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Multiple sclerosis prevalence among Sardinians: further evidence against the latitude gradient theory

Abstract A descriptive epidemiological survey was extended to the whole province of Sassari, northern Sardinia between latitudes 40°30' N and 41° N. Results showed a crude total prevalence rate of 144.4 per 100 000 on prevalence day (31 December 1997), and an onset-adjusted prevalence rate of 149.7 per 100 000. The total average annual incidence rate was 4.9 per 100 000 for the whole time interval studied (1968-1997), having increased from 2.0 in 1968-1972 to 6.8 in the last quinquennium considered. A substantial improvement in MS case ascertainment due to the introduction of new diagnostic procedures might account for such rates in Sardinia as well as in other Italian regions. However, when comparing our data with those obtained in the province of Ferrara, in the same time frames (1968-1997), a nine-fold versus a five-fold increase of MS prevalence was detected in Ferrara and Sassari, respectively. MS incidence temporal trend also notably increased in Sassari, but remained substantially stable in Ferrara. The progressive shortening of the time interval between clinical onset and diagnosis, and the proportion of benign-mild MS cases, were similar in both studies, thus suggesting a similar diagnostic accuracy. In our opinion, the repeatedly assessed increase of MS frequency in our province, at least partially does represent an actual rise of MS risk among Sardinians, thus disproving the latitude gradient-based theory (i.e. prevalence rates correlate with geographical latitudes) and supporting the hypothesis of a "Sardinian focus" of MS in a genetically susceptible population.

Key words Multiple sclerosis • Prevalence • Incidence • Sardinia

Introduction

Small population-based studies conducted by our research group in northern Sardinia, insular Italy, since 1980 [1] indicated that prevalence rates of multiple sclerosis (MS) have increased more than two or three times that which has been observed in the rest of continental and insular Italy in the same time interval. The aim of the present study was to extend our investigation of MS frequency to the entire population of the Sardinian province of Sassari, which constitutes one-third of the population of the island, in order to update and confirm what appears to be a temporal trend.

Methods

The study covered the province of Sassari, in northern Sardinia, that lies between latitudes 40°30' N and 41° N. It has an area of 7520 square kilometers and encompasses 89 municipalities. In the 1991 census, the total population was 454 904 (224 984 men and 229 920 women). Over the past 30 years, the population of the province increased from 381 191 to 454 904. The population denominators were calculated using log incremental rates for intercensus data. Migration flow was moderate: in 1995, 1.7% of the total population was registered as resident from other Italian provinces and from foreign countries, whereas 1.6% had moved away from the study area. The population consisted almost entirely of Sardinian natives, the proportion of residents born outside the province of Sassari being negligible. As a result we believe that generalizations to the popula-

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tion of the whole island are warranted. The Sardinian population is ethnically and culturally homogeneous and distinct, as indicated by genetic, linguistic and historical studies. In particular, the genetic distances between Sardinia and the rest of Italy and Europe are 10-fold higher than between non-Sardinian Italians and Europeans, although Sardinians share the same Caucasoid origin [2].

Case collection and ascertainment

In 1995, a register of MS cases was created at the Neurological Clinic of the University of Sassari, to include patients diagnosed as suffering from MS according to the Poser criteria [3] for clinical or laboratory supported definite MS (CDMS, LSDMS), and clinical or laboratory supported probable MS (CPMS, LSPMS). Other autoimmune and/or immunomediated and infectious diseases such as primary and secondary CNS vasculitis, post-infectious leukoencephalopathy and other demyelinating disorders were ruled out by means of laboratory tests and neuroimaging, in addition to history and neurological examination.

Results

On prevalence day (31 December 1997), 686 subjects living in the province of Sassari had been diagnosed as suffering from MS (492 women and 194 men). Using as denominator the 1997 population, the crude overall prevalence rate was 144.4 per 100 000 (standardized rate of 141). The highest rates were observed in the age range 30-49 years, ranging from 300 to 326 in different age groups. For women, in particular, the highest rates were assessed in the age group 30-34 years (457 per 100 000).

Considering the patients who, on prevalence day, were already symptomatic but not diagnosed yet, onset-adjusted total prevalence rate was of 149.7 per 100 000. The mean age on prevalence day was 42.4 ± 12.2 years: 41.8 ± 12.1 for women, and 43.6 ± 11.9 for men.

Incidence was studied for the period 1 January, 1968 to 31 December, 1997. During that period of 30 years, 637 patients (455 women and 182 men) had the onset of MS while living in the study area. The mean age at onset was 28.0 ± 9.0 years (27.5 ± 8.9 for women and 29.5 ± 8.8 for men). The average annual incidence for the entire period was 4.9 per 100 000, 6.9 for women and 2.8 for men. The highest rates were noted in the age groups between 20 and 34 years for both sexes. The total incidence rates increased over time from values of 2.0 per 100 000 in the period 1968-1972 to 6.8 in the interval 1993-1997 (from 2.4 to 9.2 for women and from 1.6 to 4.2 for men).

Conclusions

Previous investigations demonstrated that Sardinia is a high-risk area for MS. The present research, a "spider" kind of population-based survey [4], is an update of MS prevalence to 31 December 1997 and a study of the temporal trend of MS incidence between 1968 and 1997 in the province of Sassari. Observed MS prevalence rates are notably higher than those expected in relation to Sardinia's latitude. We ruled out an increased disease duration due to longer survival, an increased number of benign or mild cases due to greater diagnostic accuracy and awareness for the disease, improved epidemiological procedures, influx of people in the high-risk age groups, and immigration of individuals from a population genetically at higher risk for MS. A comparison with a survey in the province of Ferrara, in northern Italy in 1993 [5], reveals that prevalence rates in the province of Sassari are nearly three-fold greater and that better diagnostic accuracy and improved epidemiological methodology cannot therefore fully account for the observed increased prevalence.

A significant increase of new MS cases per year was observed in the 3 decades considered. Comparing the trend of the time lag between clinical onset and diagnosis in our study versus Ferrara [5], no difference was detected to be possibly responsible for the increased prevalence. Instead, a clear dif-

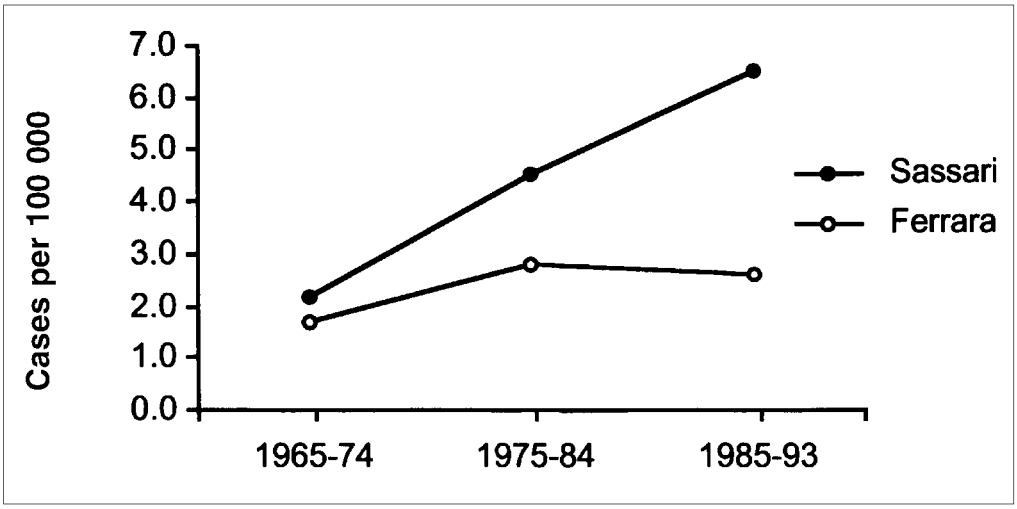

Fig. 1 Temporal trends of MS incidence rates in the provinces of Sassari and Ferrara, in the period 1965-1993

ference in the incidence trend over time was observed (Fig. 1).

Our results are consistent with those previously observed in Sardinia by the same group of researchers, confirming that Sardinia is among the areas at highest frequency of MS in the world [4]. Better diagnostic accuracy does not fully account for the steady increase of MS frequency observed over a long period of time by means of repeated assessments. A true rise of MS risk in Sardinia secondary to biological factors is therefore hypothesized. Such high rates appear to be in contrast with the latitude gradient-based theory according to which MS prevalence rates correlate with geographical latitudes, and support the hypothesis of a "Sardinian focus" of MS in a genetically susceptible population.

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Sommario *Il presente lavoro è un'indagine epidemiologica descrittiva estesa all'intera provincia di Sassari, Sardegna settentrionale, latitudine 40°30' N e 41° N. I risultati mostrano un tasso crudo di prevalenza totale di 144.4 per 100 000 al giorno di prevalenza 31 dicembre 1997, ed un tasso di prevalenza totale aggiustato per l'esordio di 149.7 per 100 000. Il tasso di incidenza totale medio era di 4.9 per 100 000/anno per l'intero intervallo di tempo studiato (1968-1997), incrementato da 2.0 nel periodo 1968-1972 a 6.8 nel periodo 1993-1997. Un sostanziale miglioramento nell'accertamento dei casi di SM legato all'introduzione di nuove procedure diagnostiche potrebbe giustificare tali tassi in Sardegna, ma tale fenomeno si è verificato anche per altre regioni italiane. Tuttavia, nel confrontare i nostri dati con quelli ottenuti nella provincia di Ferrara nello stesso intervallo di tempo (1968-1997), l'incremento della prevalenza di SM nella terza decade studiata è stato nove volte superiore rispetto alla prima a Sassari e cinque volte superiore a Ferrara. Veniva anche osservato un notevole aumento dell'incidenza a Sassari, che tuttavia restava sostanzialmente stabile a Ferrara. Il progressivo accorciamento dell'intervallo di tempo tra l'esordio clinico di malattia e la diagnosi e la proporzione di casi benigni-lievi di SM erano simili in entrambi gli studi a dimostrazione di una simile accuratezza diagnostica. A nostro avviso, l'incremento della frequenza di SM nella nostra provincia ripetutamente accertato, rappresenta, almeno parzialmente, un effettivo aumento del rischio di SM tra i Sardi, in contrasto con la teoria del gradiente latitudinale ma sostenendo l'ipotesi di un "focus sardo" di SM in una popolazione geneticamente sucettibile.*

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The prevalence of multiple sclerosis in the world: an update

Abstract The systematic study of multiple sclerosis (MS) in populations, started in 1929 by Sydney Allison, now consists of over 400 publications dealing with the prevalence of MS throughout the world. However, any attempt to redefine the pattern of geographical differences in MS frequency remains as difficult as ever. The comparison of prevalence studies carried out in different areas and times is made difficult by the variability in surveyed population sizes, age structures, ethnic origins and composition, and the difficult quantification of numerators, especially regarding the recognition of benign and very early cases. Additionally, complete case ascertainment depends on access to medical care, local medical expertise, number of neurologists, accessibility and availability of new diagnostic procedures, the degree of public awareness about MS, and the investigators' zeal and resources. Critical examination of the more recent data on MS prevalence leads to some revisions of previously held concepts, the most interesting of which is the appreciation of the greater influence of genetic factors on disease acquisition. The rarity of MS among Samis, Turkmen, Uzbeks, Kazakhs, Kyrgyzis, native Siberians, North and South Amerindians, Chinese, Japanese, African blacks and New Zealand Maoris, as well as the high risk among Sardinians, Parsis and Palestinians, clearly indicate that the different susceptibilities of distinct racial and ethnic groups are an important determinant of the uneven geographic distribution of the disease. The updated distribution of MS in Europe, showing many exceptions to the previously described north-south gradient, requires more explanation than simply a prevalence-latitude relationship. Prevalence data imply that racial and ethnic differences are important in influencing the worldwide distribution of MS and that its geography must be interpreted in terms of the probable discontinuous distribution of genetic susceptibility alleles, which can however be modified by environment. Because the environmental and genetic determinants of geographic gradients are by no means mutually exclusive, the race versus place controversy is, to some extent, a useless and sterile debate.

Key words Multiple sclerosis · Epidemiology · Prevalence · World

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Introduction

The systematic study of multiple sclerosis (MS) in populations started in 1929 when Sydney Allison ascertained 40 cases in north Wales, estimating a point prevalence of 13 per 100 000 [1]. In 1949, the majority of the patients he had studied had died but two survivors and one deceased patient had had symptoms for 43 years, providing the first examples of benign MS [2]. There are now over 400 publications dealing with the prevalence of MS throughout the world, but despite this wealth of data, any attempt to redefine the pattern of geographical differences in MS frequency remains as difficult as ever. The comparison of prevalence studies carried out in different areas and at different times is faced with a number of problems among which is the variability of the surveyed populations in terms of size, age structure, ethnic origin and composition [3]. Another concern is the difference in quantification of the numerators, especially regarding the recognition of benign and very early cases [4]. The extent to which complete case ascertainment is achieved depends on geographic and time variables such as access to medical care, local medical expertise, number of neurologists, acces-

sibility and availability of new diagnostic procedures, the degree of public awareness about MS, and the investigators' zeal and resources [4, 5]. Further problems arise from the use of different diagnostic criteria and interobserver variability in the application of the same diagnostic criteria [3]. Because of all these potential sources of bias when comparing MS prevalence rates, the present review of the worldwide geographical distribution of MS is subject to criticism, but the reader is asked to remember that the main factors influencing the reported frequencies of the disease are when, where and how these studies were conducted, and that the reported pattern of geographical distribution only partially reflects real differences in MS risk.

Europe

United Kingdom and Republic of Ireland

The combined prevalence rates reported in Fig. 1 confirm the high overall frequency of MS in the United Kingdom and Ireland. The prevalence rates estimated for Scotland and its offshore islands over the last 25 years range from 145 to 193 per 100 000 [6-10]. The ones for mainland Scotland are the highest so far detected anywhere in the world for large populations. Whereas MS prevalence used to be higher in north-east Scotland according to the first studies in the Grampian Region [8], a smoothing of the previously described gradient in MS risk has been suggested by a recent survey in south-east Scotland [10], where the prevalence rate in 1995 was 187 per 100 000. In England and Wales, the prevalence figures reported from different areas over the last 15 years have varied from 74 to 112 MS cases per 100 000 [11-19]. Mapping these figures reveals that MS appears to be evenly distributed within England and Wales. The most recent prevalence estimate of MS from Northern Ireland was reported as 168 per 100 000 [20], indicating a risk similar to that in Scotland. As far as the Republic of Ireland is concerned, the available figures are rather old: the nationwide prevalence of 66 per 100 000 dates back to 1971 [21]. This figure should be updated to make the data comparable with more recent data from the United Kingdom. To summarize, it is clear that the highest frequency of MS in the United Kingdom and, most likely in the world, is in Scotland. This supports the hypothesis that Scottish ancestry is associated with or reflects a greater genetic susceptibility to the disease.

Scandinavia

Scandinavia comprises Norway, Sweden, Denmark, Finland and Iceland. The Nordic countries are not homogeneous with respect to the distribution of MS (Fig. 2).

In Norway, there is a marked difference in MS risk between north and south: in Hordaland county, in the south-west of the country, the prevalence in 1983 was 75 per 100 000 [22], and in Oslo, in the south-east, the prevalence in 1995 was 132 [23]. Both these figures are notably higher than those reported from the northernmost counties of Tröms and Finmark, where in 1983 they were 37 and 21, respectively [24]. Such a south-north decreasing gradient in MS frequency has been attributed to the high proportion of

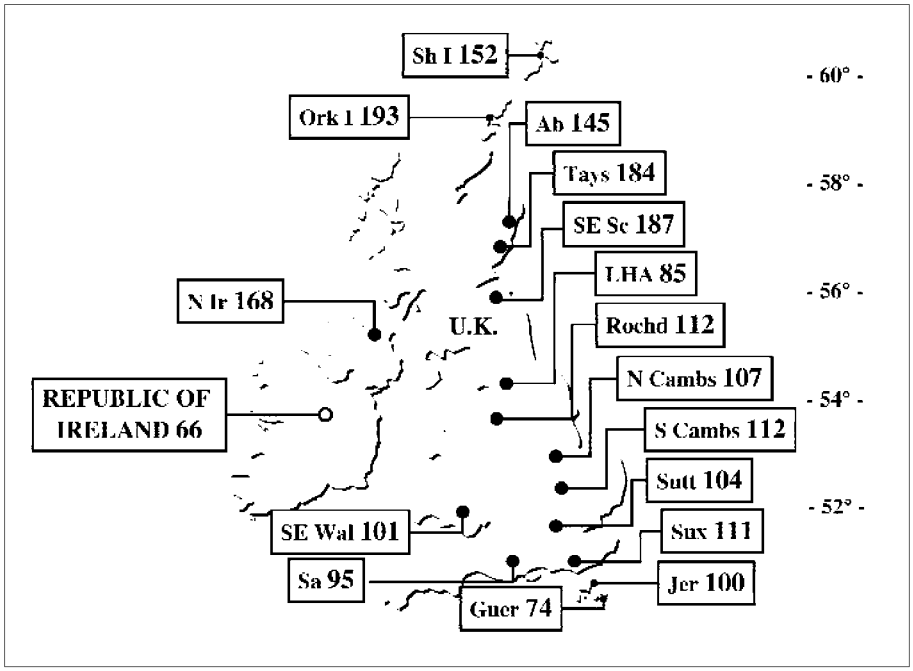

Fig. 1 Distribution of MS in the UK and the Republic of Ireland. Study area (prevalence year): *Sh I*, Shetland Islands (1974); *Ork I*, Orkney Islands (1983); *Ab*, Aberdeen (1980); *Tays*, Tayside (1996); *SE Sc*, South East Scotland (1995); *LHA*, Leeds Health Authority (1996); *Rochd*, Rochdale (1989); *N Cambs*; North Cambridgeshire (1993); *S Cambs*, South Cambridgeshire (1990); *Sutt*, Sutton (1985); *Sux*, Sussex (1990); *Jer*, Jersey (1991); *Guer*, Guernsey (1991); *Sa*, Southampton (1987); *SE Wal*, South East Wales (1985); *N Ir*, Northern Ireland (1996); Republic of Ireland (1971)

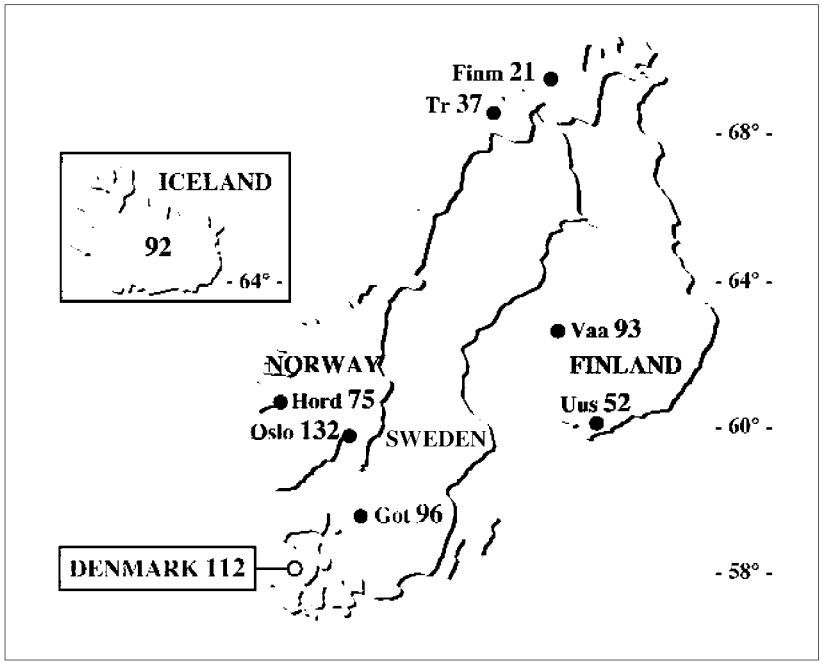

Fig. 2 Distribution of MS in Scandinavia. Study area (prevalence year): *Finm*, Finmark (1983); *Tr*, Tröms (1983); *Hord*, Hordaland (1983); *Oslo*, Oslo (1995); *Got*, Gothenburg (1988); *Vaa*; Vaasa (1979); *Uus*, Uusimaa (1979); Iceland, (1989); Denmark (1990)

Samis in the northernmost Norwegian populations. The low frequency of MS in those regions, associated with the statement that in the Scandinavian neurologists' clinical experience MS very rarely affects Samis, supports the belief that Samis are resistant to the disease because of their genetic differences from Norwegians [24]. However, as Samis constitute only 10% of the populations of Tröms and Finmark counties, that alone cannot explain the strikingly low risk of MS in the northernmost part of Norway.

The only area recently surveyed in Sweden is Gothenburg, where an MS register has existed since the early 1950s. The MS prevalence in Gothenburg was updated in 1988 and, with a rate of 96 per 100 000 [25], was similar to that reported for southern Norway.

An MS register has existed in Denmark since 1949. The nationwide prevalence of MS was updated in 1990, indicating a rate of 112 per 100 000 [26], close to that observed in Gothenburg in 1988 [25] and in Oslo in 1995 [23]. Taking into account that Danes, Norwegians and Swedes have an almost identical ethnic background, they may share a similar genetic susceptibility to the disease.

In Finland, MS cases have been registered since 1964. The ethnic background as well as the language are quite different from the rest of Scandinavia. The most recent data from the western province of Vaasa and the southern province of Uusimaa confirm the uneven distribution of MS in Finland; in 1979, the prevalence rates were 93 in Vaasa and 52 in Uusimaa [27]. On the basis of the frequent familial occurrence of the disease in the Jalasiärvi district of the province of Vaasa, the difference in MS risk between the people of the two provinces has been attributed to gene enrichment and loss, related to the geographic isolation of many rural communities in the western part of Finland and leading to a higher genetic susceptibility to the disease [27].

In Iceland, the nationwide prevalence of MS in 1989 was reported as 92 per 100 000 [28], indicating a risk similar to that in England, Denmark, Sweden and southern Norway in the early 1990s. Although Iceland was settled in the ninth and tenth centuries by Vikings from the west coast of Norway, blood group studies have indicated that Icelanders are genetically closer to the populations of the British Isles and to the Irish, rather than to Norwegians [28].

Germany, Switzerland and Austria

The prevalence rates of MS recorded in Germany in the early 1980s varied from 43 per 100 000 in the district of Halle to 69 in the region of Rostock (Fig. 3) [29-32]. Ten years later, it was reported as 85 for southern Hesse [33], 95 for the city of Bochum [34] and 108 for Southern Lower Saxony [35]. The overall distribution of MS frequency in Germany does not reveal a latitudinal gradient. The prevalence figures from Germany in the early 1990s suggest a rather homogeneous distribution of MS and appear to be similar to those reported from England and Wales, Iceland, Denmark, Sweden and southern Norway in the same years.

In Switzerland, the most recent data were reported as 110 per 100 000 for the Canton of Berne [36], a risk similar to that found in Germany in the early 1990s. The prevalence figures from Austria are probably underestimates. They were presented at the MS conference held in Hamburg in 1985 and were then cited by Bauer in 1986 [37]. There are reasons to believe

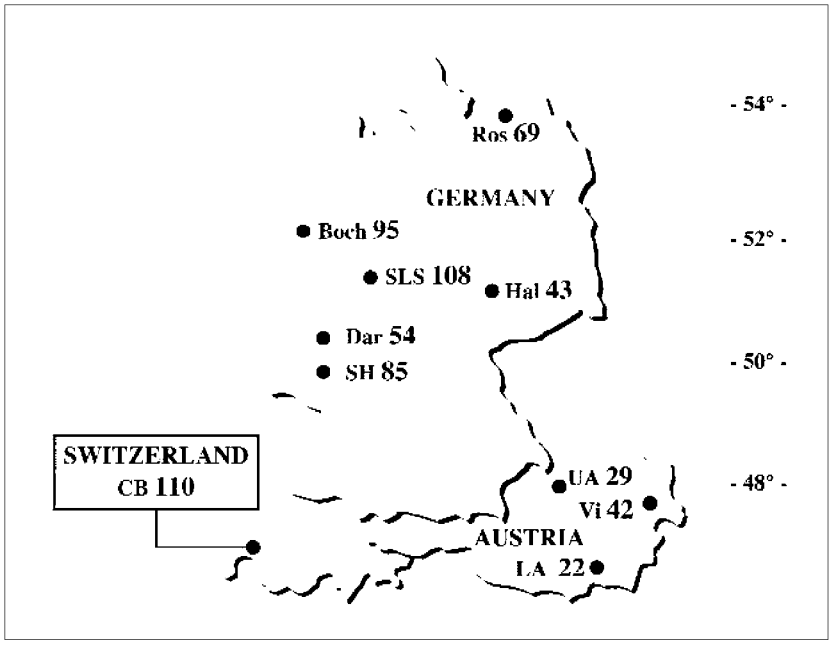

Fig. 3 Distribution of MS in Germany, Switzerland and Austria. Study area (prevalence year): *Ros*, Rostock (1983); *Boch*, Bochum (1990); *SLS*, South Lower Saxony (1992); *Hal*, Halle Distr. (1984); *Dar*, Darmstadt (1982); *SH*, Southern Hesse (1992); *CB*, Canton of Berne (1986); *UA*, Upper Austria (1981); *LA*, Lower Austria (1981); *Vi*, Vienna (1981)

that the reported rates, ranging from 22 to 42 per 100 000 (Fig. 3), do not reflect the actual frequency of Austrian MS.

The Netherlands, Belgium and France

In the Netherlands, MS frequency was assessed for the province of Groningen in 1992, giving a prevalence of 76 per 100 000 (Fig. 4) [38]. In Belgium, the prevalence in Flanders was given as 74 in 1992 (Fig. 4) [39]. This figure is identical to that estimated in the province of Groningen in the same year, suggesting a similar frequency of MS throughout the Netherlands and Belgium.

The risk for MS in France (Fig. 4) is notably lower than in other European countries at the same latitude. The prevalence rates for communities surveyed in Brittany in 1978 were up to 28 per 100 000 [40]. In the 1980s, those reported from other French regions varied from 37 to 58 per 100 000 [41-44], indicating a MS prevalence similar to that found in Spain and Italy, with the exception of Sardinia. The highest rates were for Chalon sur Saône and Avignon in southeastern France [42]

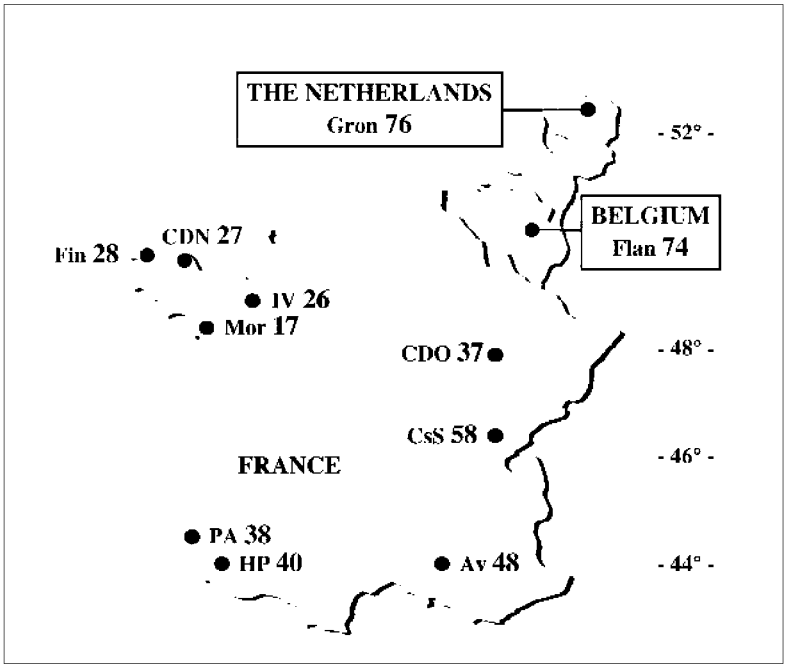

Fig. 4 Distribution of MS in The Netherlands, Belgium and France. Study area (prevalence year): *Fin*, Finistére (1978); *CDN*, Côtes Du Nord (1978); *IV*, Ille et Vilaine (1978); *Mor*, Morbihan (1978); *CDO*, Côte D'Or (1983); *CsS*, Chalon sur Saône (1984); *Av*, Avignon (1984); *PA*, Pyrénées Atlantiques (1988); *HP*, Hautes Pyrénées (1983); *Gron*, Groningen (1992); *Flan*, Flanders (1992)

and the lowest for Côte-d'Or in the northeast [41] and the Pyrénées-Atlantiques in the southwest [43]. The population-based prevalences so far noted in France fail to reflect a latitudinal gradient in MS frequency. The nationwide study conducted by INSERM in 1986 suggests a clustering of high-risk areas in the northeastern country [45], but the reported geographic distribution of MS was most likely biased. The study was based on a national epidemiological sample derived by questionnaires returned by MS patients in reply to a television announcement. To test the survey's reliability, the reported geographic distribution of MS should have insured that the percentages of responders from each of the 95 departments and the 21 regions of France represented the same proportion of the MS population actually residing in each of them. It is most unlikely that this condition was fulfilled.

Poland, the Czech Republic and Hungary

The prevalence of MS in Poland was assessed in 1981 for the western part of the country, yielding a rate of 45 per 100 000 [46], and in 1992 for the north-western region of Szczecin, finding a rate of 62 per 100 000 (Fig. 5) [47]. In western Czechoslovakia, now the Czech Republic, the prevalence of MS in 1984 was 71 per 100 000 (Fig. 5) [48]. In 1992, a prevalence rate of 89 per 100 000 was calculated for three Bohemian districts in the northern part of the Czech Republic [49].

The MS prevalence rates found in Hungary in the years between 1992 and 1996 ranged from 32 to 79 per 100 000 (Fig. 5) [50-52]. The lowest rate was in Baranya county [50] and the highest for Fejer county [52]. The prevalence rate of 5 per 100 000 obtained for Gypsies in Baranya county suggested that they are less susceptible to the disease. However, in Gypsies living in Fejer county, the prevalence of MS was 98 per 100 000, similar to that in Hungarians.

Considering that the availability of new diagnostic tools, in particular magnetic resonance imaging, is notably lower in these countries than in Germany and in Western European countries, it is likely that most of the reported prevalence rates are underestimated due to a less accurate ascertainment of early and benign cases. In the light of all these considerations, the overall MS frequency in these countries may not significantly differ from that in Germany.

The Iberian Peninsula

Prior to the late 1980s, Spain and Portugal had been included in the low-medium frequency zone for MS [53]. This conclusion was based primarily on hospital records and mortality data. From the beginning of 1990s, along with the modernization of the public health system, a series of population-based prevalence studies were conducted in Spain [54-60] that revealed rates ranging from 32 per 100 000 in the province of Teruel [58] to 65 in the Gijon health district (Fig. 6) [54]. These studies indicate that the actual overall frequency of MS is nearly 50 per 100 000 in Spain, evenly distributed throughout the country.

Information as to the risk for MS in Portugal is quite limited. The prevalence of 47 per 100 000 recently found in Santarem (Fig. 6) [61] suggests a risk similar to that in Spain.

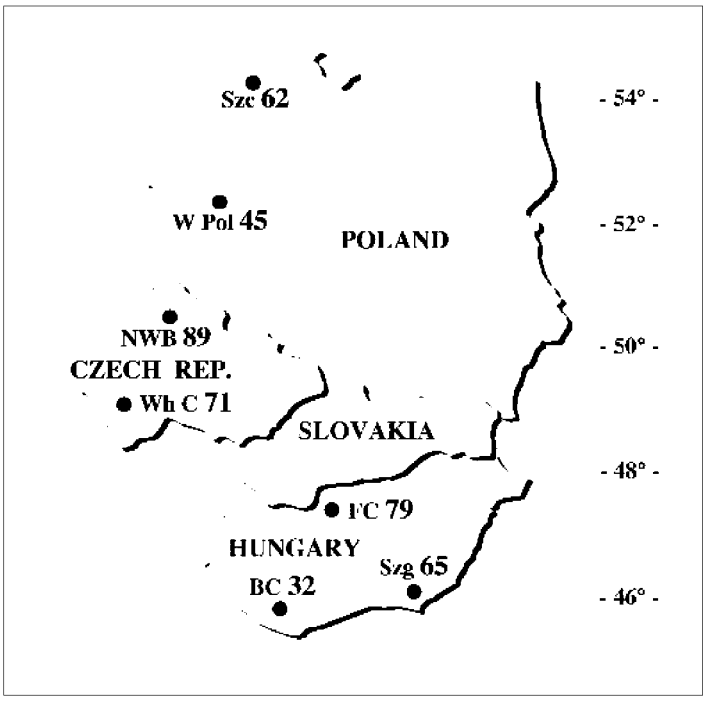

Fig. 5 Distribution of MS in Poland, the Czech Republic and Hungary. Study area (prevalence year): *Szc*, Szczecin Region (1992); *W Pol*, Western Poland (1981); *NWB*, North West Bohemia (1992); *Wh C*, Whole Country (1984); *FC*, Feyer County (1992); *Szg*, Szeged City (1996); *BC*, Baranya County (1993)

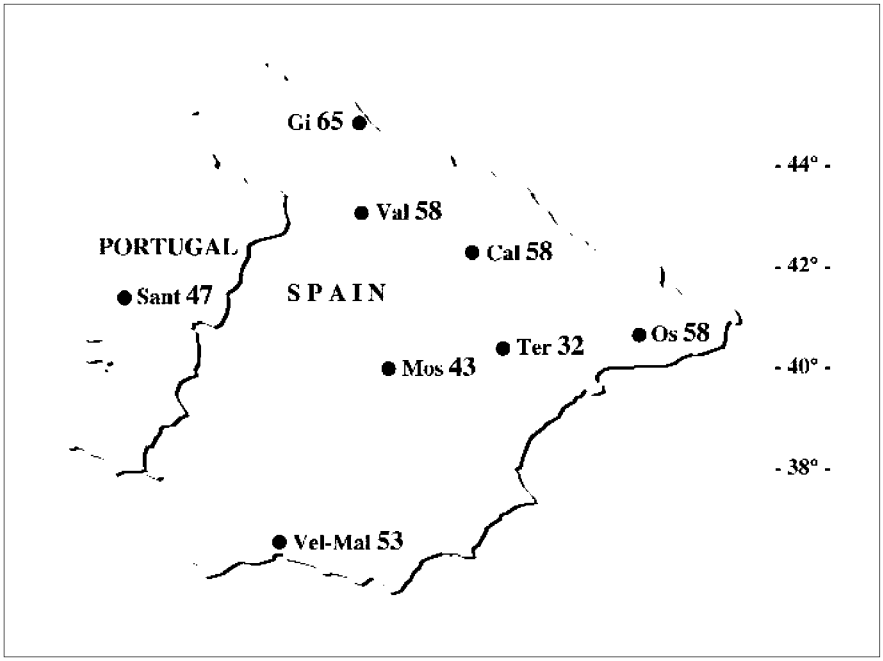

Fig. 6 Distribution of MS in the Iberian Peninsula. Study area (prevalence year): *Gi*, Gijon (1994); *Val*, Valladolid (1997); *Cal*, Calatayud (1995); *Os*, Osona (1993); *Mos*, Mòstoles (1998); *Ter*, Teruel (1996); *Vel-Mal*; Vélez-Malaga (1991); *Sant*, Santarem (1998)

Continental and insular (Sicily, Sardinia) Italy and Malta

During the last 20 years, the frequency of MS in the Italian peninsula and its two major islands, Sicily and Sardinia, has been studied in detail and by means of repeated assessments. The prevalence rates found in different areas of the Italian mainland ranged from 40 to 70 per 100 000 [62-71], with the exception of Salerno and Valle d'Aosta where they were 35 and [72] and 90 [73], respectively (Fig. 7). However, the rate in Salerno in 1998 was based on the information received from general practitioners and is likely an underestimate. With regard to the study in Valle d'Aosta, the prevalence rate may in fact exceed those reported from other regions of continental Italy because of the peculiar characteristics of the investigated population that speaks a French dialect, has remained isolated in the Alps for centuries and has an ethnic background different from other Italians. The prevalence studies carried out in Sicily since 1975 [74-78] found rates

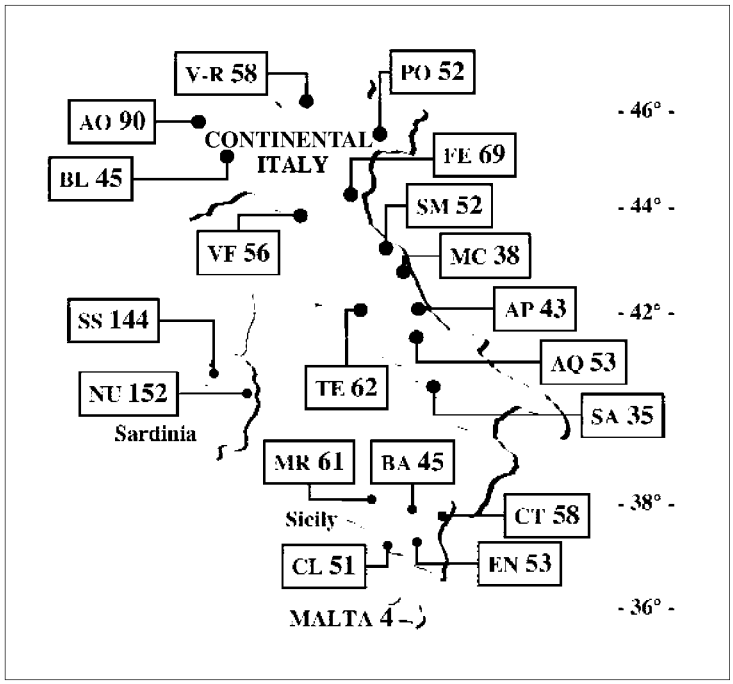

Fig. 7 Distribution of MS in continental and insular (Sicily, Sardinia) Italy, and Malta. Study area (prevalence year): *V-R*, Vallagarina-Rovereto district (1981); *AO*, Valle d'Aosta (1995); *PO*, Pordenone (1987); *BL*, Biella (1987); *FE*, Ferrara province (1993); *SM*, San Marino Republic (1982); *VF*, Valdarno-Firenze district (1991); *MC*, Macerata province (1988); *AP*, Ascoli Piceno province (1988); *TE*, Terni province (1994); *AQ*, L'Aquila province (1996); *SA*, Salerno (1998); *SS*, Sassari province (1996); *NU*, Nuoro province (1994); *MR*, Monreale (1991); *BA*, Bagheria (1994); *EN*, Enna (1975); *CT*, Catania province (1995); *CL*, Caltanissetta (1986); Malta (1978)

ranging from 45 in Bagheria city [77] to 61 in Monreale city [76], similar to those reported from peninsular Italy.

The island of Sardinia represents a striking exception to the even distribution of MS in Italy. The most recent survey on large populations confirms the results of previous studies on small populations, indicating that this Italian island has the highest frequency of MS in Mediterranean Europe and one of the highest in the world. The prevalence of MS was 152 per 100 000 in the province of Nuoro in 1994 [79] and 144 in the province of Sassari in 1997 [80]. Because of their peculiar genetic structure, Sardinians are probably more susceptible to the disease as compared to other Italians. The genetic distance of Sardinians from most present-day Europeans is second only to Samis and exceeds that of Basques; it is reflected by an unusually high frequency of some blood groups, HLA phenotypes and thalassaemia variants that are rare elsewhere. These characteristics reflect several millennia of genetic drift in a small and isolated population [81]. The studies carried out in Nuoro and Sassari showed a notable increase in MS incidence over that observed in the continental province of Ferrara in the same years, and appear to confirm at least in part, a real change in the frequency of the disease over time. If this interpretation is correct, the very high frequency of MS among Sardinians could also reflect the environmental and social changes that have occurred on the island following the end of its geographic and historical isolation.

Malta, with a rate of 4 per 100 000 in 1978 [82], has the lowest prevalence of MS so far recorded in the Mediterranean areas. This may be related to the Maltese' genetic background, but major problems in case ascertainment cannot be excluded.

Slovenia, Croatia, Yugoslavia and Rumania

A national survey carried out in Slovenia in 1992 revealed a prevalence rate of 83 per 100 000 (Fig. 8) [83]. The frequency of MS in Slovenia, where a large proportion of the population is of Germanic descent, is thus similar to that reported in Germany. The more reliable prevalence studies of MS in Croatia were reviewed by Materljan and Sepcic a few years ago [84]. The rates ranged from 28 per 100 000 in Istria in 1981 [85] to 40 in Zagreb in 1979 (Fig. 8) [86]. An exception to this range of frequency was represented by the small mountain community of Gorski Kotar, where the MS prevalence was 124 per 100 000 in 1986 [87], identical to that recorded in the neighbouring region of Kocevje [88], a small community in the mountainous part of Slovenia. This spatial cluster of MS across the frontier between Croatia and Slovenia may reflect the Germanic descent of a large proportion of the population living in both Gorski Kotar and Kocevje. However, the higher frequency of MS in small communities that have remained isolated in mountain regions for a long time may also be explained by their tendency towards consanguinity.

Prevalence data from Yugoslavia are very limited. A prevalence rate of 20 per 100 000 was estimated in central Serbia in 1981 (Fig. 8) [89], but the cases were ascertained only through hospital records. In Rumania, the MS prevalence in 1977 was 27 for Arges County [90] and 42 for the city of Bucharest (Fig. 8) [91]. In 1984, a survey on the MS frequency in 34 counties representing 76% of the entire Rumanian population estimated a mean prevalence of 26 per 100 000 [92]. This figure is probably biased by incomplete case ascertainment: the patients were identified through the

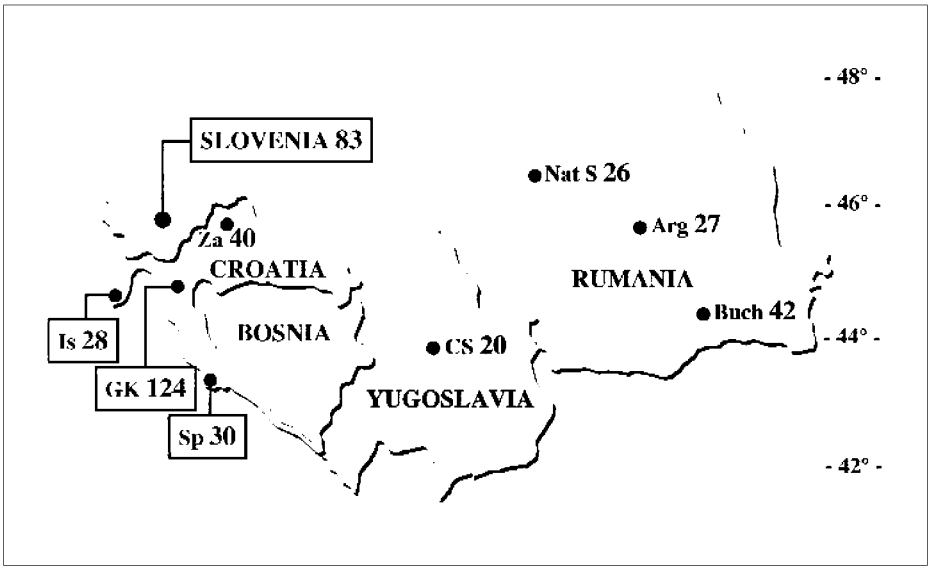

Fig. 8 Distribution of MS in Slovenia, Croatia, Yugoslavia and Rumania. Study area (prevalence year): Slovenia (1992); *Nat S*, National Survey, 34 counties (1984); *Arg*, Arges County (1977); *Buch*, Bucharest (1977); *Za*, Zagreb (1979); *Is*, Istria (1981); *GK*, Gorski Kotar (1986); *Sp*, Split (1981); *CS*, Central Serbia (1981)

records of the hospital neurological departments and the risk for MS was found to be identical in women and men.

Bulgaria, Macedonia, Albania, Greece and Cyprus

The prevalence rates recorded in different areas of Bulgaria in the 1990s [93-96] ranged from 30 per 100 000 in Sofia [93] to 43 in the region of Pavlikeny [96], showing no significant difference in MS frequency distribution within the country (Fig. 9). In the urban area of Sofia and the rural town of Somokov, the risk of MS appeared to be significantly lower in Gypsies [95]. As previously reported, an apparent resistance of Gypsies to MS was also observed in Hungary, in the county of Baranya [50] but in contrast, not in the county of Fejer [52]. To draw a definite conclusion with respect to this question, the disease frequency should be examined in a group of Gyspsies in Central Europe, but this approach would likely encounter serious difficulties.

In the Republic of Macedonia, the overall MS prevalence in 1991 was reported as 16 per 100 000 [97], based exclusively on patients treated at the Neurological Clinic of Skopje.

The first survey of MS prevalence in Albania was carried out in 1988 and assessed a rate of 10 per 100 000 [98]. Because of difficulties in case ascertainment believed to be related to the low socio-economic level of the population, the author of the study concluded that the true MS frequency in Albania was probably much higher.

In Greece, the most recent prevalence study of MS was carried out in the provinces of Macedonia and Thrace in 1984, yielding a rate of 29 per 100 000 [99]. It is probable that this figure does not reflect the true frequency of MS in the country. Greeks share the same genetic background as Sicilians and other southern Italians, with a prevalence of about 50 per 100 000. The chances of ascertaining early and benign cases of MS is undoubtedly higher in Italy than in Greece. In the Greek community of Cyprus, the prevalence of MS was 43 per 100 000 in 1993 [100], remarkably higher than in Greece. If this is correct, the role of environmental factors might be crucial in explaining these differences in MS risk between populations that are ethnically the same. However, because Cyprus is sparsely populated, more intensive case-finding and a tendency towards consanguinity may contribute to this figure.

European Russia and other countries of the former Soviet Union

The prevalence studies of MS carried out in Russia and other countries of the former Soviet Union after 1970 have been recently reviewed by Boiko et al. [101, 102]. The interpretation of the data from this vast territory is particularly difficult because of important differences in the ethnic composition of the populations, the variability in the geographic and social characteristics of the surveyed areas, the high rates of migration and the poor organization of the epidemiological studies. Viewed as a whole, the published rates give the impression that the Baltic Republics, Belarus, Ukraine and European Russia, mostly inhabited by Russian and other people belonging to the Slavonic group, have a similar risk for MS. The ranges for prevalences from Estonia, Latvia, Lithuania, Belarus and Ukraine were 25-55 per 100 000 (Fig. 10). Similar rates, varying from 24 to 55 were estimated for European Russia. Thus, the rates in

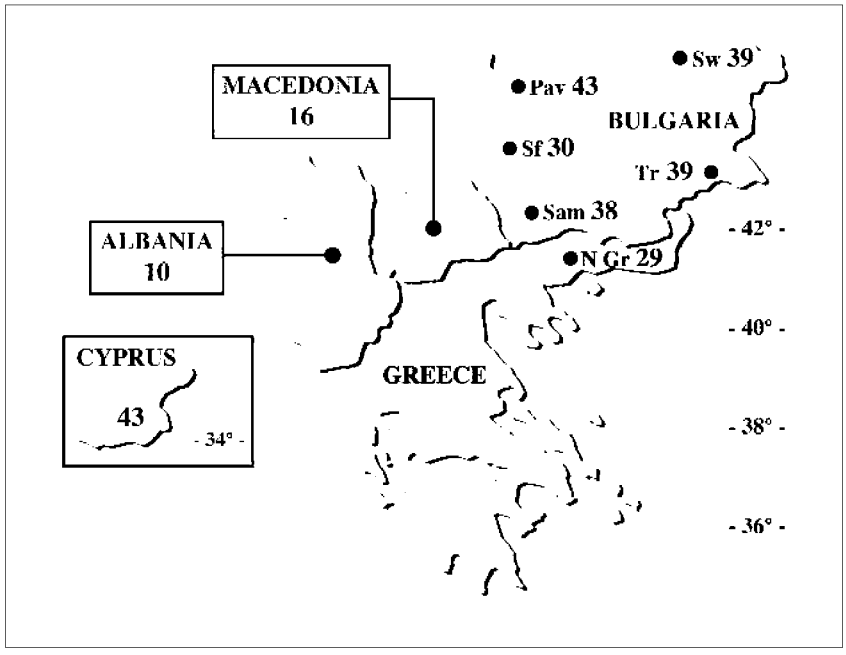

Fig. 9 Distribution of MS in Bulgaria, Macedonia, Albania, Greece and Cyprus. Study area (prevalence year): *Pav*, Pavlikeny (1998); *Sw*, Swoge (1995); *Sf*, Sofia (1992); *Sam*, Samokov (1998); *Tr*, Trojan (1995); Macedonia Republic (1991); Albania (1988); *N Gr*, Northern Greece (1984); Cyprus, Greek Community (1993)

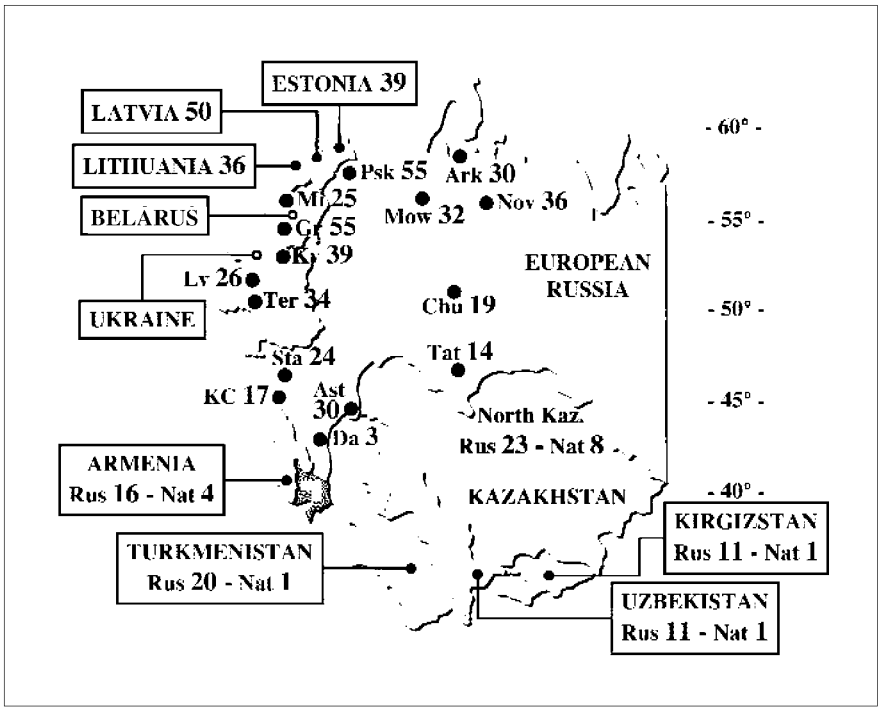

Fig. 10 Distribution of MS in European Russia and other countries of the former Soviet Union. Study area (prevalence year): *Ark*, Arkhangelsk (1980); *Psk*, Pskov (1980); *Mow*, Moscow (1973); *Nov*, Nizhnyi Novgorod, Gorki (1980); *Chu*, Chuvasia (1990); *Tat*, Tataria (1978); *Ast*, Astrakhan (1980); *Sta*, Stavropol, N-W (1990); *KC*, Karachay-Cherkessia (1990); *Da*, Daghestan (1990); Estonia (1991); Latvia (1970); Lithuania (1980); *Gr*, Grongo (1988); *Mi*, Minsk (1988); Armenia, Russians and natives (1981); *Kv*, Kiev (1985); *Lv*, Lvov (1985); *Ter*, Ternopol and Herson (1995); Turkmenistan: Russians and natives (1983); Uzbekistan: Russians and natives (1983); Kyrgyzstan: Russians and natives (1980); North Kazakhstan: Russians and natives (1985)

northern Russia were 55 for the Pskov region, located close to the Baltic Republics, and 30 for the Archangelskyi region; the rates in central Russia were 32 for Moscow and 36 for the Nizhnyi Novgorod region; the rates in southern Russia were 24 for the Stavropol region and 30 for the Astrakan region. Lower rates were recorded in regions with native populations of Turkic descent (Chuvasians, Tatars, Bashkirs, others) or the northern Caucasus group (Circassians, Chechens, Dagestanians, others). The prevalence rates were 19 in Chuvasia and 14 in Tatarstan. Those from the northern Caucasus fluctuated from 17 in Karachevo-Caucasia to 3 in the mountain districts of Dagestan. The frequency of MS among the native populations of the southern countries of the former Soviet Union was found to be notably lower than that among Russians living in the same areas. The rates in Armenia were 4 for Armenians, 3 for Azerbaijanis, 4 for Kurds and 16 for Russians. In Turkmenistan they were near 1 for Turkmen and 20 for Russians. In Uzbekistan, the prevalence among Uzbeks was near 1, but 11 among Russians. In the northern part of Kazakhstan, they were 8 for Kazakhs and between 20 and 30 for Russians, Ukrainians and Germans living there. In Kyrgyzstan, the rates were 1 for Kyrgyzis and 11 for Russians.

These data seem to stress the importance of genetic factors in modulating the geographic distribution of MS. However, the risk of MS among Russians born or living in the southern former Soviet Union was lower than that detected among Russians in the mother-country, thus confirming the complementary role of environmental factors in determining the geographic distribution of the disease.

The Americas

Canada

The studies carried out in Canada in the years before 1990 showed a prevalence of MS averaging around 90 per 100 000. From east to west, the rates were 55 for Newfoundland in 1984 [103], 68 for Ottawa in 1975 [104], 94 for London, Ontario in 1984 [105], 111 for Saskatoon, Saskatchewan in 1977 [106], 87 for Cardston, Alberta in 1988 [107], and 91 for British Columbia in 1982 (Fig. 11) [108]. These rates seemed to indicate a gradient of increasing frequency moving from east to west. A possible explanation for this apparent gradient was the higher density of French-speaking people in the eastern seaboard and Newfoundland, as compared to western Canada, where people of British and North European ancestry are more represented [109]. However, the numbers reported from Newfoundland were probably underestimated. In fact, it has now moved to values higher than 100 per 100 000 (W. Pryse-Phillips, personal communication). More recently, the reappraisal of MS frequency in some areas of Saskatchewan and Alberta has shown a notable increase in the prevalence rates. This was most dramatically noted in the study from Saskatoon where it increased from 111 in 1977 [106] to 248 in 1999 [110], the highest rate ever reported worldwide in population of comparable size. In Saskatoon, after the survey conducted in 1977, the identification of cases continued until December 1998 by long-term surveillance, collecting information from the local MS clinic registries, medical records, and community and provincial resources. For Alberta, excluding surveys

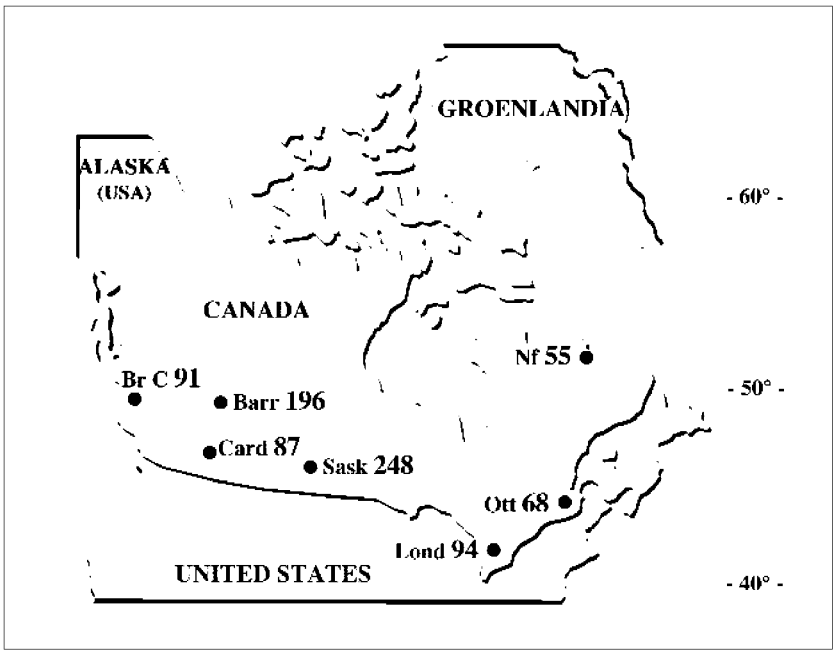

Fig. 11 Distribution of MS in Canada. Study area (prevalence year): *Nf*, Newfoundland (1984); *Br C*, British Columbia (1982); *Barr*, Barrhead, Alberta (1990); *Card*, Cardston Region, southern Alberta (1988); *Sask*, Saskatoon, Saskatchewan (1999); *Ott*, Ottawa (1975); *Lond*, London and Middlesex County, Ontario (1984)

on very small populations such as that from Westlock County [111], the prevalence reported in Barrhead County was 196 in 1990 [112]. In view of the fact that people living in these areas were ethnically similar to those in the rest of western Canada, it was felt that research should focus on these regions in order to identify environmental factors influencing the risk for MS. However, it soon became clear that the reported rates were probably more related to the recent changes in circumstances favouring an exceptionally high case ascertainment, than a true association with risk factors. The institution of universal medical insurance coverage programs giving equal access to medical care, the widespread availability of sophisticated procedures for the diagnosis of MS, the creation of MS clinics, the periodic reassessments of MS frequency in several provinces and the high degree of public awareness of the disease, all support the view that the most recent prevalences from Canada reflect the overall MS case distribution encompassing all levels of disability (benign or mild to severe) as well as ethnic and socio-economic categories [4]. In other words, the Canadian studies demonstrate the highest level of saturation of prevalent cases.

The North American Indians living in Canada have shown a low risk for MS [113]. The majority of Indians with MS had a Caucasian ancestor, suggesting that the admixture with Caucasian genes increases these aboriginal people's susceptibility to the disease [113, 114]. A low frequency of MS was also observed among the Canadian Hutterites, a socially isolated ethnic group originally immigrated from Southern Germany to Canada as well as to other parts of North America, forming closed communities, where social mixing and marriages outside the group are still rare today [115]. They constitute a rare exception to the relationship between MS risk and northern European ancestry in Canada. A tendency towards consanguinity and social isolation, perhaps also pure chance, are all factors that could make the Hutterites less susceptible to the disease despite their residing in regions where MS is otherwise frequent.

The United States

By comparison with Canada and Western Europe, the number of localized population surveys on MS in the United States is modest and leaves much of the country undefined as to the distribution of the disease. Moreover, comparison of the reported rates is rendered difficult because of a number of problems such as variations in the characteristics of the denominator, case-finding methods, and the period of the prevalence surveys.

A north-south gradient of MS prevalence in the United States was originally suggested by localized surveys conducted between 1948 and 1967 [116]. In the 1970s, this gradient was confirmed by the national survey of MS prevalence sponsored by the National Institute of Neurological and Communicative Disorders and Stroke [117]. The national survey estimated that the overall prevalence of probable MS in the United States in 1976 was 46 per 100 000, being 53 north, and 30 south of 37° latitude (Fig. 12). Case finding in this national survey was accomplished through a probability sample of physicians and general hospitals in the contiguous United States. MS service organizations and direct audits of neurology case records were not used as case finding sources. Therefore, possible and probable MS cases not known to (or not remembered by) the medical providers were not included in the prevalence estimate. The extent to

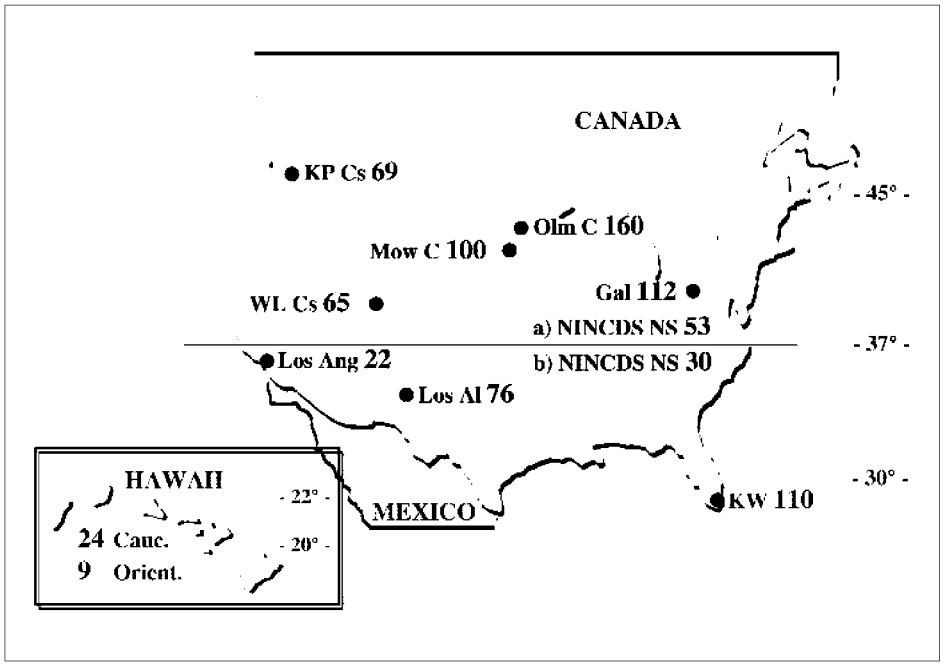

Fig. 12 Distribution of MS in the United States. Study area (prevalence year): *KP Cs*: King-Pierce Counties, WA (1970); *Olm C*, Olmsted County, MN (1985); *Mow C*, Mower County, MN (1978); *Gal*, Gallion, OH (1987); *WL Cs*, Weld-Larimer Counties, CO (1982); *Los Ang*, Los Angeles County, CA (1970); *Los Al*, Los Alamos County, NM (1979); *KW*, Key West Island, FL (1983); Hawaii: Caucasians and Asians (1969); *NINCDS NS*, NINCDS National Survey (1976), regions above (a) and below (b) the 37th parallel

which such bias restricted the identification of MS cases is uncertain.

Evidence coming from a subsequent study of MS prevalence conducted in Weld and Larimer Counties of northern Colorado [118] indicates that U.S. surveys of MS, which neglect case-finding sources such as MS service organizations and neurology practice chart reviews, may underestimate MS prevalence by as much as 20%-40%. On this basis, the prevalence undercount in the 1976 national survey was not only seriously underestimated but also of different degree in the different regions of the United States.

Local surveys of MS conducted in the United States since 1970 seem to corroborate its uneven distribution but raise some doubts about the appropriateness of the partition of the country into high (north) and low (south) prevalence zones. The reported rates suggest a higher frequency of MS in the northeastern and southern regions of the country. In the midwest, the rates were found to be 160 for Olmsted County, Minnesota in 1985 [119], 100 for Mower County, Minnesota in 1978 [120], and 112 for Galion city, Ohio in 1987 (Fig. 12) [121]. In the west and the south, the rates were 69 for King-Pierce Counties, Washington in 1970 [122], 65 for Weld-Larimer Counties, Colorado in 1982 [118], 22 for Los Angeles County, California in 1970 [122], 76 for Los Alamos County, New Mexico in 1979 [123], and 110 for Key West, Florida in 1983 [124]. The pattern of geographic distribution of MS as suggested by these rates, is, however, adversely affected by the low level of comparability of the studies. The studies for Olmsted County, controlled by the Mayo Clinic, are exceptional in terms of high case ascertainment over a long time period and the revised rate of 160 estimated in 1985 is not comparable to any of the other figures so far reported from the United States. The same comment can be made for the rate of 100 reported from the neighbouring Mower County. Neurologists for the outreach program in Mower County are provided by the Mayo Clinic, and all diagnoses made in the program are indexed by the diagnostic file at the Mayo Clinic; this greatly facilitated identification of cases. Another source of bias when comparing the reported rates is the notable difference in the size and the structure of the surveyed populations. The rates reported for Galion, Los Alamos County and Key West were based on small populations, ranging from about 15 000 to 26 000. Comparison of the data is also biased by methodological differences. The rates from King-Pierce and Los Angeles Counties are not directly comparable with those from Olmsted and Mower Counties, since the former were reported for white individuals born in those two countries and the latter only for cases with symptom onset in the study area.

The modest number of local surveys of MS and the low level of comparability of the reported rates preclude finding a reliable pattern of the disease distribution in the United States. The major support for the oversimplified but commonly accepted belief that MS frequency in the United States is directly related to latitude still derives from the analysis of MS distribution conducted by Kurtzke et al. [125] more than 20 years ago, of a cohort of 5305 U.S. Army veterans with respect to residence at service entry. They found high rate above and low rates below the 37th parallel.

The association between MS and latitude has also been investigated by two ongoing prospective studies of American women, the Nurses' Health Study (NHS), of women born between 1920 and 1946, and the Nurses' Health Study II (NHS II), of those born between 1947 and 1964 [126]. In the NHS, MS incidence was found to be higher among women

residing in the northern tier compared to those in the southern one, after adjusting for age, ancestry and longitude zone. For NHS II women, no increase in the risk of MS was detected among those living in the north. This difference between the two cohorts was interpreted as consistent with an attenuation over time of the north-south gradient of MS prevalence in the United States.

Geographic distribution of MS in the United States is undoubtedly influenced by the varying genetic susceptibility to the disease of different racial and ethnic groups. In the 1976 national survey of MS [117], the prevalence rates of probable MS among whites and non-whites were 49 and 26, respectively. Among U.S. Army veterans [125], the risk of MS in blacks was half that assessed in whites; the risk was also notably lower in Asians and American Indians. In Hawaii [127], the rates were 24 for Caucasians and 9 for Asians. Simlarly, Detels et al. [128] found low MS rates among foreign-born and American-born Japanese and Chinese on the West Coast. In the early 1990s, Bulman and Ebers [129], by re-analysing and re-interpreting the U.S. Army veterans' data that favoured a north-south gradient in the United States [125], showed that the distribution of MS within the country correlated with the distribution of individuals of western European ancestry, the highest correlation being with people of Scandinavian origin. On this basis, Bulman and Ebers concluded that the geographic distribution of MS in the United States may better reflect ethnic migration patterns and genetic susceptibility rather than environmental factors.

Central and South America

Information about the distribution of MS in Latin America is limited (Fig. 13). The few estimates of MS frequency published before 1990, suggesting prevalence rates of 2 in Venezuela, 4 in Peru and 4 in Brazil, are unreliable. They were provided by Christensen [130] in the 1970s on the basis of published reports, without any way of judging the accuracy of the diagnosis and the quality of the studies. The hospital-based survey of MS in Mexico City [131], which estimated a rate of about 5 in 1985, has also to be considered with caution.

The quality of the studies in some Latin American countries has improved during the last decade. In the Caribbean area, reliable data have been reported from Cuba and Martinique. Around 1990, the prevalence of clinically definite MS in the different Cuban provinces varied from 5 to 10 per 100 000 [132]. In the island of Martinique, with a French Afro-Caribbean population, the prevalence of definite and probable MS in 1997 was 14 per 100 000 [133]. Interest in MS has also increased in Brazil, Uruguay and Argentina. In Brazil, by using standardized diagnostic criteria, the prevalence of MS was found to be 14 in Sao Paolo City in 1997 [134] and 5 in Rio de Janeiro in 1999 [135]. In the Atlantic South Project, which started in 1994 with the purpose of defining MS in Brazil by using a database, in a population of 509 patients classified according to the Poser criteria, 72% was Caucasian Brazilian and the rest was Afro-Brazilian

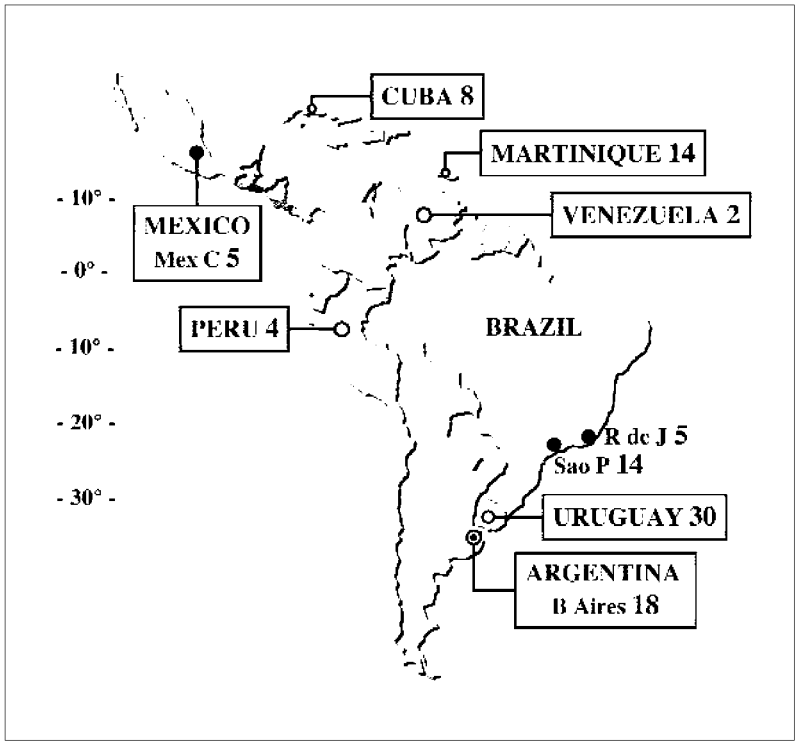

Fig. 13 Distribution of MS in Central and South America. Study area (prevalence year): *Mex C*: Mexico City (1985); Cuba (1984); Martinique (1997); Venezuela (1970); Peru (1970); *Sao P*, São Pãulo (1997); *R de J*, Rio de Janeiro (1999); Uruguay (1996); *B Aires*, Buenos Aires area (1996)

[136]. On this basis, the previous rate of 5 from Rio de Janeiro was believed to have been due to a high proportion of non-Caucasians in the surveyed population rather than to the geographic location close to the Equator [135]. By the same token, the rate of 14 from Sao Paolo was interpreted as more likely due to the high proportion of people of southern and central European origin. In Uruguay, where the vast majority of the population is of European origin, a 1996 national survey of MS estimated an overall prevalence of 30, using the Poser diagnostic criteria [137]. As to Argentina, having a high proportion of people of European origin like Uruguay, the capture-recapture assessment of MS risk in the metropolitan area of Buenos Aires yielded a rate of 18 in 1996 [138]. Studies from Brazil, Uruguay and Argentina have emphasized the low risk of MS among the South-American Indians and those of African descent as compared to the Caucasian inhabitants of the Continent.

The published morbidity data are not sufficient to define the geographic distribution of MS in Latin American countries, but they do give the impression that the major determinant will turn out to be the different genetic susceptibility to the disease of the various ethnic and racial groups living in this vast area.

Asia

Siberia

The risk of MS in Asiatic Russia has long been estimated to be low. Following a major migration of Russians to the East along with a large-scale industrialization and a marked increase of the resident population, the frequency of MS in Siberia has gradually increased.

Most of the data on MS prevalence in Siberia are to be found only in the proceedings of local meetings published in Russian, but have recently been reviewed by Boiko et al. [101, 102]. The most recent reports from Siberia indicate prevalence rates ranging from 12 to 41 per 100 000 (Fig. 14). The rates from western Siberia around 1985 were near 20 for the Tomsk, Kemerovo and Novosibirsk regions, and 16 for the Altai. MS surveys in eastern Siberia in the years between 1985 and 1990 yielded rates of 14 in Irkutsk, 17 in the Chita region, 12 in Yakutsk, 40 in the central western part of Amur region, 31 in the south-western part of the Amur region, 41 in Khabarovsk, and 20 in the Primorski region. Almost all the MS patients were Russians living there. Of these, 80% belonged to the third generation, the children of Siberia-born parents. MS was found to be very rare among the native Siberian peoples. In fact, until 1972, no MS case had been observed among the native Siberian peoples, when four cases were reported in Buriats, and more recently a first case among Yakutes. MS is apparently still absent in the smaller Siberian tribes.

The most interesting feature of MS epidemiology in Siberia is the enormous difference in rates between the indigenous populations and the Russians, clearly supporting a leading role of ethnic factors in determining the distribution of the disease. The restricted access of native Siberians to specialist medical care cannot explain a difference of such a degree, which must therefore reflect a lower genetic susceptibility to MS. The data also indicate that the overall prevalence of MS in Russians born and living in Siberia is lower than that reported for Russians born and living in

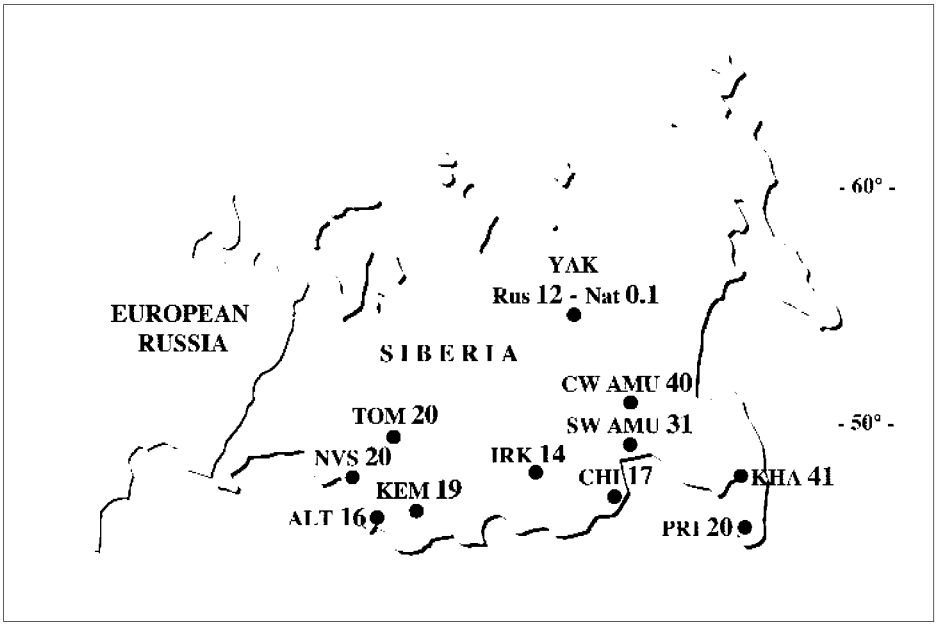

Fig. 14 Distribution of MS in Siberia. Study area (prevalence year): *TOM*, Tomsk Region (1984); *NVS*, Novosibirsk Region (1984); *KEM*, Kemerovo Region (1984); *IRK*, Irkutsk Region (1985); *CHI*, Chita Region (1985); *CW AMU*, central-western Amur Region (1985); *SW AMU*, south-western Amur Region (1985); *KHA*, Khabarovsk Region (1990); *PRI*, Primorsky Region (1985); *YAK*, Yakutsk, Russians and natives (1985); *ALT*, Altai (1985)

Europe. This seems to support the view that the geography of MS is greatly influenced by environmental factors, but the lower prevalence in Russians living in Siberia could result from local factors such as a less complete case-finding and ascertainment. In this regard, it has to be emphasized that the rates from the Far East regions of Amur and Khabarosk, with a better organized health system, are identical to those reported from the northwestern and central regions of European Russia [101].

India, China, Taiwan and Japan

MS is generally believed to be rare in India. Cases have been reported from various regions of the country and, despite the serious lack of prevalence estimates, it has been suggested that the disease may be more common in the north, which was settled mostly by Indo-Europeans, than in the south where Tamil and Dravidian populations predominate [139]. To date, some prevalence data are available only for the Bombay area. On the basis of 30 MS patients diagnosed in hospitals and private clinics in Bombay in the years 1957 to 1972, Singhal and Wadia [140] estimated a MS prevalence rate of 1 per 100 000 among Indians (Fig. 15). The fact that 6 of these 30 patients were Parsis suggested that MS was more frequent among them than in other ethnic groups. This was confirmed by two subsequent studies of Parsis, one in Bombay [141] and the other in both Bombay and Poona [142]. In 1988, the prevalence of MS among Parsis was 28 in Bombay and 58 in Poona. Parsis are of Persian origin and practise the Zoroastrian religion; their ancestors had migrated to the Bombay area in the seventh century [142]. Information about MS prevalence among other Indian ethnic groups is lacking. With regard to diagnostic accuracy, differentiating MS from HTLV-I associated paraparesis (HAP) is a crucial concern in India. In his chapter on neurological diseases in South India, Mani [143] mentioned seven cases of MS including three cases of Schilder's disease, but 45 cases of HAP in the same time period.

The few studies so far available from China and Taiwan indicate that MS is rare among Chinese, with a prevalence of 1 in Taipei, Taiwan in 1980 [144] and also in Hong Kong in 1986 (Fig. 15) [145]. A door-to-door survey in Lang Cang Lu Hu Zu County of the Chinese Yunnan province estimated a rate of 2 in 1986 [146].

In 10 Japanese cities extending from north to south, MS prevalence varied from 1 to 4 per 100 000 in the years between 1975 and 1983 (Fig. 15) [147, 148]. The rate distribution in Japan was interpreted as being consistent with a north-south gradient [147], but it was based on a small numbers of cases and failed to establish any relation to latitude. Doubts about the validity of MS diagnosis in the Japanese reports have been raised by the widespread use of the 1972 Japanese criteria [149], which also affect some Chinese reports. The higher prevalence observed among Japanese living in Hawaii or in the western coast of United States [127, 128] may therefore reflect methodological differences rather than the influence of environmental factors.

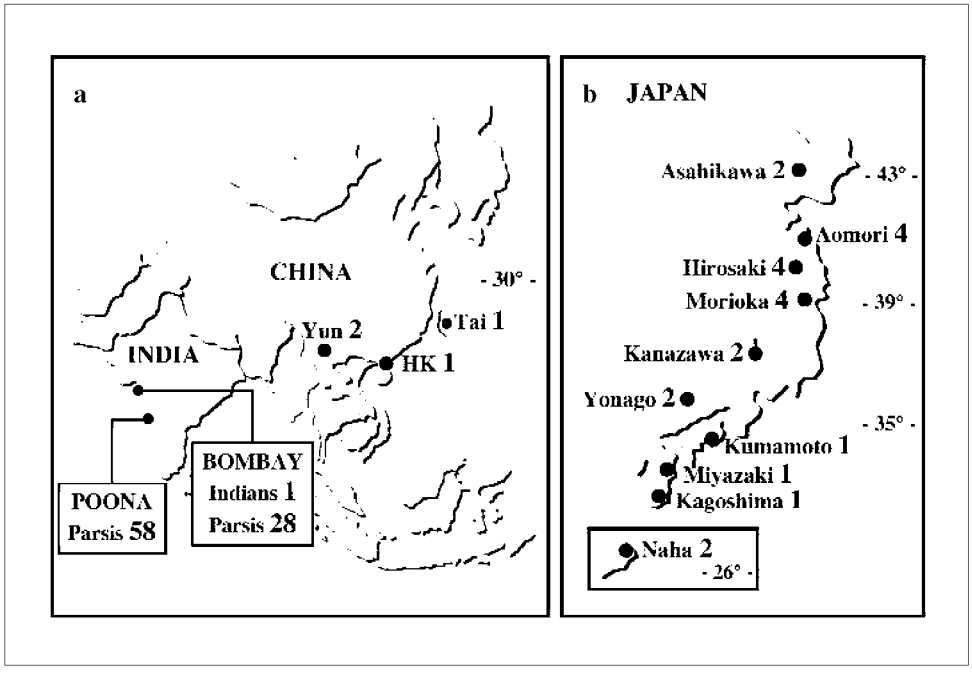

Fig. 15a,b Distribution of MS in (a) India, China, Taiwan and (b) Japan. Study area (prevalence year): Bombay: Indians and Parsis (1988); Poona, Parsis (1988); *Yun*, Yunnan Province, La Cang Hu Zu Country (1986); *Tai*, Taipei, Taiwan (1980); *HK*, Hong-Kong (1986); Japan: prevalence between 1975 and 1983

The Middle East

Data from the Middle East emphasize the importance of the genetic-historical factor in determining the distribution of MS. MS prevalence among Arabs was reported to be 4 in Baghdad, Iraq in 1969 [150], 7 in Jordan in 1977 [151], and 8 in Saudi Arabia in 1977 (Fig. 16) [152]. In Kuwait, with a population of 2 010 000, of whom 1 457 472 were Arabs and 552 528 non-Arabs, the overall MS prevalence rate in 1988 was 10 per 100 000 [153] based on 201 patients classified according to the Poser criteria. The rate based on the 186 Arab patients, the vast majority of whom were Kuwaitis, Palestinians and Egyptians, was 13. Among non-Arabs, 95% of whom were Southeastern Asians, the rate was 3 based on 15 MS patients. The prevalence among Kuwaitis was 10 as compared to 24 among Palestinians. Such a significant difference in rates between Kuwaitis and Palestinians cannot be explained in terms of environmental factors alone. About 60% of the Palestinians in Kuwait were born there and the majority of the remaining 40% had migrated to Kuwait more than 20 years prior to prevalence day. A better explanation is provided by differences in the genetic control of disease susceptibility. The distributions of the AB0 blood groups as well as of the HLA-DR and HLA-DW haplotypes were reported to be different between Kuwaitis and Palestinians. Palestinian MS patients showed an association with HLA-DR2 and HLA-DQW1 similar to that reported in Caucasians, such association not being found in Kuwaitis [153].

Data from Israel are difficult to interpret (Fig. 16). In a recent study on MS prevalence among native-born Israelis of different origins and among immigrants to Israel [154], the rate in native-born Israelis whose father had been born in Europe or America was found to be as high or even higher than that found in immigrants from Europe or America, thus eliminating environmental factors. On the contrary, the rate among native-born Israelis whose father had been born in Africa or Asia was significantly higher than that among immigrants from Africa or Asia, pointing to environmental factors. The prevalence of MS among native-born Israelis of European or American origin was significantly higher than that among those of African or Asian origin, once again stressing genetic factors.

Africa

The Canary Islands, North Africa and sub-Saharan Africa

In the Canary Islands, the prevalence of MS was found to be 6 in Las Palmas in 1980 [155] and 15 in Lanzarote in 1986 (Fig. 17) [156]. These rates are much lower than those reported from southern Spain in the 1990s, which suggests a significant influence of place on the risk of MS for people of same ethnicity. However, it must be emphasized that the rates from the Canary Islands are similar to those reported from Spain in the same years [56]. Many of the studies conducted in Spain in the 1980s, including those from the Canary Islands, were based on hospital records, while the higher figures reported from Spain in the 1990s resulted from population-based studies.

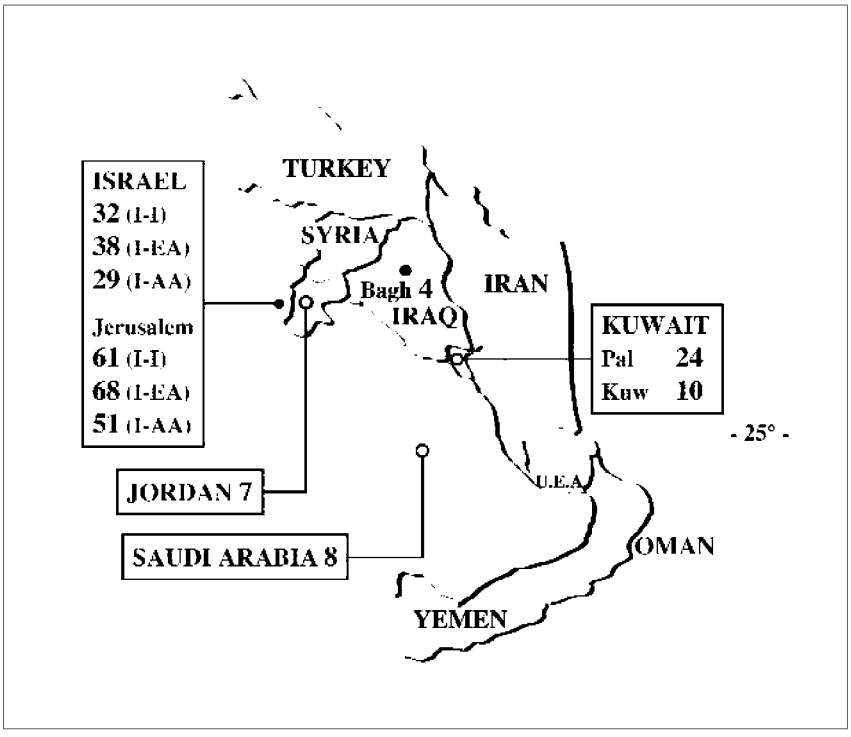

Fig. 16 Distribution of MS in the Middle East. Study area (prevalence year): Jordan (1977); Saudi Arabia (1977); Kuwait: Palestinians and Kuwaitis (1988); Israel: Native Israelis, father born in Israel (I-I); Native Israelis, father born in Europe or North America (I-EA); Native Israelis, father born in Asia or Africa (I-AA) (1985)

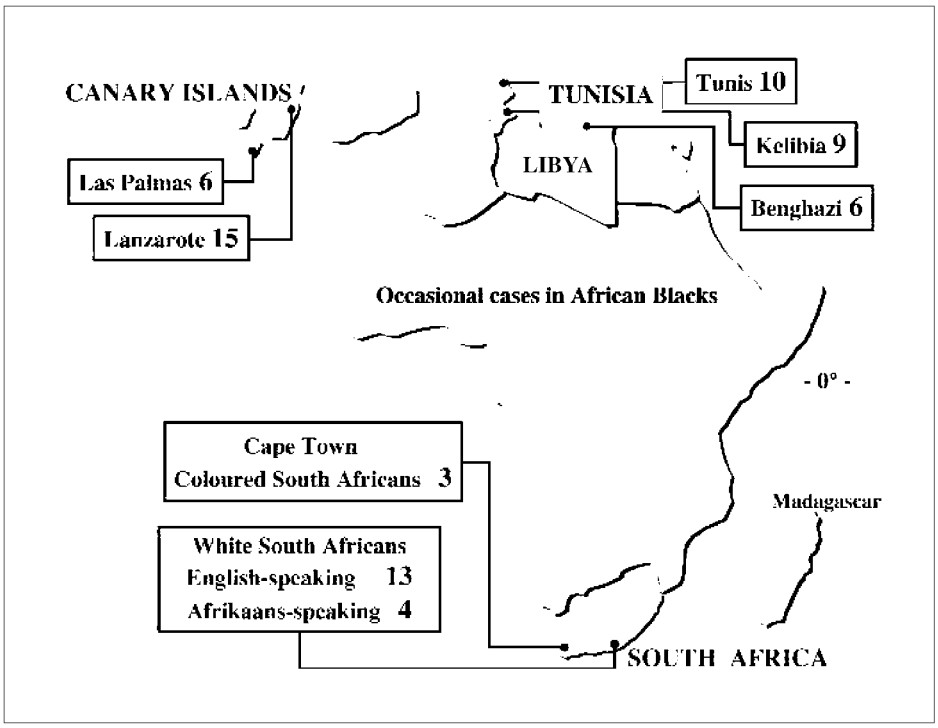

Fig. 17 Distribution of MS in the Canary Islands, North Africa and sub-Saharan Africa. Study area (prevalence year): Lanzarote (1986); Las Palmas (1980); Tunis (1975); Kelibia area (1985); Benghazi (1984); South Africa: Cape Town (1985); White South Africans (1960)

In Tunisia, the prevalence rates of MS were found to be 10 in Tunis in 1975 [157] and 9 in Kelibia in 1985 (Fig. 17) [158]. In Benghazi, Libya the prevalence was 6 in 1984 [159]. These rates are similar to those reported for Arabs in the Middle East. With the exception of Palestinians, MS prevalence appears to be rather evenly distributed among Arabs, regardless of place of residence.

With regard to the sub-Saharan Africa, for many years physicians working there claimed that MS did not exist in black Africans. Current evidence, however, clearly indicates that MS does occur, albeit rarely, in black Africans. In a review of the literature on MS in tropical countries, Poser [160] quoted a number of well documented cases, including four autopsied cases, that showed the incontrovertible existence of the disease in black Africans in Senegal.

In South Africa, the famous study by Dean [161], who advanced the hypothesis of a critical age of exposure to develop MS, reported a 1960 prevalence of 13 in English-speaking white South Africans and 4 among Afrikaners, pointing to a difference in susceptibility (Fig. 17). By that time, he had not identified any affected black South African. In a subsequent report, however, Dean et al. [162] described 6 MS cases in South African blacks. A survey conducted in Cape Town in 1985 [163] estimated a prevalence rate of 3 in "coloured" South Africans but its significance is obscured by their mixed genetic background. The extremely small number of MS cases so far reported in the black population of South Africa by highly trained observers working in a very good medical care system represents the most convincing argument corroborating the black Africans' high resistance to MS. Since the South African black population includes tribal groups such as Zulu and Xosa who do not live elsewhere in Africa, it is possible that they possess an even lower susceptibility to the disease [160].

Australasia

Australia and New Zealand

In the early 1980s, MS surveys were conducted in nine separate regions of Australia and New Zealand (Fig. 18) [164-167], reporting prevalence rates varying from 11 in north Queensland, Australia [164] to 69 in Otago-Southland, New Zealand [167], excluding possible MS. The geographic distribution indicated a south-north gradient, which was interpreted as favouring an environmental cause [168]. In New Zealand, where such a gradient was more appreciable, the rate distribution was interpreted as also reflecting the higher proportion of people of Scottish ancestry in the south [167], and thus a concomitant role for genetic influences. In Australasia, different racial and ethnic groups share the same environment; the statement that the main determinant of the south-north gradient is environmental is probably an overly simplified explanation. The reported distribution of MS may also reflect the heterogeneity of the white populations living in the different regions of Australia and New Zealand [81]. In New Zealand, MS was reported to be rare in Maoris. They constitute 16% of the Waikato, 7% of the Wellington and 3%

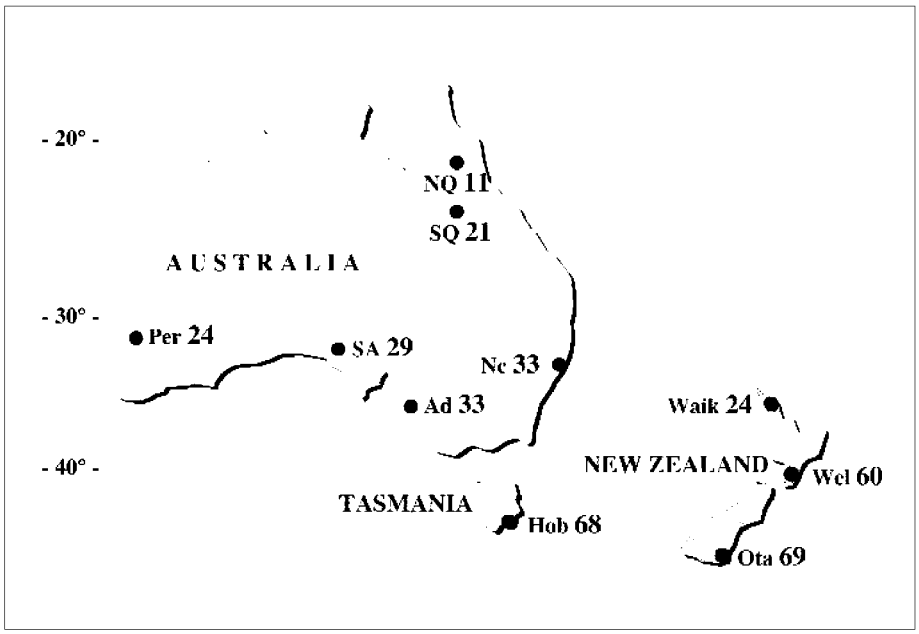

Fig. 18 Distribution of MS in the Australia and New Zealand. Study area (prevalence year): *NQ*, North Queensland (1981); *SQ*, South Queensland (1981); *Per*, Perth (1981); *SA*, South Australia (1981); *Nc*, Newcastle, New South Wales (1981); *Ad*, Adelaide (1981); *Hob*, Hobart (1981); *Waik*, Waikato (1981); *Wel*, Wellington (1983); *Ota*, Otago (1981)

of the Otago-Southland populations [167]. Thus, it is likely that the higher proportion of whites with some Maori ancestry in Waikato has given them a lower susceptibility to the disease, and therefore a lower prevalence in Waikato, compared to the South Island of New Zealand.

Conclusions

Critical examination of the more recent data on MS prevalence leads to some revisions of previously held concepts. The most interesting ones are the appreciation of the greater influence of genetic factors on the acquisition of the disease. The rarity of MS among Samis, Turkmen, Uzbeks, Kazakhs, Kirghizis, native Siberians, North and South Amerindians, Chinese, Japanese, African blacks and New Zealand Maoris, as well as the high risk among Sardinians, Parsis and Palestinians, clearly indicate that the different susceptibility of distinct racial and ethnic groups is an important determinant of the uneven geographic distribution of the disease. The higher frequency of MS in English-speaking whites in South Africa, compared with Afrikaners, and the low frequency among Canadian Hutterites, also hint at a difference in susceptibility.

The updated distribution of MS in Europe, showing many exceptions to the previously described north-south gradient, requires more explanation than simply a prevalence-latitude relationship [3]. In Europe, there are genetic differences across relatively small geographic distances and the geography of MS also correlates with the genetic clines for markers of susceptibility to the disease [109, 169]. The north-south gradient in the United States, which has traditionally been interpreted as reflecting an environmental effect [170], also matches patterns of migration from Europe, the highest frequencies occurring in areas populated mostly by people of Scandinavian ancestry and the lowest correlating with the distribution of black peoples [171].

The prevalence rates for the white populations of Australia and New Zealand, excluding aboriginal peoples, have been interpreted as suggesting that a latitude effect exists in the absence of demonstrable racial gradients [168]. It has to be emphasized, however, that a proportion of the population from the North Island of New Zealand claiming to be white has up to 50% of Maori ancestry [172]. Therefore, the gradient observed in New Zealand may also reflect the lower susceptibility of whites living in the north compared to those living in the south. For Australia, the heterogeneity of the white people who migrated from northern and southern European countries at different ages probably persists, influencing the reported rates [81]. Since genetic differences are an important determinant of MS distribution in Europe [3, 81], it is logical to expect them to also play a role among Australians of European origin.

Despite the evidence that genetic susceptibility is important in influencing the acquisition of MS, the role of environment and its expression in terms of latitude cannot be ignored. In Australia, the highest prevalence rate reported from communities largely originated from the United Kingdom and Ireland is not much more than half the frequency observed in most parts of the British Isles [172], suggesting that environment can modify the risk for MS among individuals belonging to the same ethnic group. The influential migration studies in South Africa [161], Israel [173] and among West Indians migrating to the United Kingdom [174] indicate that MS prevalence can vary with place of residence

early in life irrespective of genetic factors. Twin studies show that almost 60% of monozygotic twins are not concordant for MS [109], pointing to a complex interplay of genes and environment.

A substantial increase in MS incidence has been reported from different regions [24, 27, 79, 80, 119, 175, 176]. If such an increase reflects a real change in the impact of biological factors on the frequency of MS, it can only be reasonably attributed to a change in environmental conditions; population genetics shapes the disease much more slowly [81]. It is difficult to decide whether the reported rises in the risk of MS incidence reflect, at least in part, a true change in MS risk or merely depend on better case ascertainment, earlier diagnosis or demographic factors. A recent comparison between the temporal trends of MS incidence observed in Sardinia and in Ferrara province, northern Italy, seems to prove that the increasing frequency among Sardinians indicates, at least in part, a real change in MS risk [79, 80], probably related to the environmental and social changes following the loss of geographic isolation after World War II.

In summary, prevalence data imply that racial and ethnic differences are important in influencing the worldwide distribution of MS and that its geography must be interpreted in terms of the probable discontinuous distribution of genetic susceptibility alleles [171]. Racially and ethnically influenced differences in the risk of MS, however, can be modified by environment [177]. Because the environmental and genetic determinants of geographic gradients are by no means mutually exclusive, the race versus place controversy is, to some extent, a useless and sterile debate. Researchers must consider the available evidence and direct their efforts towards multicenter studies of similar ethnic groups living under different environmental conditions. Such an approach may provide significant clues for both pathogenetic and triggering mechanisms of MS.

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Sommario *I primi studi sistematici sulla sclerosi multipla (SM) furono intrapresi nel 1929 da Sydney Allison. Attualmente, esistono oltre 400 pubblicazioni scientifiche riguardanti la prevalenza della malattia su scala mondiale. Tuttavia, ogni tentativo di ridefinire il pattern di distribuzione geografica della frequenza di SM si presenta a tutt'oggi difficile, poiché il confronto degli studi di prevalenza, condotti in aree geografiche e tempi diversi, risente della variabilità delle caratteristiche della popolazione in studio (dimensione, struttura dell'età, origine e composizione etnica) e della quantificazione del numeratore dei tassi resa problematica e complessa dal diverso grado di accertamento di casi benigni ed iniziali. La completezza di tale accertamento dipende, inoltre, da numerosi fattori, quali l'accessibilità alle strutture sanitarie, in particolar modo ai servizi diagnostici, la disponibilità di medici esperti, il numero di neurologi, il grado di informazione e conoscenza della malattia da parte del pubblico, le capacità e le risorse dei ricercatori. L'analisi critica dei dati più recenti sulla prevalenza della SM porta a riconsiderare alcuni concetti precedentemente accettati ed orienta verso un maggiore apprezzamento del ruolo del fattore genetico nell'acquisizione della malattia. La rarità della SM tra i Lapponi, i Turkmeni, gli Uzbeki, i Kazaki, i Kirgizi, i Siberiani nativi, gli Amerindi, i Cinesi, i Giapponesi, i neri Africani ed i Maori della Nuova Zelanda, così come l'elevato rischio tra i Sardi, i Parsi ed i Palestinesi, indicano chiaramente che la suscettibilità alla malattia varia nei diversi gruppi razziali ed etnici ed è un fondamentale determinante della disomogenea distribuzione geografica della malattia. Il pattern dell'aggiornata distribuzione di SM in Europa richiede una interpretazione più articolata della semplice correlazione prevalenza-latitudine e costituisce, pertanto, un'eccezione alla teoria del gradiente nord-sud frequentemente citata. La geografia della SM deve invece probabilmente essere interpretata in termini di una distribuzione discontinua di alleli di suscettibilità genetica, la cui frequenza relativa può tuttavia essere influenzata da variazioni della concentrazione di fattori ambientali. Infine, poiché determinanti ambientali e genetici non sono mutualmente esclusivi nel determinare gradienti geografici di malattia, la controversia "razza-luogo" è per certi aspetti sterile ed inutile.*

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