‘The marvellous harmony of the nervous parts’: The origins of multiple sclerosis

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ABSTRACT – Working in the 1660s, William Croone wrote on the nature of connections between nerve and muscle. A previously unknown copy of his essay, wrongly attributed to Thomas Willis, has recently come to light. Croone left the challenges of clinical neurology to his successors. The story of multiple sclerosis begins early in the nineteenth century. Despite much information on the aetiology and pathogenesis, the origins of that disease remain obscure. Here, the hypothesis is advanced – based on the epidemiology, clinical neurology, immunology and genetics of demyelinating disease, linked to European history and population genetics – that multiple sclerosis evolved from a related disorder, neuromyelitis optica (or Devic’s disease). Genetic drift and stratification altered the immune response to a common pathogen and changed the disease phenotype. Against this background, the sustained epidemic of multiple sclerosis arose when cultural changes led to a subtle but crucial alteration in the age at which genetically vulnerable individuals are exposed to Epstein Barr infection.

KEY WORDS: epidemiology, genetics, MHC, mitochondrial haplogroups, multiple sclerosis, neuromyelitis optica, optico-spinal, TH1, TH2, William Croone

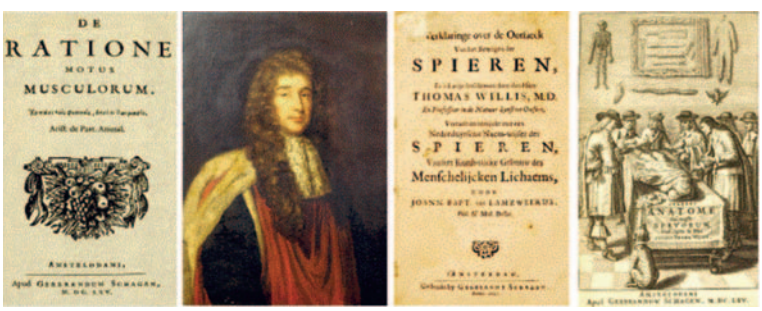

Fig 1. Left to right: **Title page from the Amsterdam edition of *Cerebri anatome* containing Croone’s essay; William Croone; title page of the Dutch *De ratione motus musculorum* (1667) attributed to Thomas Willis; engraved frontispiece from the Schagen edition of *Cerebri anatome* (1665/6)** showing the circle around Willis – William Croone is not identified.

In her will of 21 September 1706, Lady Sadleir endowed two lectures in memory of her first husband, William Croone (1633–1684). The one at the Royal College of Physicians was to be on the brain, nerves and muscles. Why nerve and muscle? Given that his reputation rests on one slim pamphlet, Croone has been rather well marketed. *De ratione motus musculorum* was published anonymously in 1664. Curiously, between 1664 and 1676, it was appended to Dutch editions of Thomas Willis’s *Cerebri anatome* with a separate title page but no author identified. Willis published his own version of events as *De motu musculorum* in 1670. And that was the end of the matter until 2003 when an edition of *De ratione motus musculorum*, published in Dutch and formalising the plagiarism by claiming Thomas Willis as the author, surfaced in the antiquarian book-trade.[1] The Dutch *De ratione motus musculorum* is previously unrecorded and appears to represent the survivor of an hitherto unknown edition of Croone’s essay (Fig 1).

But the continental editions of *Cerebri anatome* published by Caspar Schagen have a broader significance. They contain a unique figure showing the circle around Willis responsible for the gestation of clinical neuroscience. *De ratione motus musculorum* is more than just an essay on the twitching of muscle fibres. It offers a general theory on how the nervous system works:

> *muscular contraction* [is] *brought about through the action of a spirituous liquor that passes from the nerves and interacts with substances in the muscle ... the soul acts upon the body through the nerves composed of a medullary substance full of juice with a double membrane which surrounds that substance; an infinite number of little cords within these membranes are inserted into parts of the muscles … all objects of the senses are carried to the brain where different and distinct movements are perceived by the mind.*

Adopting the Greek position on health as a state of harmony arising from equilibrium of earth, fire, air and water, Croone reflected:

> *This is the origin of the marvellous harmony of the nervous parts. Perhaps we shall shed light on this very difficult question: why does sensation persist in paralysis after the movement is lost and conversely?*

This clinical question was addressed *inter alia* by John Cooke in his Croonian lectures given to the College of Physicians between 1819 and 1821 (Cooke 1820–23) – the first to deal extensively with the nervous system. As the polishing touches were put to his last, in December 1822, a young English nobleman – Augustus D'Este – travelled to Scotland to visit a friend who he found to be dead on his arrival. There, D'Este lost vision in both eyes. This recovered but recurred in 1826. Further episodes occurred and by 1843 D'Este was well established on a chronic progressive course with superimposed relapses. Later, he became paralysed, lost the use of his arms, and eventually died in December 1848, having had symptoms intermittently for 26 years. D'Este had multiple sclerosis[2] – and he is not alone. Now, multiple sclerosis is the commonest potentially disabling disease affecting the nervous system of adults in the Western world.

The story of multiple sclerosis

German clinico-pathologists added details to the first depictions of multiple sclerosis by Robert Carswell (1838) and Jean Cruveilhier (c 1841) prior to the definitive accounts by Jean-Martin Charcot and his school at the Salpétrière from 1865. Charcot recognised multiple sclerosis as a distinct entity. His contributions were in making the story coherent but, in some respects, Charcot's analyses would now be challenged. For him, multiple sclerosis was primarily a disorder of astrocytes from which inflammation followed. With his pupil Joseph Babinski, Charcot saw but did not perceive the nature of remyelination, misreading this for partial demyelination. But in two important respects, his school was ahead of the game. They understood the pathological and clinical importance of axonal degeneration; and, with the most primitive concepts of neurophysiology, made intuitive speculations on pathophysiology.

The central concept underlying ideas on the pathogenesis of multiple sclerosis is that a cascade of inflammatory events culminates in acute injury of axons and their myelin sheaths. Brief exposure of the exposed (rat) spinal cord to nitric oxide, produces reversible conduction block in normal or hypomyelinated axons.[3] Hence, one mechanism of symptom onset is the direct effect of inflammatory mediators on conduction through myelinated axons. It follows that, in situations where structural damage may not have occurred, recovery follows removal of these inflammatory mediators, reversing the functional deficit affecting intact myelinated axons.

Although axonal dysfunction is initially reversible, a separate and destructive sequence of calcium-dependent excitotoxic events follows more prolonged exposure to inflammatory mediators. Electrically active axons are especially vulnerable and show irreversible conduction block with demyelination and axonal degeneration after prolonged exposure to nitric oxide.[4] Despite structural damage, function may yet recover through neuronal and cortical plasticity, and remyelination. That said, although the lesions of multiple sclerosis contain oligodendrocyte progenitors, many seem unable successfully to engage naked axons[5] and endogenous remyelination is limited to the acute phase of brain inflammation. This failure to complete the process of remyelination may be crucial in sealing the fate of surviving but vulnerable axons. So, why does remyelination fail and does this matter?

A number of clinical trials have now made the point that the suppression of inflammation in chronic multiple sclerosis rarely does much to limit the accumulation of disability through sustained progression.[6] One interpretation of these observations is that axonal loss and inflammation occur independently. But the *in vitro* evidence suggests that cells of the oligodendrocyte lineage support neuronal survival by both contact-mediated and soluble mechanisms, and that IGF-1 contributes this effect through the PI3 kinase/Akt signalling pathway. Furthermore, differentiated oligodendrocytes increase neurofilament phosphorylation and axonal length due to an effect of glial cell derived nerve growth factor (GDNF) acting through the MAP kinase/Erk pathways. Loss of these mechanisms may explain the chronic axonal attrition characteristic of multiple sclerosis.[7]

Taken together, the phases of symptom onset, recovery, persistence and progression in multiple sclerosis can be summarised as:

- functional impairment with intact structure due to direct effects of inflammatory mediators
- demyelination and axonal injury with recovery through plasticity and remyelination
- chronic axonal loss due to failure of enduring remyelination from loss of trophic support for axons normally provided by cells of the oligodendrocyte lineage.

But bits are missing from this story. Pathologists have dissected the unitary concept of multiple sclerosis and proposed heterogeneity. Multiple sclerosis is not one disease but four.[8] Each has inflammation as its basis but, thereafter, the processes diverge:

- macrophage mediated demyelination (type 1)
- antibody and complement mediated mechanisms (type 2)
- ischaemia (type 3)
- oligodendrocyte sensitivity (type 4).

Key Points

A new edition of William Croone's essay, *De ratione motus musculorum* (1667), is announced

The origins and aetiology of multiple sclerosis are unknown but the phenotype of multiple sclerosis differs amongst racial groups

The neolithic founders of Europe introduced neuromyelitis optica

Genetic drift and stratification changed the mechanisms and phenotype of optico-spinal multiple sclerosis

Cultural changes led to alterations in public health that triggered the development of relapsing-remitting multiple sclerosis in the nineteenth century

These histopathological categories cluster within patients arguing against the interpretation that they merely represent snapshots in the temporal evolution of tissue injury. The suggestion is that types 1 and 2 depend on specifically different genetic predisposing factors, whereas types 3 and 4 represent innate tissue vulnerability. So what is known about aetiology and where should the search start?

John Sutherland established differential prevalence rates for multiple sclerosis in Scotland during the early 1950s.[9] These mapped more closely to the distribution of Nordic people than to any geographical gradient. Orkney and Shetland still have the highest frequency of multiple sclerosis yet recorded. Later, the idea evolved that multiple sclerosis was disseminated throughout Europe by Norse invaders, thus accounting for its contemporary distribution – the Viking hypothesis.[10] In asking, 'Who are the Orcadians?',[11] Roberts re-evaluated the historical and archaeological evidence which told of a succession of peoples in Orkney of Neolithic origin, followed by Picts, Celts, the Norse and the Scots. Genetic analysis confirmed considerable distance from Iceland, Northern Ireland and the Gaelic fringe of western Europe, and with proximity to Scandinavia and countries bordering the North Sea. Although there were surprising differences from modern gene frequencies for a population generally believed to be of Norwegian ancestry, Roberts assumed that the Scandinavian founder group in the Orkneys also (by chance) had unusual gene frequencies – including those increasing susceptibility to multiple sclerosis. These have been maintained whereas modern-day Scandinavians have progressively achieved equilibrium with other Europeans, shifting gene frequencies away from their original profile. Roberts considers the Orcadians to be an extreme ultra-European population.[11]

The origins of multiple sclerosis

Eugéne Devic (1858–1930) described the combination of myelitis with bilateral optic neuritis. The prognosis was poor and autopsy showed a single spinal focus of acute necrotic myelitis together with optic nerve lesions.[12] Later, the term neuromyelitis optica was introduced to describe this disorder. Until recently, the diagnosis was reserved for patients having a single episode of spinal cord and optic nerve or chiasmal disease, occurring in either order. Now, it is recognised that both the optic nerve and spinal cord features may recur – sometimes on several occasions – but without clinical involvement elsewhere in the central nervous system. Magnetic resonance imaging typically shows a long diffuse spinal abnormality, quite unlike the discrete circumscribed lesions of multiple sclerosis, and with high signal in the optic nerves or chiasm but a relative absence of brain lesions. Whilst there is often an excess of white cells, the cerebrospinal fluid is conspicuous for the usual absence of oligoclonal bands.[13] Pathologically, the extensive spinal lesions are associated with necrosis and cavitation, acute axonal injury, loss of oligodendrocytes, inflammatory infiltrates and peri-vascular deposition of immunoglobulin (IgM) and complement. These are the features of a predominantly Th2 immune response with prominent humoral mechanisms, and they epitomise the type 2 pathology of multiple sclerosis.[8,14] Affected individuals may respond to plasma exchange.

Epidemiological studies of demyelinating disease have tended to separate neuromyelitis optica (as originally defined) from multiple sclerosis – whilst noting that the latter often has a specifically different phenotype with disproportionate involvement of the spinal cord and optic nerves in Asian populations. Lumping neuromyelitis optica (monophasic or relapsing) with the Asian (optico-spinal) phenotype of multiple sclerosis allows the frequencies of demyelinating disease confined to the optic nerves and spinal cord and relapsing-remitting multiple sclerosis, as seen in the West, to be compared. The result is rather striking (Fig 2).

With the availability of local expertise in clinical neurology, it became clear that demyelination in Africa, Asia, the Orient and Aboriginal populations is typically optico-spinal whereas (throughout most of the twentieth century) relapsing remitting multiple sclerosis matching the phenotype seen in northern Europeans has been distinctly uncommon. Osuntokun first applied sound epidemiological principles to the study of neurological disease in Nigeria,[15] finding two possible cases of multiple sclerosis, 12 with acute disseminated encephalomyelitis, 95 with neuromyelitis optica and a further 33 either with acute bilateral optic neuritis or transverse myelitis. Thus, over 90% of all patients had optico-spinal disease. Each and every study, large and small, from the African continent has reinforced this point.[16,17] The high frequency of optico-spinal disease is again apparent in India,[18] Malaysia,[19] Korea,[20] and Hong Kong.[21] Between 1890 and 1952, there were 124 cases of neuromyelitis optica (72%) and 48 with multiple sclerosis (28%) in Japan,[22] unlike northern European populations studied during this era.[23] The same is true for the aboriginal populations of north America in whom five of six (83%) patients showed an aggressive relapsing neuromyelitis optica phenotype.[24] In South America the native population has optico-spinal multiple sclerosis at a high frequency.[25] Those who reached the north American continent by sea, bringing African and French ancestry to Martinique, also retain a higher frequency of optico-spinal multiple sclerosis than occurs in Northern Europeans,[26] as does the admixed African-American mainland population.[27]

Asia, the Orient, the Americas, Austraslasia and into Europe is the route taken by man coming out of Africa. Contemporary analyses of human origins now use a combination of ephemeral, archeological, linguistic and molecular genetic analyses of mitochondrial or Y chromosome markers to chart these movements.[28,29] Phylogenetic dendrograms have been improved by networks allowing the appearance of mutations to act as temporal and spatial markers of migration and population genetics.[30,31] The original lineage of *homo sapiens* (L) arose from *homo erectus* in Africa 150,000 years BP. L1 re-emerged, expanded but remained mainly in Africa and the Mediterranean, including Sardinia, from 100,000 BP with displacements by L2/L3 from 80,000 BP (Fig 3). L3 left Africa for Arabia via the Yemen in 50,000 BP. Her descendants, N and M, made it to Australia, Asia and Turkey by 30,000 BP, and from Asia to north (25,000 BP) and

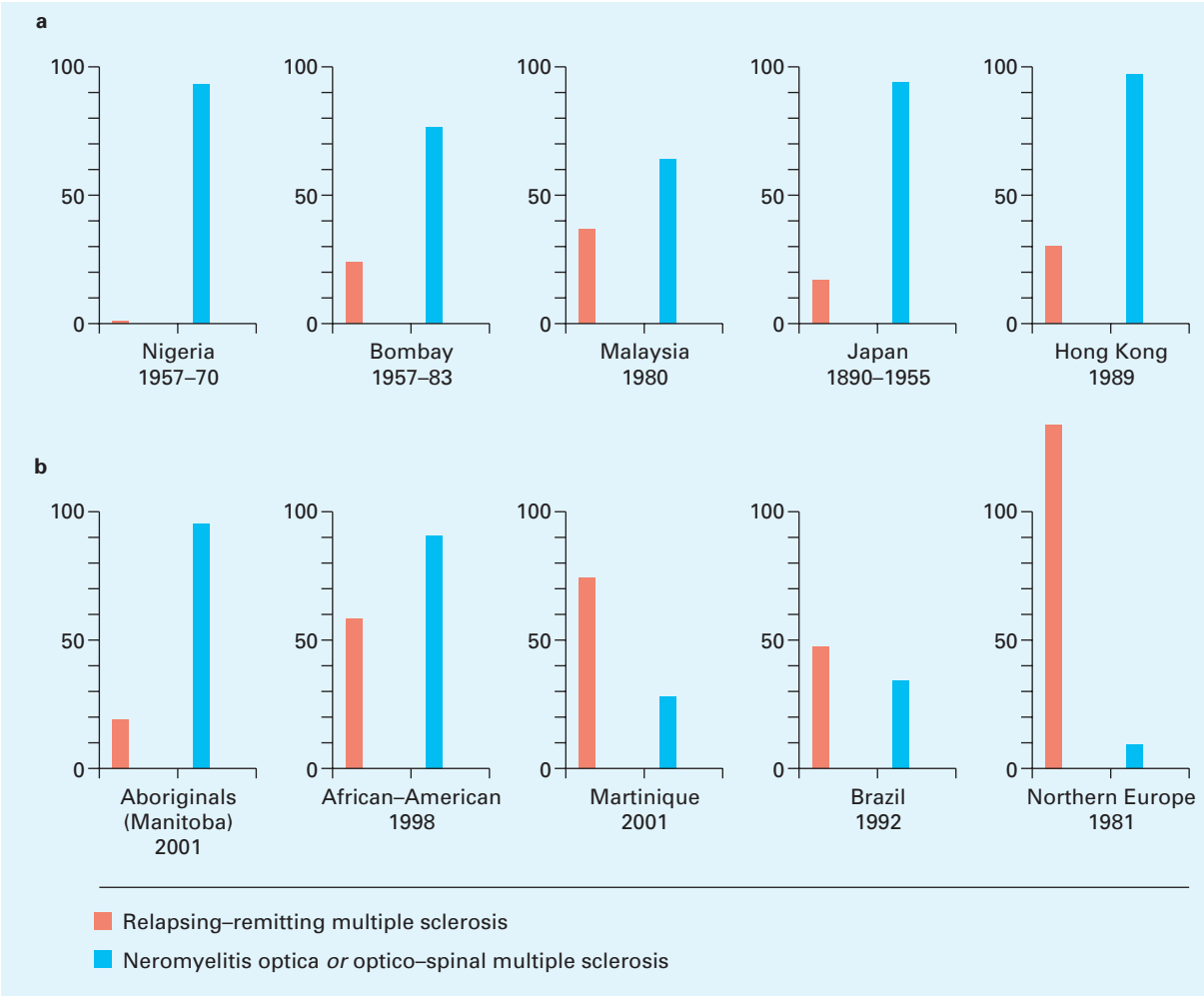

Fig 2. The relative frequency of relapsing-remitting multiple sclerosis and neuromyelitis optica or optico-spinal multiple sclerosis in (a) Africa, India, Asia, and the Orient; (b) aboriginal populations of North America and South America, admixed Afro-Americans/ Europeans, and northern Europeans – in the twentieth century.

South America (14,000 BP). Mitochondrial markers identify discrete subpopulations of N and M in European, Indian, African, Asian (and American), and Australian populations.

Europe was settled in the Upper Paleolithic (40,000 years BP) and this group is marked by mitochondrial (mt) DNA haplogroups U5, H, V, I, W, T and K. Survivors chilled out during the last Ice Age (20,000 BP) in Iberia, the southern Mediterranean and the Ukraine, eventually giving rise to 70–80% of European descendants. With retreat of the ice (15,000 BP), re-population occurred in the Neolithic period (10,000 BP) from Iberia (haplogroup V) and the Ukraine. But in came a new wave from Anatolia carrying mt DNA haplogroup J (originating from N) around 8500 BP, drifting thereafter with the movement of farming as hunter-gatherers ate their way into northern Europe, and gaining a further contribution of the H, T and K haplogroups. Their descendants represent 20% of the present population. The language markers of these founders are Finno-Ugrian, proto-Indo-European (Neolithic arriving with the Anatolian wave and haplogroup J) and Basque (ice-age survivors), respectively. Orkney and Shetland have no Paleolithic history. They were populated from meso- or early-Neolithic mainland Scotland, tweaked by the Norse interests of the fifth and sixth centuries AD imposing *elite dominance*, and again from Scotland in the fifteenth century.

The relevance of this history is that multiple sclerosis in general and the optico-spinal form in particular is associated with haplogroup J/T[32–34] in northern Europeans but not Basques in whom the frequencies of haplogroups J and T are reduced.[35] Is it too glib to suggest that optico-spinal multiple sclerosis, present at low frequency in the out-of-Africa population, reached Europe with the Neolithic migration – and carried not in saddlebags but tucked in the genes?

Perhaps transitional cases provide the evidence. Harding *et al* described eight women presenting with bilateral sequential optic neuropathy and later developing symptoms consistent with demyelination outside the visual system.[36] Magnetic resonance imaging abnormalities typical of demyelination were present in seven patients who were scanned. All eight had matrilinear relatives affected by Leber's hereditary optic neuropathy, and the 11778 mutation. In a subsequent review of Leber's

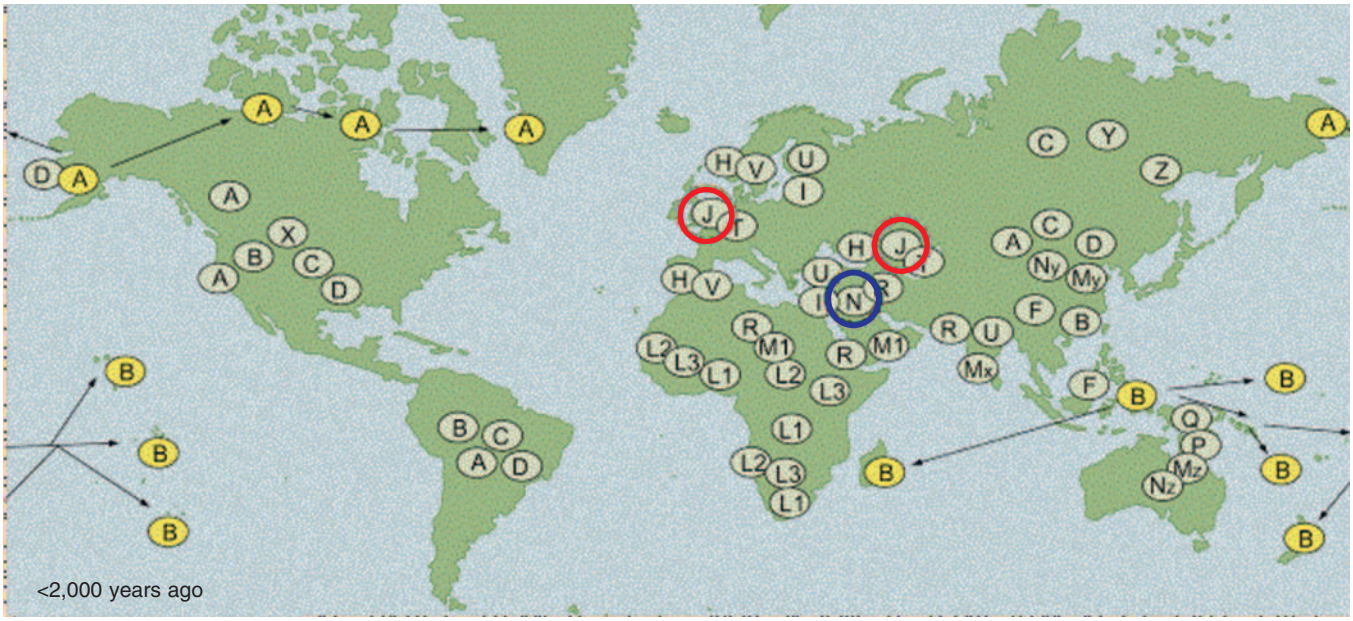

Fig 3. Mitochondrial markers for populations emerging from Africa and migrating to Europe in the Paleolithic and Neolithic (kindly provided by Dr Peter Forster).

hereditary optic neuropathy, Riordan-Eva *et al* reported that 45% of 24 women with the 11778 mutation had a multiple sclerosis-like illness.[37]

But there the genetic trail goes cold. Pathological mutations of mtDNA are not associated with multiple sclerosis in systematic screening of unselected patients. Kellar-Wood *et al* found no mutations at the 11778 mitochondrial DNA site in 307 unrelated patients with multiple sclerosis, randomly selected with respect to clinical presentation.[38] Kalman *et al* studied 22 patients with prominent optic nerve involvement, 20 of whom met criteria for clinically definite multiple sclerosis.[39] None had the 14798, 11778 or 3460 mutations of mitochondrial DNA. And focusing on the most informative group, the neuromyelitis optica phenotype amongst Caucasians is also not associated with mutations of mitochondrial DNA.[40,41] Even in Japan, Nishimura *et al* screened 80 patients, of whom 18 were women with bilateral visual failure but no mutations were found.[42] Nor was there a clue to a pathological mtDNA mutation in 20 Korean patients with multiple sclerosis.[43] Thus, haplogroup J and T are population markers but do not harbor a pathological mutation. In that case, where should the search for genes that determine susceptibility to multiple sclerosis be focused?

Because of linkage disequilibrium, susceptibility genes making even a small contribution to a disease process may still be identifiable by screening nearby anonymous markers, obviating the need directly to hit the disease locus itself. When polymorphisms that increase susceptibility to disease arise in a founder group, these will initially be located amongst a large group of linked genes. This block is subject to recombination during subsequent meioses and is gradually whittled down as the population expands. It follows that the progeny of this founder will share segments of DNA identical-by-descent over many generations. But in time, this linkage disequilibrium degrades. Susceptibility genes can then no longer be identified by association mapping. The population is now in linkage equilibrium. For younger populations, or more recently introduced alleles, the degree of linkage disequilibrium may be sufficient to use markers remote from the disease promoting polymorphism to track the genetic basis for susceptibility. Although the loss of founder mtDNA markers is significant, those that are transmitted survive longer as population markers than nuclear genes. Therefore it may be easier to identify a mtDNA population marker than the nuclear genes putatively introduced with that founder group.[44] It follows that the ancient susceptibility genes for multiple sclerosis will be hard to identify by association mapping. Conversely, susceptibility genes over-represented in the European population may still be trapped in large blocks of linkage disequilibrium and easier to find. Although estimates for the extent of linkage disequilibrium are changing, empirical evidence suggests that this may be relatively extensive. Recombination is not uniformly distributed, as assumed, but concentrated in hot spots separating regions of marked linkage disequilibrium averaging around 25 kilobases.[45]

Starting with the founder alleles that arrived, by chance, with haplogroup J/T in the proto-European population, genetic drift and selection for survival from epidemic disasters of the Middle Ages may have concentrated the optico-spinal susceptibility genes and exposed the expanding population to the immunological consequences of these and additional mutations. Systematic filtration of high-risk groups would have culled individuals and genotypes not well suited to surviving the waves of infectious disease, and selecting others for their immunological advantages. Identification of the events that drove these changes in genetic make-up of the emerging European population remain shrouded in the mists of history but the answer must lie in one or more public health upheavals of the fifteenth to seventeenth centuries

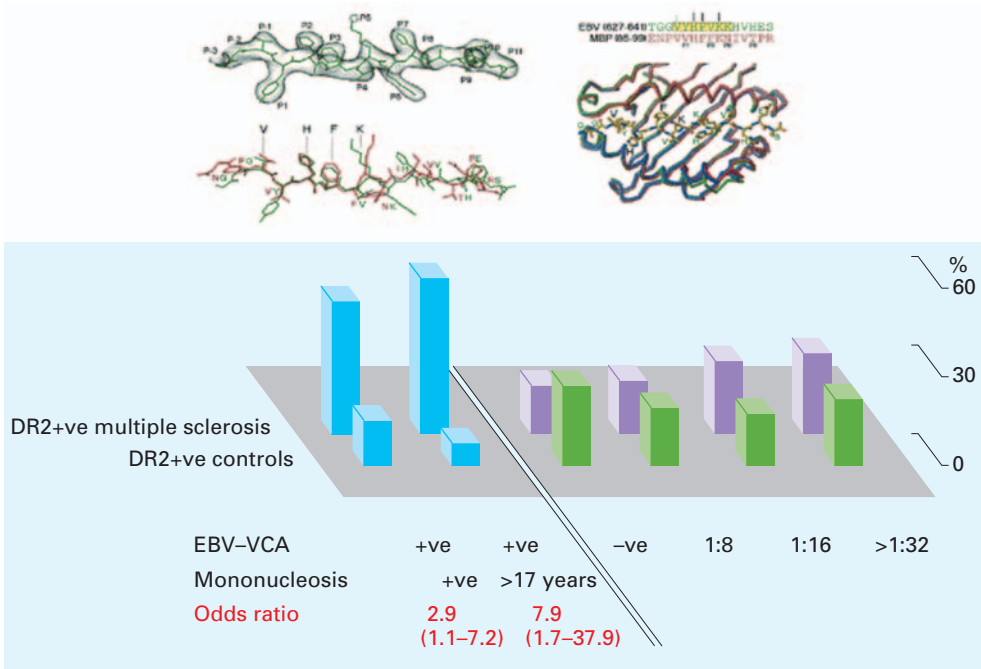

Fig 4. Molecular mimicry between epitopes of myelin basic protein and Epstein Barr virus (EBV): risks for multiple sclerosis depending on age at acquisition of infectious mononucleosis, and distribution of serum antibody titres to EBV in HLA-DR2 matched individuals with multiple sclerosis and controls.

resulting from infectious disease and wars.[46] The price paid is autoimmunity, and the major suspect for having got the genetics wrong is the major histocompatibility complex (MHC). Its many polymorphisms are considered to be the tombstones of 'long-standing battles for supremacy between the immune system and infectious pathogens'.[47] Removed from the microbial environment, these alleles saddled the progeny of their ancestral survivors with an inconvenient pro-inflammatory genetic heritage.

The MHC consists of 3,600 megabases DNA mapped to chromosome 6p21.3.[48] It contains 224 genes at an unprecedented density – 1 in every 16 kilobases. The sex-averaged recombination rate across the MHC is 0.49 cM per megabase but with three recombination hotspots.[49] It is predicted that 128 genes are expressed, of which 40% are likely to have products influencing immune function. Multiple sclerosis is associated and linked to alleles of the major histocompatibility complex, especially DR15/DQ6 (DRB1*1501, DRB5*0101, DQB1*0602) in Europeans.[50]

It takes rather little licence to speculate that although the immune repertoire was fixed long before *homo sapiens* made an appearance, modifications of the proto-European genetic repertoire changed the nature and style of the immune response. *Neo*-multiple sclerosis – the Western phenotype – may have emerged because the Th2 immune response of neuromyelitis optica switched as a result of this genetic filtration and a changing microbial environment. Now a Th1 immune response enhancing T cell and memory responses dominated, overriding the optico-spinal specificity, exposing new and more ubiquitous antigens, increasing the frequency of episodes – thus altering the course and phenotype. Thereafter, relapsing-remitting multifocal multiple sclerosis became the pattern as frequency of the disease increased during the nineteenth century and beyond due to population expansion, increased awareness and (perhaps) a genuine increase in incidence. This analysis is no different from the MHC-regulated response to *Mycobacterium lepra* determining the Th1 tuberculoid (DR2[15]/3 associated) and Th2 (DR1/7 associated) lepromatous varieties of that infection.[51]

Until recently, whole genome linkage disequilibrium mapping was considered impractical and dependent on chance co-localisation of susceptibility genes and markers applied randomly and distributed at low density. In GAMES (the Genetic Analysis of Multiple sclerosis in EuropeanS), 19 groups researching multiple sclerosis in 16 countries each performed a low resolution screen of the genome for linkage disequilibrium by typing 6,000 microsatellite markers in pooled DNA. Meta-analysis of these data identified the most consistently associated markers, several of which were then genotyped individually in 3,392 cases and 3,201 controls. The most strongly associated were encoded within MHC. The best of the rest to emerge from this analysis was D20S894. This marker lies 45kb from *JAG1*, and immediately under a peak of linkage at 20p12 identified in a meta-analysis of linkage screens (GAMES and the Transatlantic Multiple Sclerosis Consortium, unpublished). Jagged1 binds notch1 to induce Hes5 which inhibits the differentiation of oligodendrocyte precursors.[52] Areas of poor remyelination are characterised by expression of Jagged1 on reactive astrocytes, in the vicinity of Notch1 and Hes5 positive oligodendrocyte precursors. Conversely, remyelination is characterised by the absence of Jagged1. The implication is that the Notch1/Jagged1 system controls the degree of remyelination in the lesions of multiple sclerosis.[53] It requires no intellectual leap to suggest that a genetic polymorphism in receptor or ligand might determine the success or otherwise of remyelination, perhaps making the difference between a mild or severe course or, even,

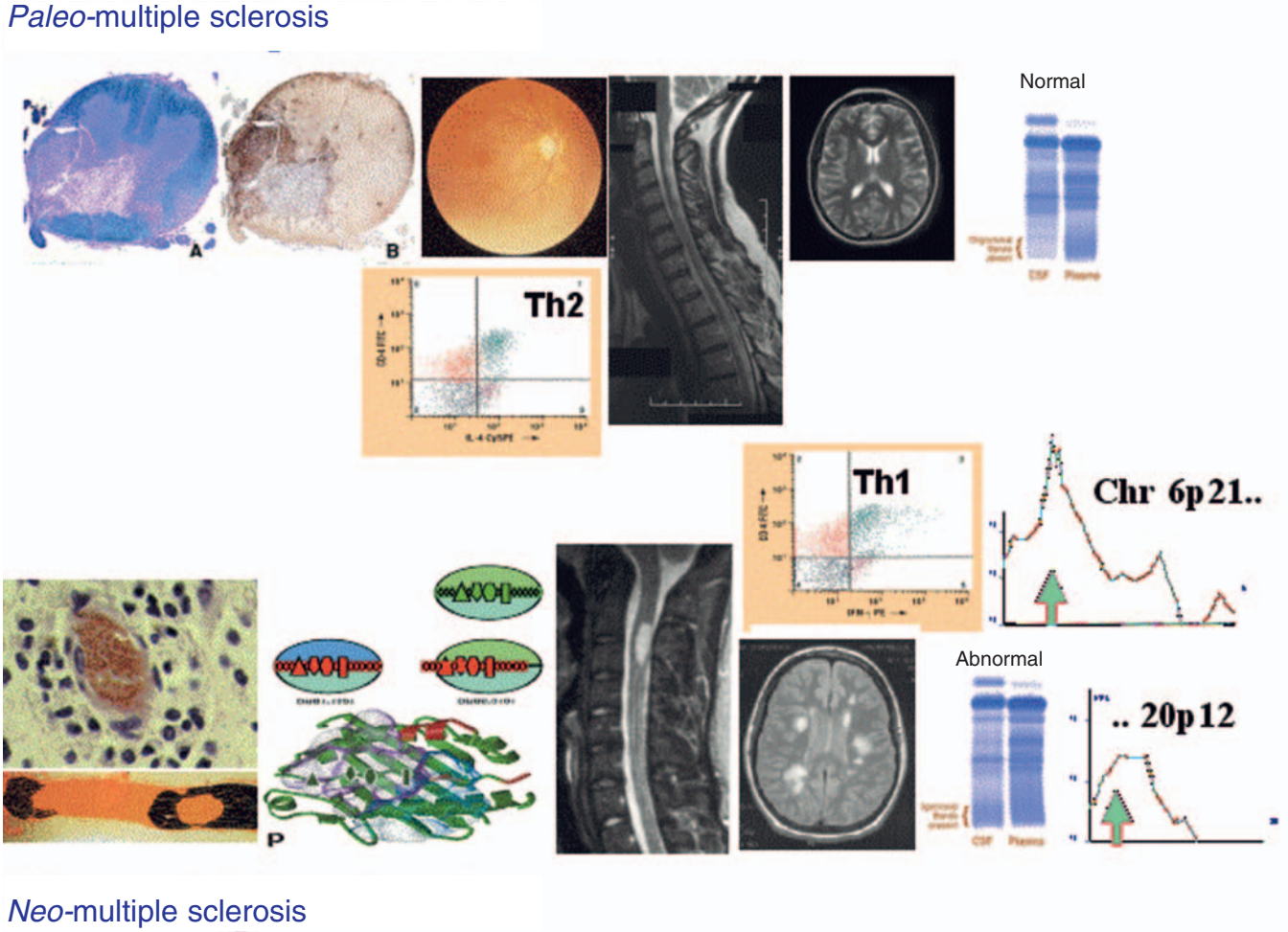

Fig 5. The comparative features of neuromyelitis optica and relapsing-remitting multiple sclerosis.

no pathological and clinical phenotype at all despite cycles of inflammatory injury.

If there was a genetic time bomb waiting to go off, what lit the fuse? At some point, a specific microbial challenge occurred which led to the appearance of multiple sclerosis and its subsequent increase in frequency. Lang *et al*[54] showed that a T cell receptor specificity present in multiple sclerosis (Hy.2E11) recognises a residue of myelin basic protein (85–99) in the context of DRB1*1501 restriction, and an epitope of EBV (residues 627–641) in association with DRB5*0101. Four T cell receptor peptide contacts are identical for myelin basic protein and EBV. Thus, there is molecular mimicry. Studies on the molecular evolution of EBV suggest that the two types (EBV-1 and -2) arose from recombination between a proto-EBV strain and an unknown member of the lymphocryptovirus (and perhaps a third organism), creating genome sequences of the two present day viruses.[55] These changes are thought to have occurred about 10,000 years BP but, apparently, multiple sclerosis makes no appearance until the early nineteenth century. Could cultural change have exposed a window of autoimmune opportunity through changes in age at infection and with markedly different biological consequences – as is well established for enterovirus infection and paralytic poliomyelitis? Patients with demyelinating disease report later age at infection by measles, mumps, rubella and, especially, EBV infection compared to controls selected for the same frequency of HLA-DR2 so as to match for at least one marker of genetic susceptibility.[56,57] Infectious mononucleosis after the age of 18 years carries a relative risk for multiple sclerosis of 7.9 (95% CI 2–38: Fig 4).

Multiple sclerosis: an evolutionary hypothesis

Multiple sclerosis did not begin with wandering Vikings distributing their genetic material throughout Europe and, through their descendants, to other parts of the globe. It evolved from a disease already present in more ancient populations and leaving traces in the present day spectrum of disease (Fig 5). That disease was neuromyelitis optica. Th2 and humoral mechanisms acting against a particular genetic background targeted the disease process to the optic nerves and spinal cord producing long necrotic lesions carrying a poor prognosis for functional recovery. The disease was never common but, by chance, the susceptibility factors were brought to Europe with the small

founder group from Anatolia which contributed to the re-population of northern Europe after the last Ice Age – around 10,000 years BP. That founder group is marked by the mitochondrial haplogroup J/T and traces of the association remain – with multiple sclerosis in general and the optico-spinal phenotype in particular. Thereafter, genetic drift and selection pressure from waves of epidemic disease favoured the emergence of high immune response genotypes clustered within the major histocompatibility complex. Those changes were sufficient to induce the Th1–Th2 switch in immune response, triggering more frequent episodes and eventually breaking down the optico-spinal specificity perhaps, immunological and neurological checks and balances made the lesions smaller, more sharply defined and (individually) of less immediate functional significance. Thus arose relapsing remitting multiple sclerosis. The triggers were infectious disease with EBV playing a particular role – its impact emerging most floridly with cultural change consequent upon expansion of the population and industrialisation in the nineteenth century.

Even now, the switch from optico-spinal to relapsing-remitting multiple sclerosis is seen, on a smaller scale, by the shifting epidemiology and clinical phenotype of multiple sclerosis in migrants and in Japan following cultural changes and industrialisation from the 1960s.[58] These social shifts expose the innate vulnerability of those few individuals harbouring alleles that later underwent concentration and stratification amongst progeny of the Neolithic founders. Epidemiological studies of multiple sclerosis in migrants fast-forward the collision of genetic, environmental and social risk factors that evolved over 10,000 years to create the modern epidemic of multiple sclerosis in Europe. The intrinsic vulnerability is exposed in at-risk individuals experiencing a new microbial environment at a crucially altered phase of maturation in their immune repertoire, either on migration or through altered domestic conditions. Thus, the phenotype, immunopathogenesis and histological complexity change, whilst the frequency of susceptibility genes determines the prevalence of demyelinating disease in each population. In suggesting a relationship between neuromyelitis optica and relapsing multiple sclerosis, the issue of how other inflammatory demyelinating disorders – especially acute disseminated encephalomyelitis and primary progressive multiple sclerosis – fit this perspective remains to be discussed.

This formulation makes many assumptions but goes further than previous analyses. Several commentators have come close. Cosnett[59] saw a link between neuromyelitis optica disease and multiple sclerosis in Africa; Cree *et al*[60] gathered and described much of the clinical epidemiological evidence but did not draw the strands together; Kira *et al*[58] used the experience of multiple sclerosis in Japan to great effect, spotted the Th2/Th1 polarities and elaborated many perceptive points including the effect of cultural change on phenotype but separated the Asian and western forms of multiple sclerosis. An evolutionary approach to the origins of multiple sclerosis is novel but risky and leaves many issues unexplained. It is testable using the available matrix of informative populations, mitochondrial and nuclear genetic markers, and discrete clinical phenotypes. The zoological record is in the spectrum of pathological changes, dubbed heterogeneity, and the transitional clinical cases. The archeological record is in the global epidemiology of demyelinating disease.

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