Editorial

Surveying multiple sclerosis in the United Kingdom

Making lists of those in whom the diagnosis of multiple sclerosis has already been made, or identifying persons with one particular feature of the disease, is not a difficult exercise and as a result the disease has been surveyed in many places and on many occasions. The usual reason has been to use temporal and geographical trends in morbidity and mortality to generate hypotheses for the cause. For this purpose, it is essential to know that the individual studies can reliably be compared so as not to base hypotheses for the aetiology of multiple sclerosis on shaky epidemiological foundations. Taken together, the conceptual yield from these epidemiological surveys has been poor given the effort that has gone into the enumeration of cases; many questions have been left unanswered and the results have proved tantalisingly vague in providing a detailed understanding of factors which determine the frequency and distribution of the disease.

Every student of the subject is taught that the epidemiology of multiple sclerosis shows a latitudinal gradient in frequency.[1] Some commentators take the view that this reflects differences in exposure to an environmental trigger which is unevenly distributed.[2] Others conclude that the gradient arises from the non-uniform distribution of susceptibility genes among different racial groups.[3] Although it is interesting to interpret the epidemiology of multiple sclerosis through the social history of northern Europeans,[4] the epidemiological sands of multiple sclerosis are shifting with the migrations of the peoples whose neurological disorders they seek to understand, making serial and comparative studies difficult to interpret. In the end, the race or place debate is of doubtful impact as ideas on polygenic and multifactorial disease leave plenty of room for proposing an interplay between genetic and environmental factors.[5]

The study of multiple sclerosis in the United Kingdom has been of special importance as the disease has at one time been more common in the north eastern corner of the British Isles than anywhere else in the world. In 1986, the distribution of multiple sclerosis in the United Kingdom was reviewed in this *Journal*[6] using published figures for prevalence, incidence, and mortality and confining the analysis of prevalence to definite or probable cases; we concluded then that a frequency gradient exists which correlates with a genetic cline marked by the HLA-DR2 susceptibility allele. Williams *et al*[7] subsequently reanalysed mortality statistics, calculating annual age and sex specific figures standardised to death rates in the United Kingdom for 1974; they found less evidence for the north-south gradient and considered (on the basis of a fall in mortality) that the incidence of multiple sclerosis had been falling in Scotland. Mortality is adequate as a measure of disease frequency only when no

distinction is made between death with and death from multiple sclerosis but Williams and colleagues considered only those with multiple sclerosis as the underlying cause of death and so underestimated absolute numbers by between 30% and 50%. While confirming the general trend towards a reduction in death rates throughout the United Kingdom, they showed that this was more pronounced in Scotland (39%) and Northern Ireland than in England and Wales (10%) and highlighted the conspicuous reduction in mortality for Scots aged >65 years. Although the failure to show a correlation between temporal and geographical trends for mortality and prevalence invites the comment that the mortality returns used by Williams *et al*[7] were too crude for useful analysis, we argue later in this review that the same criticism can be levied at figures for prevalence—traditionally considered the more robust statistic.

One of several concerns about each of these analyses has been the quality of the primary information and this led Swingler, Taylor, and Hall (RJ Swingler, personal communication) to compare statistics for multiple sclerosis based on entries for 3 617 890 people into the Value Added Medical Products (VAMP) system for storing general practice records in England and Wales, with the 527 736 listed in the General Practice Administration System for Scotland (GPASS). The standardised prevalence ratio for England and Wales was 116 (95% confidence intervals (95% CIs) 112–120) and for Scotland it was 158 (95% CI 147–170); in reducing the comparison between morbidity statistics for multiple sclerosis to a single rate each for Scotland and for England and Wales, the national difference in frequency (137 (95% CI 126–148) % more multiple sclerosis in Scotland) is demonstrated without undue emphasis on district or regional variations—often the result of demographic peculiarities such as the location of facilities for the young disabled.

Recent epidemiological studies confirm the high overall frequency of multiple sclerosis in the United Kingdom and, with notable exceptions, continue to show a temporal trend of increasing prevalence in each newly surveyed district; thus to the previously reported prevalences of 117/10⁵ in south east Wales,[8][9] 115/10⁵ in the urban area of Sutton close to London,[10] 99/10⁵ in Southampton,[11] and 178/10⁵ in north east Scotland[12] can be added figures of 130/10⁵ for south east Cambridgeshire[13] and 153/10⁵ in rural Suffolk.[14] This issue of the *Journal* contains reports of first surveys for the Mid-Downs and Brighton districts of Sussex in southern England[15] (111/10⁵) and for two Bailiwicks of the Channel Islands[16] (Jersey—113/10⁵ and Guernsey—87/10⁵), which come within the administrative boundaries of the United Kingdom but, being

70–100 miles south of the English mainland, are latitudinally comparable with western France (lying 10–30 miles to the west) and represent something of a genetic bouillabaisse by comparison with southern England.

In 1995, an overview of published surveys of multiple sclerosis in the British Isles seems to show three trends; a difference in frequency between the north east mainland and off-shore islands of Scotland compared with other parts of the United Kingdom; a steep rise in prevalence with repeated survey in all areas except some parts of north east Scotland; and, consequentially, a gradual levelling of the previously shown gradient in frequency.

This gradient was most apparent when the estimate for prevalence of multiple sclerosis had been serially updated in north east Scotland[12 17-20] and in the Orkney islands,[21-23] where by 1974 the figure for Orkney stood at 309/10[5], and very few other parts of the United Kingdom had been surveyed. In their definitive study, Poskanzer and colleagues[23] searched archival material and concluded that the first example of disseminated sclerosis occurred in an Orcadian who died in 1898; a second case was reported 10 years later and thereafter the diagnosis became more common, coinciding with a general increase in awareness and the adoption of clinical criteria for the diagnosis in neighbouring parts of Scotland. Changes in disease frequency in the first few decades of the 20th century can reasonably be attributed to alterations in nosological fashion and this led Poskanzer to conclude that multiple sclerosis may have been no less frequent an illness in 19th century Orcadians, than it later became. Estimates of prevalence, however, carried out on four occasions showed a steady rise from 111/10[5] in 1954[21] to 309/10[5] in 1974[23] for Orkney, and from 134/10[5] to 184/10[5] in Shetland over the same period.[21-23] Recognising that these changes did not necessarily reflect increased incidence, Poskanzer *et al* defined (as accurately as possible) the date of onset in 66 Orcadian and 53 Shetland cases incident between 1930 and 1969, and showed an average annual incidence of 2·2/10[5]/year for Orkney and 1·6/10[5]/year in Shetland with stable quinquennial rates over this period.[23]

Later, Cook and colleagues[24] documented the annual incidence from 1941 to 1983 and suggested that there had been a steady reduction from 1964. Between 1941 and 1964, 53 patients with probable multiple sclerosis were identified in a population of 500 000 whereas only 12 patients developed the disease among the population of 320 000 living on the islands between 1965 and 1982. By 1983, the quoted prevalence had also fallen from 309/10[5] in 1974 to 224/10[5] (the figures were 257/10[5] and 193/10[5] for probable cases only, in 1974 and 1983 respectively). This reduction in frequency of multiple sclerosis apparent in north east Scotland is matched by epidemiological surveys from other regions that border the North Sea and several authors have argued that a change has occurred in environmental factors determining the frequency of multiple sclerosis in these places.[25-27] If these trends reflect a change in biological factors that determine the frequency of multiple sclerosis, this can only reasonably be attributed, as has been claimed, to a change in environmental conditions; population genetics shape the distribution of disease more slowly. Elsewhere the systematic increase in morbidity statistics for prevalence with time and gradual erosion of the latitudinal gradient probably result from a catching up effect of more recently surveyed areas with those areas that have been repeatedly studied over a longer period.

Poskanzer *et al* identified several factors which maximise the prevalence of multiple sclerosis surveyed serially and on islands; systematic depopulation of Orkney and Shetland by the young led to an older population after the 1960s, less at risk of developing multiple sclerosis; the opposite is the case for the rural survey from Suffolk where those aged <35 years are over-represented.[14] Prevalence rising out of line with incidence was attributed by Poskanzer *et al*[23] to increased survival (from 26 to 40 years in Orkney and from 24 to 34 years in Shetland between 1954 and 1974); the change in prevalence also resulted from improved recognition; and the criteria for diagnosis had also been altered. Several of these factors have influenced the steady rise in prevalence with repeated survey seen in other parts of the United Kingdom. Despite the completion of contemporary surveys for several regions of England and Wales, however, comparisons are not made easy by inconsistent use of classification systems and inclusion criteria, and by the failure to standardise morbidity statistics for population structure, so that even now it is difficult to construct a comprehensive multipoint prevalence map of multiple sclerosis in the United Kingdom. A quick glance at published figures for prevalence is not sufficient; more detailed scrutiny of diagnostic criteria, inclusion or omission of suspected cases, quotation of confidence intervals, variable citation of crude and age adjusted figures, reworking of statistics for time of onset not diagnosis,[28] and adjustment for a standardised population (but, if so, which one?) are all methodological variables which restrict epidemiological vision. One need look for confirmation no further than the tables of Rice-Oxley *et al*[15] and Sharpe and colleagues[16] quoting entirely different standardised prevalence ratios for multiple sclerosis in published studies relating to the British Isles (this *Journal*; table 3, page 29; and table 2, page 24 respectively).

Until the mid-1980s, studies of multiple sclerosis in the United Kingdom used the system of classification suggested by Allison and Millar.[29] Adopting the Poser criteria,[30] which were introduced to take account of advances in the laboratory investigation of multiple sclerosis, does not materially affect estimates for the total number of prevalent cases or the standardised prevalence ratios based on this numerator. Differences arise, however, when surveys are restricted to the categories of definite and probable (Poser) and probable and early (Allison and Millar) cases as the proportion in the suspected (Poser) and possible (Allison and Millar) categories needing exclusion differs significantly between the two classifications. Allison and Millar categorised cases as probable (usually a remitting history and always with signs attributable to more than one lesion), early (remitting symptoms with no signs), and possible (progressive or static symptoms at a single site, and with no other identified cause). Laboratory investigations were not taken into account and indeed few were available at that time. The most widely cited version of the Poser criteria[30] does not deal with suspected cases; these are assumed to be all those thought to have demyelinating disease but with neither clinical symptoms or signs, or laboratory evidence, for more than one lesion. Some surveys have used the Poser criteria but ignore features such as age at presentation and particular laboratory investigations.[8 15] Both classification systems were first used in parallel for the initial survey of south Glamorgan.[8]

For all these reasons, it is not possible to compare the analysis of probable cases defined using the Allison and Millar classification that we performed in 1986[6] with any of the more recent publications on multiple sclerosis. The full range of inconsistency that has contaminated the description of these morbidity statistics for the United

Major contemporary United Kingdom multiple sclerosis prevalence studies (all figures per 100 000)

| Study | Latitude | Year | Population | Cases (n) | Allison and Millar | | | | | | | |
					All	95% CI	MS	Pt No	95% CI	Poss	Pt No	95% CI
Shetlands	60	1954	18 715	25	134	90–198	118	22	77–179	16	3	5–50
Shetlands	60	1962	17 537	29	165	115–238	120	21	78–184	46	8	22–91
Shetlands	60	1970	17 327	31	179	126–258	133	23	88–200	46	8	23–92
Shetlands	60	1974	18 445	34	184	132–258	152	28	105–220	33	6	15–73
Orkneys	59	1954	20 746	23	111	74–167	82	17	51–132	29	6	13–65
Orkneys	59	1962	18 531	33	178	127–250	168	31	118–238	11	2	3–43
Orkneys	59	1970	17 077	40	234	172–319	222	38	162–305	12	2	3–47
Orkneys	59	1974	17 462	54	309	237–404	257	45	192–344	51	9	27–99
Orkneys	59	1983	19 182	46	240	180–320	209	40	153–284	31	6	14–70
Aberdeen	57	1970	440 176	557	127	116–137	105	464	96–115	21	93	17–26
Aberdeen	57	1973	440 176	634	144	133–156	117	517	108–128	27	117	22–32
Aberdeen	57	1980	471 000	839	178	166–191	145	682	134–156	33	157	29–39
N Ireland	55	1951	1 370 709	700	51	47– 55	41	555	37– 44	11	145	9–12
N Ireland**	55	1961	1 425 000	1146	80	76– 85	57	808	53– 61	24	338	21–26
N Ireland	55	1987	86 500	119	138	115–165	104	90	85–128	34	29	23–48
SE Wales	52	1985	376 718	441	117	107–129	84	316	75– 94	33	125	28–40
SE Wales	52	1988	376 718	453	—	—	—	—	—	—	—	—
Suffolk	52	1988	31 379	62	198	154–253	185	58	143–240	13	4	5–34
Cambs	52	1990	288 410	374	130	117–144	107	309	96–120	23	65	18–29
Cambs	52	1993	290 700	441	152	138–167	120	349	108–133	32	92	26–39
Sutton	51	1985	170 000	195	115	100–132	104	176	89–120	11	19	7–18
Southampton	51	1987	417 000	411	99	90–109	92	384	83–102	7	28	5–10
Sussex	51	1991	596 594	810	136	127–145	120	718	108–133	32	92	26–39
Jersey	49	1991	84 082	95	113	92–138	106	89	86–130	7	6	5–19
Guernsey	49	1991	61 164	53	87	66–113	74	45	55– 99	13	8	7–26

**Standard population. For Allison and Millar; All = probable early and possible cases; MS = probable and early cases; Poss = possible cases only. For Poser; All = definite, probable, and suspected cases; MS = definite and probable cases; Susp = suspected cases only.

Kingdom (and the problems are no less elsewhere) is shown in the table, which lists major surveys reporting the prevalence of multiple sclerosis in parts of the United Kingdom reported since the 1950s, and the figure, which plots the most recent estimate for prevalence at each location against latitude. The 1961 study from Northern Ireland is included as this forms the yardstick from which standardised prevalence ratios have, in most cases, since been calculated.[31] This figure was updated in 1987.[32] Some other studies performed in the United Kingdom over this period cannot be worked into the overall analysis of morbidity statistics for multiple sclerosis and are not included as they are based on small numerators and denominators, used neither the Allison and Millar nor the Poser criteria, or were restricted to one particular racial group. These include surveys of the Western Isles in 1954[17] and 1979,[33] Northumberland and Durham,[34] Carlisle,[35] Yorkshire,[36] Cornwall in 1950[37] and 1958,[38] and immigrants from the new Commonwealth countries.[39] Whereas we are confident that our reporting of

these figures is accurate, assiduous readers will notice some differences from the primary literature. These mainly affect confidence intervals—an important and often omitted feature of prevalence studies. The most appropriate method of calculation varies depending on the size of the numerator; for the range represented in these surveys, we calculated confidence intervals as:

Upper limit = (numerator/denominator measured in 10^5) × Z
Lower limit = (numerator/denominator measured in 10^5)/Z
where Z is given as: exp (1·96 × [square root of 1/numerator])

In some surveys, enough information is given to allow calculation of rates which compare more closely to figures quoted for other regions. For example, the published prevalence for Suffolk[14] is $153/10^5$ (confidence intervals not given) but this refers only to probable cases and excludes both the early and possible categories of Allison and Millar; we have derived a figure of $198/10^5$ (95% CI 154–253) for all cases of multiple sclerosis, as shown. The figure for Southampton shows an internal
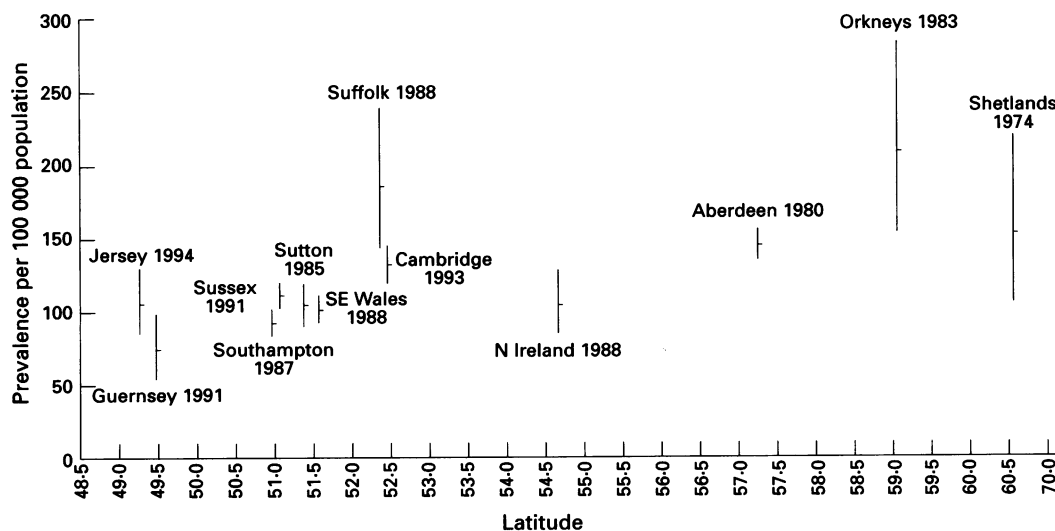
Latitudinal gradient in contemporary United Kingdom studies on prevalence of multiple sclerosis.

Poser										
All	Pt No	95% CI	MS	Pt No	95% CI	Susp	Pt No	95% CI	SPR	95% CI
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	153	140–166
—	—	—	—	—	—	—	—	—	221	184–261
—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
117	441	107–129	101	380	91–112	16	60	12–21	139	126–150
120	453	110–132	101	379	91–111	20	74	16–25	—	—
130	374	117–144	112	322	100–125	19	54	14–24	121	108–133
152	441	138–167	131	380	118–145	21	61	16–27	142	129–157
—	—	—	—	—	—	—	—	—	129	111–147
99	411	89–109	95	395	86–105	4	16	2–6	115	104–127
136	810	127–145	111	665	103–120	24	145	21–29	—	—
—	—	—	100	84	81–124	—	—	—	120	96–144
—	—	—	74	45	55–99	—	—	—	96	70–121

inconsistency and we have assumed the total number of cases as 412 (probable = 384; early and possible = 28) and not 411 as published.[11] Minor corrections are also included for other surveys based on recalculations of the prevalence figures. The most recent prevalences for Orkney differ from the published figures[23] because, in line with the general principles for estimating prevalence, we have included the three cases with definite or probable disease living on the islands in 1983 but with onset elsewhere. Although the standardised prevalence ratios provide the best comparator between surveys, hitherto these have used the Allison and Millar criteria with adjustment to the population denominator of Northern Ireland in 1951. Thus the prevalence ratio published in this issue by Rice-Oxley et al[15] for Sussex (100/10[5]; CI 92–108) is based on definite and probable cases classified using the Poser criteria without standardisation to a reference population. In situations where the total number of cases (definite, probable, and suspected—Poser; probable, early, and possible—Allison and Millar) is identical using either classification (south east Wales,[8 9] Southampton,[11] and Cambridgeshire), this will not matter; but the pronounced differences which emerge with the restriction of cases to the definite/probable or probable/early categories are well illustrated by the 19 cases who appear in the Channel Islands survey using the Allison and Millar criteria but are unclassifiable under the Poser scheme. Furthermore, there is inconsistency of approach, using either system, to the isolated demyelinating episode with symptomatic recovery and no recurrence at the same or another site. This is apparent in the paper by Rice-Oxley et al,[15] who omit 40 such cases using the Allison and Millar criteria which others might well have included, over and above the 52 with persistent spinal cord syndromes featured as having possible multiple sclerosis. A superficial assessment of the prevalences for southern parts of the British Isles published between 1985 and 1990, and with classification using the Poser criteria, seems to show a lower figure for Southampton than elsewhere; however, when the figures for definite and probable multiple sclerosis only, or the standardised prevalence ratios, are compared, this difference is lost indicating the extent to which the inclusion of suspected cases introduces noise, and generally obfuscates the overall picture.

For the future, it is clear that more consistency of approach is needed. To some extent this can be achieved by agreeing ground rules for diagnostic criteria, deciding on the inclusion or omission of suspected cases, and through insistence on the quotation of confidence intervals and the use of standardised prevalence ratios. Less easy is the adoption of a population for standardisation that is appropriate for surveys being conducted throughout the world and involving peoples of different genetic background and demographic characteristics.

Can anything now be said about the distribution of multiple sclerosis in the United Kingdom? With the steady rise in prevalence for southern parts of England and the more stable rates in north east Scotland, there does seem to have been a reduction in slope of the previously demonstrated gradient in frequency. Without knowing the extent to which surveys of multiple sclerosis in north east Scotland have saturated prevalent cases, and with continuing uncertainty on whether other parts of the country have yet reached a steady state, it is difficult to predict how much further the gradient will collapse. The probability remains that the north east of Scotland genuinely has a higher frequency of multiple sclerosis than other parts of the United Kingdom; and if so, differences in features of the population at risk, correlating with genetic clines, still offer an attractive, but not exclusive, explanation. When the confounding effect of comparing repeatedly surveyed regions with virgin territories, and the wide confidence intervals for many of the studies based on small denominators, are taken into account, the evidence for a systematic change in prevalence of multiple sclerosis with latitude in the United Kingdom now seems less secure.

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Neurological stamp

Mistletoe

The mistletoe was worshipped by the Druids. It seemed to defy nature by living its entire life aloft in the branches of trees, never descending to the earth, which seemed to be a plant's natural habitat. In former times it was surrounded by an aura of awe as the key to the supernatural.

For centuries the mistletoe had a therapeutic reputation and its medicinal virtues have included its use as a sedative, treatment for epilepsy, headache, paralysis, hypertension, lung ailments, and debility. A sprig of mistletoe was the "golden bough" of the famous Trojan hero Aeneas. When Aeneas visited the underworld, the prophetess Sibyl bade him arm himself with the golden bough and together they descended to the "Land of Shades".

The mistletoe is shown on a Christmas stamp issued by Guernsey in 1978 (Stanley Gibbons 176, Scott 172). The display of the mistletoe at Christmas and New Year dates back to a Norse tradition.

L F HAAS