Environmental factors and multiple sclerosis

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Studies in Canada have provided strong evidence that environmental factors act at a population level to influence the unusual geographical distribution of multiple sclerosis (MS). However, the available data accommodate more than one type of environmental effect. Migration studies show that changes to early environment can greatly affect risk, and there are recent indications that risk can be altered in situ. The rising incidence rates of MS in Canada implied by longitudinal increases in sex ratio place this effect in temporal context and narrow the candidates for mediating the effect of environment. Similarly, geographical patterns in Australia imply that modifiable environmental factors hold the key to preventing some 80% of cases. Genetic epidemiology provides overwhelming evidence that genetic background has an important complementary role. If genetic factors are held constant, the environment sets the disease threshold. Although these could be independent additive risk factors, it seems more likely that susceptibility is mediated by direct interactions between the environment and genes.

Introduction

Nature versus nurture arguments about the pathogenesis of multiple sclerosis (MS) have given way to evidence that both are important. Independent of seminal South African migration studies by Dean,[1] the low prevalence of the disorder among people of east Asian descent in Canada compared with that in people of north European descent has long been recognised. A similar relative dearth of cases in Queensland is obvious to local practising neurologists familiar with the prevalence of the disorder in Sydney and Melbourne. And these impressions have been confirmed by real data.[2] It is more timely to ask if and how nature and nurture interact rather than debate their relative importance. Identification of environmental factors might pinpoint biological pathways, and vice versa.

The limited ability of case–control studies to identify differences led to a temporary de-emphasis of the study of environmental factors. The environment does not necessarily differ for affected and unaffected individuals in the same family, and geographically separate regions have the same risk. Several recent studies discussed here refocus attention on environment, which is so clearly important in pathogenesis.

The study of genetic factors, perceived a decade ago to be more tractable than that of environmental influences, has been slow in fulfilling initial promise. Claims for linkage on nearly every chromosomal arm suggest systematic methodological failures.[3] Two recent small but confirmed effects leave half of the genetic contribution to MS unexplained.[4,5] Re-examination of the conceptual and practical importance of the environment in the pathogenesis of MS seems timely.

Given that the effect of the environment in MS is not necessarily mediated by singular or discrete events, it may be useful to separate susceptibility, triggering, and outcome. Here we focus on the first of these. Although there is convincing evidence that environment affects outcome and clinical features,[6] few studies have examined differences in long-term outcome by geographic location.

Non-specific viral (and perhaps bacterial) infections seasonally precede both onset and relapses (and MRI activity) in perhaps a quarter of MS cases[7] despite common disparity between biological and clinical onset. The relation of relapses to long-term disability is surprisingly unclear[8] and the dissociation of the two is evident in early studies of interferon.[9]

See Online for webfigure 1

Geography

The uneven geographical distribution of MS is central to understanding the role of environment and has influenced epidemiologists since Davenport's report that ethnicity affected risk of MS in veterans of World War I.[10] US Veteran's Administration data enabled Kurtzke's pivotal studies of the geographic gradients noted by Davenport.

US data revealed north–south and east–west gradients.[11] Distribution of MS in the USA resembles that of Scandinavian immigration; thus the geography reflects both genetic and environmental clines. Migrants commonly go to places with opportunities for portable skills—for Scandinavians in the 1850s, the US northwest provided opportunities for which their skills as woodsmen stood them in good stead. Suggestions that geographical distribution is entirely explained by genetic clines[12,13] seem improbable. More likely, gradients reflect gene–environment interactions.

McLeod[2] shrewdly concentrated on medium-sized epidemiologically tractable communities. His Australian data had more ethnic homogeneity than the US Veterans Administration data. Differences in susceptibility related to differences in place of birth and subsequent domicile suggested that MS risk can be altered up to early adulthood.[14] The broad Antipodean picture showed that the environment is important in setting thresholds for genetic penetrance.

The Agricole health-care system for French farmers and their families provides a nearly ideal population for study: ethnically homogeneous, sedentary by domicile, and geographically evenly distributed.[15] This population shows a striking north–south gradient as seen in Europe and in north America as a whole but the pattern is more complex than that. There is an east to west gradient, unlike the west to east for the northern USA,[11] and there is focal irregularity (see webfigure 1). The low risks in

Corsica and Côte d'Azur are continuous along the Atlantic coast, and even this curvilinear coastal band of disproportionately decreased risk has some discontinuity. Poitou-Charentes[15] has an anomalously low prevalence of 47 per 100 000 and is bordered to the east by areas with prevalences greater than 70 per 100 000. This microheterogeneity suggests a climatological influence.

The amount of winter sunlight parallels the range of prevalence, with high sunlight associated with low prevalence (see webfigure 2). To avoid any temptation to make maps of prevalence fit preconceived notions we have arbitrarily split the regions of France into thirds in contrast to the case for webfigure 1. The co-occurrence of low prevalence of MS and high ultraviolet exposure in Poitou-Charentes and much of the Atlantic coast support a role for sunlight exposure (figure 1). The data used in these maps to describe UV radiation are satellite-derived, corrected for cloud cover and its density, and have been validated with ground measurements.

If MS risk is related to sunshine alone, the far north of Norway should have the highest incidence, because the sun does not clear the horizon for two months of the year. However, incidence in Finnmark and Troms seems to be lower than in Scotland or England and only half that of landlocked Oppland further south.[16] This pattern must lie at the heart of the main environmental influence and suggests possible interactions between diet and sunlight. There is a plausible role for the consumption of oily fish, which is higher by virtue of accessibility and accepted wisdom in areas of low prevalence (figure 2).[16,17] This interaction might also explain the low prevalence on the French Atlantic coast.

Migration studies

In Australia, prevalence in Tasmania is five to six times that in Queensland, a difference far too large to result from a genetic cline, mirroring findings in British migrants to South Africa. Conversely, migrants from east Asia to the west coast of North America have a low prevalence and large populations in Vancouver, Canada, retain low risk; although small recent increases in prevalence have been reported in these migrant populations and in Japan.

In the UK and North America, the risk of MS in migrants from the far East remains low, whereas in migrants from India the risk of MS increases in the second generation, although there may be heterogeneity within this diverse population.[18] Differences between migrants and their offspring could reflect early timing of environmental exposure or inevitable selection processes affecting migrants or perhaps both. Migration data were instrumental in Acheson's proposal of a role for sunshine in disease pathogenesis:[19] FMR Walshe's snort, "Sunshine? More likely to be the moonshine, my boy!" to the suggestion at a neurology conference was indelibly imprinted on the young Acheson.

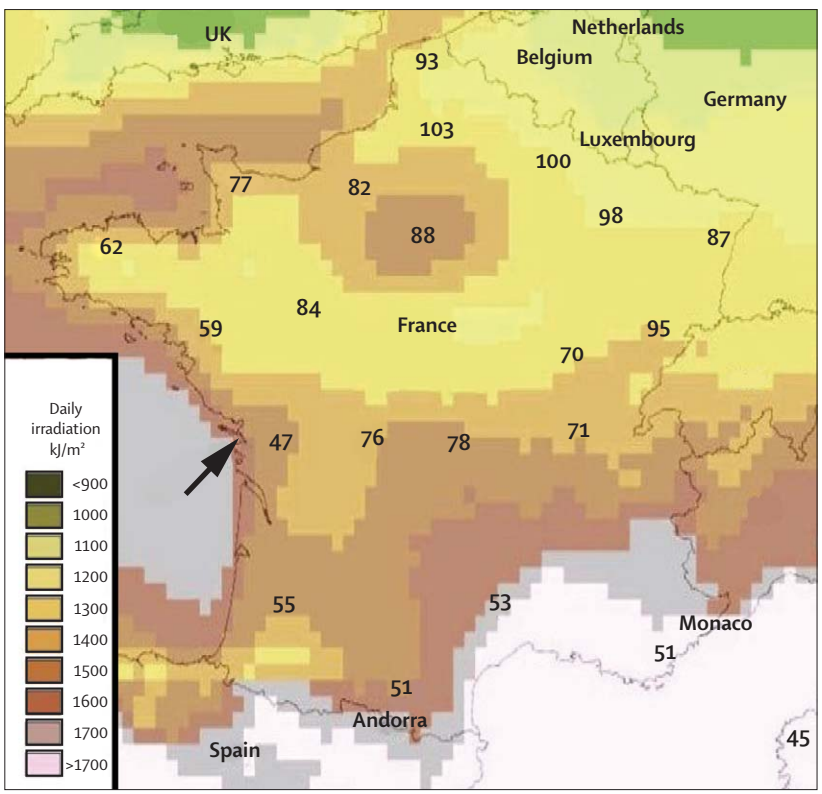

Figure 1: **August monthly mean ultraviolet irradiation and MS prevalence in France**
Prevalence figures per 1000. UV data reproduced from the SoDa service with permission from Ecole des Mines de Paris/Armines. Arrow indicates the Poitou-Charentes region of anomalously low MS prevalence.

For **the SoDa service** see http://www.soda.is.com

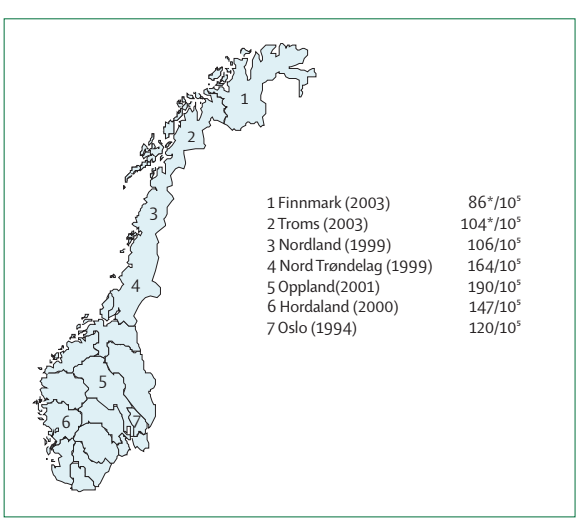

Figure 2: **Anomalous distribution of MS prevalence in Norway**
If MS prevalence were influenced by sunlight alone, the maximum would be in the north. But the highest prevalence is in landlocked Oppland in the south. *Estimates based on patients included in this study. Reproduced with permission from Springer Science and Business Media.[16]

See **Online** for webfigure 2

Migration studies are typically unable to establish timing of environmental exposures owing to small numbers. Whether there is a discrete time of exposure is open to question, and although clinical onset is commonly

***Panel:* Findings and unresolved questions in MS twin studies**

Findings

MZ concordance is greater than DZ concordance[22]

MZ rate much exceeds the DZ rate in high-risk regions,[22] suggesting caution in the use of concordance rates to estimate genetic complexity

High MZ concordance rates are mainly derived from the female pairs[22]

Age at onset in concordant MZ twins is similar[22]

Concordance is determined by stochastic or chance factors and by environment

Outcome is under partial genetic control

Sibling rates in twin families are identical to sibling rates from several other sources including avuncular and parent-child families[22]

There is an association between MS, concordance, and microchimerism in twins but cause cannot be distinguished from effect[26]

Unresolved questions

Is concordance related to the presence of *HLA-DRB1*1501* and other susceptibility and resistance alleles, genetic load, stochastic factors, or a combination?

Age at onset in DZ concordant pairs versus siblings. If risk is related to intrauterine exposure, age at onset may resemble that of MZ twins rather than non-twin siblings

The relation of chorionicity to concordance is unknown because placental structure was rarely recorded

DZ twin concordance is higher than that of siblings; differences are only nearly significant

MS may be under-represented in DZ twins[27,28]

MZ=monozygotic. DZ=dizygotic.

discrete, resistance or susceptibility could be entrained by cumulative exposures.

Genetic epidemiology and environmental factors

Family studies

Twin studies have been influential in separating genetic from environmental influences on MS susceptibility. Studies of other family relationships provide useful epidemiological insights; each type of relative pair illuminates potentially different features related to whether or not relatives are colineal or vertically related, and to differential common exposure. Comparisons of risks in relatives more distant than half siblings (eg, first cousins, nieces, and nephews) have limitations. The latency of learning of the disease in relatives increases and even long-term awareness of it generally decreases with genetic distance.

Twins

The first demonstration of statistically higher concordance for MS in monozytic than in dizygotic twins[20] had a large effect but was mostly unwelcome at a time when neurovirology dominated MS research. This study was the first to compare concordance in monozygotic and dizygotic twins with that in siblings, similarly ascertained.[20] Serial, proband-wise replications in the same population[21,22] and in other large national studies[23–25] were reassuring, but points about ascertainment need to be made. Ascertainment biases related to the social nature of volunteerism and the special characteristics of monozygotic twin relationships favour females, monozygosity, and concordance of participants in such studies. Population-based Canadian studies avoided these biases.

Comparison of concordance rates in monozygotic twins versus dizygotic twins illustrates how excess concordance comes from female pairs. For females, the updated Canadian monozygotic twin concordance of 38% and dizygotic twin concordance of 4% (Ebers and Sadovnick, unpublished) are similar in direction to findings from Denmark and Italy (panel).[27,28]

Discordance in monozygotic twins is inevitably taken as proof of environmental causation but does not necessarily support this conclusion. Stochastic effects, informatively illustrated in single cells,[29] might account for discordance. By way of explanation, in the north Atlantic, waves of 70 feet or more will occur once a year in a given location but are largely random in time. Disease triggering might be akin to such misfortune of time and place. Once again a unitary explanation evades us, even for concordance.

If environmental risk were determined at a broad population level, it might reasonably be expected to be equal within monozygotic twin pairs. Recent evidence strongly implies that differing monozygotic concordance rates between populations reflect differential environmental effects. In monozygotic twins, concordance is clearly influenced by background prevalence or incidence, implying that population effects are independent of, or interact with, susceptibility genes.

Because of heterogeneity among those affected by traits that are genetically complex or determined by several loci, the minimum threshold for disease might be far exceeded in some individuals, thereby raising disease penetrance and concordance in risk-prone monozygotic twins. The frequencies of susceptibility and resistance alleles[30] might differ in concordant versus discordant pairs. Furthermore, microchimerism in affected twins with MS could explain some discordance.[26] The striking female-specific predilection for concordance first noted in Canadian data implies gender-specific gene–environment interactions.[31]

The use of monozygotic and dizygotic concordance rates to estimate numbers of susceptibility loci[32] seems unreliable. Variable concordances by background prevalence and inability to specify validated inheritance models mean that assumptions made are open to challenge. Estimates of 10 to 15 or more genes obtained with this method are not supported by genome searches, and although small effects have been shown for the *IL7R* and *IL2R* genes[33] these would not affect the inheritance pattern unless larger effects were to be seen in individual families.

Accurate concordance rates in dizygotic twins are needed, and if they are higher than those for siblings, a dramatic shift in the search for environmental factors could ensue because gestational, or even epigenetic,

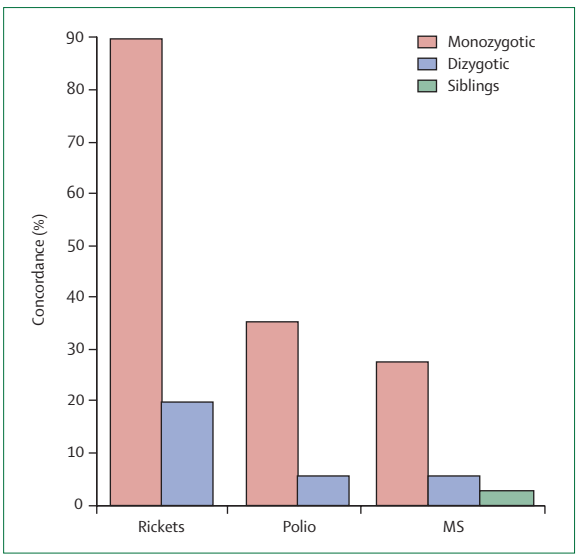

Figure 3: **Twin and, where available, sibling concordance rates for rickets,[35] polio,[36] and MS[22]**

factors are implicated. Such rates have been consistently higher but lack significance in the three independent Canadian cohorts.[20–22] There are stronger age-at-onset correlations in concordant monozygotic pairs (r=0·78) than in siblings (r=0·18),[34] but few concordant pairs of dizygotic twins exist, so this relation is inadequately studied. Dizygotic twins might be like monozygotic twins, because they share intrauterine environment and birth timing, or like non-twin siblings whom they resemble genetically. In opposite sex twin pairs, the inherent matching for maternal environment and birth timing might be useful in the isolation of factors related to development. The concordance pattern for MS, an autoimmune disorder, can be compared with that seen in rickets, caused by a vitamin D deficiency, and polio, an infectious disease (figure 3).

Adoptees

About 1% of individuals in North American countries are adopted at or near birth, and this population can provide useful insights into genetic and environmental influences in MS. Among 1201 first-degree non-biological relatives of adoptees with MS, one case of MS was found—equivalent to the general population rate—whereas the expected number for matched biological relatives was 25.[37] Biological parents (mostly mothers, because fathers were difficult to trace) of affected adoptees had the prevalence expected for natural mothers who had kept their children.[37] There was no risk associated with growing up with someone destined to get MS unless there was a biological relationship.

Half siblings

Conveniently, there are almost equal numbers of half siblings raised together and separately. Those raised apart often have had no contact owing to parental disharmony. In a population of about 3500 half siblings,[38] common intrafamilial environment had no detectable effect on increasing MS risk over those raised apart, confirming conclusions from adoptees.

In individuals who had only one parent in common, paternal and maternal half-siblings' risks could be directly compared, and showed a significant excess of affected maternal half siblings.[38]

The maternal half-sibling rate when compared with risks in full siblings from the same families surprisingly showed half-sibling risks at odds with twin-sibling concordance data. Risk dropped steeply from monozygotic twins to siblings, the latter having half the proportion of genes in common compared with the former. No parallel drop emerged in the comparisons between siblings and half siblings, who share the same same relative proportions of genes as twins versus siblings. Indeed the prevalence of MS in maternal half siblings was more than half that in full siblings.[38] This conspicuous inconsistency with polygenic models seems to have gone unnoticed in the rush for whole genome association studies. If more than a few tiny effects exist, they are producing little, if any, effect on the inheritance pattern. Monozygotic concordances probably cannot be compared with those of more distant relatives for determining gene number because they seem to be disproportionate to other pairs of relatives.

Stepchildren

A single study found the risk of disease in stepchildren brought into a family with MS had the same risk as the general population,[39] which is further evidence against involvement of the familial microenvironment.

Conjugal MS

Systematic investigation in the Canadian population showed no attributable risk for spouses of patients with MS, even without discounting for undoubted assortative mating.[40] Among 13 550 individual patients, there were 23 spousal cases, which is consistent with the population rate (point prevalence 0·1%, lifetime risk 0·2%). The absence of conjugal cases among 43 families with three or more (including two with 13 and 18) affected members adds further evidence against adult transmission.[40,41]

Risks for offspring of couples in which one partner has MS are similar to those for full siblings of patients. Slightly higher rates among siblings of probands could simply reflect increasing rates of MS. Corrected dominance variance approaches zero, so inheritance can be described as pseudominant with incomplete penetrance. Offspring of two parents with MS have a risk approaching 20% which is four to five times greater than the risk for offspring of a single affected parent.[40,41] Among consanguineous couples, many identitical loci in offspring translates into a nearly three times higher risk (9% *vs* 3·5%) than that in siblings from random matings.[42]

Genetic isolates

Reports of reduced MS risk in religious isolates are convincing. Despite common European origins, prevalence is an order of magnitude lower in western Canadian Hutterites than in neighbouring provincial communities,[43] and there is a less pronounced decrease among Mormons.[44] These differences might result from founder effects and genetic drift, but agrarian sects also differ in many environmental exposures from their more urban secular neighbours.

Timing of environmental effects

Gestation and neonatal period

A marginally significant excess risk in dizygotic twins compared with non-twin siblings, coupled with evidence for maternal effects, potentially implicate gestational or early life timing in susceptibility, even if remote in time from the typical adult onset of MS. More direct evidence comes from studies of month of birth in several northern countries, which have latitude-correlated increased risks for May births and decreased risks for November births.[45] The polarity of this distribution reverses in the southern hemisphere. Unaffected sibling controls differed in birth month distribution from the general population as much as their affected brothers and sisters did, but in the opposite direction.[45] Highly significant results in five distinct populations, including more than 42 000 patients with MS, were dismissed by some experts who likened them to signs of the zodiac.[46] Much evidence from veterinary science shows commercially important effects of birth season on various developmental and later measures. Processes in development are implicated by this timing relationship. Remarkably, the effect derives from patients with relapsing-remitting MS,[6] indicating that phenotype is also influenced by early seasonal life events.

Early childhood, adolescence, and adulthood

Timing precision cannot be expected from migration data, limited as they are by small numbers and possible heterogeneity. Early studies implied that migration before age 15 years was needed to affect risk[47] but reliable Australian data suggest that risk could be altered into the third decade.[14] These findings point to factors after birth, in childhood, and beyond puberty. The Australian data could suggest a more prolonged exposure, which lengthens vulnerable periods not only for risk but also for potential intervention. By apparent contrast, results in UK migrants studied from gestation to the third decade of life suggest risk increases in the second generation.[18] Hence, risk might be influenced in each of the periods of gestation (month of birth effect and maternal effect in half siblings), childhood (migration data and case–control evidence showing space-time clustering),[48] adolescence, and early adulthood.[14] However, the data are not incompatible with a type of environmental imprinting, and the existence of more than one environmental factor could explain the apparent breadth of time for exposure.

	Prevalence
General population rate	1/1000
Adoptive siblings	1/1000
First cousin	7/1000
Paternal half sibling	13/1000
Half sibling reared apart	21/1000
Maternal half sibling	24/1000
Full sibling risk	35/1000
HLA identical sibling	80/1000
Sibling in consanguineous mating	90/1000
Child or sibling	197/1000
Offspring conjugal pair	200/1000
Monozygotic twin risk	270/1000

Table: **Population-based prevalence rates in relatives of MS probands**

Birth order

Results of studies in 30 000 Canadian families pose problems for three popular hypotheses. First, the hygiene hypothesis, as in asthma,[49] is unsupported: in large families, MS risk is greatest in those born later rather than earlier.[50] Second, the suggestion[51] that the presence of infants increased risk for their older siblings is unsupported.[50] Third, absence of birth-order effects outside large (>9 siblings) families fits uneasily with transmissibility. The older sibling in pairs not cohabiting with their affected sibling by virtue of two-decade age differences actually had higher risk than cohabitating siblings adjacent in order. The increased risk among later-born siblings is greater among females than males, a finding that has led to detailed examinations of sex ratio.

Basal population rates of one per 1000 in Canada were unaltered by serially increasing degrees of environmental sharing through familial exposures, which contrasts dramatically with risks associated with genetic sharing (table). These data are epitomised by the risks for half siblings who have never cohabited being more than an order of magnitude greater than for non-biological siblings raised together.

Sex ratio

Sex ratios in MS have received inadequate attention. A recent monograph took no note either of the variability, both geographically and longitudinally, in the female to male ratio or of its significance.[45] Brain's conclusion that males and females were equally affected agreed with early reviews of all features of MS.[52] In retrospect, dismissals of oft-repeated findings of equal sex ratios in the early 1900s seem puzzling. Year of birth very strongly predicted the sex ratio in Canada[31] leaving no doubt that the female-to-male ratio has been changing over much of the 20th century in North America. This change has potential both as an indirect measure of incidence change

and as an outcome target for prevention studies. In native-born Canadians, estimated female-to-male ratios changed from 1 in the early 1900s to 3·5;[31] a similar increase is seen in European migrants to Canada (Ebers, Orton, and Sadovnick, unpublished data). Notably, this increase began long before the introduction of oral contraceptives, refrigeration, or perhaps the increase in popularity of smoking in women. In Scotland, a similar change is more recent, the ratio being at unity in the 1950s[53] but now exceeding 3. These findings further indicate that individuals who have the same genetic background change their risk of MS through environmental differences.

Infectious causes and genetic epidemiology

Chlamydia is a typical example of an infectious association with MS that was promptly investigated and later disproved.[54] The conspicuous stand-alone nature of proposed Faroe epidemics[55] and lack of clustering among Danish cohorts further weaken the case for transmissibility.[56] Although studies from Italy suggest space–time clustering in early childhood, the pattern could result from the variable geography.[57]

These studies cannot exclude the possibility that MS is an infectious disease determined by host characteristics and ubiquitous exposure, but maintain the emphasis on host factors. This argument, equally applicable to non-infectious exposures, owes its continued currency to possibilities for prevention. Direct support for infectious causes has been resoundingly absent. Reports implicating specific infectious causes commonly fail to account for the genetic epidemiology and pay no heed to the measles-antibody story, soberingly summarised by Norrby.[58] Among the many lessons from these studies was the importance of controls: patients with diseases such as chronic active hepatitis and lupus had much higher measles antibody titres than did those with MS. The parable of the shepherd crying wolf comes to mind, since so many putative viral associations have been declared present, causal, and then summarily excluded.

Clusters

There are few, if any, documented examples of clusters of MS. If the incidence rate in the US is five per 100 000, a rate of 25 per 100 000 would be needed to reach statistical significance. One cluster was brought to my attention by one of three patients who later developed MS who worked in a single small-town Ontario doughnut shop. Although the number of patients was accurate, the proposed denominator of seven employees at the stricken doughnut shop was not, as all connections between the three individuals must be taken into account. This necessarily imprecise larger number must factor in prior probability that such an occurrence is not independent of Ontario's world-leading doughnut shop frequency. Such a cluster, given sufficient duration of observation, must eventually arise by chance alone.

Viral candidates

Nearly 100% of patients with MS are seropositive for Epstein-Barr virus (EBV) compared with 90% of healthy people, and this difference is greater in some small populations of children with MS.[59,60] Children with MS get EBV at a slightly later age than healthy individuals. Among Danish people who tested positive for heterophile EBV antibodies, there was an increased risk for MS.[61] Coassociation with determinants of susceptibility also related to age or probability of EBV infection must be considered. Age-of-acquisition curves for EBV, which are steep in the early to middle teens, are affected by geographical and socioeconomic factors. Matching of cases and controls in studies of these factors must be scrupulous to avoid biases. Some patients with MS have EBV-positive foci in their brains; these foci should be sought in additional control groups.[62]

Measles virus held MS researchers in thrall for nearly two decades, during which time we learned much more about the virus than the disorder. Age at onset of measles was later in patients with MS than in controls. Reported differences between recalled early childhood infection in patients and controls[63] have not been replicated in powerful prospective Danish databases;[64] this discrepancy highlights the problem of recall bias.

The lack of success in identifying environmental exposures with case–control methods promoted belief that genes for susceptibility would be more easily found. We concede, uncomfortably, that this was overly optimistic but the search is finally bearing fruit.[30,33] Cases themselves do not necessarily hold the answer, and parental exposures in the context of epigenetic influences warrant study.

Latitude, sunlight, vitamin D, and photobiology

No factor is more strongly associated with MS risk than latitude,[65] a finding that inevitably raises questions of photobiology. When Acheson proposed associations between MS risk and sun, successful trials in rickets prevention had been completed, and Dean had shown the low risk of MS in UK migrants to sunny South Africa. Goldberg specifically pointed to a role for vitamin D in MS[66] when Holick's work on metabolic pathways showed that sunshine was the main determinant of its concentration.[67,68]

An association between multivitamin intake and lower MS risk in nurses was credited to intake of vitamin D. However, the amounts taken could have hardly budged serum concentrations, and the timing of intake did not agree with abundant data indicating that risk is established earlier in life.

Achieving a vitamin D intake of over 400 units per day is difficult because unsubstantiated fears of toxicity prejudice public-health recommendations.[69] Coassociations undoubtedly occur between vitamin intake and outdoor activity, exercise, and other healthy lifestyle factors. Outdoor activity as an occupational

exposure is associated with lower MS risk[70] and vitamin D could mediate this risk. This suggests adult modification of risk, which offers hope for prevention. As part of a complex that influences the regulation of about 1000 genes, vitamin D has many proven and potential roles.[71] Vitamin D deficiency is endemic in northern cities, such as Toronto and Boston,[72] and affects nearly two-thirds of the Scottish population at winter's end. Seasonal deficiency is not yet convincingly associated with any non-bony disease.

No direct evidence from affected adults implicates vitamin D exposure early in life in susceptibility to MS. Given the potential for recall bias, epidemiological methods have limitations in separating vitamin D exposure from other photobiological effects. Coastal vitamin D intake through oily fish (one of the few dietary sources) might compensate, but there are other possible influential factors in such diets.

The increased prevalence of MS among people born in May might reflect maternal end-of-winter deficiencies in vitamin D, but the equally and discretely reduced risk for November is much less plausibly explained. Certainly the remarkably symmetrical deviations imply some natural cycle. The risk of MS among French farmers and their families is not obviously different from that of the general population, but the effect may not be independent of low female-to-male sex ratios for the disease in France and does not necessarily apply to higher sex ratios that are characteristic of northern Europe. Gestational serum samples from mothers whose children develop MS are not readily available but would test the hypothesis of maternal deficiency. One model integrating vitamin D into genetic and environmental susceptibility in MS postulates that vitamin D epigenetically modifies genes important in development of the brain, immune system, or development of axonal resilience or immunological tolerance.

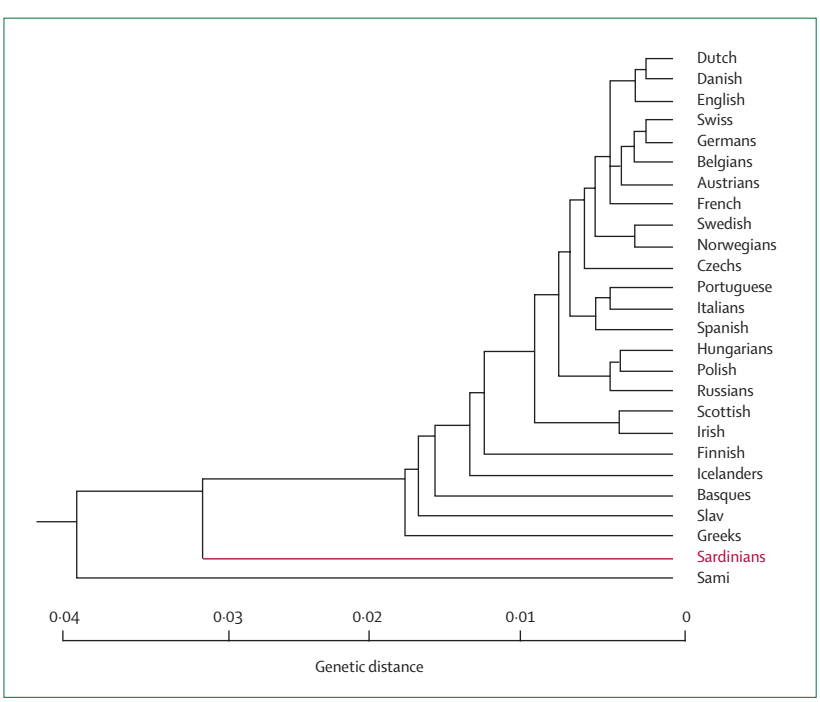

Figure 4: **A European family tree—the key role of the Samis and Sardinians in the understanding of MS**
Reproduced with permission from Princeton University Press.[79]

Age at onset data

Although migration data imply that early-life exposures determine risk of MS, few data bear on exact timing and whether exposure needs be discrete or prolonged. If discrete, age at onset curves give little indication of it. Unlike myasthenia gravis and rheumatoid arthritis incidences, which increase with age, MS incidence peaks at age 24 years and almost returns to baseline by age 60 years, which is contrary to what would be expected if risk were determined by age-related mutations. Although age at onset in concordant siblings is only slightly more similar than in unrelated individuals, a similar age at onset in monozygotic twin pairs implies genetic basis.

Smoking and risk

Studies in separate cohorts have confirmed an association between smoking and MS that is independent of latitude and ancestry. Preliminary dose-response studies hint at causality.[73]

Diet and vitamins

The inability to show non-genetic familiality for risk weighs against individual dietary factors, which are typically familial. As with infection, ubiquitous dietary exposures or deficiencies at a population level could support these findings. Vitamin intake, associated with protection in case–control studies, was based on use in adulthood in the important US Nurses Study.[74,75] The human dietary Achilles heel of vitamin D insufficiency may increasingly come into play at high latitudes. Vitamin D intake in diet is more or less restricted to oily fish, shiitake mushrooms, and reindeer stomach contents, and the latter two are only inconsistently available for those who have a taste for them.

Paediatric MS

The vanguard of any change in demographics, phenotype, or incidence should first appear in children. Collaborative studies of paediatric populations such as Kids with Multiple Sclerosis (KIDMUS)[76,77] that collect important baseline material should yield valuable harbingers of temporal trends in MS. Comprehensive studies of class II MHC alleles in this population would help address uncertainties in disease homogeneity.

Evolutionary considerations

Dobzhansky said that nothing in biology makes sense except in the context of evolution. We speculate here on an adult-onset and largely post-reproductive disease of northern European populations. The relation between

skin colour and environment and how it arose has been reviewed by Jablonski.[78] This relatively recent story has played out over the past 50 000 years. MS and other diseases of white northern Europeans, such as type 1 diabetes and inflammatory bowel disease, might result from rapidity of biological change exceeding evolutionary capability. Populations migrating out of Africa had to navigate between the opposing dangers of the Scylla of folate deficiency—aggravated by destruction of folate in capillaries of fair skin exposed to sunlight—and the Charybdis of vitamin D deficiency.

Sami and Sardinians are remarkable exceptions to expected geographic patterns: the former reside in the far north and have little MS; the latter have a high incidence not just in comparison with their Mediterranean neighbours, but with other populations further north. The genetic map of European origins compiled by Cavalli-Sforza (figure 4)[79] shows these two populations at the root of a proto-European tree, suggesting that mutations crucial for MS happened after the divergence of the Sami.

Rickets, like epidemic and endemic infections, must have been a powerful selective pressure in northern climates. A deformed rachitic pelvis could be lethal to a pregnant woman and her child and can thus provide an end to maternal lines that are unable to adapt to the diminished effective ultraviolet B radiation with northwards migration. Lightening of skin colour with increasing northern latitudes would have been protective. Could the heterozygote advantage for phenylketonuria implied by its geographical distribution in northern Europe, which is similar to that of MS, have resulted from subtle skin lightening? The question of how environment and genes interact naturally draws attention to the possibility of climate-related epigenetic modification.

Conclusions

Much is known about the characteristics of environmental effects in MS. The most influential risk factor operates early in life and determines geographical gradients in ethnically homogeneous populations. Perhaps distinct from this, or primed by early exposure, are later influences that seem also to be geographically distributed. The possibility of more than one effect leaves undiminished strong implications that genes determine familial risk. Major environmental influences, directly or indirectly climate-related, are operative at a population level. Sunshine and vitamin D are testable candidates but dietary interactions might explain some of the geographical inconsistencies. Many answerable questions remain and the importance of these factors and their practical relevance to preventiion of the disease has not received proportionate consideration. Future studies should investigate the environment in conjunction with our rapidly advancing understanding of how genes produce susceptibility and how they could interact with the environment.

Search strategy and selection criteria

All articles containing the search term "multiple sclerosis" from 1997–2007 were obtained from *Scopus*. This approach yielded some 24 746 titles and the abstracts of those related to the broadest definition of epidemiology were read. On the basis of abstract content, relevant papers were read specifically to provide context for this review rather than to comprehensively catalogue all publications. This review summarises the epidemiology of MS with emphasis on population-based studies. Among these the most dependence was on the Canadian Collaborative Study on Genetic Susceptibility to Multiple Sclerosis. In progress for 25 years, the ascertainment, size, longitudinal self-correcting nature, and systematic replications of this study provided several definitive observations.

If, as seems increasingly probable, sunlight or vitamin D are major environmental risk factors, studies of disease prevention might begin.[80] Hurdles include long latency separating intervention and outcome and the identification of young investigators with patience and doggedness. Nevertheless, we have calculated that if there is an effect in late adolescence, as Australian data indicate, prevention studies giving interim results within 3–4 years could be done in Canada. Implications are too great for prevention to remain an unrequited speculation. The story is told of an English army major posted to India who was unhappy with his new home's treeless vista. His request for the planting of a row of trees was met with protestations that it would take 20 years to make a difference. His reply was, "In that case we should plant this afternoon!"

Conflicts of interest

I have no conflicts of interest.

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