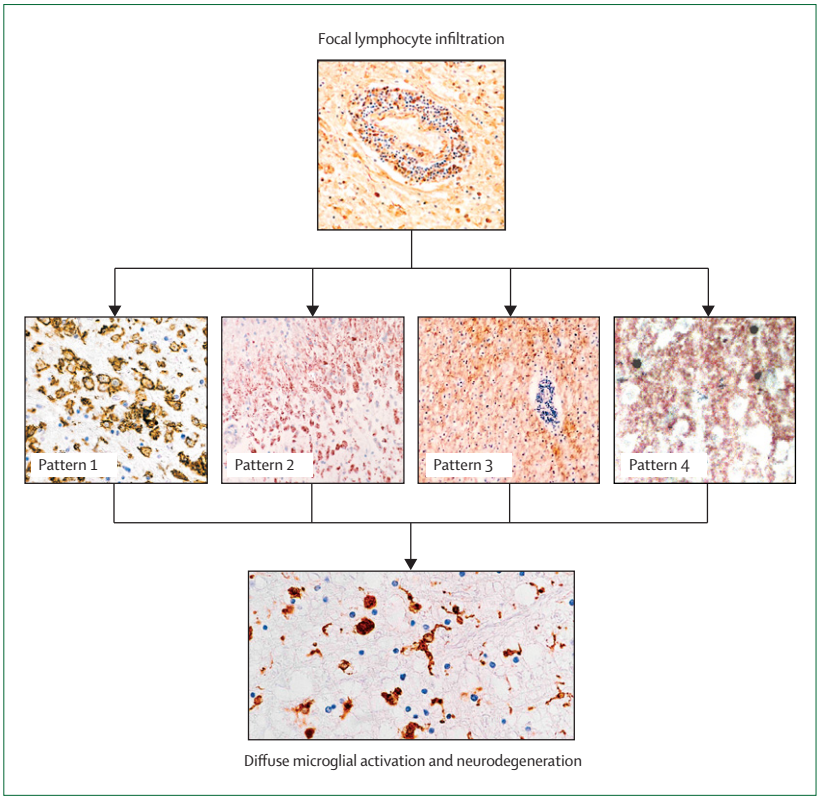

Figure 5: **Pathological heterogeneity**
The four principal patterns of multiple sclerosis pathology[108,109] arising from the common mechanism of inflammation and leading to the common terminal path of neurodegeneration and microglial activation. Histological panels are from reference 1.

reduce the environmental triggers of multiple sclerosis. γ interferon promoted relapses of multiple sclerosis,[134] whereas β interferon reduced their frequency, albeit to no greater extent than was noted with azathioprine[135] which had been largely dismissed as toxic and insufficiently effective. Yet, because the β interferons have a fairly innocuous profile of adverse effects, they began to be used at earlier stages of the disease once modest efficacy had been shown. At this stage, copaxone (glatiramer acetate) emerged from the attempt of one laboratory to generate new agents promoting experimental allergic encephalomyelitis; nowadays, this drug is believed to act by inducing tolerance or anergy of myelin-reactive lymphocytes.[136] At present, least contentious is the use of the β interferons (eg, Rebif, Avonex, and Betaseron) and copaxone in relapsing-remitting disease, for which the pivotal studies initially showed a reduction in frequency of new episodes by about 30% for 2–3 years.[129–133] Research from extension studies suggests that this effect persists beyond 2 years of treatment.[131,137]

Common sense suggests that if early intervention reduces disease activity, it will necessarily also increase the interval between episodes and delay conversion to multiple sclerosis—defined either by a second clinical episode or the accumulation of new MRI lesions—in patients with

clinically isolated syndromes. And, since a proportion of episodes do not recover fully, the accumulation of fixed disabilities in relapsing-remitting multiple sclerosis, and after conversion from a clinically isolated syndrome, will also be decreased. Crucially, whether such treatment delays entry into the secondary progressive phase of multiple sclerosis is uncertain. The interferons certainly reduce the conversion rate to multiple sclerosis from 45–50% with placebo to 28–35% over 2–3 years in the CHAMPS, ETOMS, and BENEFIT trials; a trial of copaxone in unifocal clinically isolated syndrome, yet to report in full, suggests a similar effect.[138–141] In an extension of the CHAMPS study, of 5 years total treatment, no gain in terms of disability with interferon treatment was recorded;[142] however, the BENEFIT trial, perhaps the best of the three studies, showed a marginally significant effect of interferon on the accumulation of disability over 3 years.[140] These therapies have no useful treatment effect on the secondary progressive phase of the disease,[143–146] except in those unusual cases of progressive multiple sclerosis continuing to have high relapse rates.[147,148] Likewise, no agent has been shown to affect primary progressive multiple sclerosis.[149] The main adverse effects of interferon β are local injection-site reactions and flu-like symptoms with hyperthermia, perhaps due to cytokine release. 5–30% of treated patients develop persistent neutralising antibodies, usually in the first year of treatment and more commonly in those receiving interferon β-1b. Their presence is associated with reduction in the treatment effect on relapse activity.[150]

New trials have been designed further to inform prescribing. These aim to position the individual therapies in an increasingly competitive market, with an emphasis on earlier and broader prescribing indications, dose responsiveness favouring increased exposure, and the use of MRI surrogates to anticipate clinical activity. Two studies have compared the efficacy of the interferons. The EVIDENCE trial,[151] which reported greater efficacy with high-dose subcutaneous Rebif (interferon β-1a) three times per week than with low-dose Avonex (interferon β-1a) given once per week, lasted only 24 weeks. The 2-year INCOMIN trial[152] showed greater efficacy with Betaferon (interferon β-1b) given on alternate days than with Avonex given once per week. The recent BEYOND trial showed no difference in clinical efficacy between two doses of Betaferon and copaxone.[153]

Some dampening of enthusiasm occurred with the systematic review of interferons in multiple sclerosis[154] concluding that evidence exists only for a reduction in relapse frequency during the first year of treatment with no convincing efficacy thereafter and no effect on the accumulation of disability. The failure to confirm treatment effects in these reviews partly reflects the large confidence intervals generated by trials that end early or contain many drop-outs. A systematic review concluding that glatiramer acetate does not alter relapse rate or progression in multiple sclerosis[155] inevitably elicited vigorous responses. Nowadays, there is a suggestion that efficacy might be enhanced by prescribing a higher dose than that which is approved at present.[156]

Two other drugs are now licensed. Mitoxantrone (an anthracenedione antineoplastic drug which intercalates with DNA and inhibits both DNA and RNA synthesis) is probably more efficacious than the interferons or copaxone, but its use is confined to cases that are characterised by disease which is sufficiently aggressive to justify its toxic effects (eg, cumulative cardiotoxicity and acute leukaemia in 0·2% of patients).[157] In particular, it slows the accumulation of disability in difficult cases of rapidly worsening multiple sclerosis with frequent relapses, but has less or no effect on non-relapsing progressive disease.[158,159] It is now licensed in the USA for patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis but not those with primary progressive multiple sclerosis.

The demonstration that an antibody against the α4β1 integrin on the surface of lymphocytes could reduce lymphocytic infiltration and clinical disease in animals with allergic encephalomyelitis[160] led to clinical trials of a humanised anti-α4 integrin antibody, natalizumab (Tysabri). Given indefinitely by monthly infusion, this antibody showed greater efficacy against placebo than is seen with the interferons, reducing the relapse rate at 1 year by 68% and the chance of acquiring fixed disability over 2 years by 42%.[161] An unpublished interim analysis of these data led to a US licence being issued for natalizumab in relapsing multiple sclerosis, only for the drug to be withdrawn from the market months later when two case of progressive multifocal leucoencephalopathy were identified in a trial combining Avonex (IFNβ-1a) with natalizumab.[162] As a result, natalizumab is licensed as monotherapy for severe relapsing-remitting multiple sclerosis, which is defined in the UK by the National Institute for Health and Clinical Excellence as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions or a significant increase in T2 lesion load on MRI. Since licensing, the FDA has warned that two further cases of PML have been identified in the second year of natalizumab monotherapy, from roughly 12 000 patients exposed for over 12 months.[163]

The future of treatment

> "Some London neurologist has injected serum into a woman's spine with beneficial results, and as her disease is the same as mine, they wish me to try it too. I may be able to walk again, to write etc, my life prolonged"
>
> *W N P Barbellion, 1889–1919*[164]

In 1993, there were no licensed therapies for multiple sclerosis. Now several exist. For the future, debate will hinge around the complex interplay of efficacy, safety, and convenience in which individual patients and practitioners may set different priorities. Some will see efficacy as the overwhelming issue: others will regard

oral versus parenteral therapy as important; yet more will be rightly cautious concerning safety; and some may regard a long interval between administrations as practical and psychologically advantageous. Against that background, as new therapies are identified offering improved efficacy, profiles of adverse effects have also changed. Therefore, a new dilemma arises. Should a more liberal attitude to the clinical risk-benefit ratio be adopted, perhaps leaving a few individuals compromised through having received a novel but complicated treatment early in the course, even though this approach stabilises the disease process for many recipients?

Oral agents have emerged as possible treatments of multiple sclerosis. In a phase 2 trial of 281 patients over 6 months, fingolimod reduced the relapse rate from 0·77, on placebo, to 0·35.[165] Its adverse effect profile remains unclear, and is the subject of current phase 3 trials. In a trial of 306 patients over 36 weeks, high-dose oral laquinimod reduced the number of enhancing MRI lesions by 40% compared with placebo;[166] and in a similar study of oral fumarate in 257 patients over 24 weeks, MRI enhancing lesions were reduced by 69% compared with placebo.[167] Furthermore, strategies are appearing to abrogate highly selective immune processes; in general these processes are technically demanding and have shown only limited efficacy, as emphasised by vaccination with attenuated autologous antimyelin T-cell lines.[168] Alternatively, monoclonal antibodies can be used to block specific cell surface targets (eg, CD25[169]) or delete particular lymphocyte groups; in a phase 2 trial of rituximab in 104 patients over 48 weeks, the number of patients having a relapse was halved compared with placebo (20% *vs* 40%).[170]

The early experience with the pan-lymphocyte depleting antiCD52 antibody, alemtuzumab, is promising. Initial studies focused on secondary progressive multiple sclerosis in which alemtuzumab effectively suppressed clinical and radiological disease activity. Nonetheless, patients continued to have progression of their disability, correlating with continued brain atrophy that was attributable to axon degeneration. The degree of progression and tissue loss were related to the MRI inflammatory load before treatment, suggesting that these are post-inflammatory events.[171] The lesson is that effective immunosuppression is required early to stabilise the cascade of events that culminates in irreversible disability. There followed open-label treatment of such cases[172] and a phase 2 single-blind trial comparing alemtuzumab and Rebif (IFNβ-1a). This trial shows that alemtuzumab reduces the relapse rate compared with Rebif by up to 74%, and the chance of accumulating disability by up to 71%, over 3 years.[173]

Comparable suppression of the immune system can be achieved with bone-marrow transplantation, with similar results. A review of 183 cases from the European Blood and Marrow Transplantation Group (EBMT) database with severe multiple sclerosis showed that mortality was 5·3%, but was restricted to the years 1995–2000 when busulphan-based regimens were mainly in use rather than BEAM (carmustine, etoposide, cytarabine, melphalan) or antithymocyte globulin without graft manipulation. Improvement or stabilisation of neurological conditions occurred in 63% of patients at a median follow-up of 42 months.[174] As with alemtuzumab, disease progression is not checked if the intervention is given later in the course. This clinical analysis accords with pathological studies of cases studied at autopsy after bone-marrow transplantation that show extensive axonal loss in the absence of active inflammation.[175]

Taken together, the results of clinical trials allow the conclusion that inflammation is necessary for new lesion formation and also conditions axon degeneration. Immunological therapies might prevent progression of disability if given before the cascade of events, leading to an irretrievable loss of tissue integrity. This notion explains the present restrictions of immunotherapy in patients with secondary progressive multiple sclerosis. The goal of future therapies in multiple sclerosis should be to limit the neurodegenerative contribution to disease progression. This aim might need: prevention of immunological chronicity by inhibition of diffuse microglial activation; protection of intact axons from acute injury with anti-excitotoxic and membrane-stabilising agents; provision of trophic support to persistently demyelinated axons with growth factors and strategies that enhance remyelination; and promotion of plasticity and axon regeneration by manipulation of extracellular matrix molecules and inhibitory environments.

Most patients expect stem-cell biology to deliver a dividend for remyelination and repair in multiple sclerosis. Validation of the evidence already gathered in experimental studies will need several issues to be settled, which are outlined in panel 3.

***Panel 3:* Remyelination and repair in multiple sclerosis**

- Will cessation of the inflammatory process allow sufficient repair and reversal of deficits, and does suppression of the inflammatory process inhibit remyelination?
- Is the potential for enhancing endogenous remyelination real enough to make the notion of exogenous rescue unnecessary?
- Is there a critical period when the naked axon can be rescued by reclothing it in myelin?
- How many axons must be remyelinated to achieve useful conduction through a critical pathway, and can axon outgrowth be promoted to increase the so-called arena of remyelinaton?
- Which intervention provides the best medicine and how can it most effectively be delivered?

Multiple sclerosis: past, present, and future

Multiple sclerosis made a fleeting appearance on the stage of neurological description early in the 19th century;

was given full clinico-pathological characterisation in the late decades of that century; began to reveal the mysteries of aetiology and pathogenesis in the 20th century; and yielded somewhat to disease modifying therapies as the millennium ended. Future studies will resolve the issues of heterogeneity and complexity in multiple sclerosis, and we can expect a mechanism-based classification that informs successful strategies to limit and repair the damage.

Conflict of interest statement

Our department has received grant funding from Genzyme and funding to undertake clinical trials on alemtuzumab, and we have both received travel expenses and honoraria for speaking at meetings about alemtuzumab.

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