Article abstract—Geographically, multiple sclerosis (MS) seems to be distributed into three zones of high, medium, and low frequency. High-frequency areas, with prevalence rates over 30 per 100,000 population, include Europe between 65° and 45° north latitude, southern Canada and the northern United States, and New Zealand and southern Australia. These regions are bounded by areas of medium frequency with prevalence rates of 5 to 25 per 100,000, which include southern Europe, the southern United States, and most of Australia. Known areas of Asia and Africa (save for one white group in South Africa) are all low, with prevalence rates under 5 per 100,000 population.

All high- and medium-risk areas are among predominantly white populations: In America, blacks and Orientals have much lower rates of MS than whites but still demonstrate the geographic gradients found for whites. Migration studies indicate that on the whole, migrants retain much of the risk of their birthplace. However, this risk is clearly not defined at birth: MS death rates for migrants born in one risk area and dying in another are intermediate between the rates characteristic of their birthplaces. Prevalence studies for migrants from high- to low-risk areas indicate the age of adolescence to be critical for risk retention; those migrating under age 15 years acquire the lower risk of their new residence. Furthermore, several low-to-high studies show that those migrating in childhood or adolescence increase the risk of MS.

The migrant data, plus the geographic distributions, serve to define MS as an acquired, exogenous (environmental) disease whose acquisition in ordinary circumstances takes place years before clinical onset. The data fit best the "simple" or "prevalence" hypothesis: that the cause of MS will be found where the clinical disease is common. Further evidence for this viewpoint is provided by the occurrence of two epidemics of MS: one (definite) in the Faroe Islands, the other (probable) in Iceland. Both followed the occupation of those lands by British forces during World War II. If this relation is causal, MS is not only acquired but also transmittable.

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Epidemiologic contributions to multiple sclerosis: An overview

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Epidemiology. For over a century, multiple sclerosis (MS) has intrigued workers in all the neural sciences, but it still remains a disease of unknown cause, inadequate treatment, and unpredictable outcome. To attack all these areas of ignorance, a number of investigators have turned to epidemiology.

One definition of epidemiology is the study of the natural history of disease. Its content and uses are described in figure 1. The epidemiologic unit is a patient with a diagnosed disorder. The basic question, after diagnosis, is how common the disease is, and this in turn is delineated by measures of the number of cases (numerator) within defined populations (denominator). These ratios, with the addition of the time factor to which they pertain, are referred to as rates. The population-based rates in common use are the incidence rate, the mortality rate, and the prevalence "rate." All are ordinarily expressed in unit-population values. For example, 10 cases among a community of 20,000 inhabitants represents a rate of 50 per 100,000 population, or 0.5 per 1000 population.

The incidence or attack rate is defined as the number of new cases beginning in a unit of time within the specified population. This is usually given as an annual incidence rate in cases per 100,000 population per year. The date of onset of clinical symptoms ordinarily decides the time of accession, although occasionally the date of first diagnosis is used.

The mortality or death rate refers to the number of deaths with this disease as the underlying cause occurring within a unit of time and population, and thus an annual death rate per 100,000 population. *The case fatality ratio* refers to the proportion

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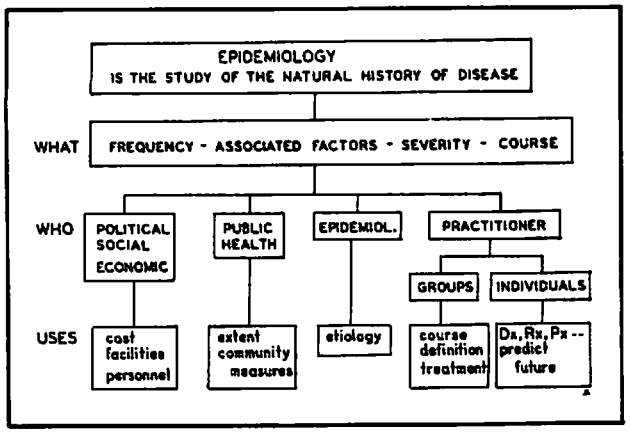

Figure 1. Epidemiology: content and uses. From Kurtzke (1974).[1]

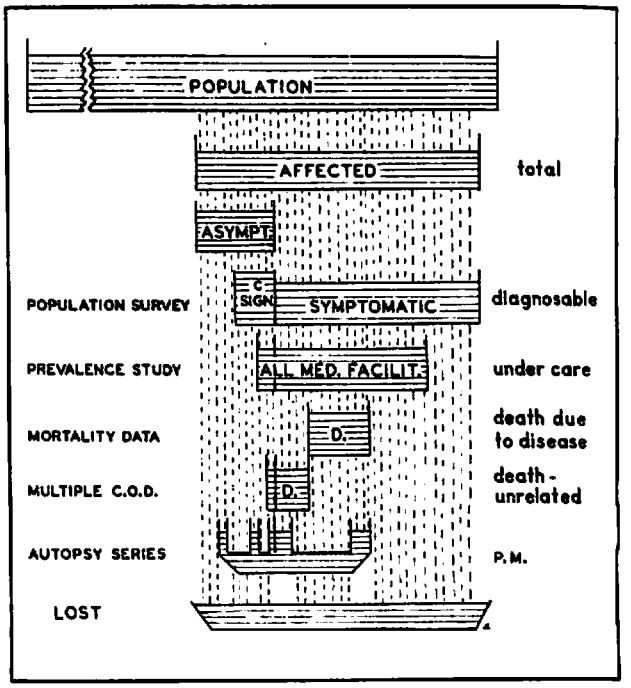

Figure 2. Catchment diagram of case ascertainment of disease within a population. From Kurtzke and Kurland (1973).[2]

of the affected who die from the disease. When this is high, as in glioblastoma multiforme, accurate death rates reflect the disease well. When it is low, as in epilepsy, death data may be strongly biased.

The point prevalence "rate" is more properly called a ratio and refers to the number of affected within the community at one point in time, again expressed per unit of population. If there is no change in case fatality ratios or annual incidence rates over time (and no migration), the average annual incidence rate times the average duration of illness in years equals the point prevalence rate.

When the numerator and the denominator refer to the entirety of a community, their quotient is a *crude rate, all ages,* for the entity in question. When both terms of the ratio are delimited by age, sex, color, or other criteria, we are speaking of *age-specific, sex-specific,* or similar rates.

Because different communities will differ in their age distributions, the proper comparisons among communities are for the age- (and sex-) specific rates. Such comparisons become unwieldy when more than a few surveys are considered, and the proper step then is the calculation of *age-adjusted* rates. One method of age adjustment is to take the age-specific rate for each age group from birth on and multiply it by a factor representing the proportion of a standard population that this same age group contains. The sum of these individual adjusted figures provides an *age-adjusted rate, all ages,* or a *rate all ages, adjusted to a standard population.* One standard population often used is that of the United States for a censal year. This method is important when dealing with common disorders that affect primarily either end of the age spectrum. It is less indicated when considering rare entities that have no notable age (or sex) predilection.

Both incidence and prevalence rates of diseases are derived from surveys for the disease in question as it occurs within circumscribed populations. Mortality rates come from official published sources. Characteristics of the diseased in terms of associated factors, course, and treatment should come from the population prevalence studies as well, but much of our current information on these aspects is actually derived from case series from hospitals.

Figure 2 is a diagram reflecting how cases of a given disease are ascertained within a community. Within the finite resident population, there will be at any one time a finite number of persons affected with the disease. As is true of almost every illness, some of these will be asymptomatic, whereas a proportion will have symptoms appropriate to the condition. Among the asymptomatic, a subset will have abnormalities discoverable by examination or laboratory methods, whereas the remainder will then be, by all known criteria, free of disease even though affected. By examining the entirety of the population or an appropriate sample thereof, one can discover the symptomatic and abnormal asymptomatic cases. This is called the population survey in figure 2 and has been used for common diseases, but it is impractical for rare entities. What has generally been done in neurology is the ascertainment of all the affected who have come to medical attention. This I have loosely referred to as the "prevalence study" rather than a true "population survey."

One step still further removed from complete enumeration of cases is a listing of deaths that the disease has caused. Such data originate in death certificates, specifically that item written thereon

as the "underlying cause of death." On the standard certificate there are also places for "contributory causes of death" and "associated conditions." In selected instances they too can be obtained, and they provide another (undefined) fraction of the affected. The (underlying) cause of death on the official death certificate is coded according to a three- or four-digit number, which represents a specific diagnosis within the International Statistical Classification of Diseases, Injuries, and Causes of Death (ISC). In the United States, a slightly altered version known as the ICDA is used. The ISC is revised every 10 years, and the last two revisions—the eighth and the new ninth—each had major changes over prior editions.

The autopsy series is really a subset of hospital case series, with all the biases implicit in such material.[3] To these are added its own unique biases. Even if all autopsies are collected from all the resources of the community (including the medical examiner), they will still represent a very fragmentary portion of the affected. In most areas, far from all the deceased are subject to postmortem examination (selection bias). Of pertinence to neurology, not all autopsies done include the examination of the brain by neuropathologists, and the spinal cord is seldom included. Aside from that, we must accept that the autopsy series is limited to some who die because of the disease, plus some who die with the disease known but for other reasons, plus some who die with the disease clinically manifest yet undiagnosed, plus some in whom the disease would have been impossible to determine during life.

At every step along this pathway, then, we must miss a proportion of the affected. And the further we get from a true survey of the subject population, the larger this proportion will be—and the more undefinable its setting within the range of the illness.

In the period since World War II especially, there have been an increasing quantity and quality of works designed to define the natural history of MS. Thus, we do have today some useful information on survival, risk factors, and prognostic features. Here, though, we shall concentrate on the geographic distribution of MS and what it seems to tell us.

It is well to recall that in virtually all series of MS cases, whether defined for the laboratory or for an epidemiologic inquiry, we are dealing with a clinical diagnosis without recourse to a pathognomonic diagnostic test or to pathologic verification. A number of schemes for diagnostic criteria have been put forth, none with universal acceptance. In almost all of these, however, there are several grades relating to the degree of confidence in the correctness of the label. If we limit attention to the classes considered "best," and discard "possible MS" and "uncertain MS," we do in fact have defined groups that are quite similar one to another in time and space. Thus, the assessments that follow are based upon series of cases variously labeled "definite," "clinically definite," and "probable" MS.

Geographic distribution of MS. The geographic distribution of MS has been best delineated from prevalence surveys, whose number at present is approaching 200. Almost all have been performed since World War II. In 1975, I tried to collect all such studies and to rate them as to quality.[4]

Figure 3 shows the studies then available for Western Europe, with the prevalence rates per 100,000 population for "probable MS" correlated with the latitude of the locus of the study.[4] The solid circles are what I consider Class A studies, which represent proper surveys with well-defined and reasonably comparable methodology and diagnostic standards. Those I rate Class B (open circles) are good surveys, but there are reason(s) why they are not fully comparable to those of Class A. Surveys denoted by diamonds are Class C. They have obvious defects that make them unreliable. Open boxes are Class E surveys, which represent an estimate of the prevalence from the ratios of MS to amyotrophic lateral sclerosis (ALS) cases in series from hospitals. Taking this ratio and a likely prevalence for ALS of 5 per 100,000, we can calculate estimated prevalence rates for MS. The vertical bars in the figures define the 95% confidence intervals for each rate. Thus, if the cited rate arose from a random sample of its parent universe, the "true" rate for this universe would be found to lie within this interval 19 times out of 20. Therefore, one should not pay too much attention to the precise digits for any given rate.

It seems to me that in Western Europe MS is distributed according to latitude within two clusters: a high-frequency zone with prevalence of some 30 to 80 (or more) per 100,000 population extending from about 43° to 65° north latitude, and a medium-frequency zone with prevalence of some 5 to 25 per 100,000, and mostly 10 to 15, from about 38° to 46° N. Later surveys have in essence confirmed this distribution.[5] This includes eight new studies from Italy and Sicily. Kelly and Dean,[6] however, have reported a prevalence of 52 per 100,000 with 15 cases from a small city in Sicily.

Similar prevalence data for Eastern Europe are shown in figure 4. Note the relative paucity of good-quality studies. There still seems to be a disposition of rates into the same two frequency zones—high from about 45° to 65° and medium from 32° up to possibly 50°—but latitude alone does not serve fully to separate the two. As to later information, we do have available a good study from Bucharest, Romania. The prevalence for probable MS was 41 per 100,000 with 798 patients

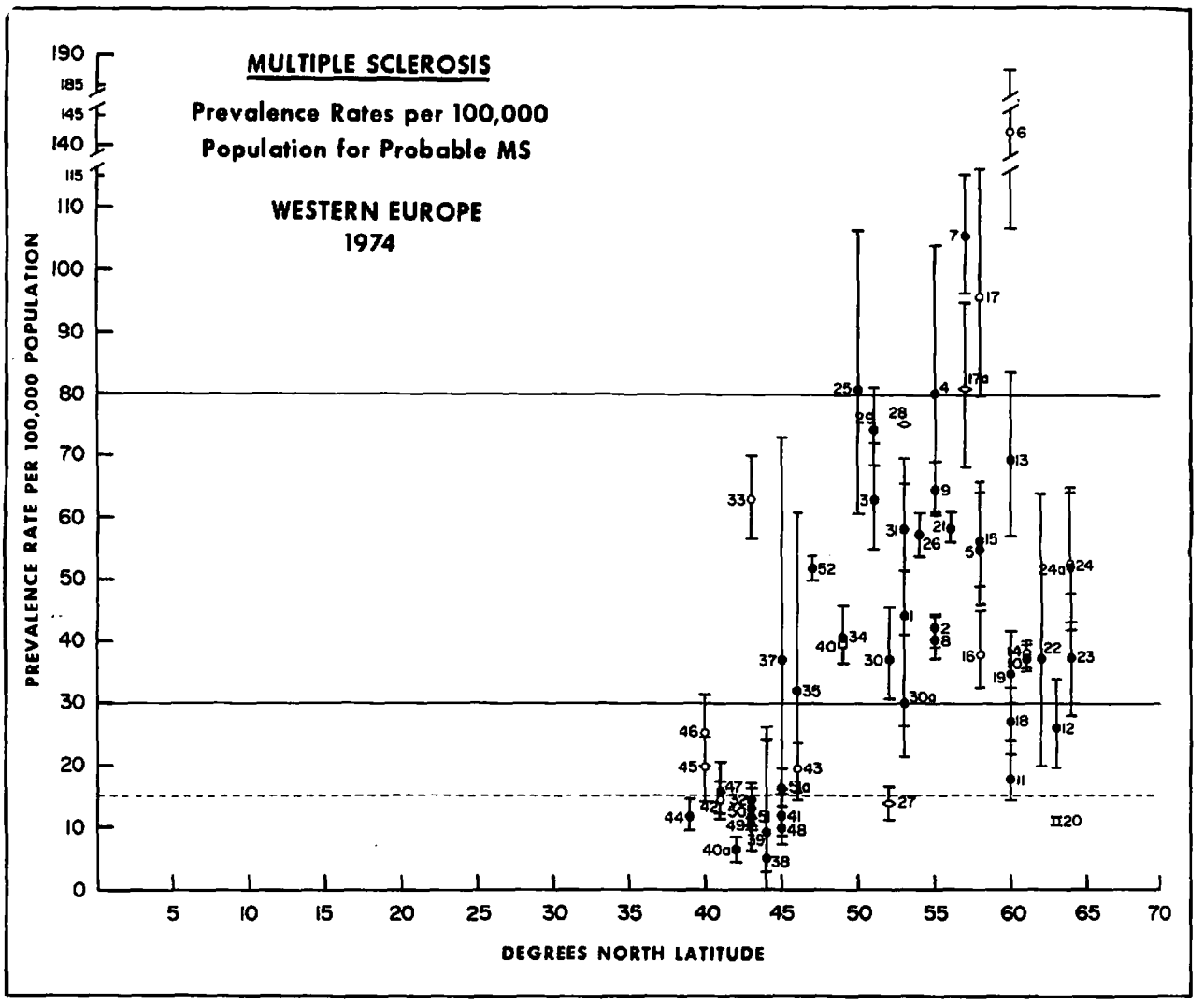

Figure 3. Prevalence rates per 100,000 population for probable MS in Western Europe, correlated with geographic latitude. Numbers identify the survey in Kurtzke (1975).[4] Solid circles represent Class A studies, open circles Class B, diamonds Class C, and squares Class E. Vertical bars define 95% confidence intervals on the rates. From Kurtzke (1975).[4]

as of January 1977.[7] Bucharest lies in southern Romania at 44° N. In the northwestern part of its western neighbor, Yugoslavia, the Rijeka region is at 45° N. This area provided a prevalence of 32 per 100,000 with 95 probable MS on December 31, 1969.[8]

Data were presented previously to indicate clustering of MS in Switzerland and Scandinavia, and the statement was made that the disorder in the latter region comprises a "Fennoscandian focus" extending from the waist and southeastern plains of Norway across the southern part of Sweden to southwestern Finland, and thence back to Sweden near Umeå.[9] This focus is taken to define the northern boundaries of high MS in Europe.

The geographic distribution of MS in Europe may thus be considered to follow the pattern of figure 5. The high-frequency region of Northern Europe is rather sharply separated, both north and south, from a medium-frequency area. The more recent studies suggest that the high-risk zone may include not only that part of the Balkans to the south of the dotted line but also its extension from the head of the Adriatic Sea to the Black Sea. This is based on the recent Romanian and Yugoslavian works.[7,8]

Prevalence surveys from the Americas are denoted in figure 6. Here we see all three risk zones: high-frequency from 37° to 52°, medium-frequency from 30° to 33°, and low-frequency (prevalence less than 5 per 100,000) from 12° to 19° and from 63° to 67° north latitude. The coterminous United States and southern Canada are represented by all the surveys from Number 88 to 119a, except for Numbers 106 (Greenland), 109 (Jamaica), 113 (Alaska), 117 (Netherlands Antilles), and 118 (Mexico City).

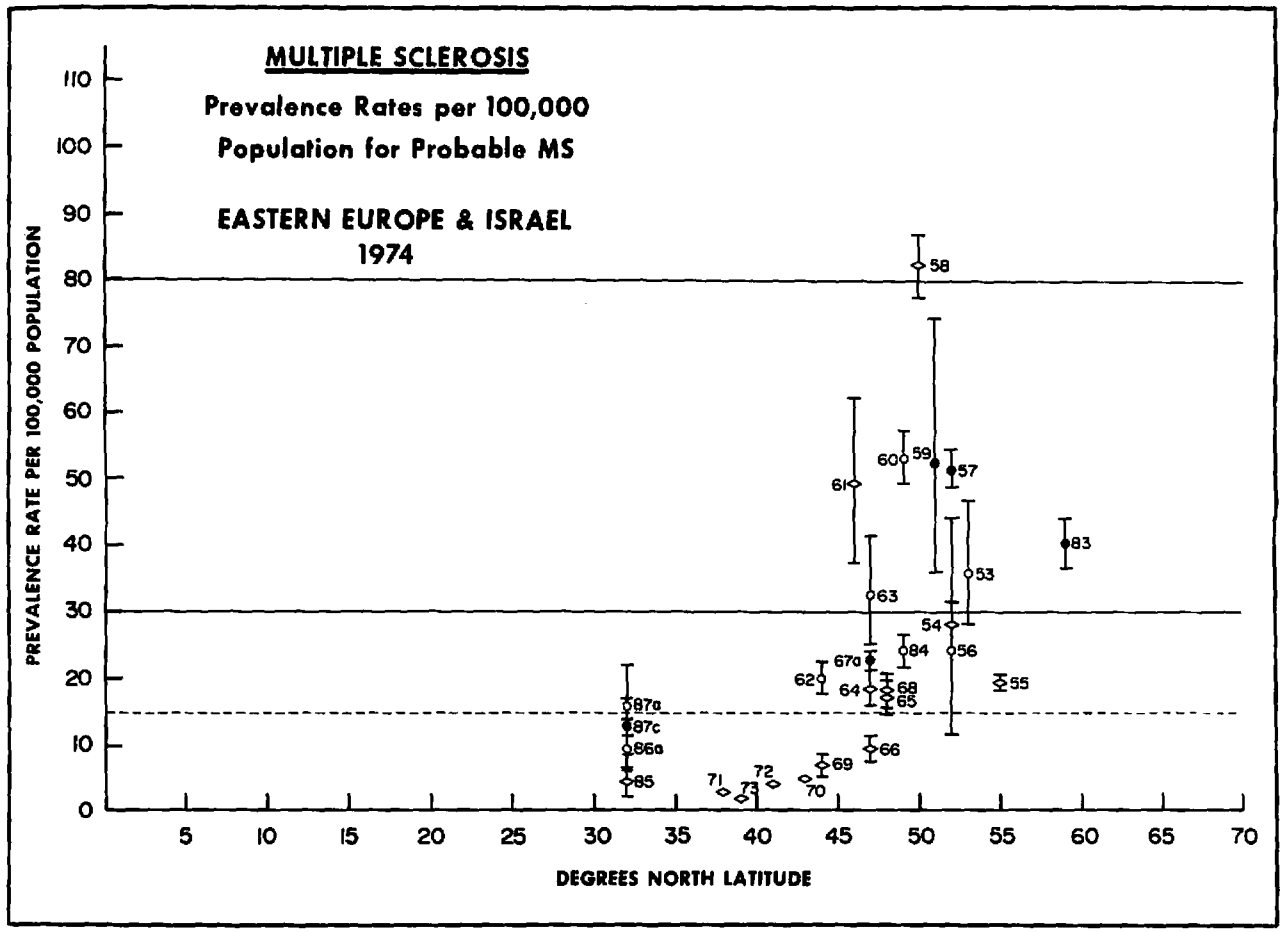

Figure 4. Prevalence rates per 100,000 population for probable MS in Eastern Europe and Israel, as in figure 3. From Kurtzke (1975).[4]

The Alaskan rate of 0 refers to natives of that state. The prevalence rates for the northern United States and southern Canada, then, are quite similar to the high frequency rates of Western Europe. Note that there are no data referable to South America.

However, Christiansen[10] has published prevalence estimates for several regions of that continent, based on the ratio of MS to ALS cases seen at major clinics in Buenos Aires, Tucamán, and Mendoza, Argentina, and in Montevideo, Uruguay, and Lima, Peru. All but the last gave estimated prevalence rates of 15 to 21 per 100,000; in Lima the estimate was 5, using an expected prevalence of 5 per 100,000 for ALS. Thus, it would seem that South America from 36° south latitude as far north as perhaps 12° south might fall within the medium-prevalence zone for MS.

In the United States, the modest number of prevalence surveys in figure 6 leaves much of the country undefined as to the distribution of MS. Visscher et al[11] recorded a prevalence of 69 per 100,000 for probable MS among 399 native-born whites of King and Pierce Counties, Washington, and 22 among 356 whites of Los Angeles County, California, as of April 1970. These rates confirm the high-north and medium-south partition of the country but still leave wide gaps in our knowledge. However, by taking advantage of our recent history, we can provide a rather detailed delineation of the disease throughout the United States.

In the World War II period, some 16.5 million Americans served in the armed forces. In the Korean conflict there were 6.8 million, including 1.5 million who had also served in World War II. Veterans of these wars who are judged "service-connected" for MS provide a nationwide series of unprecedented size. "Service-connection" requires evidence of disease either during or within 7 years after discharge from the military service. By matching these individuals with their military peers, we then have a large, national, unbiased, preillness case-control series.

Table 1 summarizes our series of 5305 cases and matched controls by sex and race.[12] In figure 7 are the case-control ratios for white males in World War II according to state of residence upon entry into service. Note the strong north-south gradient. This distribution is quite similar to that for death rates in the United States.[2]

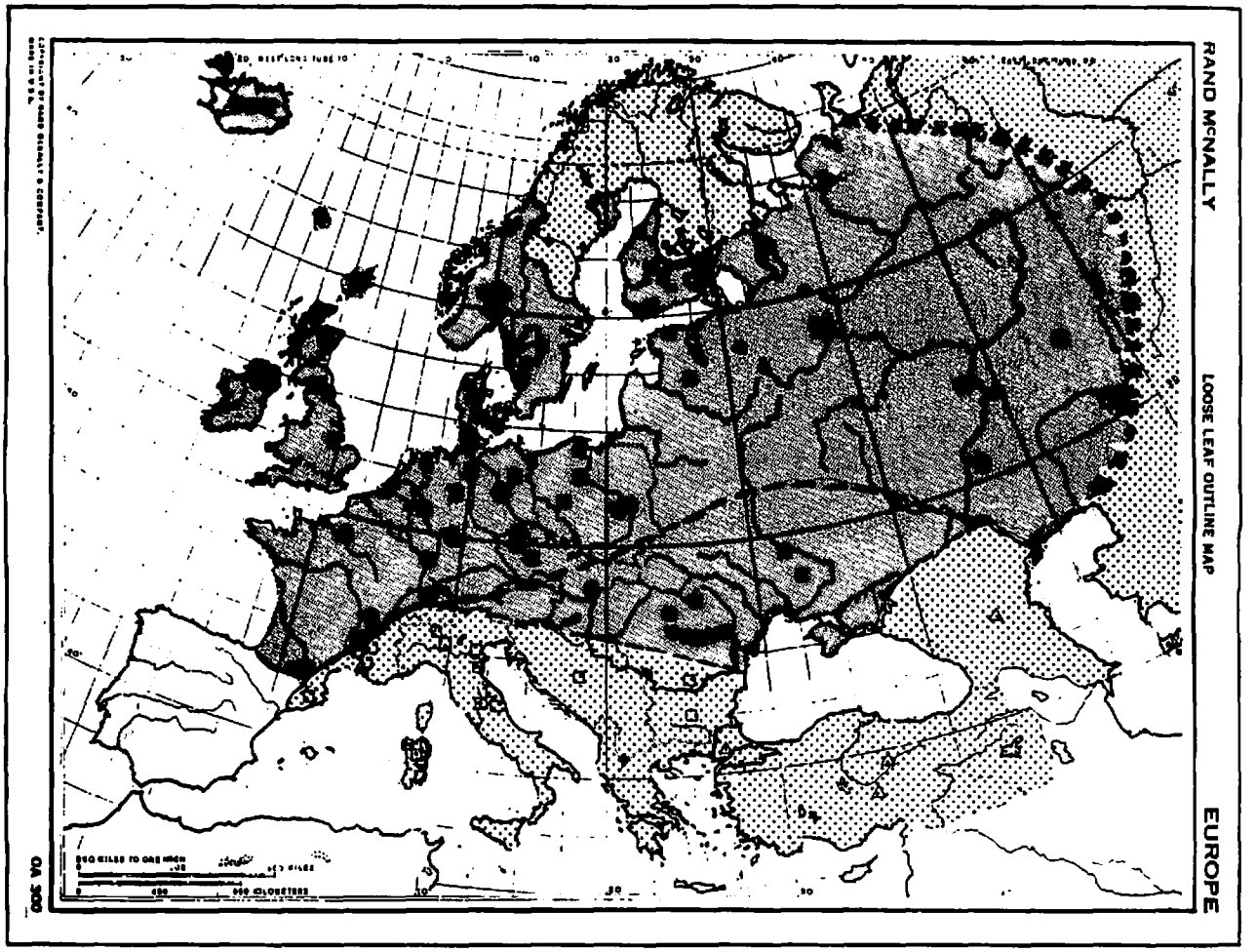

Figure 5. MS prevalence zones of Europe as of 1974 with survey sites spotted on the map. Heavy shading represents high-frequency MS (prevalence, 30 or more per 100,000); dotted shading, medium-frequency MS (prevalence, 5 to 25); no European area is low (prevalence, 0 to 4). Solid squares are high-frequency rates, open squares medium-frequency, and triangles likely but not surely medium-frequency. Dashed line may be the proper dividing line between high and medium, but later data suggest a line more southerly than even the solid line, and extending from the northern Adriatic to the Black Sea. Surveys are listed reagrdless of quality. From Kurzke (1977).[3]

Returning to the international prevalence studies, we see that Australia-New Zealand include principally a high-frequency zone for 44° to 34° south latitude and a medium-frequency region for 33° to 15° south (figure 8). The recorded rates that are considered high, though, are toward the lower end of this range.[4]

Rates from Asia and the Pacific in the northern hemisphere are all low, except that Hawaii (Numbers 145 and 146) is likely to be in the medium zone (figure 9). These study sites extend from 8° to 47° north latitude. Later hospital series in Asia and prevalence studies in Japan indicate that there is no site in Asia that has thus far been demonstrated to have more than a low frequency for MS.[5]

In the southern hemisphere, with surveys from 30° to 6° south, all rates from Asia and Africa are also low, except for English-speaking native-born whites (Number 156) of South Africa (figure 10). Their rate of 11 contrasts with that of 3 for the Afrikaans-speaking native-born whites, a difference still without an explanation. It should be noted, though, that over the entirety of this vast continent, there are data otherwise available only for Ethiopia, Natal, and Senegal. In particular, there is no information on the Mediterranean littoral, where some recent hospital data from Tunisia suggest a prevalence rate within the medium-risk range.[5] Ben Hamida and Samoud[13] reported seeing about 50 new cases of MS a year in their neurologic clinic in Tunis, an area of perhaps 700,000 population.

We may thus consider the worldwide distribution of MS as presently known to comprise three zones of frequency or risk. The high-risk zone, with prevalence rates over 30 per 100,000 population, includes Northern Europe, the northern United States and southern Canada, New Zealand, and

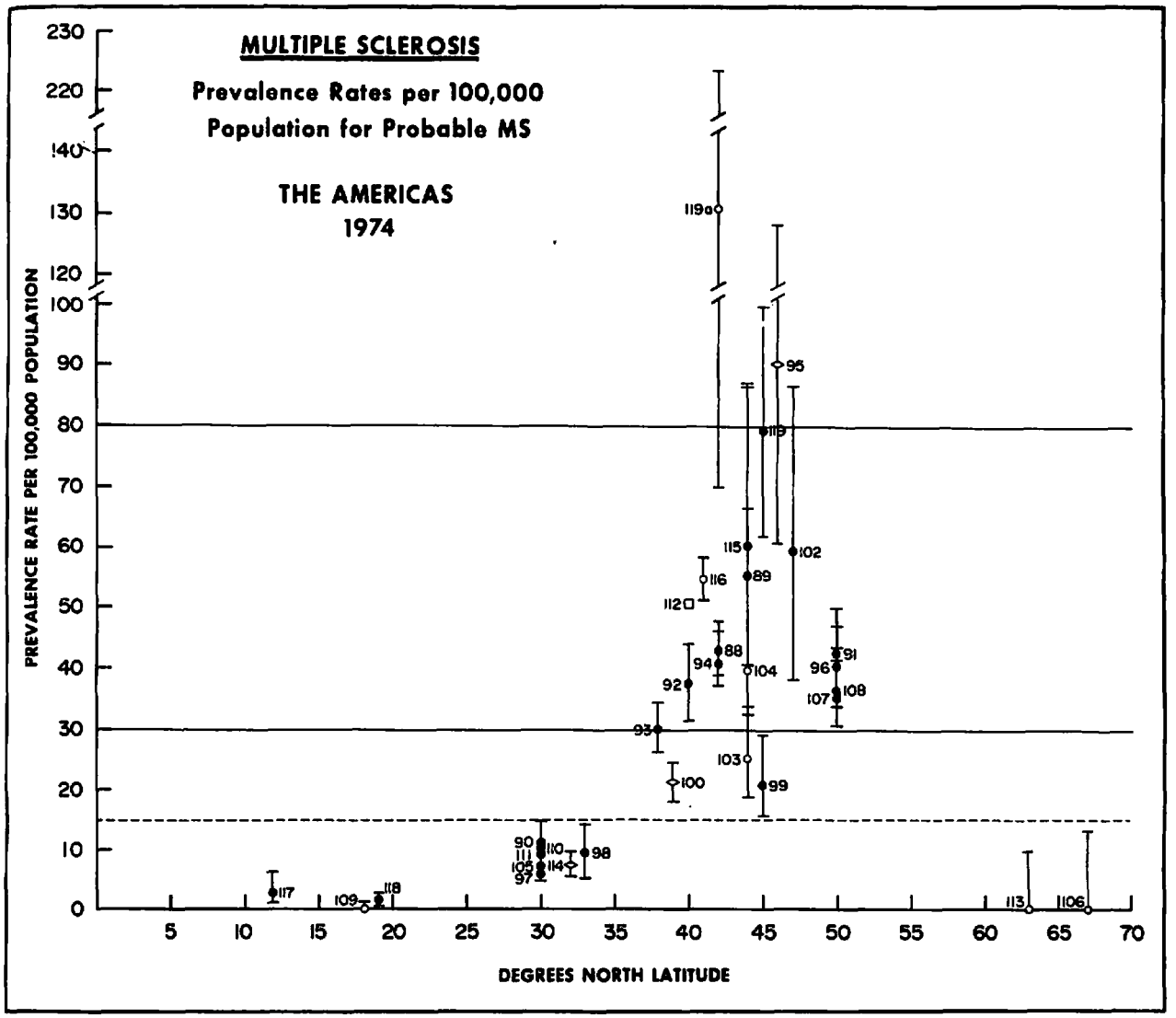

Figure 6. Prevalence rates per 100,000 population for probable MS in the Americas, as in figure 3. From Kurtzke (1975).[4]

Table 1. Multiple sclerosis: Case/control ratios by race and sex for veterans of World War II and/or Korean conflict "service-connected" for MS[12]

Race and sex	Ratio	Case/control
White male	1.04	4923/4741
White female	1.86	182/98
White total	1.05	5105/4839
Black male	0.45	177/390
Black female	1.33	4/3
Black total	0.46	181/393
Other male	0.23	17/73
Other female	—	2/—
Other total	0.26	19/73
All male	0.98	5117/5204
All female	1.86	188/101
All total	1.00	5305/5305

southern Australia. These regions are bounded by areas of medium frequency, with prevalence rates between 5 and 25 per 100,000. Asia, Latin America, and almost all of Africa are of low frequency, with prevalence rates less than 5 per 100,000, but much of Africa and all of South America remain unknown from formal prevalence studies (figure 11).

Race. All the high-risk and medium-risk areas for MS have predominantly white populations. Regardless of residence in the United States, in our veteran series, blacks or Negroes have only half the risk of white males (table 2). The group consisting of the "Other" races suggests a paucity as well in American Indians and in Orientals (table 3). Detels et al[14] in California have presented good evidence for a low prevalence among Japanese-Americans. The apparent deficit we found among

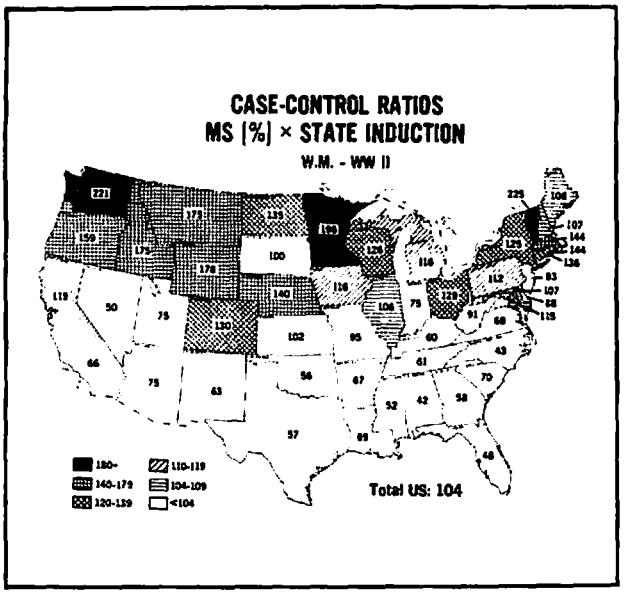

Figure 7. Case-control ratio percentages for MS according to state of residence at entry into active duty (EAD): white males of World War II. Data of Kurtzke, Beebe, and Norman (1979).[12]

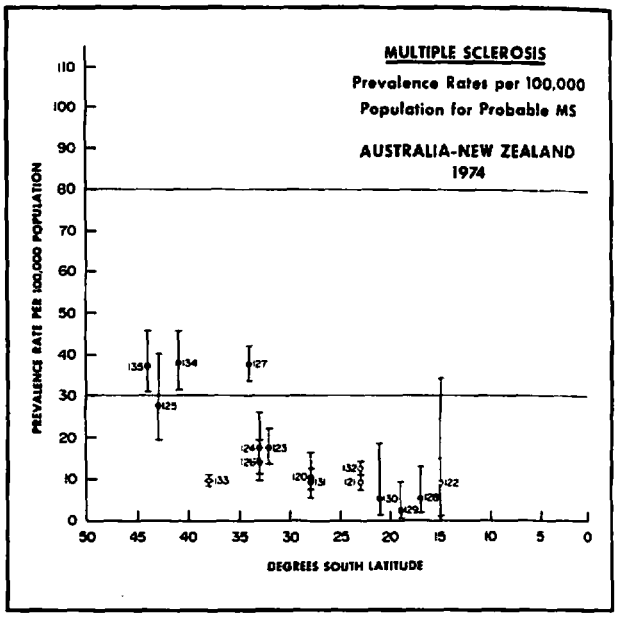

Figure 8. Prevalence rates per 100,000 population for probable MS in Australia-New Zealand, as in figure 3. From Kurtzke (1975).[4]

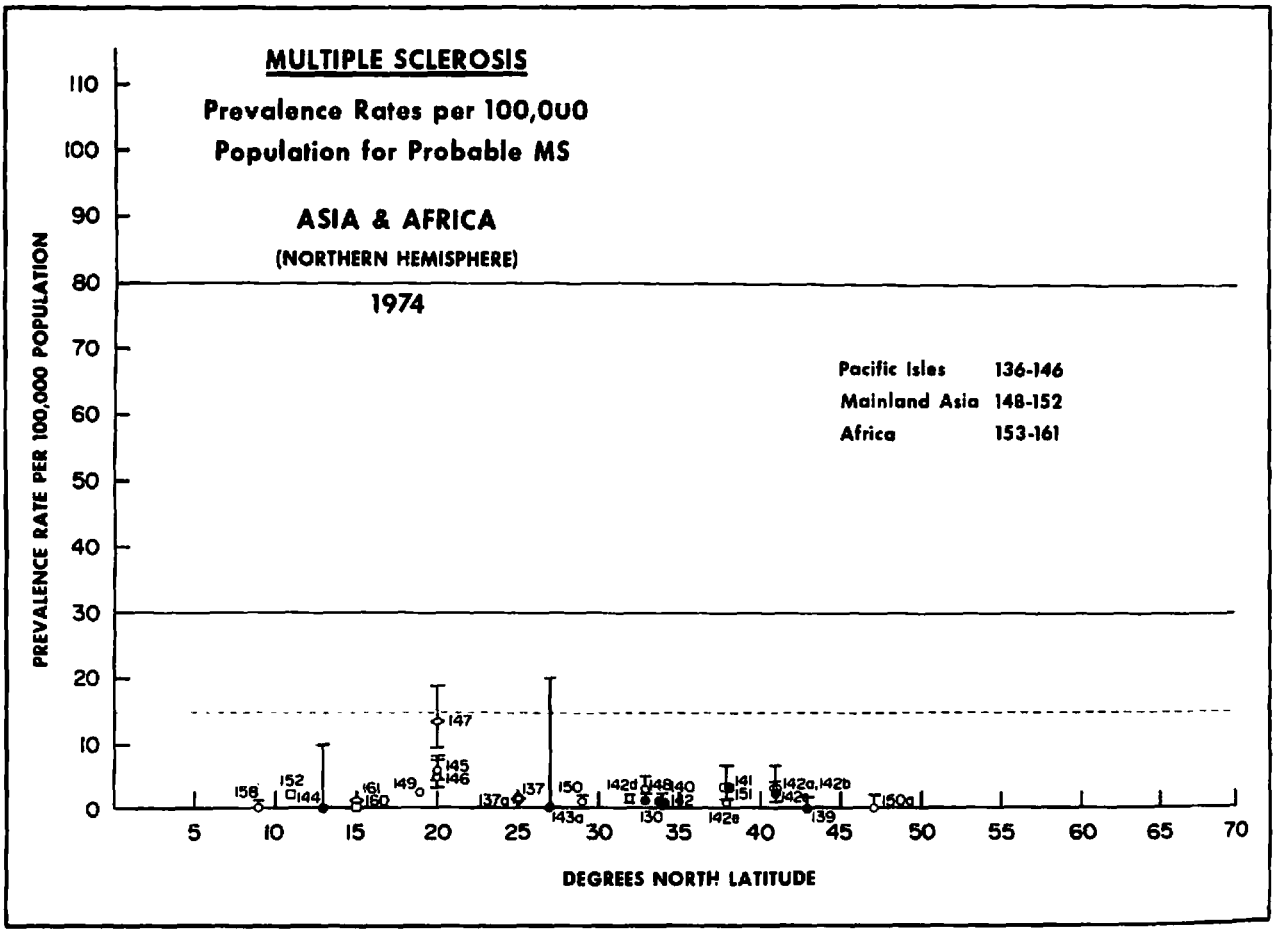

Figure 9. Prevalence rates per 100,000 population for probable MS in Asia and Africa (northern hemisphere), as in figure 3. From Kurtzke (1975).[4]

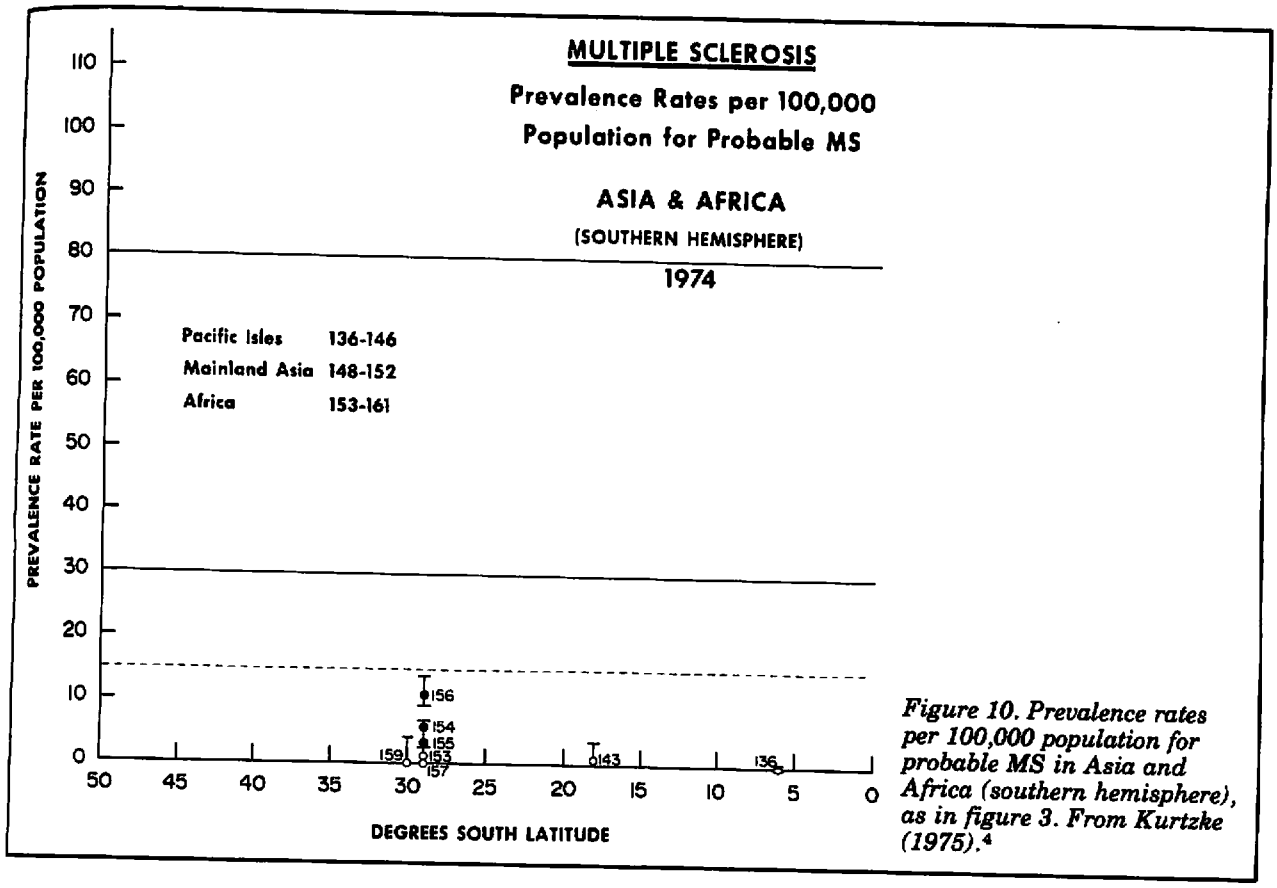

Figure 10. Prevalence rates per 100,000 population for probable MS in Asia and Africa (southern hemisphere), as in figure 3. From Kurtzke (1975).[4]

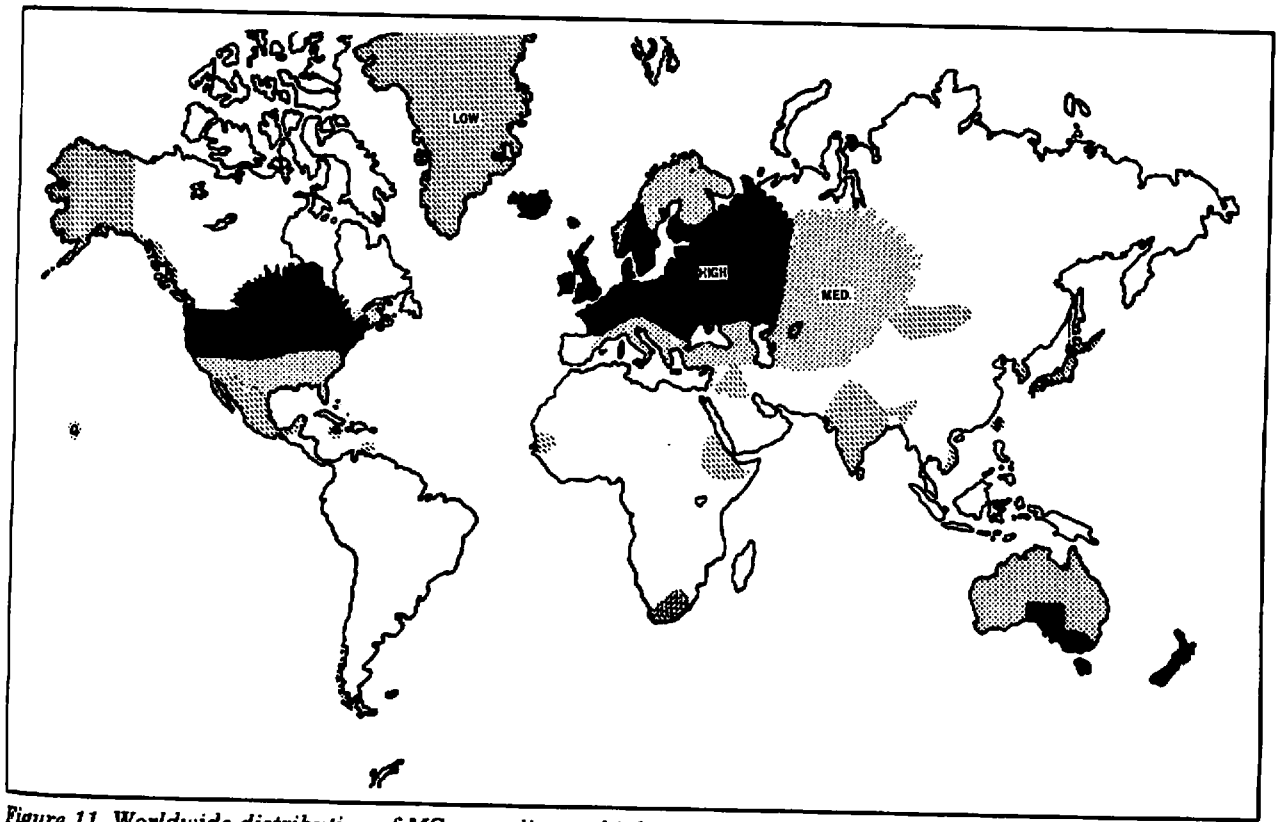

Figure 11. Worldwide distribution of MS according to high- (solid), medium- (dotted), and low- (diagonal dashed) risk areas as of 1974. The high-risk area of Europe may reach the head of the Adriatic Sea in the Balkans. From Kurtzke (1979).[5]

Table 2. Multiple sclerosis: Case/control ratios by tier of residence at entry into active duty (EAD) for the major sex and race groups, entire series[12]

Sex and race	Tier of residence at EAD			
	North	Middle	South	Total*
		(MS/C Ratio)		
White male	1.41	1.02	.58	1.04
White female	2.77	1.71	.80	1.86
Black male	.61	.59	.31	.45
Total series†	1.41	1.00	.53	1.00
		(MS/Control)		
White male	2195/1544	2059/2022	668/1161	4922/4737
White female	97/35	65/38	20/25	182/98
Black male	28/46	88/150	61/194	177/390
Total series†	2323/1647	2213/2219	762/1425	5298/5291*

* Excludes 1 male case and 11 male controls inducted in foreign countries.
† Includes Black females and Other (nonwhite, nonblack) persons.

Table 3. Multiple sclerosis: Case/control ratios for "other" males by birthplace and race, entire series[12]

Birthplace and race	Ratio	Case/control		
		Total	N*	S*
Coterminous United States	0.48	11/23†	6/12	5/11
Amerindian	0.38	3/8	3/6	0/2
Mexican—Spanish American	0.60	6/10	1/1	5/9
Japanese	0.50	2/4	2/4	0/0
Mexico, Latin America, total	0.29	6/21		
Mexican—Spanish American	0.00	0/5		
Puerto Rican	0.38	6/16		
Hawaii, total	0.00	0/15		
Japanese	0.00	0/10		
Other	0.00	0/5		
Asia, total	0.00	0/14		
Chinese	0.00	0/4		
Filipino	0.00	0/9		
Other	0.00	0/1		
Total	0.23	17/73		

† Includes 1 Filipino control.
* N = Northern and middle tier of birth, S = Southern. For white males, the MS/C ratios are 1.2 N and 0.6 S.

Spanish-Americans would seem more a reflection of geography than of race. This is borne out when comparisons by each race are made among the foreign-born cases in the veteran series (table 4).

Migration. The fate of migrants among regions of differing risk for MS is vital to interpretation of the distribution. Table 5 summarizes material on prevalence rates (all ages) among immigrants to and from different MS risk areas. The rates are calculated regardless of age at immigration and time of clinical onset of MS in reference to migration. In broad terms, the immigrants do tend to retain much of the MS risk of their birthplaces. The evidence for risk retention is better for immigrants from high-risk areas to low than for the reverse, where data are limited.

Information on low-risk to high-risk area migration remains sparse. Dassel[15] recorded three instances of MS among immigrants from Indonesia

Table 4. MS case/control ratios according to race and birthplace in selected regions, entire series[12]

Region	Ratio	Case/control			
		Total	White	Black	Other
Mexico, Central America	0.14	2/14	1/9	1/-	-/5
Puerto Rico	0.42	14/33	6/14	2/3	6/16
Hawaii	0.06	1/16	1/1	-/-	-/15
Japan, Korea	—	4/-	4/-	-/-	-/-
China	0.00	-/4	-/-	-/-	-/4
Philippines, SE Asia	0.00	-/12	-/2	-/-	-/10

Table 5. Prevalence rates per 100,000 population for probable multiple sclerosis among native-born and immigrants[3]

Immigration site according to its MS risk	Native-born	Prevalence rates among immigrants from risk areas		
		High	Medium	Low
High				
(1) So. Australia	38	37	4	...
Medium				
(2) Perth, W. Aust.	40*	87*	...	...
(3) Perth, W. Aust.	14	22	...	...
(4) W. Australia	10	31	...	...
(5) Queensland	9	15	...	...
(6) Israel†	9‡	-----19‡-----		6‡
(7) Israel	4	33	8	3
Low				
(8) South Africa	6	48	15	...
(9) Netherlands Antilles	3	59	...	...
(10) Hawaii†	5	-----35 -----		...

* Age-specific rate, 40 to 49 years.
† May include "possible" MS.
‡ Age-adjusted to 1960 United States population.

to Holland. Their onsets were at ages 17, 23, and 25 years and took place, respectively, 7, 9, and 8 years after their arrival in the Netherlands. They are probably whites of Dutch origin, but neither this information nor the population at risk was provided. Regardless, three cases out of what is likely to be a small migrant group looks impressive. Unfortunately, this group could not be traced any further (Dassel: personal communication, 1977).

Three instances of exacerbating-remitting MS have been found among a series of some 3400 persons who were born in Vietnam of Vietnamese mothers and French fathers and came to France before the age of 20.[16] The three MS patients each had clinical onset about 15 years after immigration, which for them was before the age of 10. The cumulative risk of MS, which was also their prevalence rate, was 89 per 100,000, with a 95% confidence interval of 18 to 260. The age-specific prevalence rate was 169 per 100,000, ages 20 to 29 (confidence interval, 35 to 494). Both measures are rather similar to such rates for Denmark, but the confidence intervals are very wide. Even so, their lower limits are clearly higher for these half-Orientals than are the rates for Vietnamese in Vietnam.

Age of migration. If the risk of MS is defined at or near birth (or the disease is innate), birthplace alone and time of birth would be the critical point, and for low-to-high migrants there would be no increase in the risk of MS. The fact that the latter

is unlikely to be the case has already been indicated, but additional evidence may be found when age of migration is assessed.

In the United States, death rates for MS are distributed so that the states to the north of 37° north latitude have twice the rates of those to the south.[2,3] For MS deaths in the United States from 1959 to 1961, those who exchanged risk areas (between north and south) between birth and death demonstrated an obliteration of the north-south difference, and all death rates were closer to the national mean than were death rates for the nonmigrants. The death rate for US southern-born MS patients who had died in the north (0.68) was significantly higher than the rate for the southern-born who died in the south (0.46). Thus, it would appear that moving north does increase the risk of MS.

Further evidence supporting this point is provided by the veteran case-control series. In table 2, their residences were allocated within three horizontal tiers for the coterminous United States: a northern tier of states above 41° to 42° north latitude, a middle tier, and a southern tier below 37° including California from Fresno south. Migrants would be those born in one tier who entered service from another. In table 6 are the data for white males with World War II service. The marginal totals provide the ratios for birthplace and for residence at service entry. The major diagonal (north-north, middle-middle, south-south) gives the case-control ratios for nonmigrants. Cells off this diagonal define the ratios for the migrants.

All ratios decrease as we go from north to south. This is true for birthplace and for residence at service entry. The nonmigrant ratios are: 1.41 north, 1.04 middle, and 0.56 south. Among the migrants, those born in the north and entering service from the middle tier have a ratio of 1.26; if they enter from the south, their ratio is 0.70, only half that of the nonmigrants. Birth in the middle tier is marked by an increase in the MS:C ratio for northern entrants to 1.30 and a decrease to 0.72 for the southern ones. Migration after birth in the south seems to raise the ratios to 0.62 (middle) and 0.73 (north). The migrant risk ratios are intermediate between those characteristic of their birthplace and those characteristic of their residence at entry.

Therefore, the risk of MS is altered by changing residence between birth and entry into service, and thus well before clinical onset. This is further evidence that MS is an acquired, exogenous, environmental disease, and that it is acquired well before the onset of clinical symptoms. The environmental factor would appear to be either more common or more effective in geographic areas where the disease itself is more common.

From the marginal totals of table 6, residence at birth has about the same gradient of risk as does residence at service entry, and therefore is at about age 24 years for these World War II veterans. For the migrants, there is no clear difference in risk for moves from high-risk to low-risk regions versus low to high. If we assume that migration took place at an even rate between birth and service entry, there are still two hypotheses as to a likely age of acquisition of MS: If the disease is acquired over a short interval, the point midway between birth and age 24 would seem the most reasonable to account for our findings. This would therefore indicate age 10 to 15 years, which would be in accord with other data on migrants (see below). However, the findings are equally compatible with the idea that prolonged or repeated exposure to the presumed pathogen is required for its

Table 6. MS/control ratios for white males in World War II* by tier of residence at birth and at entry into active duty (EAD): United States only[17]

Birth tier	EAD tier			Birth total
	North	Middle	South	
		(MS/C ratio)		
North	1.41	1.26	.70	1.38
Middle	1.30	1.04	.72	1.04
South	.73	.62	.56	.57
EAD total	1.39	1.04	.58	1.04
		(Case/control)		
North	1611/1140	112/89	32/46	1755/1275
Middle	125/96	1544/1482	68/94	1737/1672
South	16/22	42/68	439/788	497/878
EAD total	1752/1258	1698/1639	539/928	3989/3825

* Includes those who also served in Korean conflict.

acquisition, and that what we are seeing here is a dose-response curve to duration of exposure during the earlier years of life. In either event, though, the disease does seem to be acquired well after birth and well before clinical onset.

From ages of maximal clustering of MS in Denmark and several other features, it was "tentatively concluded that [for natives of high-risk areas] the actual onset of MS appears to take place on the average between the ages of 10 and 15 years, and that there is probably a 'latent' or 'incubation' period of some 20 years before the onset of clinical symptomatology."[18] Even more precise were the results of a survey of European immigrants to South Africa.[19,20] The MS prevalence rate, adjusted to a population of all ages, was 13 per 100,000 for immigration before age 15, which is the same medium-prevalence rate as for the native-born English-speaking white South Africans. But for all older age groups, the prevalence was some 40 to 80 per 100,000, the same as expected from their high-risk homelands. This change was sharp and occurred exactly at age 15 years.

Two other high-to-low migrant surveys also suggest, though with small numbers, that age 15 divides those who retain the risk of their birthplace from those (younger) who acquire a lower risk. These pertain to immigrants to Israel[21] and Hawaii.[22] On low-to-high migration, Alter, Kahana, and Loewenson[23] have suggested that Afro-Asian immigrants arriving in Israel before the age of 5 years have age-specific incidence rates similar to rates for immigrants from Europe, whereas those arriving beyond age 5 tend to differ: European rates appear higher. However, the number of cases, especially for those under age 15 at immigration, would appear too small for meaningful interpretation.

There are, however, major problems with migration studies. "The question of risk of MS in migrant populations gets very involved, being dependent not only on a sufficiency of people who change their residence from one risk area to another but also on their ages at immigration, their length of stay in the new land, *and* their ages at prevalence day.... Another problem further to confound the issue is the apparent racial predilection for MS, regardless of geography...."[24]

The true population at risk according to age at survey, age at migration, and age at clinical onset can be very difficult to define, and the choice of denominator—or the type of rate required (incidence, prevalence, death, or cumulative risk)—can get very involved. In addition, the desired population denominator is generally not available from routine sources.[5]

Risk of MS. It was particularly to attack the problems of migrants that I attempted to provide, for one area at least, estimates as to the risk of MS by age, sex, and interval.[25] Table 7 gives a summary of the period risk for MS in Denmark by age at entry for both sexes combined. The cumulative lifetime risk from birth is 201 per 100,000, or 1 chance in 500. At age 20, the risk of MS beginning within the next 5 years is 34 per 100,000. After 20 years this figure is 142, and after 30 years it is 181. Conversely, at age 10 the 5-year risk is only 2 per 100,000 and the 20-year risk is 92. By 30 years, it reaches 159. For entrants age 50, the lifetime risk of 13 per 100,000 is attained within 10 years.

If we assume that the duration of MS is constant regardless of geography, the ratios of prevalence

Table 7. Period cumulative risk of multiple sclerosis in Denmark: Approximate number of new cases expected by period per 100,000 population of given age at entry, both sexes combined*

	Period						
Age entry	5 yr	10 yr	15 yr	20 yr	25 yr	30 yr	Lifetime
0	0	2	4	20	52	89	201
5	2	4	21	54	94	128	211
10	2	19	53	92	126	159	210
15	17	51	90	125	158	181	209
20	34	74	109	142	165	181	193
25	40	75	108	131	148	157	160
30	35	69	92	108	118	120	120
35	34	58	74	83	86	86	86
40	24	41	50	53	53	53	53
45	17	27	30	30	30	30	30
50	10	13	13	13	13	13	13
55	3	3	3	3	3	3	3
60	0	0	0	0	0	0	0

* Data of Kurtzke (1978).[25]

Table 8. MS: Number of cases per 100,000 population expected to develop in given intervals among a disease-free cohort of a high-risk populace*

Interval (years)	Cases per 100,000
5	14.1
10	28.8
15	44.4
20	61.3
25	77.9
30	92.2
life	121.2

* Risk estimates for Denmark applied to 1960 US population distribution.

rates in different areas are equivalent to the ratios of incidence rates. Then too, such ratios can also be applied to these risk estimates. In this case, if 100,000 Japanese were to migrate to Denmark at age 10, they would be expected to provide 4 MS cases after 20 years if they retained the low risk of their birthplace, but there would be 92 cases if they acquired the high risk of Denmark.

More informative might be a statement as to the number of cases expected to occur within given intervals among a disease-free sample of the general population. Table 8 presents such figures derived from the Danish risk estimates and the 1960 US population distribution.[5] In 5 years there will be only 14 cases per 100,000 population, or some 12% of the total anticipated. After 20 years we will have accumulated only half the total cases expected. It is this kind of information that must be borne in mind when trying to interpret data for MS among migrants.

MS epidemics. There has been in the past no reason to consider that MS has occurred in the form of epidemics. All known geographic areas that had been surveyed at repeated intervals have provided either stable or increasing prevalence rates, the latter compatible with better case ascertainment and perhaps improved survival. The incidence of MS has been stable over 25 years in Northern Ireland[26] and over 60 years in Rochester, Minnesota.[27] Epidemics of MS would serve to define the disease as not only acquired but also transmittable.

We seem to have encountered two separate epidemics of MS, which in fact may have common precipitants and which occurred in the ethnically similar lands of the Faroe Islands and Iceland.

The Faroes are a group of small islands lying between Norway and Iceland at 62° north latitude and 7° west longitude. The population in 1978 was approximately 42,000. Beginning in 1972, Kay Hyllested of Copenhagen and I have been attempting to ascertain all instances of known or suspected MS that had occurred in the Faroes. As of July 1977, there were 78 potential cases found. Among these were 25 native-born resident Faroese with our diagnosis of MS.[28] In clinical characteristics they were similar to other series of MS patients, but their occurrence over time showed striking anomalies.

Taking the living cases at various dates, there were marked variations in the prevalence rates. In 1950 the rate was 41 per 100,000 population; in 1961 it was 64; in 1972, 38; and in 1977, 34 per 100,000 (table 9). For 1939, the prevalence was 0. Even more discrepant from other series were the durations of illness at these prevalence days. There was a mean duration of 4 years in 1950, 10 years in 1961, 20 years in 1972, and 25 years in 1977. The mean ages of the patients at prevalence day also rose with time, though less steeply, from 31 years of age in 1950 to 48 in 1977.

Plotting these cases by calendar year of onset gave good evidence that in the Faroes, MS has suddenly appeared, and suddenly disappeared

Table 9. MS in the Faroes: Some characteristics of the MS series, accepted cases, as of various prevalence days[28]

	Prevalence day*				
Characteristic	1939	1950	1961	1972	1977
Number of cases	0	13	22	15	14
(number of males)	—	(7)	(12)	(6)	(6)
Prevalence rate per 100,000	—	40.9	63.6	38.3	33.7
Mean age at P.D.	—	30.85 –	35.73	42.67	48.43
Mean age at onset	—	26.85 –	25.32	23.07	23.71
Mean duration (yrs)	—	4.00	10.41	19.60	24.72
Time of onset:					
Mean	—	7/46	11/50	11/52	9/52
Median	—	1946	1949	1951	1951

* July 1.

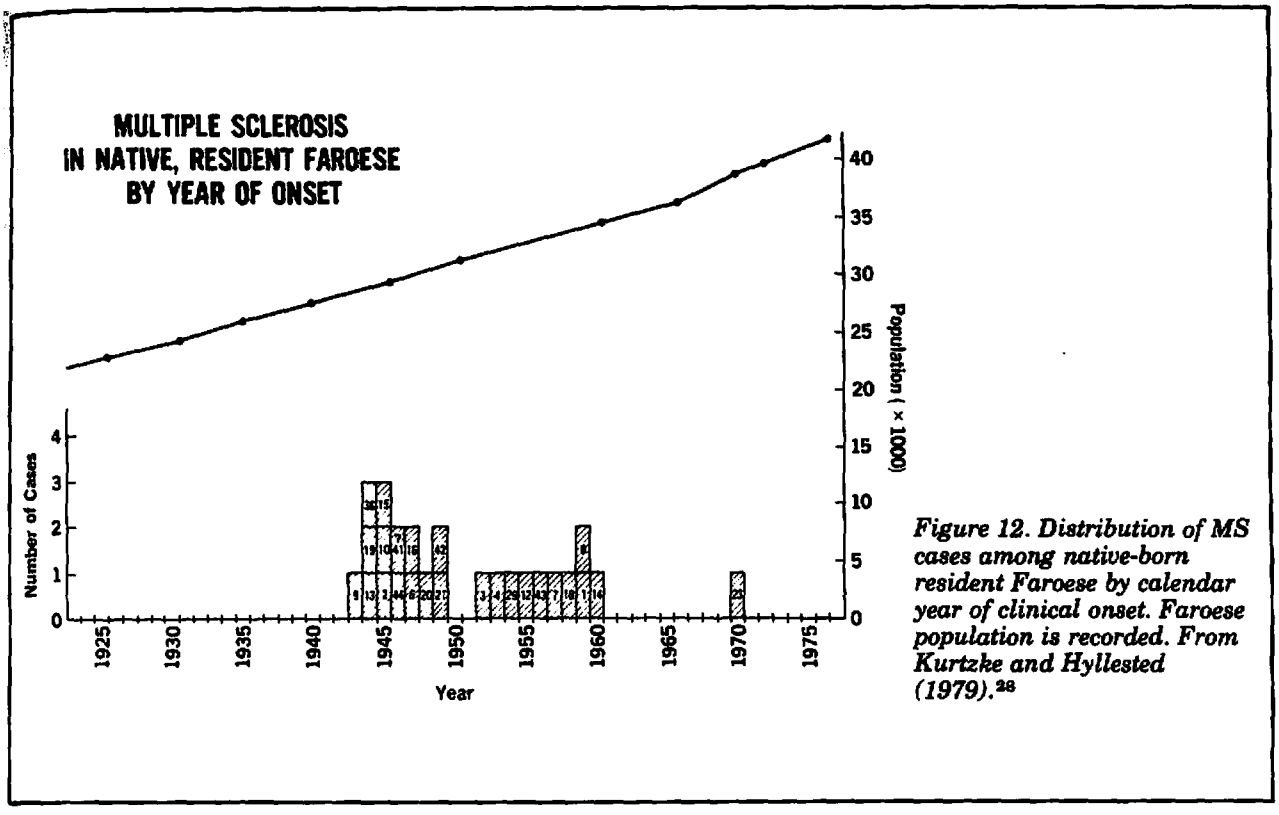

Figure 12. Distribution of MS cases among native-born resident Faroese by calendar year of clinical onset. Faroese population is recorded. From Kurtzke and Hyllested (1979).[28]

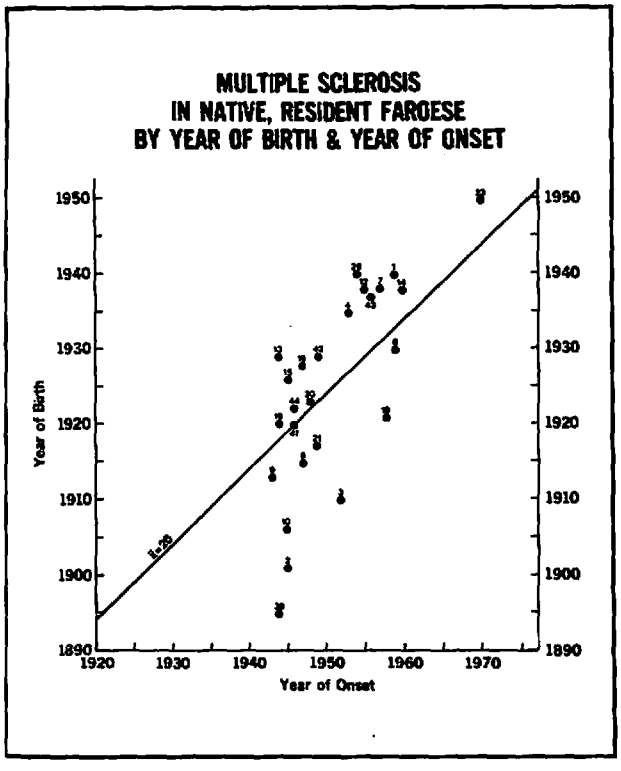

Figure 13. Distribution of MS cases among native-born resident Faroese by calendar years of birth and onset. Diagonal represents the mean age at onset. From Kurtzke and Hyllested (1979).[28]

(figure 12). All cases but one began between 1943 and 1960. It is these 24 cases of 1943 to 1960 that meet the criteria of an epidemic: disease occurrence clearly in excess of normal expectancy, and disease likely to be derived from a common or propagated source. In figure 13 we have plotted the cases by calendar year of both birth and onset of symptoms. The diagonal represents the mean age at onset of 26 years, and one would ordinarily expect the cases to cluster about this mean throughout the entire period.

The primary conclusion from these data is that the MS cases of 1943 to 1960 constitute a "point-source" epidemic, the result perhaps of a single cause that was introduced into the Faroes at a single time before 1943.

The major unusual event that we have found so far in the Faroes was their occupation by British forces for 5 years in World War II. Denmark was overrun by Germany on April 9, 1940, and on April 13 a detachment of Royal Marines landed in the Faroes. Within 2 months they were replaced by the permanent occupation forces. The latter are said to have numbered some 8000 men,[29] or almost 1 Briton for every 3 Faroese (figure 14). Residences during World War II matched the known locations of the British troops for all but three patients, and they too had had direct contact with the British (figure 15).

An obvious next question concerned what had

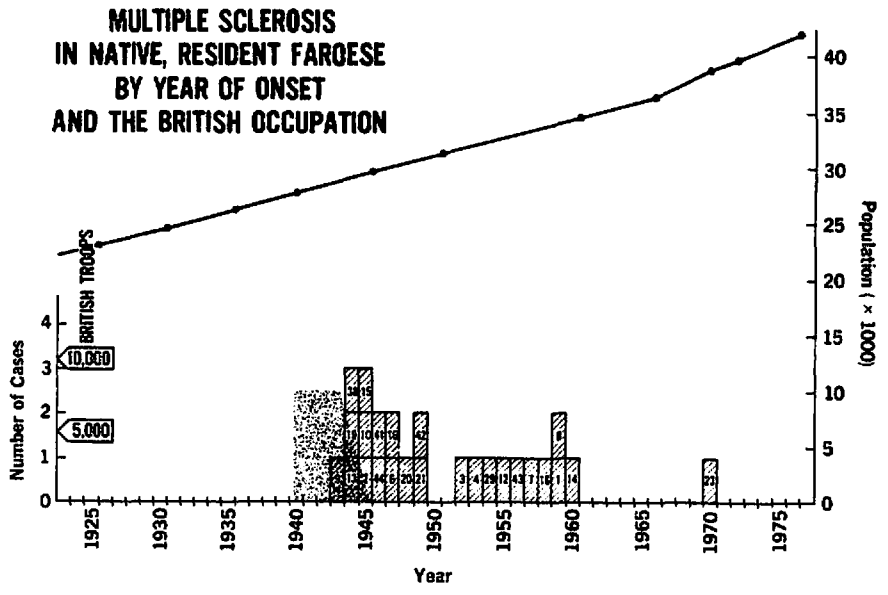

Figure 14. Distribution of MS cases among native-born resident Faroese by calendar year of clinical onset, and provisional estimates of British troops during their occupation, 1940 to 1945 (shaded area). From Kurtzke and Hyllested (1979).[28]

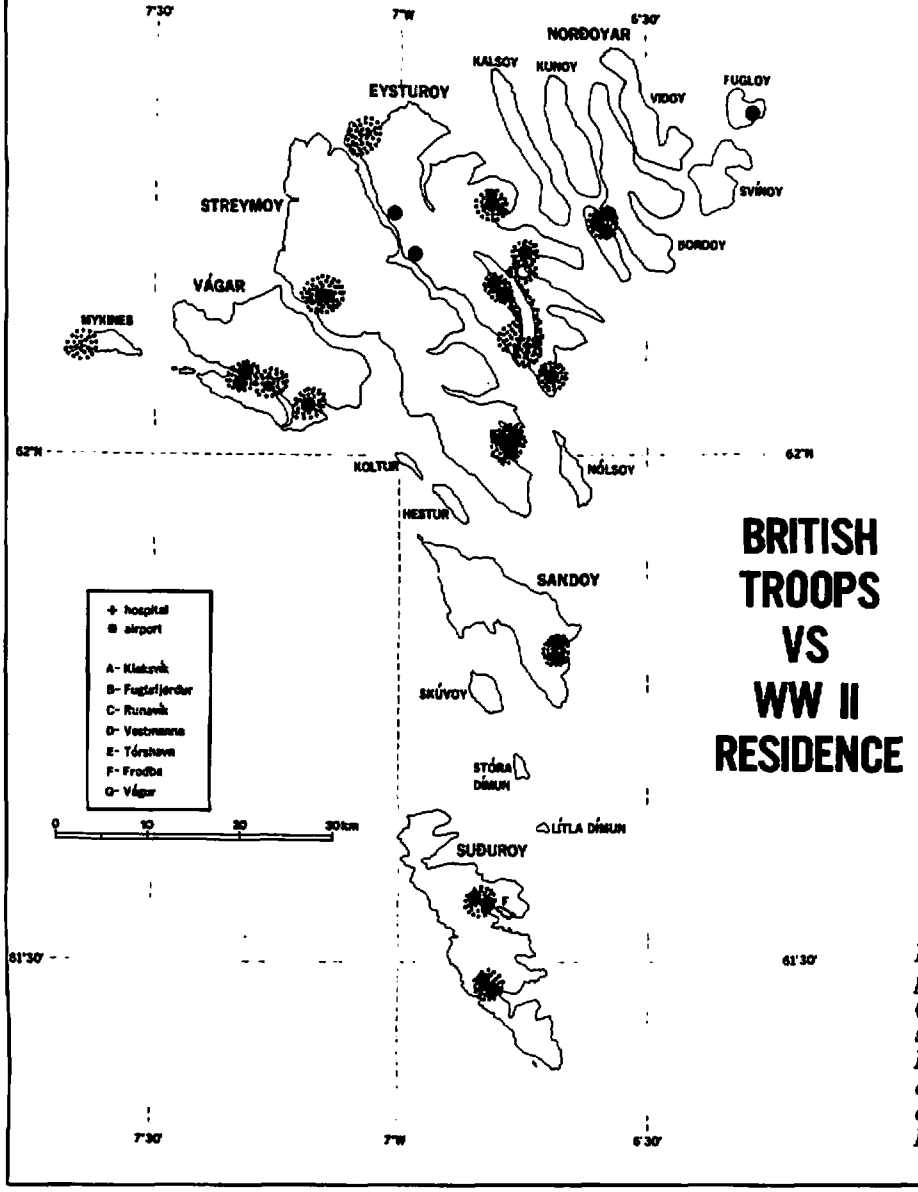

Figure 15. Residences of MS patients during World War II (large solid circles) superimposed on locations of British troops (dotted areas) during the 1940 to 1945 occupation. From Kurtzke and Hyllested (1979).[28]

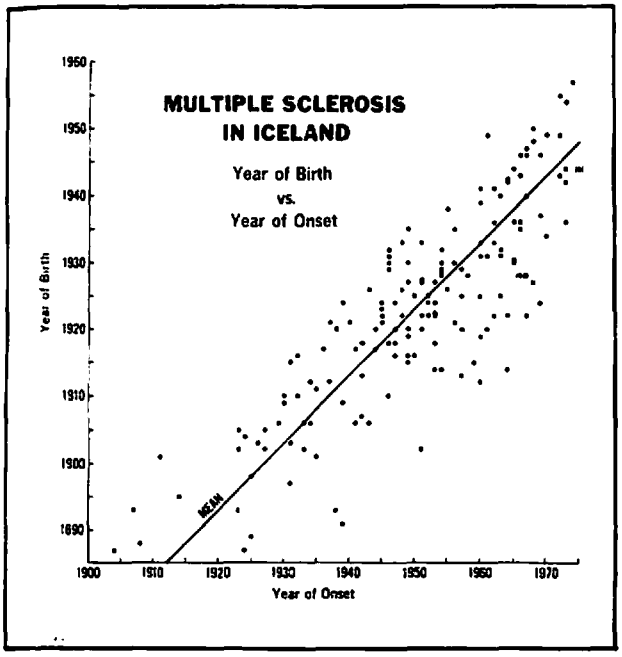

Figure 16. Distribution of MS cases in Iceland, 1900 to 1974, by calendar years of birth and of onset as of 1976. Diagonal represents the mean age at onset. Two cases in parentheses are foreign-born. Data of Kurtzke, Gudmundsson, and Bergmann (1980).[30]

happened with MS in Iceland. The same Norse Vikings settled Iceland at about the same time as they settled the Faroes. Like the Faroes, Iceland has been a county of Denmark, but it had attained its semi-independence in the 1920s. Also like the Faroes, it was occupied in World War II, not only by the British but also by the Canadians and the Americans. Iceland declared its independence as a nation during that war.

With the late Kjartan Gudmundsson, we collected between 1974 and 1976 all MS cases known in Iceland from 1900 on.[30] Figure 16 shows the correlation of these cases by calendar year of birth and onset, the same as in figure 13 for the Faroes. There is certainly no abrupt appearance and no disappearance, but there does seem to be some degree of clustering of cases for 10 years or so after 1945. In figure 17 are the MS cases by year of onset alone. Overall, there seem to be three rather distinct phases in the chronology of MS in Iceland: a low and sporadic occurrence before World War I, a sudden rise in 1923 and then a plateau to 1944, and then a sudden rise and an irregular plateau from 1945 on. The war periods are denoted by asterisks. We are now updating this series.

Calculation of annual incidence rates reveals more clearly that there does in fact seem to have been at least one definite epidemic of MS in Iceland beginning in 1945 (figure 18). The average annual incidence rate from 1923 to 1944 was 1.6 per 100,000. For 1945 to 1954 it was 3.2, and for 1955 to 1964 it was 1.9. With our update, the average rate for 1965 to 1974 also will be 1.9.

As stated, Iceland was heavily occupied during World War II, and US military bases are still present there. In World War I, Iceland might possibly have been a coaling station for the Royal Navy and may have been a link in the convoys to the United Kingdom, but there was then no formal occupation. The British did lay mine fields, though, between Iceland and the Faroes in both world wars.

However, at least for World War II, it is likely that in Iceland too the disease was reintroduced, or at least reinforced, concomitant with the occupation. We may possibly see here also a "critical mass" of population required to maintain the disease within a relative geographic isolate. Throughout this century, the population of Iceland has been about five times that of the Faroes. Al-

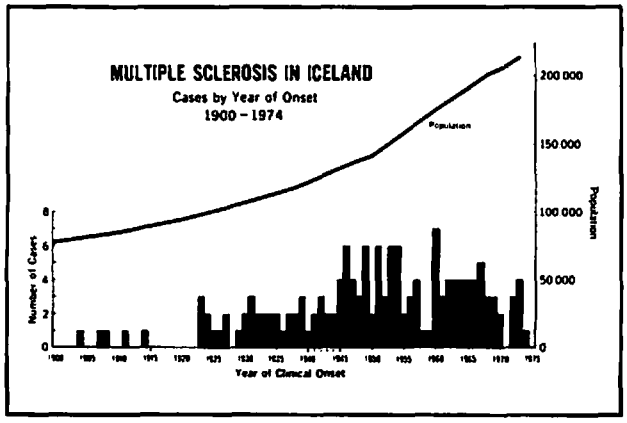

Figure 17. Distribution of MS cases in Iceland, 1900 to 1974, by calendar year of onset as of 1976. Icelandic population is noted. Shaded cases are foreign-born. Data of Kurtzke, Gudmundsson, and Bergmann (1980).[30]

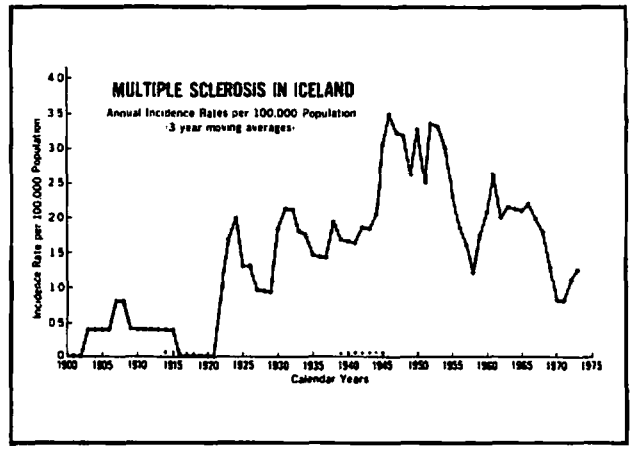

Figure 18. Annual incidence rates per 100,000 population for MS in Iceland, 1900 to 1974, calculated as 3-year centered moving averages as of 1976. Data of Kurtzke, Gudmundsson, and Bergmann (1980).[30]

though not as definitive, then, as the situation in the Faroes, this Icelandic saga may warrant as detailed scrutiny as we are attempting to accomplish for the Faroes in terms of the introduction and epidemic occurrence of MS.

Summary. Epidemiology is the study of the natural history of disease. Measures of disease frequency involve a numerator (cases) and a denominator (population at risk). Incidence and death rates refer to new cases and to deaths per unit population; prevalence rates refer to cases present at one time per unit time and population. Incidence and prevalence rates arise from specific surveys for the disease within circumscribed populations; death rates come from standard published governmental sources. Selection bias grows as the source of cases deviates from a true population survey, and it is maximal in autopsy series.

As to MS, the best measures of geographic distribution come from prevalence studies, of which there are now nearly 200. These works indicate that, geographically, MS is distributed throughout the world within three zones of high, medium, and low frequency. High-frequency areas, with prevalence rates over 30 per 100,000 population, comprise Europe between 45° and 65° north latitude, southern Canada and the northern United States, and New Zealand and southern Australia. These regions are bounded by areas of medium frequency with prevalence rates of 5 to 25 and mostly 10 to 15 per 100,000, which comprise Southern Europe, the southern United States, and most of Australia. Known areas of Asia and Africa (save for one white group in South Africa) are all low, with prevalence rates under 5 per 100,000 population.

All high- and medium-risk areas are among predominantly white populations: In America, blacks, Orientals, and possibly Indians have much lower rates of MS than do whites, but each group still demonstrates the geographic gradients found for whites.

Migration studies indicate that on the whole, migrants retain much of the risk of their birthplace. However, this risk is clearly not defined at birth: MS death rates for migrants born in one risk area and dying in another are intermediate between the rates characteristic of their birthplaces. Prevalence studies for migrants from high- to low-risk areas indicate the age of adolescence to be critical for risk retention: Those migrating after age 15 retain the MS risk of their birthplace, and those migrating before age 15 acquire the lower risk of their new residence. Several low-to-high studies show that those migrating in childhood or adolescence do in fact increase the risk of MS. The best data supporting this point arise from a nationwide series of MS cases with preillness controls from the US military-veteran population. For white male veterans of World War II service, case-control ratios are clearly decreased by moving from north to south between birth and entry into military service, and are clearly increased by similar moves in the opposite direction.

The migrant data, plus the geographic distributions, serve to define MS as an acquired, exogenous (environmental) disease whose acquisition in ordinary circumstances takes place years before clinical onset. The data fit best the "simple" or "prevalence" hypothesis: that the cause of MS will be found where the clinical disease is common.

Further migrant studies are required to support (or refute) this interpretation. However, all migrant studies are beset with major difficulties in ascertaining the denominator—the true population at risk—because this is a threefold function of age at migration, duration of residence, and age at prevalence day—each aspect of which will have a major influence in defining the expected numbers of cases. To obviate those difficulties in some measure, period risk estimates have been calculated for MS in Denmark. They indicate that after 5 years a disease-free population (all ages) would be likely to provide only some 12% of the MS cases expected over its lifetime, and only half the expected total would be found even after 20 years of follow-up.

Recently, two epidemics of MS have been defined: one (definite) in the Faroe Islands, the other (probable) in Iceland. Up to 1977, Hyllested and I have been able to identify in the Faroe Islands 25 cases of MS among native-born resident Faroese. All but one had clinical onset of MS between 1943 and 1960; one began in 1970. The median year of onset was 1949. The 24 included cases for 1943 to 1960 met all criteria for a point-source epidemic. Present evidence as to a source for this epidemic points to the British troops who occupied the Faroes in large numbers for 5 years from April 1940. Residences of all but three patients during the war were locations where the troops were stationed, and these three also had direct contact with the British.

With the late Kjartan Gudmundsson, all cases of MS in Iceland have been collected. As to their numbers, there seem to have been two stepwise increases in the occurrence of new cases of MS: after World War I, and after World War II, with plateaus following each of these increments. The annual incidence rate of 3.2 per 100,000 for 1945 to 1954 was twice as high as the rate for 1923 to 1944, and appears to have returned thereafter nearly to this earlier level. Iceland, which shares its ethnic origin and history with the Faroes, was also heavily occupied during World War II, not only by the British but also by Canadians and Americans.

If these findings are valid, both these studies would indicate the definition of MS as not only an acquired disease but also a transmittable one. This in turn requires further search for a viral origin.

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