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Epidemiologic Evidence for Multiple Sclerosis as an Infection

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INTRODUCTION

In the occident, multiple sclerosis (MS) is among young adults the most common disease with primary pathologic changes in the central nervous system. It has been characterized as a disease of unknown cause, inadequate treatment, and unpredictable course.

The name derives from the gross appearance of the scattered lesions or plaques found in the white matter of the central nervous system; when old, these lesions are hard, or sclerotic, because of gliosis. Histologic stains reveal their essential pathology as loss of the myelin sheath with preservation of the axon. The clinical course is usually one of exacerbations and remissions, but with an increasing proportion of the affected patients entering a chronic progressive phase as the years go by. A proportion of patients, however, shows little disability throughout life. The major clinical features of the disorder are weakness, incoordination, and sensory, visual, and sphincter disturbances. Diagnosis remains a clinical decision, although there are frequent abnormalities in laboratory tests, such as averaged evoked potentials, cerebrospinal fluid (CSF) gamma globulin levels, computerized tomography, and especially magnetic resonance imaging. None of these, however, are pathognomonic.

The prevailing view as to the etiology of MS is that it is an immunopathologic disorder, perhaps autoimmune, with various environmental factors acting in a genetically susceptible host (182, 254, 277). Murrell et al. (200), from the ecological viewpoint, believe MS to be ". . . multi-factorial in aetiology. Non-specific infections . . . operating in the presence of dietary lipids, suspect genes and socioeconomic factors, are all ecological variables interacting selectively. . . ." Analogous to this concept would be that for the Guillain-Barré syndrome, which is considered "an autoimmune disorder of the peripheral nervous system, usually but not always initiated by an exogenous factor such as an infectious agent or vaccine (44)."

In my view, the weight of the epidemiologic evidence, in particular that from the Faroe Islands (which I shall discuss), suggests that an immune system process is the "cart" rather than the "horse," that there is a real possibility of (predominantly) one horse and not a herd of animals, and that this horse is a specific, albeit unidentified, infection.

MS Diagnosis

Clinicians have generally divided their cases into "MS" and "possible or suspected MS." An early grouping for epidemiologic purposes was that of Allison and Millar (8): probable, early probable and latent, and possible. Some later workers added "definite" and "clinically definite." Some included first bouts as "probable MS," while others considered them "possible MS." Until very recently, many investigators carrying out clinical and epidemiologic studies used some variant of the criteria of the Schumacher Panel (249) as (clinically definite) MS.

The Schumacher criteria essentially are objective evidence of central nervous system involvement (criterion 1) attributed to two or more lesions (criterion 2), which indicate chiefly white-matter (long-tract) involvement (criterion 3), which have occurred over time either as multiple episodes or progressively for at least 6 months (criterion 4), and for which a competent clinician concludes MS the most likely cause (criterion 6). Criterion 5, age 10 to 50 at onset, has been thought by most workers carrying out epidemiologic and clinical studies to be too stringent, and for those who use the Schumacher criteria in field studies, there has also been a tendency to retain Allison and Millar's probable MS, primarily for cases excluded by criterion 5. Comparisons among studies are best made by limiting consideration to the most specific classes assigned by the author, usually definite and/or probable, and excluding possible MS.

A decade ago, a new set of criteria "for research purposes" was proposed by Poser and colleagues (219). In essence, this set adds abnormalities in CSF or evoked potentials to the Schumacher requirements to provide nine subsets of labels ranging from "clinically definite MS" to "laboratory-supported probable MS." More cases are considered definite and/or probable MS than with only clinical criteria. Even though not part of these criteria, the use of magnetic resonance imaging has become an important measure that for many investigators and clinicians is an adequate laboratory finding for elevating a suspect case to definite MS (209).

The problem with these criteria—and with all others—is that there is no possible in vivo proof of the diagnosis. Save for that small proportion of cases in which an alternative diagnosis is established, the thesis is "once an MS, always an MS." Whether the Schumacher or the Poser classifications are the more "correct" is, at present, undefinable. This

problem is far from an academic quibble. Whether clinical aspects, treatment or laboratory studies, or especially epidemiologic comparisons are being considered, some assurance that proper choices are being made for inclusion or exclusion of a given subject is needed. Epidemiologically, it appears that the nonspecific clinical criteria of Allison and Millar really are not very different from the modified Schumacher set, and comparability among the many studies published does seem, for the most part, to be of an acceptable level—especially when possible MS is excluded. In fact, except for the laboratory-supported probable MS subset of Poser, most of the remaining categories of the Poser set of criteria can be made to fit the earlier classifications (152). Still, these different sets of criteria do add yet another level of complexity when studies are being compared.

EPIDEMIOLOGY

For well over a century, MS has been the subject of study by workers in all the neural sciences. In recent years, especially, these studies have included epidemiologic inquiries. While there are others, one useful definition of epidemiology is the study of the natural history of disease. The epidemiologic unit is a person with a diagnosed disorder. The basic question, after diagnosis, is how common is the disease? Frequency 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 (140, 149).

Rates

The population-based rates in common use are the incidence rate, the mortality rate, and the point prevalence "rate." All are ordinarily expressed in unit population values. The incidence, or attack, rate is defined as the number of new cases of the disease beginning in a unit of time within the specified population. This number is usually given as an annual incidence rate, in cases per 100,000 population per year. The date of onset of clinical symptoms ordinarily denotes the time of input, 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 is expressed as an annual death rate per 100,000 population. The point prevalence rate is more properly called a ratio and refers to the number of affected individuals within a community at a given point in time; it is expressed per unit of population. If over time there is no change in case fatality ratios or annual incidence rates and no migration, then the average annual incidence rate times the average duration of illness in years equals the point prevalence rate.

When both the numerator and the denominator for the rates refer to the entirety of a community, their quotient provides a crude rate, all ages. When both terms of the ratio are delimited by age, sex, race, or other criteria, the result is age-specific, sex-specific, or similar rates. Since different communities differ in their age distributions, the proper comparisons among communities are those for the age (and sex)-specific rates. Such comparisons become unwieldy when more than a few surveys are considered; 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 to multiply it by a factor representing that 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 for all ages, adjusted to a standard population. One standard population often used is that of the United States for a census year. This method is especially important in dealing with common disorders that affect primarily either end of the age spectrum.

Case Ascertainment

Within the finite resident population of a community, there will be at any one time a finite number of persons affected with the disease under study. As is true for almost every illness, some of these persons will be asymptomatic, while a proportion will have symptoms appropriate to the condition. Among the asymptomatic persons, a subset will have abnormalities discoverable by examination or laboratory methods, while the remainder will then be, to 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 methodology is called a population survey, and it has been used for common diseases; however, it is impractical for rare entities. What has generally been done in neurology is to ascertain the number of all affected persons who have sought medical attention. I loosely refer to such a study as a prevalence study rather than a true population survey (140).

One step further removed from the 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 a standard certificate there are also places for "contributory causes of death" and "associated conditions." In selected instances, they too can be obtained and can provide another (undefined) fraction of affected persons. The autopsy series is really a subset of hospital case series, with all the biases implicit in such material (140). To these are added its own unique biases. Even if all autopsy reports are collected from all the resources of the community, they will still represent a very fragmentary portion of the affected persons. In most areas, only a small proportion of deaths are examined by autopsy (selection bias). Of pertinence to neurology, not all autopsies done include the examination of the brain by neuropathologists, and the spinal cord is seldom examined.

Therefore, at every step of the pathway, a proportion of the diseased will be missed. The further one moves from a true survey of the subject population, the larger and the more undefinable will be this proportion.

Morbidity data. Morbidity data are made available by means of three general kinds of population surveys, which I refer to as the Assyrian, the in-law, and the spider (140). As Byron put it in *The Destruction of Sennacherib*, "The Assyrian came down like a wolf on the fold." The Assyrian survey is the type common to most population surveys. It consists of the deployment of a team of workers throughout a community to identify the numerator (cases) and to perform whatever examination, laboratory, and questionnaire procedures had been planned. All the data required are obtained in a short period, after which the surveyors retire from the field. This kind of survey has been directed toward the ascertainment of cases within the population by door-to-door inquiry of its entirety or of a representative sample—what I refer to as the (true) population survey. It has also been directed to the ascertainment of cases known to the medical resources of the community without investigation of

the population at large—what I refer to as the prevalence study.

The in-law survey is a very expensive but important method for carrying out population surveys. A team moves into a community, screens the residents, and then remains to keep the community under direct surveillance with ongoing or repeated assessments over a prolonged period. Such surveys are limited to regions expected to have little migration, and practicality requires them to be limited to small communities. This last point is important: even after decades, the case material will be small.

In the spider survey, rather than investigators seeking out patients, patients come to investigators. When an excellent medical facility serves a defined community as its sole health resource and when the reporting and retrieval systems permit the collection of complete and accurate data, there is a potential for many epidemiologic studies. A variant of the spider survey is a nationwide disease registry, which Denmark has for MS.

Mortality data. The (underlying) cause of death on an official death certificate is coded with a three- or four-digit number that represents a specific diagnosis within the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD), the eighth revision of which was in use for 1968 to 1978 and the ninth revision of which was in use thereafter (287, 287a, 288). In the United States, a slightly altered version known as the ICDA had been used for hospital purposes. This version is now known as the ICD9CM (clinical modification). The ICD is revised about every 10 years, and the changes in both the eighth and the current (ninth) revisions were major ones (143). The 10th revision, well overdue, has yet to appear.

Risk

According to Fox et al. (74), "The basic premise of epidemiology is that disease does not occur randomly but in patterns which reflect the operation of the underlying causes . . . [and] that knowledge of these patterns is not only of predictive value with respect to future disease occurrence, but also constitutes a major key to understanding causation." The "patterns" mentioned are those that represent the "risk factors" for a disease. To consider risk factors, one must first define risk (147).

Over time, a cohort of 1,000 healthy people in a circumscribed population will undergo a certain number of events, such as strokes. If 10 strokes occur in 1 year, the annual frequency of strokes is 1%. Thus, the experience of a population cohort over time provides a measure of the cumulative frequency of an event over time, and this experience is the best estimate of the chance or probability of the event. This estimate is the risk of the event and, for this defined cohort, it is the absolute risk.

Risk is measured on the basis of the frequency of later events in a population cohort defined at the start of the observation period. Incidence and mortality rates are based on the number of events over time within the average population during the interval. For short periods, the difference is trivial, and an annual risk of stroke occurrence or death from stroke is well approximated by the annual incidence or mortality rate. Cumulative risk would be the sum of annual rates corrected for survivorship.

Attributes that alter the expected absolute risk or probability of disease are called risk factors. For strokes, for example, age is a very strong risk factor. However, with risk factors, one cannot necessarily infer cause or pathogenesis. In one sense, they are mathematical abstractions, characteristics that are associated with a significant alteration in the frequency of disease, regardless of reason. It is the function of the clinical scientist to ascertain reasons, for among the myriad of risk factors for any disease will be the cause(s) and precipitant(s) of the disorder. Conversely, if the evidence is strong enough, the lack of an association could rule out a putative risk factor as being relevant to the disease.

Relative risk. If the absolute risk (or the incidence rate) in two population subgroups that differ as to the presence of a factor is known, then the ratio of the risk for those with the factor to that for those without the factor provides the relative risk for that factor. If the annual incidence rate for those with factor x is 8 per 100,000 population and that for those without factor x is 4 per 100,000, then the relative risk of disease for factor x is two. When true incidence rates are unknown, prospective studies of two population subgroups, one with and one without the factor, can also provide a measure of relative risk.

Odds ratio. When prospective studies are not feasible, comparisons of groups of the affected persons with appropriate controls can provide an approximation of relative risk. In such retrospective case-control comparisons, the odds ratio is defined as the quotient of a ratio whose numerator is the product of the "hits" for the risk factor (number of cases with the factor present times number of controls with the factor absent) and whose denominator is the product of the "misses" (number of cases with the factor absent times number of controls with the factor present).

The choice of the control group is critical but can be very difficult. If age is matched, one cannot study age as a risk factor. If hospital controls are used, their own risk factors for other diseases may distort the findings. If neighbor controls are used, "overmatching" for socioeconomic status and prior lifetime events may occur. In each study, the definition of the control group is as important as the definition of the cases, and the composition of the control group must be carefully defined—before the study.

Attributable risk. The excess of the rate of occurrence of disease in persons exposed to a risk factor beyond the rate in those not exposed is a measure of the amount of disease that can be "blamed on," or attributed to, that factor. Attributable risk chiefly describes the burden of illness that can potentially be modified by altering risk factors; relative risk is concerned more with factors of importance in the cause or precipitation of disease. Neither type of risk nor odds ratio, though, provides a direct measure of the predictive value of a risk factor—how often it results in disease when it is present. A "cost/benefit" ratio must be considered before researchers aim to influence disease occurrence by manipulating risk factors.

GEOGRAPHY AND MS

The geographic distribution of MS has been the subject of many mortality and morbidity surveys as well as the topic of several symposia (15, 72, 100, 121, 128). Other reviews of the epidemiology of MS are those of Acheson (1–4, 4a), Alter (11), Dean (50), Detels (60), Gonzalez-Scarano et al. (81), Koch-Henriksen (115), Kurland (123), Kurland et al. (124), Kurtzke (140, 141, 144, 145, 148, 150, 151, 153, 154), Kurtzke and Kurland (168, 169), Kurtzke et al. (171), Martyn (183), Poskanzer (221, 222), and Wynn et al. (289). Much of this paper is based on my 1977 review (140) and its successive updates (especially references 148, 151, and 154). The reader should be forewarned that the presentation that

TABLE 1. Average annual age-adjusted (to the 1950 U.S. population) MS death rates per 100,000 population in selected countries for 1951 to 1958 (80) and 1967 to 1973 (185)[a]

Country	Death rate for:		Country	Death rate for:	
	1951–1958	1967–1973		1951–1958	1967–1973
Northern Ireland	3.3	2.1	New Zealand	1.2	1.1
Scotland	3.0	2.1	Sweden	1.0	0.8
Ireland	2.9	2.1	United States	0.9	0.8
Switzerland	2.2	1.8	Finland	0.9	0.6
Czechoslovakia	2.0	1.6	Australia	0.7	0.6
West Germany	2.1	1.5	Iceland	0.3	1.0
Denmark	2.0	1.5	Italy	0.7	0.6
France	2.7	0.8	Uruguay	0.6	0.6
The Netherlands	2.0	1.5	Israel	0.5	0.6
Belgium	2.0	1.4	Greece	0.3	0.4
Austria	1.9	1.4	Chile	0.3	0.2
England–Wales	1.6	1.5	Colombia	0.2	0.2
Norway	1.5	1.1	Mexico	0.2	0.1
Canada	1.2	1.1	Japan	0.1	0.1
Portugal	1.2	1.1	Philippines	0.0	0.1

[a] Modified and reprinted with permission from the publisher (153).

follows differs notably in interpretations from those of many other authors, although the data themselves are rather commonly accepted (see Introduction).

International Mortality Data

The earliest analysis of MS mortality rates in many countries was made by Limburg (179), who found that death rates were higher in temperate zones than in the tropics or subtropics. He also noted higher rates in the northern United States and northern Italy than in the southern parts of those countries. The study of Goldberg and Kurland (80) provided death rates for MS in 31 countries for 1951 to 1958, all age adjusted to the 1950 U.S. population. Later data for most of these countries were presented by Massey and Schoenberg (185) (Table 1). Virtually all death rates were then notably lower than only a decade or two before, but the ranking was quite similar. In both intervals, the highest rates were those for Northern Ireland, Scotland, and the Republic of Ireland. Other western European countries, except for the northernmost areas of Norway, Sweden, and Finland and the Mediterranean countries of Greece and Italy, also had high rates. The rates for these last two groupings in the north and the south of Europe were similar to those for whites from Canada, Australia, New Zealand, and the United States; nonwhites from the United States (data not shown) had half the rate of whites from the United States. Lowest by far were rates in Asia, Africa, and the Caribbean.

U.S. Mortality Data

Age-adjusted (to the 1940 U.S. population) MS death rates by state in the United States for 1959 to 1961 are shown in Fig. 1. All states south of the 37th parallel of north latitude showed low death rates (mostly 0.3 to 0.5), while almost all states to the north of this line showed death rates well in excess of the national mean. In the east, the dividing line reached the 39th parallel. This configuration was true for residence at birth as well as at death and for whites alone as well as for all residents (170). There were few consistent differences in MS death rates between urban and rural counties within the respective census regions, although for whites the urban rates tended to be somewhat higher (171).

When defined by the 506 U.S. state economic areas (SEA), MS death rates for 1965 to 1971 were quite similar to the rates by state (184). For whites, all the statistically significantly high SEA and almost all otherwise high SEA were above the 37th parallel. Significantly low SEA were mostly below 37° north latitude, but again, especially for females, they extended in the east up to 39°. By SEA, the highest (but insignificantly so) rates for the much smaller numbers of nonwhites were mostly in the north, and the few significantly low rates were in the south.

Prevalence Data

The geographic distribution of MS has been studied extensively in prevalence surveys, particularly in the last quarter of the century. However, as far back as 1868, Charcot (41) had commented, "Après M. Cruveilhier [1835–1842], Carswell, dans l'article *Atrophy* de son Atlas (1838), a fait dessiner des lésions qui se rapportent à la sclérose en plaques. Mais cet auteur, qui a puisé surtout les matériaux

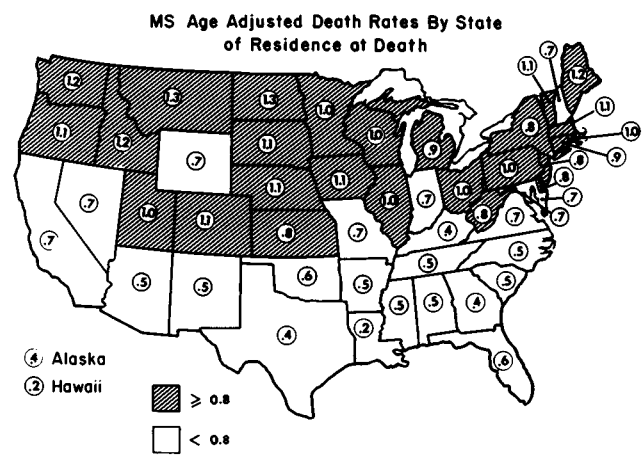


FIG. 1. Average annual age-adjusted (to the 1940 U.S. population) MS death rates per 100,000 population by state of residence at death in the United States for 1959 to 1961. Reprinted with permission from the publisher (170).

de son ouvrage dans les hôpitaux de Paris, ne relate à ce propos aucun fait clinique. Même aujourd'hui [1868], je ne crois pas que la sclérose en plaques soit connue en Angleterre." Charcot in essence pointed out that the Englishman Carswell used French material to describe MS in his article on atrophy in his 1838 *Atlas of Neuropathology* and that even in 1868 there had been no clinical case of MS known (or at least described) in England. The first case report from Britain, indeed, was that of Moxon in 1873 (198), while for most of that century in both France and Germany the disorder had already seemed quite common.

On the basis of rates for U.S. Army draftees in World War I, MS was especially common among residents of the states bordering the Great Lakes (Illinois, Michigan, Minnesota, and Wisconsin), but it was also common in Maine, Pennsylvania, Washington, Kansas, and Missouri (48). By "race," the highest rates were found for Scandinavian and Finnish sections of the country. The distribution was similar to that for MS among injuries and diseases of the nervous system in U.S. troops during that war, as were the high rates for foreign-born persons, in particular Scandinavians (22).

Prevalence surveys provide the best information on the geographic distribution of MS. However, they are expensive in terms of time, people, and money. Despite this problem, there are now well over 300 such surveys for MS. Almost all of them have been performed since World War II. Some years ago, I tried to collect such studies done up to 1980 and to rate them in terms of quality (138, 138a, 146). It is obviously impractical to list each of them here. In the references cited (138, 138a, 146) are tables that list for each survey the author, survey site, its latitude and longitude, prevalence day, population, number of cases, prevalence rate with its 95% confidence interval, and a rating as to the quality and hence comparability of the survey. Surveys done after 1980 will be summarized here, but without details.

Prevalence in Europe. Prevalence rates for Europe and the Mediterranean basin as of 1980 are plotted against geographic latitude in Fig. 2. The surveys appeared to be separated into two zones or clusters: one with rates of 30 and over per 100,000 population, considered high frequency, and one with rates below 30 but above 4 per 100,000 population, considered medium frequency. (Rates below 5 per 100,000 define regions of low frequency for MS.) On the basis of only the best (class A) studies, the high-prevalence zone extended from 44 to 64° north latitude.

Rates in the Shetland and Orkney Islands (6 and 6a in Fig. 2) were at the time the highest recorded (7, 73, 223, 262). However, Cook et al. (43, 46) found both incidence and prevalence to have declined notably in those islands by about 1980. The Outer Hebrides had a rate of 82 per 100,000 in 1979 (52). Rates in northeastern Scotland had increased from about 100 to 145 in 1980 (213, 251). The rate in Wales in 1985 was about 115, including possible MS (265, 266), while the London Borough of Sutton had a rate of 104 in the same year (286).

Later material from Scandinavia indicated a 1979 rate of 93 in Vaasa, Finland, three times the rate for 1964 (112); in 1972, the rate was 61 (19a in Fig. 2). The whole country of Finland averaged 52 in 1979 (283). The rate in Hordaland, in western Norway (11 in Fig. 2), also tripled, from 20 in 1963 to 60 in 1983, with a rise in annual incidence from 2 to 4 per 100,000 (173, 174). Conversely, Troms and Finmark, in northern Norway, had little change from 1973 to 1983; the rate for probable MS was then 28 (86). The rate in Denmark was stable at 87 for probable MS from 1955 to 1965 (117). A similar stability, at about 60 to 70, for 1955 to 1985 was reported for Iceland (27, 216).

Other material suggests that southwestern France may be of medium prevalence (9, 78), although Hautes-Pyrénées County had a rate of 40 in 1983 (32). Berne, Switzerland, had a rate of 113 in 1986 (109), while in 1976, (Germanic) Upper Wallis had a rate of 38 and (Gallic) Lower Wallis had a rate of 19 (24).

Rates in the 1980s across The Netherlands and Germany ranged from 43 to 68 per 100,000 (191, 227, 248, 284). The rate in Hungary was 37 (208), while several regions of Yugoslavia had rates of between 20 and 40 (36, 177, 186). For an isolated mountain region, the Gorski Kotar region of Croatia, Sepčić et al. (250) reported a 1986 rate of 144 and a high familial frequency.

Rates in Czechoslovakia and Poland in 1984 were 71 and 43 per 100,000, respectively (105, 279, 280). In Athens, Greece, a tentative rate of 10 was offered by Vassilopoulos (272). Romania (212, 214) had rates of 27 and 30 in 1979. The rate in Bulgaria averaged 21 in 1979 and 1983 (108, 292).

Dean et al. were the first to question the inclusion of Italy in the medium-prevalence zone: in the survey of Enna, Sicily, (51j in Fig. 2), the rate was 53 per 100,000 (53). There are now a number of other studies from mainland Italy and its islands to indicate rates of between 30 and 65 per 100,000 in the 1980s (83–85, 196, 238–241, 245). Cyprus has also been defined as a high-risk area, with a rate of 45 per 100,000 in 1988 (192).

(i) Clustering. In Europe, a number of prevalence surveys of an entire country were done by a single team at a single time, covering Norway, Denmark, Sweden, Switzerland, Northern Ireland, northern Scotland, The Netherlands, Iceland, and Finland, with repeated surveys of different generations of patients (and doctors) in Norway, Denmark, and Switzerland. While the distribution within the small area of Northern Ireland was uniform and those within The Netherlands and Iceland were rather equivocal, in all other countries surveyed there were highly significant deviations from homogeneity, and the high-rate areas tended to be contiguous, forming clusters, or foci. The differences in the rates between the highest- and lowest-rate regions in each country were on the order of sixfold or more, so the variations would seem to be of biologic as well as statistical significance (132, 133). Not only was there clustering, but in each of the three countries resurveyed a generation apart, there was a very strong correlation between the early and later distributions, with coefficients of correlation for each of about 0.8 (Fig. 3). Old and new surveys were separated by World War II for Denmark and Switzerland; the old survey in Norway provided prevalence as of 1946.

When contiguous countries were considered, the high-frequency areas in the north appeared to describe a "Fennoscandian focus" (137). This focus extended from the "waist" and southeastern mountain plains of Norway eastward across the inland lake area of south-central Sweden, then across the Bay of Bothnia to southwestern Finland, and then back to Sweden, in the region of Umeå, on the northeastern shore (Fig. 4). Hordaland, Norway, on the west coast at 60° north latitude, has now joined this focus; as mentioned above, the rate there has increased from 20 in 1963 to 60 in 1983 (173, 174). The clustering, as well as the broader geographic distributions, seems to indicate that the occurrence of MS is intrinsically related to geography.

Prevalence in Asia and Africa. (i) Northern hemisphere. Throughout the northern hemisphere, MS prevalence rates in Asia and Africa have been uniformly low (Fig. 5), aside from the Mediterranean region. There are otherwise no

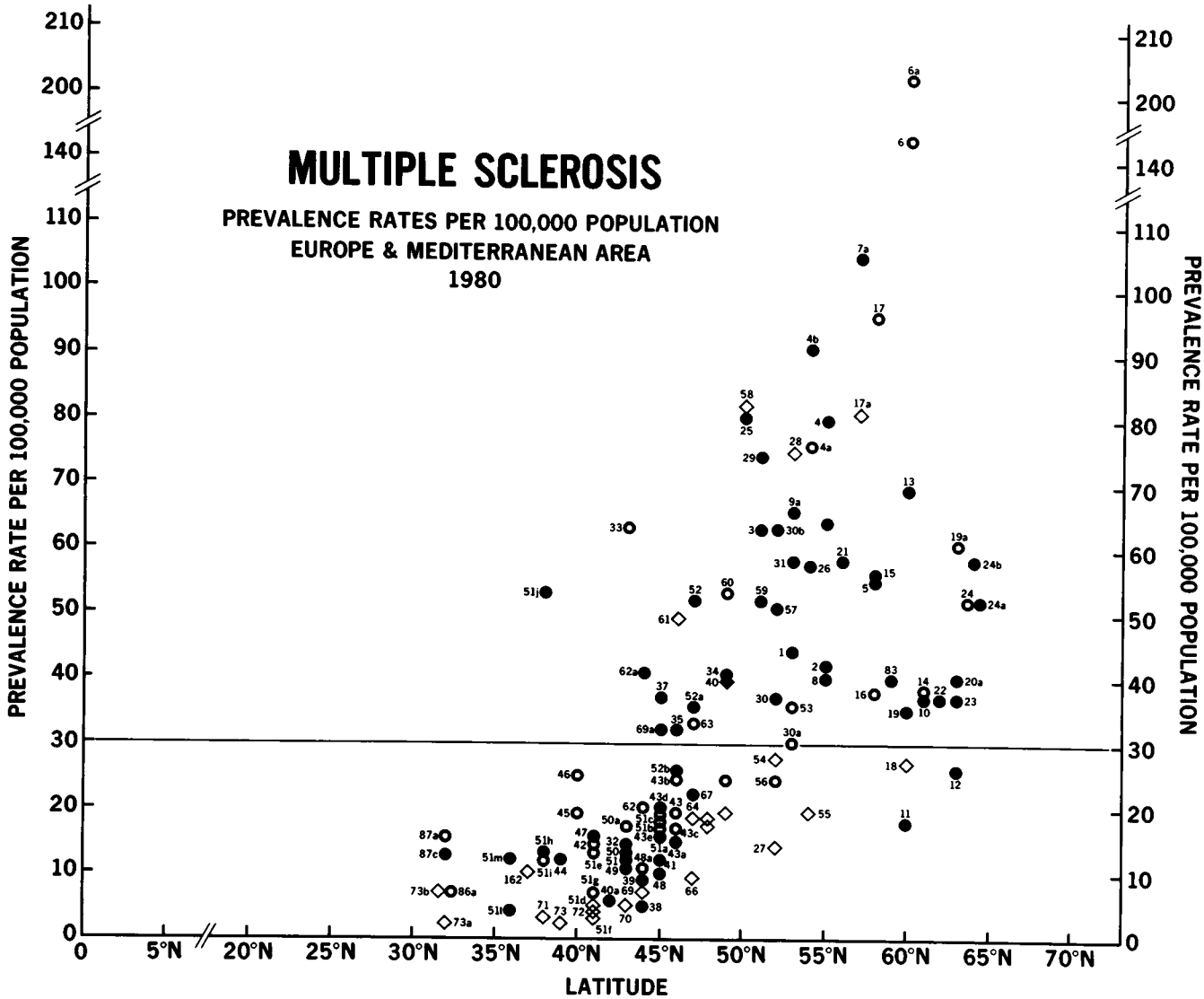


FIG. 2. Prevalence rates per 100,000 population as of 1980 for probable MS in Europe and the Mediterranean area, correlated with the geographic latitude of the survey site. Numbers identify the studies listed in references 138, 138a, and 146. Symbols: ●, class A (best) surveys; ○, class B surveys; ◇, class C surveys; □, class E surveys (MS/ALS case ratios). Class C (poor) studies are listed only if no better-quality survey was available for the specific site. Reprinted with permission from the publisher (146).

prevalence rates from mainland Asia or its major islands in excess of 4 per 100,000 population (104, 128). On the basis of MS/amyotrophic lateral sclerosis (ALS) case ratios, a hospital survey in greater Manila, in the Philippines, raised the possibility that MS among native Filipinos may be within the medium-prevalence zone: the MS/ALS case ratio was over 2:1 in 1982 (127), implying a prevalence rate of over 10 per 100,000. However, the case ratio of myasthenia gravis to ALS was even higher, and myasthenia gravis has a prevalence of about 4 per 100,000 (169).

Another subtropical locale that may really be in the medium-prevalence zone is Las Palmas Province, Canary Islands, which lie at 28° north latitude, 16° west longitude, off the southwestern coast of Morocco. Sosa Enriquez et al. (256) found 44 cases among the (white) population of 700,000 in the 10 years to 1982, for a prevalence rate of 6 per 100,000. Libya, on the Mediterranean littoral of Africa, may also be within the medium-prevalence zone, with an age-adjusted (western Germany) prevalence rate of 6 per 100,000 for the 21 patients in Benghazi in 1984 (229). Immediately west of Libya lies Tunisia. Ben Hamida (28) reported 100 cases of MS from his clinic in Tunis from 1974 to 1976; 73 of these patients had definite or probable MS, and all were native Tunisians. If all 73 came from Tunis itself, a prevalence rate of 10 per 100,000 might be inferred (162 in Fig. 2).

Kurdi et al. (122) described 32 cases of MS for the King Hussein Medical Center in Amman, Jordan. Of these, 22 were "urban." If all 22 patients came from Amman itself, a prevalence rate of 7 per 100,000 might be calculated (73b in Fig. 2); the 32 cases would indicate a minimum prevalence rate of 2 per 100,000 for the country as a whole (73a in Fig. 2). An age-adjusted (United States) rate of 8 per 100,000 was found for Kuwait on the Arabian Gulf in 1984 (5). As of 1989, the prevalence rate was 13 (6). The MS/ALS case ratio

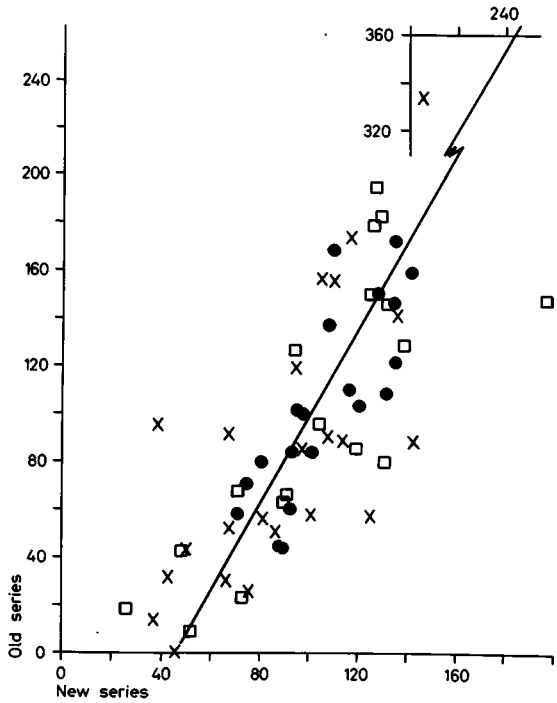


FIG. 3. Correlation of the prevalence rate distributions for MS by county between the old series and the new series of prevalence surveys in three countries, each survey covering different generations of patients: ●, Denmark; ×, Switzerland; and □, Norway. The rate for each county is expressed as the percentage of the respective national (mean) rate. Reprinted with permission from the publisher (137).

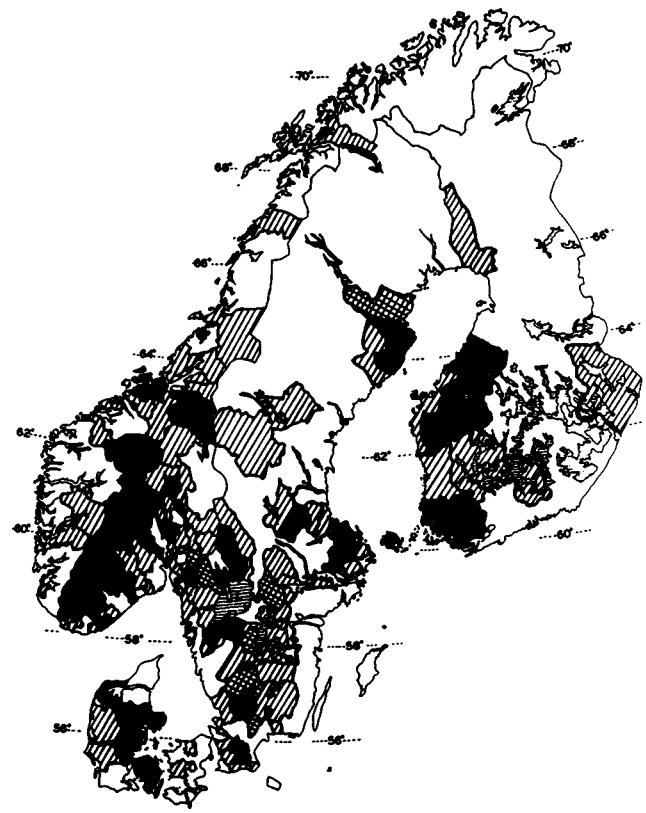


FIG. 4. Distributions in Fennoscandia. Areas with rates significantly higher than the respective national means (χ^2_a, >4.0) are in solid black; those with high rates that were of dubious significance (χ^2_a, 2.0 to 4.0) are cross hatched; those with high rates that were insignificant (χ^2_a, <2.0) are hatched; and those with rates below the respective national means are unshaded. χ^2_a = approximate χ^2 (1 df) for each unit's cases, observed versus expected. Geographic unit boundaries are omitted. Data represent cumulative death rates within 104 small units of Norway (1951 to 1965); prevalence rates for hospital cases within 106 small units of Sweden (1925 to 1934); disability prevalence rates within 20 hospital districts of Finland (1964); and childhood location prevalence rates within 23 counties for the national prevalence series of Denmark (1949). Fine horizontal shading represents lakes in Sweden and Finland. Reprinted with permission from the publisher (137).

suggests a prevalence rate of 8 per 100,000 in Riyadh, Saudi Arabia, as of 1986 (291).

The prevalence rate for native-born Israelis, age-adjusted to the 1960 U.S. population, was 13 per 100,000 in 1965 (138, 138a). Biton and Abramsky (31) presented in an abstract form an update of the material to about 1985, and they indicated a crude prevalence rate four times as high in natives with Ashkenazi (European) parents than in those with Sephardic (African-Asian) forebears (43 versus 11 per 100,000, respectively). However, when the rates as presented were age adjusted (1960 U.S. population), they were identical, 47 versus 46 per 100,000, respectively, rates that are now clearly in the high-frequency range. However, these interpretations should be viewed with caution, as the full data are yet to be published.

(ii) Southern hemisphere. In the southern hemisphere, all African-Asian rates were low, except in South Africa (Fig. 6). In that country, there was a significant difference for the prevalence rate in 1960 among native-born whites (rate, 6; 154 in Fig. 6) who were English speaking (rate, 11; 156 in Fig. 6) versus Afrikaans speaking (rate, 3; 155 in Fig. 6). Rosman et al. (242) found five new cases of MS among Afrikaans-speaking residents of Pretoria for the year ending February 1985, and they calculated an incidence rate of 1.6 per 100,000, an eightfold increase over the annual incidence rate of 0.2 per 100,000 given by Dean (49) for 1958 to 1966. For Cape Town, Kies (110, 111) recorded prevalence rates in 1986 of 14 per 100,000 for English-speaking and 11 per 100,000 for Afrikaans-speaking native-born whites. Thus, the ethnic disparity in South Africa seems to have disappeared; the Afrikaaners have "caught up" with their English compatriots, and now that nation is an area of medium risk for all whites—but still not for Cape Coloured (rate, 3) or for blacks, for whom virtually no cases are known.

Prevalence in Australia and New Zealand. Figure 7 shows the situation for Australia and New Zealand as of 1974: high-frequency areas were New Zealand (134 and 135 in Fig. 7), Tasmania (125 in Fig. 7), and South Australia (127 in Fig. 7). In all other Australian states, the rates were essentially of medium frequency, although there was a strong suspicion that the rate for Melbourne, Victoria (133 in Fig. 7), was markedly underestimated and should also have been high (138, 138a).

The two survey sites in New Zealand were Wellington (134 in Fig. 7), at the southern tip of North Island, and Christ Church (135 in Fig. 7), at the upper third of South Island. In about 1984, the prevalence rate in Wellington was 69 per 100,000 (194). However, in 1981, the prevalence rate in the Waikato region in the middle of North Island was 24 per

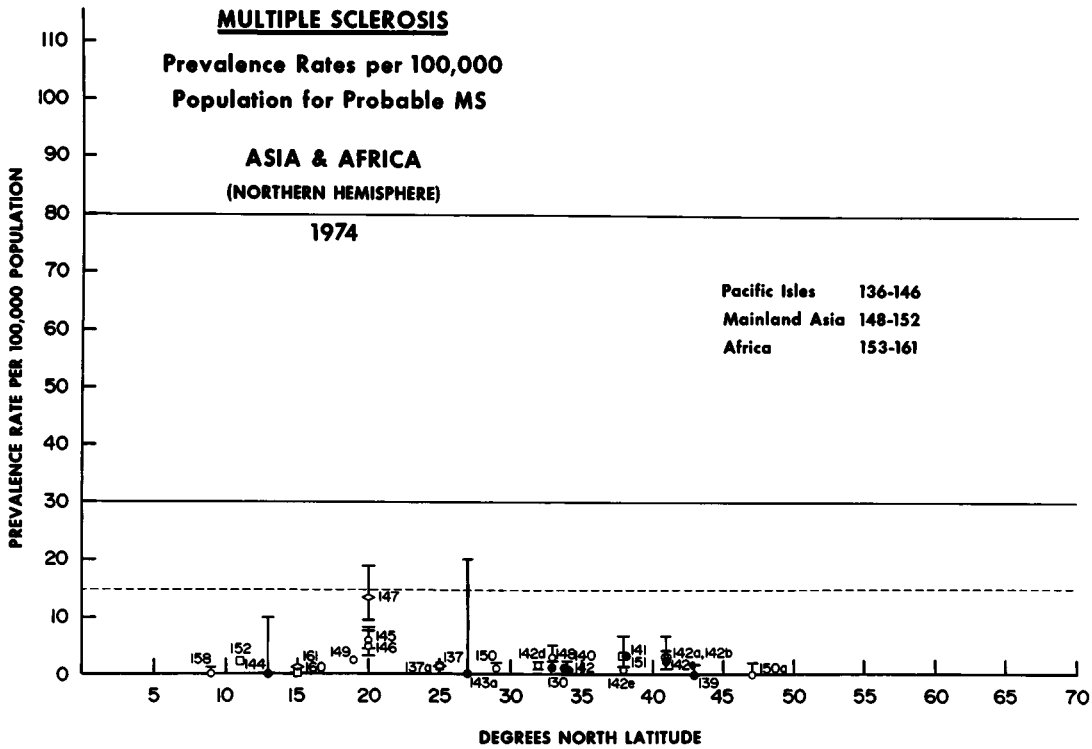


FIG. 5. Prevalence rates per 100,000 population as of 1974 for probable MS in Asia and Africa, northern hemisphere, correlated with geographic latitude of survey site, as in Fig. 2, but with 95% confidence intervals (bars) for the rates. The broken line reflects a mean prevalence rate of 15 for medium-risk surveys as of 1974. Reprinted with permission from the publisher (138, 138a).

100,000 (95% confidence interval, 18.2 to 30.1), while at the same time there was a prevalence rate of 69 for the Otago and Southland regions at the lower end of South Island (255). Both sets of authors commented on the rarity of MS among Maoris.

A nationwide prevalence survey of MS in Australia was conducted for 1981. Compared with those in an earlier survey (1961), the crude prevalence rates for 1981, including possible MS, were 18 (1961) versus 24 (1981) for Perth, Western Australia; 18 versus 34 for Newcastle, New South Wales; and 29 versus 68 for Hobart, Tasmania (92). Queensland, which is represented by 121 and 128 to 132 in Fig. 7, had a 1981 rate close to 19 per 100,000 (91). South Australia's rate was close to 30 per 100,000; no data are available for Victoria or Northern Territory (154). The state of Western Australia had a 1981 rate of 25 (93). In general, then, Australia remains largely as before: mostly of medium prevalence but with the southeastern quadrant, including Tasmania, now clearly of high prevalence.

Prevalence in the Americas. As to the distribution of MS in the Americas (Fig. 8), the prevalence rates as of 1974 appeared to fall within the same three frequency zones: high from 37 to 52°, medium from 30 to 33°, and low (a prevalence rate of less than 5 per 100,000) from 12 to 19° and from 63 to 67° north latitude (138, 138a, 146). In recent years, a number of well-done surveys have been conducted in Canada. Prevalence rates were 68 per 100,000 in Ottawa, Ontario, in 1975 (29) and 94 in London-Middlesex, Ontario, in 1984 (88). In Saskatoon, Saskatchewan, the prevalence rate was 111 (64 for those resident at onset) in 1977 (87). On the west coast, in the Province of British Columbia, the rate was 93 in 1982 (264), while on the east coast, the Province of Newfoundland and Labrador had a rate of 55 in 1985 (228).

Age-adjusted (1950 U.S. population) prevalence rates in Olmsted County (which includes Rochester) and neighboring Mower County, Minn., were, respectively, 113 and 106 per 100,000 population in 1978 (the respective crude rates were 102 and 100) (246). In the northern Colorado counties of Weld and Larimer, the prevalence rate was 65 per 100,000 in 1982 (202). The effect of immigration is seen in Los Alamos County, N.M. (98), where the prevalence rate in 1979 was 76 per 100,000 (95% confidence interval, 42 to 128) in what should be a medium-risk area; however, virtually the entire populace of Los Alamos County is migrant. No rates were recorded for regions below the equator in Fig. 8, but there are now several hospital-based estimates that suggest that the northern regions of South America are of low frequency, while the more southern regions are of medium frequency (148).

An "unusual occurrence" of MS was reported in a letter to Lancet by Sheremata et al. (252). There were stated to be 29 cases of MS among residents of Key West, Fla., for a prevalence rate of 110 per 100,000 (95% confidence interval, 74 to 158). Most patients had symptom onset between 1977 and 1982, mostly while living in Key West. The State of Florida Department of Health and Rehabilitation Services conducted a case-control survey of 22 of these patients with presumed symptom onset in Key West and 76 controls. Its official departmental report (30) states, "The above findings reveals [sic] that Key West is a high risk area for MS . . . [and] health care workers, particularly nurses (representing 41% of the cases), appear to be at a higher risk of acquiring MS than persons not employed in the health care professions." Helmick et al. (94) reported a prevalence rate of 70 for 32 cases; the 25 cases with onset in Monroe County yielded a prevalence rate of 55. Ingalls (102) discussed seven

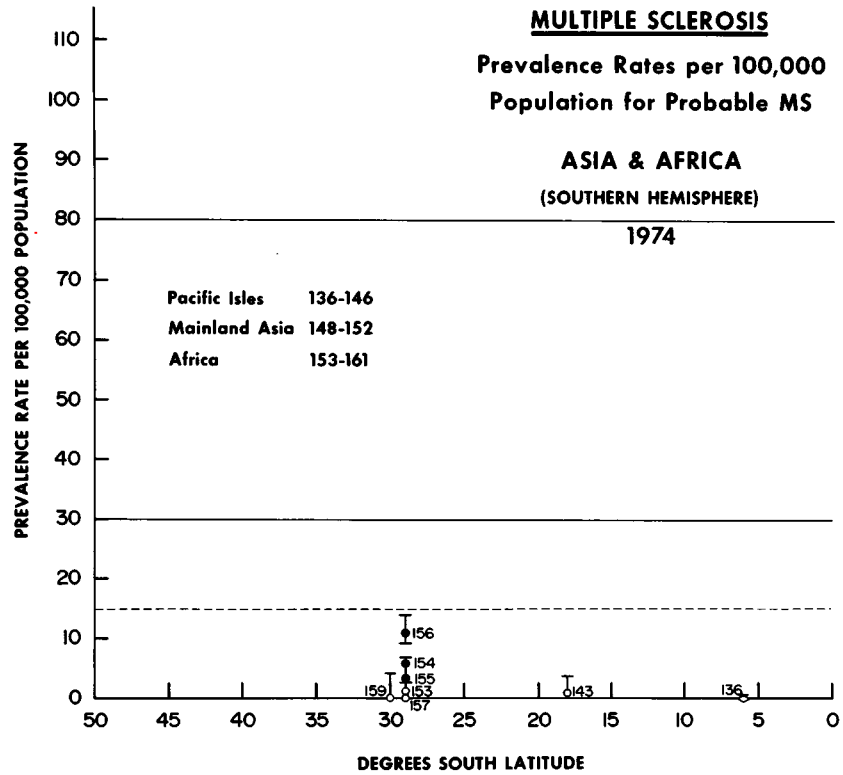


FIG. 6. Prevalence rates per 100,000 population as of 1974 for probable MS in Asia and Africa, southern hemisphere, as in Fig. 5. Reprinted with permission from the publisher (138, 138a).

affected Key West nurses. Helmick et al. (94) showed increased risk for nurses but not other health care professionals in their own case-control study.

(i) **U.S. veteran series.** Our best information as to the nationwide distribution of MS throughout the United States comes from a series of 5,305 U.S. veterans of World War II or the Korean Conflict who were adjudged by the Veterans Administration to be "service connected" for MS. Service connection essentially requires that symptoms of the illness were recorded either during or within 7 years after military service. This requirement results in a 9- to 10-year incidence series of MS cases. Each of the MS patients was matched to a military peer on the basis of age, date of entry into and branch of service, and survival of the war. This collection of data provided an unbiased, preillness case-control series of nationwide composition and unprecedented size (155).

Figure 9 shows the distribution of MS expressed as case/control ratio percentages for white male veterans of World War II by state of residence at entry into military service. In this series, a case/control ratio of 0.75 approximated a prevalence rate of 30 per 100,000 population. States below the 37th parallel, then, all fell in the medium-frequency zone, and states (and northern California) above the 37th parallel fell in the high-frequency zone, except for Virginia (ratio, 0.69) and Kentucky (ratio, 0.60). In the east, then, the dividing line for high and medium frequencies reached the 39th parallel, providing an overall distribution very similar to that for MS death rates, as shown in Fig. 1. In fact, a formal comparison of these ratios with the death rates by state of residence yielded a correlation coefficient of 0.82 ($P < 0.01$) (172). Both distributions were also quite similar to those reported from a probability sample of physicians and hospitals in the United States; with those data, Baum and Rothschild (25) had calculated a national prevalence rate of 58 per 100,000 population as of 1976.

Prevalence worldwide. In 1966 (131), it appeared that "the world-wide distribution of MS may be described within three frequency bands: (1) high frequency with prevalence of 45 per 100,000 and a range of 30–60 . . .; (2) medium frequency with prevalence of 10 per 100,000 and a range of 5–15 . . .; and (3) low frequency with prevalence of 1 per 100,000 and a range of 0 to 4. . . ." Over the years thereafter, the high- and medium-frequency bands each included higher rates, so that the former bands now have a range largely between 50 and 120 and the latter bands mostly have a rate close to 25; the rate for low-frequency bands, however, remains at less than 5 per 100,000.

I believe the general worldwide distribution of MS may still best be described within these three zones of frequency or risk (Fig. 10). I do not believe that a "super-high" grouping for rates of, for example, over 100 is warranted (yet) because of the geographic scattering of such high-prevalence figures. The high-risk zone, with prevalence rates reported up to 1989 of 30 or more per 100,000 population, includes northern and central Europe into the former Soviet Union, the northern United States and almost all of Canada, and New Zealand and southeastern Australia. Italy appears to have joined the ranks as a high-frequency area. Israel, too, now appears to have a high frequency. The high-frequency zones for southeastern Australia and for more of the Balkan states have expanded somewhat.

All the high-risk regions are bounded by areas of medium risk, with prevalence rates to date of between 5 and 29 per 100,000; these areas consist of the southern United States,

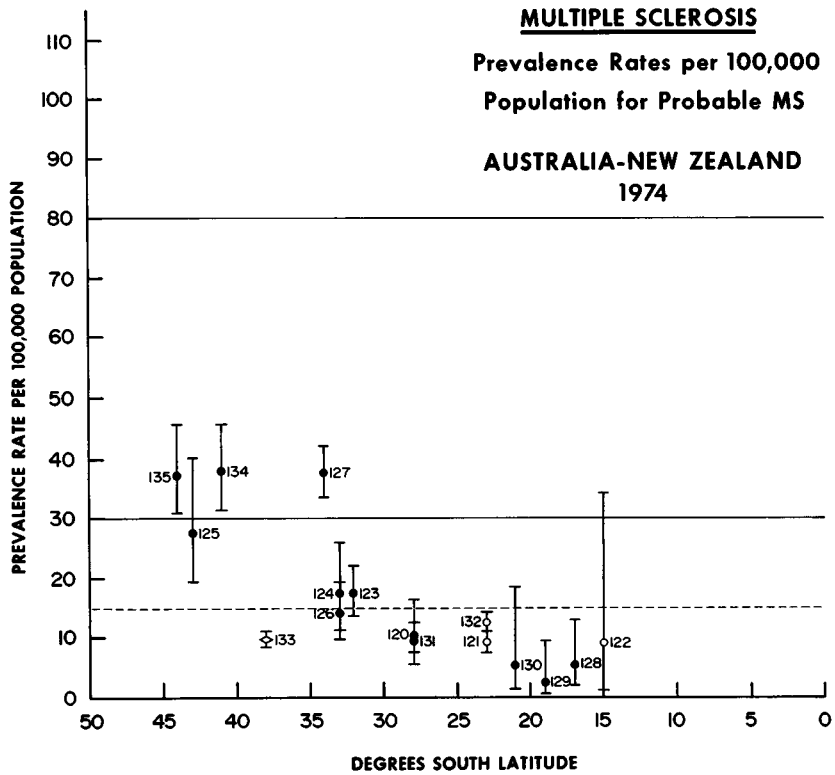


FIG. 7. Prevalence rates per 100,000 population as of 1974 for probable MS in Australia and New Zealand, as in Fig. 5. Reprinted with permission from the publisher (138, 138a).

southwestern Norway, northernmost Scandinavia, and probably Russia from the Ural Mountains into Siberia, as well as the Ukraine. Except for Italy and Cyprus (and Israel?), with the high rates discussed above, the entire Mediterranean basin is also still of medium prevalence. This classification pertains to the northern shores, but it also seems to apply to the African littoral and to the Near East nations, as far as Saudi Arabia, Jordan, and Kuwait. However, the latter findings are still rather tenuous, so I have not altered the map in Fig. 10 to incorporate them.

Much of Australia still falls in the medium-frequency zone, as do perhaps Hawaii and the middle portion of South America. Both ethnic groups of whites in South Africa now share equally in this grouping. Low-frequency areas, with prevalence rates of less than 5 per 100,000, comprise all other areas of Asia and Africa, Alaska and Greenland, and the Caribbean region, including Mexico and probably northern South America, for which data are available.

AGE, SEX, AND RACE

Prevalence Rates

The majority of the more recent prevalence studies have reported higher rates among females than among males, by a ratio now of at least 1.5:1. The sex difference is most marked at younger ages, with few differences beyond age 50. Age-specific prevalence rates are illustrated by the Danish nationwide survey of Hyllested (99) (Fig. 11) (168); the maximal age-specific rates per 100,000 were 179 for females and 137 for males. Another well-done nationwide survey of MS, that for Ireland (34), provided age- and sex-specific rates as of 1971 that were similar in all respects to those reported for Denmark 2 decades previously (Fig. 12).

Incidence Rates

The annual incidence rate for probable MS in high-risk areas at present is at least 3 per 100,000 population, with some surveys showing a rate of 5 or more; in medium-risk areas, the incidence rate is about 1 per 100,000, while in low-risk areas, it is about 1 per 1,000,000 (148, 151). There was no apparent change in incidence in Winnipeg and New Orleans, La., over several decades (259, 260). Incidence rates did not apparently change appreciably in Rochester, Minn., for 70 years (211, 246); however, in 1990, Wynn et al. (290) reported a significant increase from an annual incidence rate of 2 per 100,000 for 1905 to 1944 to about 7 per 100,000 for 1965 to 1984. Millar (193) noted stable incidence rates in Northern Ireland for over 25 years. As with Rochester, the reported incidence increased in Norway, Finland, and Italy, as discussed above, as well as in Wales (96). Denmark had "corrected" incidence rates of 5.1 for 1950 to 1959, 3.9 for 1960 to 1969, and 4.3 for 1970 to 1979; "corrections" were for delayed ascertainment. The rate for 1950 to 1959 was significantly in excess of that for 1960 to 1969 (116)—and for 1939 to 1945.

From the Danish 1949 prevalence study (99), average annual incidence rates were calculated from the cases between 1939 and 1945. An annual rate of 3.4 per 100,000 was found: 3.0 for male and 3.7 for female (134, 135). Age-specific rates rose rapidly from essentially 0 in childhood to peaks at about age 27 of more than 9 per 100,000 for females and 7 per 100,000 for males (Fig. 13). Beyond age 40 there

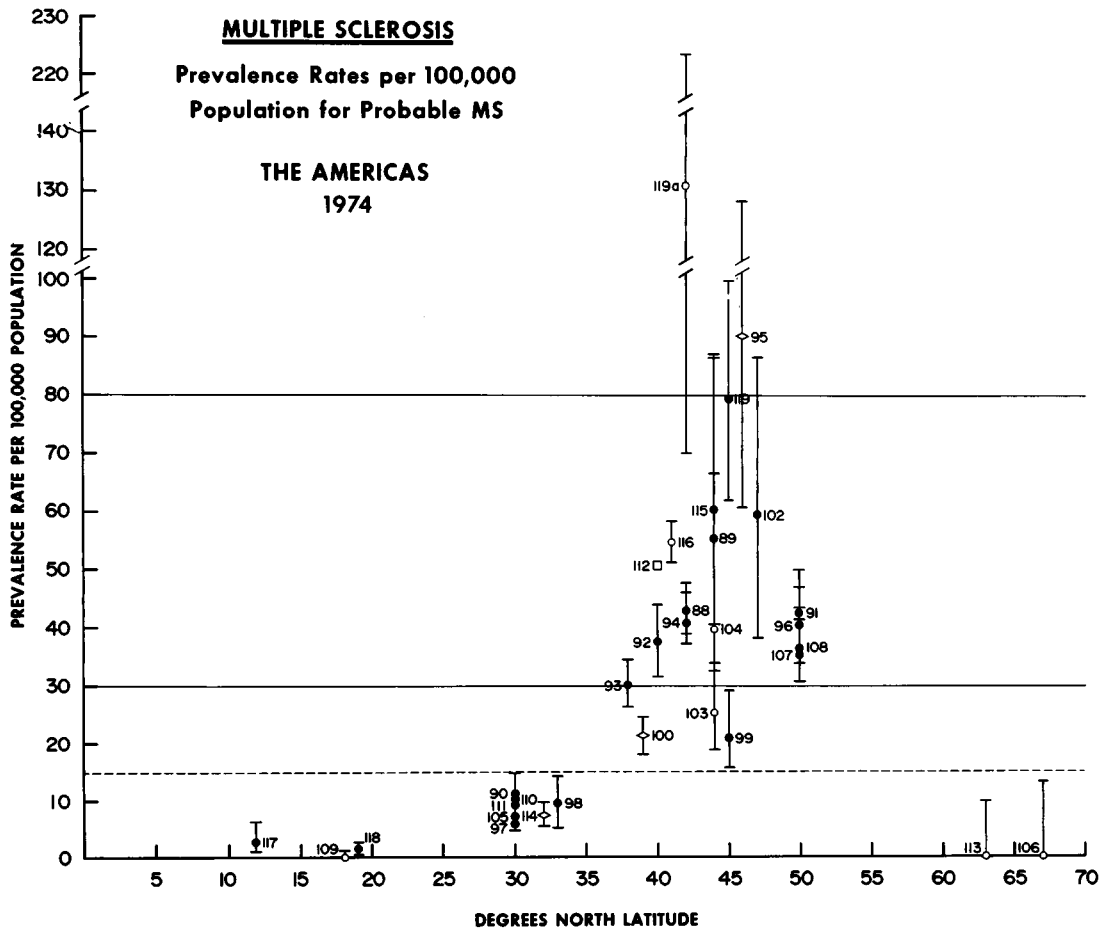


FIG. 8. Prevalence rates per 100,000 population as of 1974 for probable MS in the Americas, as in Fig. 5. Reprinted with permission from the publisher (138, 138a).

was little difference between the sexes, both of whose rates declined equally to 0 by age 60.

Japan is a low-risk area, with a likely overall prevalence rate for probable MS of about 2 per 100,000 population. Shibasaki et al. (253) pointed out the similarities in age at onset, course, and duration of MS between Orientals (Japanese) and whites in Hawaii. If the duration of illness in Japan is similar to that in Denmark, then the ratio of the incidence rates in the two countries will equal the ratio of their prevalence rates. In this manner, I estimated an average annual incidence rate for MS of 11.55 per 10 million population in Japan (148). The MS Study Group of Japan reported age at onset for 497 probable MS, 330 possible MS, and 77 Devic's disease cases (126). By adjustment of the 1968 population of Japan so that the 497 probable MS cases provide a rate of 11.55 per 10 million, age-specific incidence rates for all three conditions can be calculated. The resulting annual incidence rate for Devic's disease is 1.8 per 10 million. The age-specific incidence rate curve for probable MS in Japan shows a striking similarity to that for probable MS in Denmark (Fig. 14).

Race

From the worldwide distribution of MS (Fig. 10), it can be seen that all the high- and medium-risk areas are those with predominantly white populations. Death rates from MS in the United States demonstrated fewer deaths from MS for nonwhites. In the U.S. veteran series, black males had only half the MS risk of white males, regardless of their tiers of residence (Table 2). Note, too, that (young) white female veterans had nearly twice the risk of MS as did white male veterans. The same series, although with small numbers, indicated a paucity of Orientals, Filipinos, and American Indians with MS. An apparent lack of Latin Americans was explicable by geography, since the north and south MS case/control ratios were similar to those for whites (Table 3) and, for the foreign born, ratios for all races were alike (Table 4).

Prevalence estimates among native Japanese have been uniformly low (138, 146). Detels et al. (61, 62) have presented good evidence of low MS mortality and prevalence among Japanese and Japanese-Americans in California and Washington. Data from Hawaii (17) have suggested a low MS risk among Polynesians and Filipinos residing in the state. The illness is rare in Maoris of New Zealand (194, 255) and in Cape Coloured of South Africa, with virtually no blacks affected in that country (110, 111).

MS, then, is predominantly a white (female) burden. Nevertheless, the other racial groups still manifest the same geographic distributions as whites, but the occurrence of MS is lower.

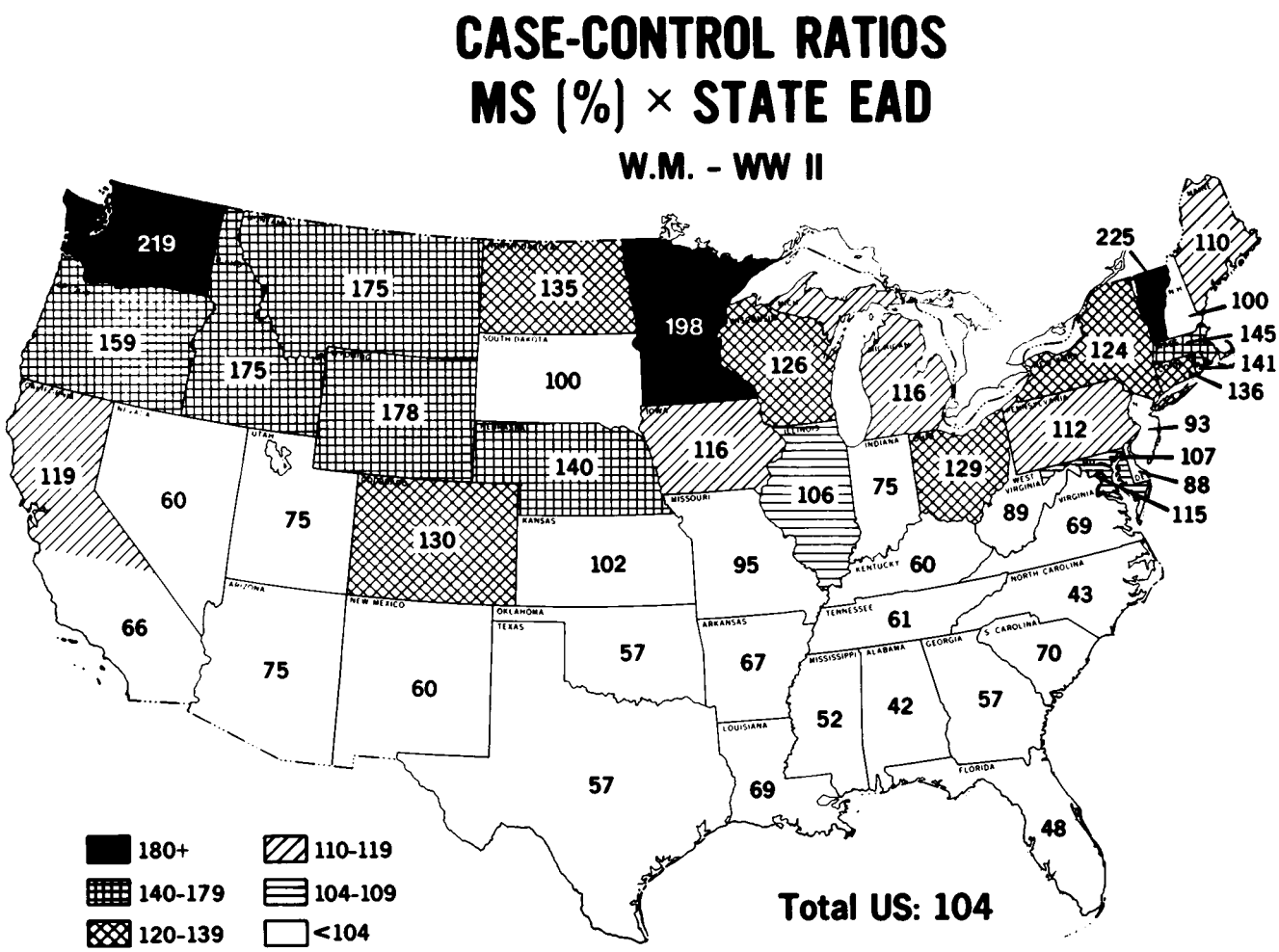


FIG. 9. Case/control ratios expressed as percentages for U.S. white male (W.M.) veterans of World War II (WW II) service connected for MS, by state of residence at entry into military service. A ratio of 0.75 reflected a prevalence rate of 30 per 100,000 population. Modified and reprinted with permission from the publisher (155).

RISK FACTORS

It is clear from the preceding discourse that age, sex, race, and geography are all important—and independent—risk factors in the expression of MS, but all are quite nonspecific (133). More discriminating characteristics are clearly needed to understand this illness.

Geographic Correlates

Attempts to identify factors that would explain the unique geographic distribution of MS have been numerous but unsuccessful (1–4, 18, 23, 148, 150, 151, 168, 169). Dietary fat (11) and trace elements and heavy metals (40, 97, 243, 278, 285) have been implicated, but these observations remain largely unsupported.

The large data set of the U.S. veteran series was analyzed as to geographic correlates for the counties of birth of the patients and their controls (204). Taken singly, all of the characteristics tested were highly significantly related to the risk of MS. However, when adjusted for latitude per se, not one of these attributes showed any significant relationship (Table 5). It was concluded (204) that "an explanation for the [marked] influence of latitude must be sought outside of the realm of conventional meteorologic variables." Multiple logistic regression analyses confirmed the importance of latitude alone (203, 205).

Population ancestry. In the U.S. veteran series, some anomalies in the distribution of MS risk by state (Fig. 9) indicated that latitude per se might not be the sole determining factor of risk, since each tier of latitude contained states with different levels of MS risk. When an explanation for such variations was sought, the hypothesis that ancestry might be a contributing factor was formed (207). The lack of ancestry data for the individual MS cases and controls in the cohort required the analysis of population-based information. The U.S. decennial census of 1980 provided these data in tabulated form (39) for about 188 million persons.

The analysis included only the 10 largest self-reported ancestry groups (English, German, Irish, French, Italian, Scottish, Polish, Dutch, Swedish, and Norwegian) as well as two additional groups of interest: Danish and "Scandinavian, not otherwise specified." Data were tabulated separately for respondents who reported "at least one specific ancestry group" (total ancestry) and for those who reported only "a single ancestry group" (single ancestry).

Proportions of residents with a specific ancestry by state were compared with case/control ratios for white male veterans of World War II by state of residence at birth and at

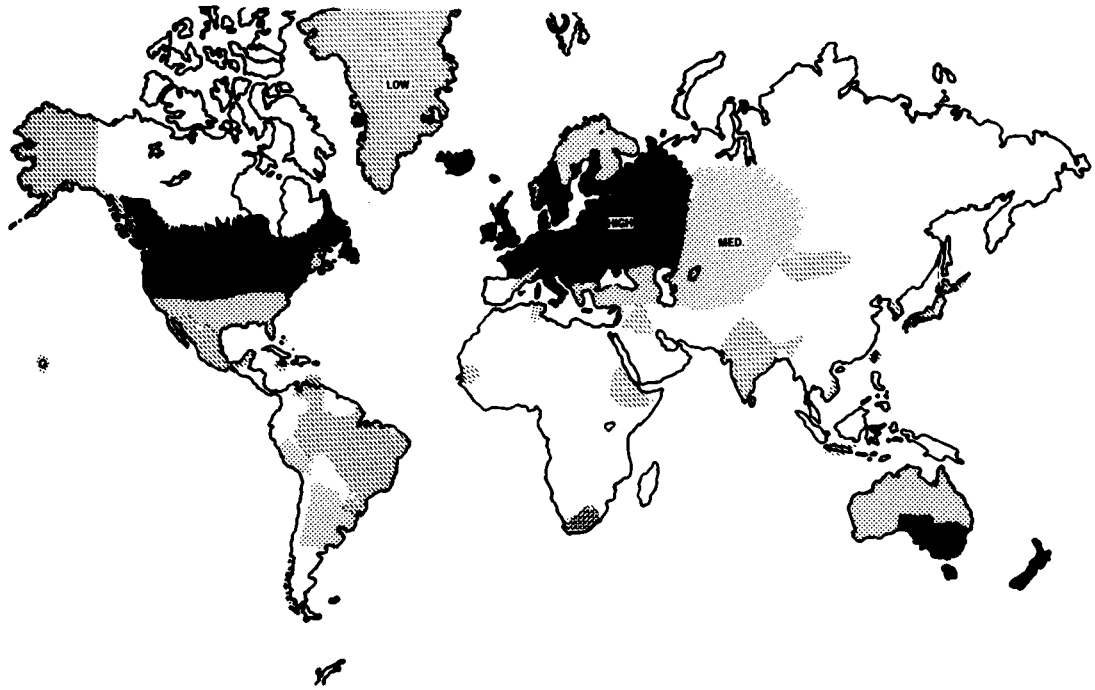


FIG. 10. Worldwide distribution of MS as of 1987. Areas of high frequency (prevalence rates of 30 or more per 100,000) are indicated by black areas, those of medium frequency (prevalence rates of 5 to 29 per 100,000) are indicated by stippled areas, and those of low frequency (prevalence rates of less than 5 per 100,000) are indicated by hatched areas. White areas indicate regions for which there are no data. South American frequencies are tentative. Reprinted with permission from the publisher (154).

entry into active duty (EAD), and correlation and regression analyses were carried out with data weighted for state population size.

Table 6 shows the correlation coefficients. Most striking were the highly significant positive correlations of Scandinavian ancestry, especially Swedish ancestry, with MS risk; these were statistically significant for all combinations of

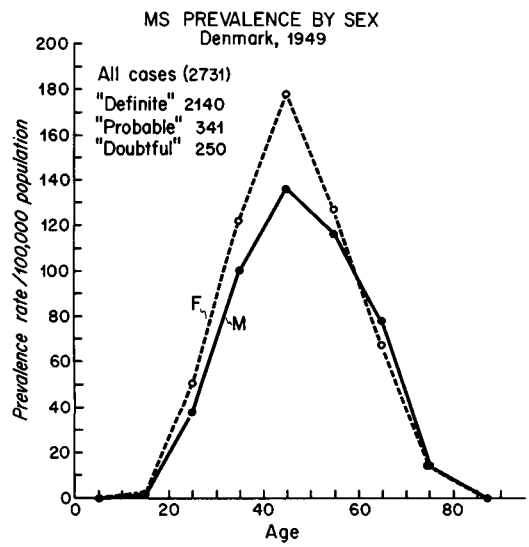


FIG. 11. Age- and sex-specific prevalence rates per 100,000 population for MS in Denmark, 1949, from the data of Hyllested (99). F, female; M, male. Reprinted with permission from the publisher (168).

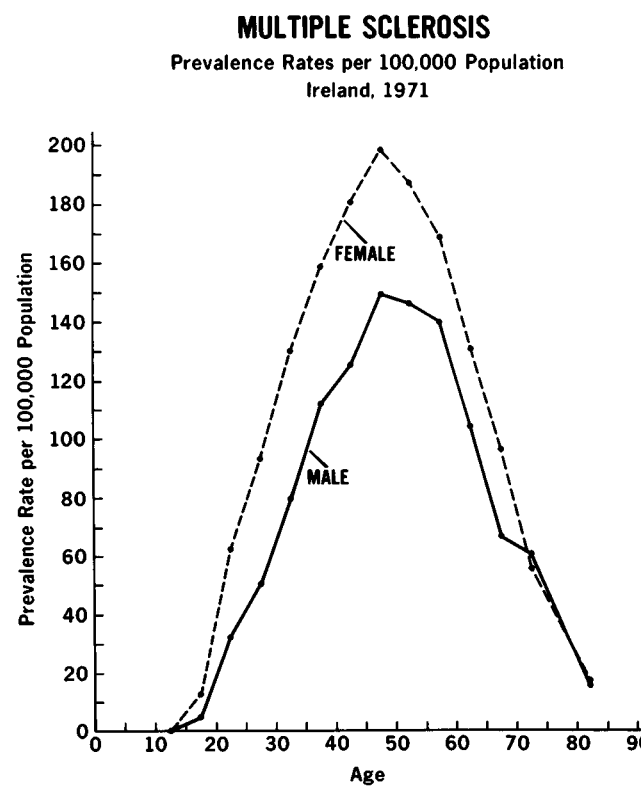


FIG. 12. Age- and sex-specific prevalence rates per 100,000 population for MS in Ireland, 1971, from the data of Brady et al. (34). Reprinted with permission from the publisher (148).

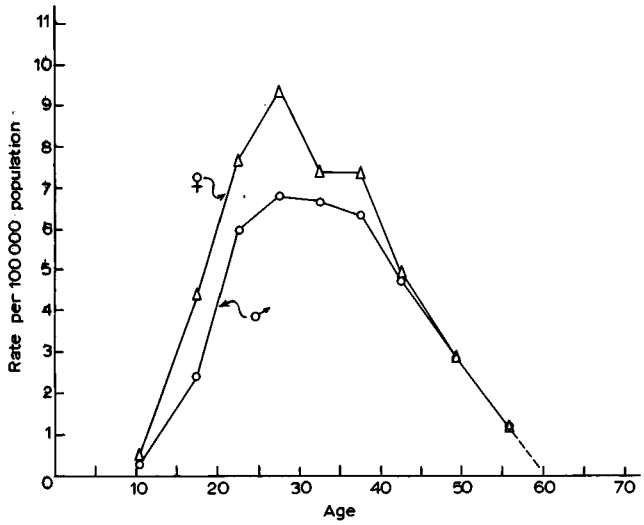


FIG. 13. Average annual age- and sex-specific incidence rates per 100,000 population for MS in Denmark, 1939 to 1945. Reprinted with permission from the publisher (135).

single or total ancestry and birth or EAD state. Thus, in a given state, the higher the proportion of persons reporting Scandinavian ancestry in the 1980 census, the higher the risk of MS among World War II white male veterans who were born in or entered military service from that state.

For more precise quantification of this association, weighted stepwise multiple regression models were fit, with all 12 ancestry groups being used to predict MS risk. Table 7 shows the sign of the regression coefficient (indicating positive or negative association) for each significant variable, along with the proportion of variance in MS risk, a measure of the strength of association.

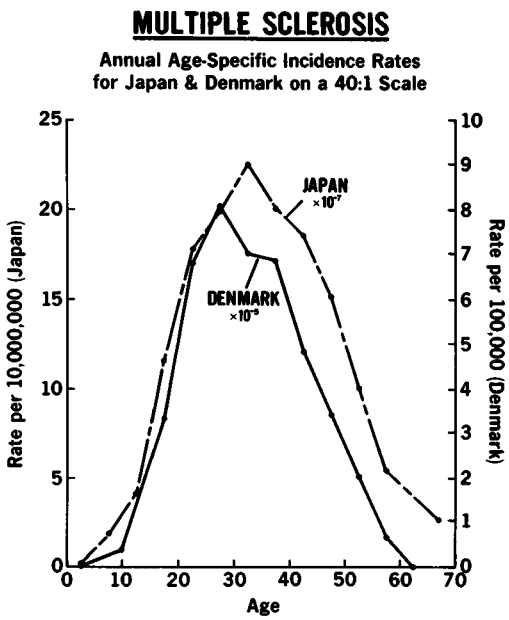


FIG. 14. Average annual age-specific incidence rates for MS per 100,000 population in Denmark (10^{-5}) and per 10,000,000 population in Japan (10^{-7}). Reprinted with permission from the publisher (148).

Thus, ancestry of the state population by itself explains nearly as much of the variations in MS risk (45 to 60%) as does geography (latitude) per se (60 to 67%). Even when ancestry is combined with geography in a joint model (data not shown), it remains a statistically significant and independent predictor of MS risk. In this latter analysis, though, the Italian correlation disappears. Although the specific ancestry groups significantly predicting MS risk vary somewhat in the different analyses, Swedish (or, in one case, Scandinavian) ancestry is always a significant positive predictor of MS risk.

Ebers and Bulman (65) had done a similar analysis of the data of the veteran series (155) and concluded that "the distribution of MS in the United States, at least in part, reflects the distribution of genetic susceptibility factors." Bulman and Ebers (37) found "the highest correlations between MS prevalence and Scandinavian birth/ancestry (r = 0.73)." They stated (37), "The analysis we report here supports a genetic explanation for the geography of MS in the U.S."

That these data provide evidence for "a genetic explanation" seems a premature statement. More appropriate would be that of Page et al. (207), who stated, "These findings provide evidence that ancestry of the resident population—a confounded measure of genetic susceptibility and cultural environment—is part of the complicated picture of MS as a disease of place."

A link between ancestry and MS risk has older antecedents. Early in this review I cited Davenport's presentation of data on drafted men in World War I (48). He reported for whites a high rate of MS in the Great Lakes region and Washington (Fig. 15). He stated that "there is some race inhabiting [these regions] that is especially subject to multiple sclerosis. . . . One thinks of the big Swedes that live in this country." However, he continued that "whether or not . . . multiple sclerosis [is] especially common among Scandinavians cannot be definitely asserted." Bailey's findings (22) also apply to MS during service in that war. Geographically, the cases were distributed like those in the report of Davenport, and Bailey did note an excess among the foreign born, in particular Scandinavians. Below I present a conjecture to explain these and other findings relating to the distribution of this disease.

Personal Characteristics

Most retrospective case-control comparisons by a number of workers have revealed no significant associations, other than the accepted geographic variations (11, 12, 20, 115, 120, 206, 220, 222, 224–226, 282). Poskanzer (220, 222) reported that patients had had a tonsillectomy in more instances than had either their spouses or their nearest siblings; however, these results have not been replicated. In the Israeli studies, there were possible inverse relationships with indices of poor sanitation and a direct relationship to some features of urbanization (12, 20). Reports implicating canine distemper or dog exposure have been published, but to date these also remain unverified (see reference 151 for information up to 1983; later data do not seem to alter this conclusion).

In Olmsted and Mower Counties, Minn., small family size was significantly associated with the risk of MS (120). Whether this association reflects socioeconomic status (see below) is uncertain, although urban residence and high educational achievement did have relative risk estimates of >1. In a small U.S. veteran twin series, Bobowick et al. (33) reported a significant excess of prior "environmental events" among affected versus unaffected twins. These

TABLE 2. MS case/control ratios by tier of residence at EAD for major sex and race groups, from the U.S. veteran series[a]

Sex and race	MS case/control ratio (no. of MS cases/no. of controls) by the indicated tier of residence at EAD[b]:			
	North	Middle	South	Total[c]
White male	1.41 (2,195/1,544)	1.02 (2,059/2,022)	0.58 (688/1,161)	1.04 (4,922/4,737)
White female	2.77 (97/35)	1.71 (65/38)	0.80 (20/25)	1.86 (182/98)
Black male	0.61 (28/46)	0.59 (88/150)	0.31 (61/194)	0.45 (177/390)
Total[d]	1.41 (2,323/1,647)	1.00 (2,213/2,219)	0.53 (762/1,425)	1.00 (5,298/5,291)

[a] Modified and reprinted with permission from the publisher (151, 155).
[b] States north of 41 to 42° comprised the North tier, and those south of 37° comprised the South tier.
[c] Excludes 1 male case and 11 male controls inducted in foreign countries.
[d] Includes black females and other (nonwhite, nonblack) persons.

events included operations, trauma, and infections as the major groups; differentiating frequencies were mostly within 20 years before clinical onset rather than in early childhood. Operskalski et al. (206), using a mailed questionnaire survey, recorded a notably increased risk with a history of infectious mononucleosis and lesser increases with moves and travel.

Poskanzer et al. (225) drew an analogy with poliomyelitis and suggested that the existence of such an infection, if more commonly acquired early in life, protected against MS in low-risk areas. This "subtle hypothesis," as Acheson (1) termed it, is that the cause of MS is much more widespread where the disease is rare than where it is common. As was true with poliomyelitis, early birth order has been reported to increase MS risk (103); however, others have found no relationship to birth order (10, 115, 275).

Beebe et al. (26) compared MS patients with matched controls from an earlier U.S. Army series, using data collected before MS was diagnosed. Among the characteristics that significantly differentiated patients from controls were geographic location at birth or service entry but not during military service before onset (see below). There was a strong positive correlation with urban residence, high socioeconomic status, and visual defects (refractive errors) at entry into service. Table 8 summarizes the first two of these factors, indicating each one to be an important variable.

TABLE 3. MS case/control ratios by birthplace and race for other (nonwhite, nonblack) males, from the U.S. veteran series[a]

Birthplace and race	Ratio	No. of MS cases/no. of controls by the indicated tier of birthplace[b]:		
		Total	North	South
Coterminous United States	0.48	11/23[c]	6/12	5/11
American Indian	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 and Latin America	0.29	6/21		
Mexican-Spanish American	0.00	0/5		
Puerto Rican	0.38	6/16		
Hawaii	0.00	0/15		
Japanese	0.00	0/10		
Other	0.00	0/5		
Asia	0.00	0/14		
Chinese	0.00	0/4		
Filipino	0.00	0/9		
Other	0.00	0/1		
Total	0.23	17/73		

[a] Modified and reprinted with permission from the publisher (155).
[b] North includes north plus middle. For white males, the MS case/control ratios were 1.2 for north and 0.6 for south.
[c] Includes 1 Filipino control.

Some Laboratory Correlates

Antibodies. As reviewed elsewhere (106, 150, 231), a number of workers have reported elevated levels of viral antibodies in the serum or spinal fluid of MS patients, including those for measles, herpes, mumps, rubella, varicella-zoster, and canine distemper. For all of these but measles, there are at least an equivalent number of negative studies. There is also conflicting evidence regarding elevated levels of measles antibodies in siblings of MS patients. Rickettsial antibody levels also have been variably noted as high or not high. Compston et al. (42) related the elevated levels of antibodies, especially those for measles, to both older age at acquisition of these infectious diseases and the presence of HLA-DR2 (see below). Visscher et al. (276) found measles antibodies to be more closely related to HLA-A3 and HLA-B7 than to the diagnosis of MS among siblings.

Recently, several workers found elevated Epstein-Barr virus (EBV) antibodies in MS patients (35, 175, 261). However, elevated EBV antibody levels have been found with alveolitis (273), rheumatoid arthritis (56), and "unexplained illnesses" (107), and the virus has been isolated from genital ulcers (215). Pedneault et al. (210) presented evidence for EBV in 18 of 24 brains with various infectious and lymphomatous encephalopathies by use of the polymerase chain reaction. Chronic EBV infection does not seem to be an unusual condition.

Koprowski et al. (119) found antibodies to human T-cell

TABLE 4. MS case/control ratios by race and birthplace for foreign-born servicemen in selected regions, from the U.S. veteran series[a]

Region(s)	Ratio	No. of MS cases/no. of controls of the following race:			
		Total	White	Black	Other
Mexico and Central America	0.14	2/14	1/9	1/0	0/15
Puerto Rico	0.42	14/33	6/14	2/3	6/16
Hawaii	0.06	1/16	1/1	0/0	0/15
Japan and Korea		4/0	4/0	0/0	0/0
China	0.00	0/4	0/0	0/0	0/4
Philippines and Southeast Asia	0.00	0/12	0/2	0/0	0/10

[a] Modified and reprinted with permission from the publisher (155).

TABLE 5. MS case-control (C) pairs by county of birth and latitude of birthplace according to geographic correlates (factor A) for the county of birth, from the U.S. veteran series[a]

Factor A	Value resulting from analysis by:					
	Latitude for case-control pairs with factor A			Factor A for case-control pairs with latitude		
	MS > C	MS < C	*P*	MS > C	MS < C	*P*
Mean annual freeze-free period (F-F)	388	359	0.15	501	320	$<10^{-9}$
Annual solar radiation (sol)	207	210	0.46	894	530	$<10^{-21}$
Mean annual h of sunshine	504	487	0.30	552	307	$<10^{-16}$
Mean annual days with a temp of >90°F (32.2°C)	394	431	0.10	333	222	$<10^{-5}$
Mean annual days with a temp of <32°F (0°C) (cold)	577	537	0.12	170	105	0.00006
Mean July relative humidity	489	486	0.47	616	338	$<10^{-18}$
Mean annual pan evaporation (pan)	269	255	0.28	565	359	$<10^{-10}$
Mean annual days of precipitation (rain)	534	517	0.31	504	300	$<10^{-12}$
Mean annual days forecasted to have air pollution	653	658	0.46	309	173	$<10^{-9}$
Ground H_2O minerals	408	392	0.30	821	508	$<10^{-17}$
Elevation, ft above sea level (1 ft = 30.48 cm)	553	509	0.09	552	286	$<10^{-19}$
Cold × rain	751	681	0.03	77	39	0.0003
Sol × pan	376	389	0.33	452	280	$<10^{-9}$
F-F × rain	669	646	0.27	187	139	0.005
Cold × pan	609	606	0.48	128	81	0.007

[a] Modified and reprinted with permission from the publisher (204).

lymphotrophic virus type I (HTLV-I) in serum and CSF for two groups of MS patients: one of 35 Swedish patients and the other comprising 17 of the patients from the Key West "epidemic" (252). Epstein and colleagues (69) were unable to confirm any HTLV-I-positive sera for 17 MS patients in metropolitan New York. Other studies reporting negative results for HTLV-I and human immunodeficiency virus (HIV) have been published from Italy, France, and the French West Indies (59, 79) and for the former from Japan (125). De Freitas et al. held a conference on this topic (57). Still, no group has yet confirmed the HTLV-I findings. Rasmussen et al. (230) found only a few sera positive for HTLV-I, HIV type 1, or HIV type 2 antibodies in 50 MS patients. Ferrante et al. (70) found HTLV-I antibodies in serum—but not CSF—in only 8 of 157 MS patients and concluded that these results "do not support the idea that HTLV-I is the aetiological agent in MS."

Cellular immunity. There is little doubt that immune system defects are present in MS (19, 21, 89, 101, 150, 182, 197, 231, 267, 268, 277). Many workers have identified abnormalities in the cellular immune response and/or abnormalities in the T-cell populations that mediate this response. Such reports have been most consistent for alterations in the T4/T8 (helper/suppressor) cell ratio, with a reduction in the latter cell type, particularly when the disease is clinically active. Nomenclature for these functionally defined lymphocytes, and in particular for subsets (or equivalents) of these groups, still seems to be in flux. A T-cell response to myelin basic protein was found in both MS-affected and unaffected members of a family with conjugal MS, independent of major histocompatibility complex class phenotype (76). Tienari and coworkers reported linkage of the myelin basic protein

TABLE 6. Correlation of ancestry (single and total) with MS risk (tabulated by birth state and EAD state), reported as Pearson correlation coefficients[a]

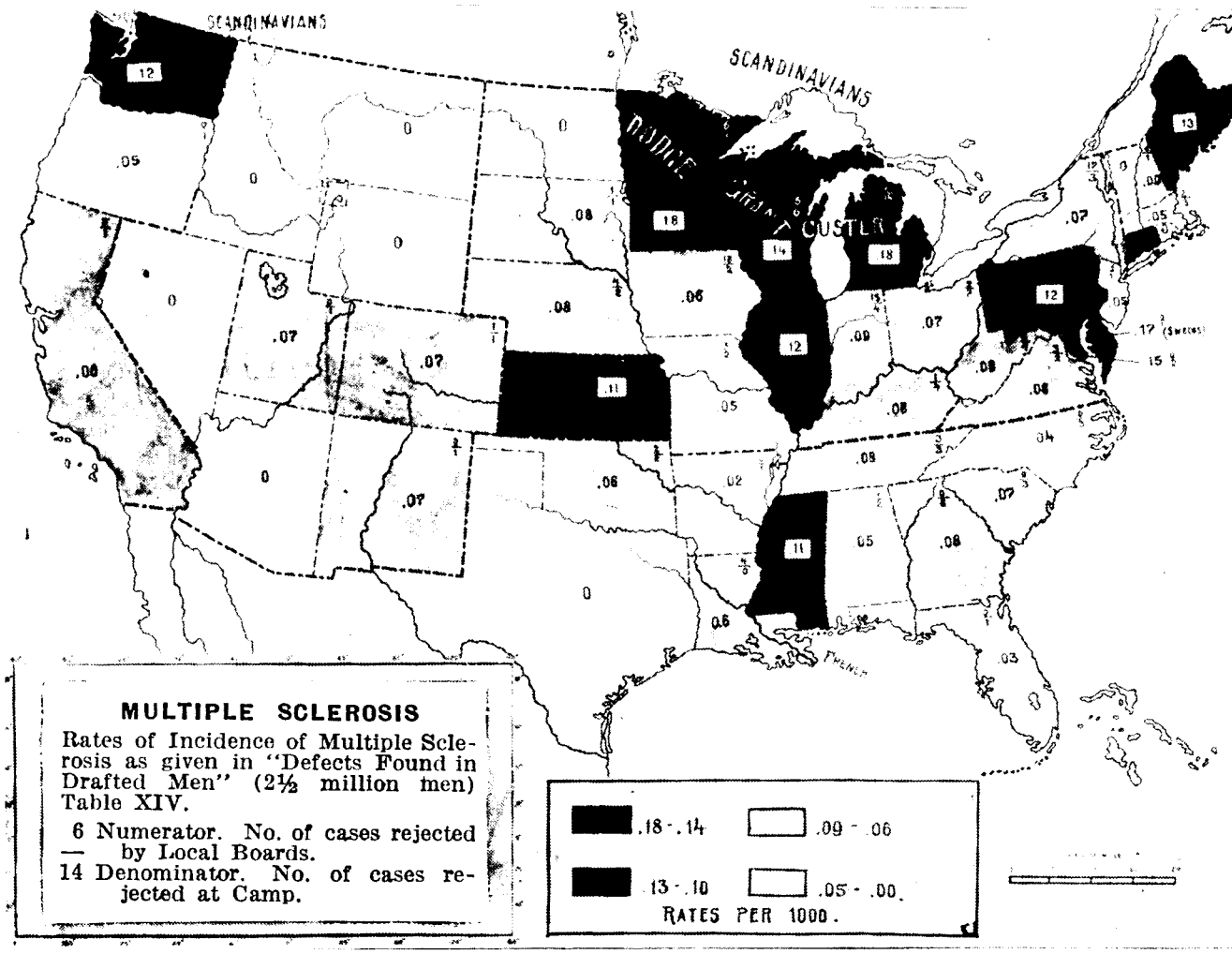
Ancestry type	Pearson correlation coefficient			
	Birth state		EAD state	
	Single ancestry	Total ancestry	Single ancestry	Total ancestry
English	−0.565[b]	−0.425[c]	−0.565[b]	−0.409[c]
German	0.250	0.276	0.260	0.309[d]
Irish	−0.136	−0.149	−0.114	−0.066
French	0.152	0.273	0.131	0.294[d]
Italian	0.212	0.238	0.207	0.228
Scottish	0.156	−0.077	0.107	0.151
Polish	0.296[d]	0.352[d]	0.283	0.349[d]
Dutch	0.077	−0.045	0.101	0.023
Swedish	0.545[b]	0.545[b]	0.631[b]	0.634[b]
Norwegian	0.401[c]	0.445[c]	0.444[c]	0.497[b]
Danish	0.306[d]	0.345[d]	0.263	0.375[c]
Scandinavian, not otherwise specified	0.489[b]	0.509[b]	0.554[b]	0.566[b]

[a] Modified and reprinted with permission from the publisher (207). Based on 1980 decennial census data aggregated by state (39).
[b] $P < 0.001$.
[c] $P < 0.01$.
[d] $P < 0.05$.

TABLE 7. Proportion of variance in MS risk, as explained by ancestry (single and total)[a]

Variable and direction of association[b]	Proportion of variance (%)			
	Birth state		EAD state	
	Single ancestry	Total ancestry	Single ancestry	Total ancestry
Swedish (positive)		29.7	39.8	40.2
Italian (positive)		16.2	15.2	17.6
Scandinavian, not otherwise specified (positive)	12.3			
Scottish (positive)	16.5			
English (negative)	31.9			
Total model	60.7	45.9	55.0	57.8

[a] Modified and reprinted with permission from the publisher (207). Based on 1980 decennial census data aggregated by state (39).
[b] Positive means that MS risk increases with increasing values for the variable; negative means that MS risk decreases with increasing values for the variable.



gene, located on chromosome 18, to MS in familial and sporadic cases (269).

Activated T cells, particularly helper cells, are found in the CSF as well. However, whether these changes reflect the cart or the horse—whether they are of etiologic importance or the consequences of the disease process—remains to be clarified.

HLA antigens. The HLA (human leukocyte-associated) antigens located on chromosome 6 have also been studied extensively. Associations with MS have been described for HLA-A3 and HLA-B7 of the major histocompatibility complex class I genes, particularly for northern European whites. More specific associations have been found for class II HLA-DR2 and/or HLA-DW2 or HLA-DR4. Excess HLA-DR2 has been suggested to be associated with MS in Cape Coloured of South Africa (71) and in Mexican Mestizos (82), and this is perhaps the most consistently elevated HLA antigen among MS patients in the United States and Europe (258, 271). More recently, HLA-DQw1 and HLA-DQβ have been proposed as the most specific differentiators (75, 180, 188). The former was found significantly elevated in Grampian Region (Scotland) patients who had no significant excess HLA-DR2 (75). Kolstad et al. (118) found HLA-DQβ in 34 of 35 MS patients and 79 of 106 controls, but such a high proportion has yet to be replicated. The association of MS with these genetically determined antigens has naturally led to the search for "MS susceptibility genes." However, no HLA subset has been thus far universally found in MS patients, but HLA-DQβ may be close, and certainly each pattern is present among unaffected persons. Further consideration of this aspect involves familial features in MS.

Familial Frequency

There have been a number of rather detailed assessments of familial frequency and genetic susceptibility in MS (90, 190, 201, 257), among which will be found some interpretations that differ from the following.

In early large published series, the frequency of multiple cases of MS in families was on the order of 6%, with a range of 2 to 17%. Among those series, the frequencies of MS among siblings and parents were about 1 and 0.5%, respectively. These respective frequencies would be about six to eight and three to four times expectations for the general population in the times and areas considered (129, 140). A large and contradictory body of literature has arisen with

TABLE 8. MS case/control ratios by socioeconomic status and by type of residence at entry into military service, from the U.S. Army World War II series[a]

Type of residence	MS case/control ratio by the indicated socioeconomic status scores[b]:					
	000–069	070–109	110–149	150–200	Total	No. of MS cases
Metropolitan	2.00	3.67	1.70	3.50	2.40	48
Other urban	1.60	1.33	2.17	1.57	1.67	40
Mixed	0.63	0.88	1.21	1.52	0.98	209
Rural	0.62	0.36	1.09	1.20	0.63	71
Total	0.70	0.81	1.33	1.61	1.00	
No. of MS cases	85	96	100	87		368

[a] Modified and reprinted with permission from the publisher (26, 153).
[b] Sum of scores for preservice occupational status (Bureau of Census codes [269a]) and for educational level, each ranging from 0 to 100; the higher the score, the higher the socioeconomic status.

regard to shared genetic components, predominantly in the HLA series, in families of MS patients. One "pro" came from the University of California at Los Angeles group on the west coast (274), and a "con" came from the National Institutes of Health group on the east coast (67). I believe that the most meaningful work, though, is that of Roberts et al. (235, 236), who assessed familial histories in cases ascertained in the aforementioned MS prevalence studies of the Orkney Islands (223, 226). In the Orkneys, MS patients did not differ from controls in HLA patterns or in other blood group, isoenzyme, or serum protein systems. They were neither more nor less inbred than controls. The only possible single-gene inheritance the authors thought at all likely was autosomal recessive with 12% penetrance. "Much more likely is a complex aetiology, the genetic contribution being polygenic and possibly subordinate to the environmental . . ." (236).

Twin studies. Unbiased data on twins, which might clarify the role of genetics, are still inconclusive. Most published twin studies on MS suffer from selection bias and retrospective family ascertainment. The only ones for which the prospective occurrence of MS within a defined cohort of twins has been assessed are those of Bobowick et al. (33), Heltberg and Holm (95), and Kinnunen et al. (113). In no instance was there a significant difference in MS concordance ratios between monozygous (MZ) and same-sexed dizygous (DZ1) twins, but the numbers were small: 1 of 6 MZ versus 0 of 8 DZ1 were concordant in the first study, 4 of 19 MZ versus 1 of 28 DZ1 in the second, and 1 of 11 MZ versus 0 of 10 DZ1 in the third.

On the basis of their retrospective but population-based series of MS cases, Ebers et al. (66) concluded that there is a major genetic factor in MS; they reported 7 of 27 MZ sets (including some clinically possible cases) as concordant, versus 1 of 43 for all DZ sets, regardless of sex, a statistically significant difference. However, even this discrepancy does not necessitate a genetic influence. If this disease not only is acquired but also is acquired in, for example, adolescence, it would not be at all surprising to find a difference between MZ and DZ1. Identical twins are much more likely to behave alike than are fraternal twins; so long as they are living together, they are much more likely to be exposed to the same environmental stimuli. "My own view has been that a genetic factor is *unnecessary* to consider in seeking an explanation for the cause [of MS] (not that there cannot be one), which cause to me lies in the environment" (140).

A most important work has just been published by the French Research Group on Multiple Sclerosis (77). In a national registry of some 8,000 MS patients as of 1986, 116 sets of twins were identified; 97 sets were contacted, and 70 sets had a living co-twin. Of these 70, 15 refused examination (although there was evidence of no disease in the co-twin). The examined sample of 54 sets showed clinically concordant MS in 1 of 17 MZ and 1 of 37 DZ. For 42 unaffected twins, the magnetic resonance imaging result was abnormal in 9 and visual evoked potentials were abnormal in 3; magnetic resonance imaging results and visual evoked potentials were abnormal in 3 and 1 MZ twins and in 6 and 2 DZ twins, respectively.

McFarland (189) properly pointed out that the French MS Registry is not population based but was "established with the help of a public appeal on national and regional TV channels" (77). McFarland noted that this fact was less important than the incomplete ascertainment, and he concluded that "the bulk of evidence continues to support a strong genetic influence in MS . . ." (189). However, I believe that this French work strengthens my statement quoted above (140) and makes even more crucial a full publication of the updated Danish work of Heltberg and Holm—at present now available only in a 1982 abstract (95).

MIGRATION IN MS

None of the material discussed thus far really solves the question of nature versus nurture. However, if one changes the risk of MS by changing the environment, then MS must be an acquired, exogenous, environmental disease(s). It is to solve this question that a number of studies of MS in migrants have been performed.

Population-based rates. Table 9 summarizes MS rates among migrants to and from the different risk areas. The rates were those regardless of age at immigration and clinical onset. In broad terms, there was a tendency for immigrants to retain much, but not all, of the risk of their birthplaces if these were high- or medium-risk areas, but there was also evidence that migrants from low-risk areas had increased their risk of MS. Later data from Australia support a higher prevalence for European immigrants, at least for the crude rates (92, 93). The data in Table 9 should be assessed from the horizontal rows, since several figures are for different age-specific prevalence rates, other figures are age adjusted, and for one survey, they are cumulative risk estimates.

The risk estimates for the Paris immigrants reflect three instances of exacerbating-remitting MS among a series of about 3,400 persons who were born in Vietnam of Vietnamese mothers and French fathers and who came to France at under the age of 20 (157). Their cumulative 18-year risk of MS to 1975 was 89 per 100,000, with a 95% confidence interval of 18 to 260. The age-specific prevalence rate was 169 per 100,000 at ages 20 to 29 (95% confidence interval, 35 to 494). Both measures were similar to such rates for Denmark (142), and both were very significantly higher than MS rates for Vietnamese in Vietnam—but they do apply to half-Orientals.

Death data. In the United States, as mentioned above, death rates for MS were distributed so that states to the north of 37° north latitude had twice the rates of those to the south (Fig. 1). If MS were innate or acquired shortly after birth and MS deaths among those who were born in the north but died in the south were compared with MS deaths among those who were born in the south but died in the north, there would be a mirror image for the distribution seen in Fig. 1.

TABLE 9. MS prevalence rates per 100,000 population among native-born persons and immigrants in different risk areas[a]

MS risk for immigration site	Reference	Publication yr	Immigration site	Prevalence rate for:			
				Native-born persons	Immigrants from the following MS risk areas:		
					High	Medium	Low
High	234	1966	South Australia	38	37	4	—[b]
	63	1978	Washington State	—	55[c]	19[c]	—
	157	1980	Paris	92[d]	—	—	89[d]
	156	1985	Northern United States[e]	49[f]	—	27[f]	—
Medium	187	1969	Perth, Western Australia	14	22	—	—
	187	1969	Perth, Western Australia	40[g]	87[g]	—	—
	263	1962	Western Australia	10	31	—	—
	244	1962	Queensland	9	15	—	—
	13	1962	Israel	4	33	8	3
	176	1972	Israel	9[h]	19[h]		6[h]
	62	1978	Los Angeles	—	30[c]	15[c]	—
	156	1985	Southern United States[i]	22[f]	29[f]	—	—
Low	49	1967	South Africa	6	48	15	—
	195	1966	Dutch Antilles	3	59	—	—

[a] Data are from Kurtzke (154).
[b] —, no comparable rates.
[c] Age-adjusted (1970 U.S. population) rates for persons 20 or older with onset after migration.
[d] Cumulative risk (20 years) in Denmark (142) for "native-born" versus cumulative risk (18 years) for half-Vietnamese immigrants to Paris (157).
[e] North plus middle tiers of states.
[f] Prevalence estimates for white MS case/control ratios.
[g] Age-specific rate (40 to 49 years).
[h] Age-adjusted (1960 U.S. population) rates.
[i] South tier of states (below 37° north latitude).

However, there was then actually an obliteration of the north-south difference, and all rates were closer to the national mean (Fig. 16). The death rate for the U.S. southern-born MS patients who died in the north (0.68) was significantly higher than that for the southern-born ones who died in the south (0.46) (170). A similar change in death rates was reported by Westlund (281) for Norway; rates for those who moved from high- to low-risk regions were decreased, and rates for those who moved from low- to high-risk regions were increased, in contrast to rates for nonmigrants of their birthplaces. These rates really represent migrations from medium- to high-risk regions, rather than those from low- to high-risk regions, as is also true for the group discussed next.

U.S. veteran series. Figure 9 showed state of residence at entry into military service for the U.S. veteran case/control series. In Table 2, these residences were allocated among three horizontal tiers for the coterminous United States: a northern tier of states above 41 to 42° north latitude, a middle

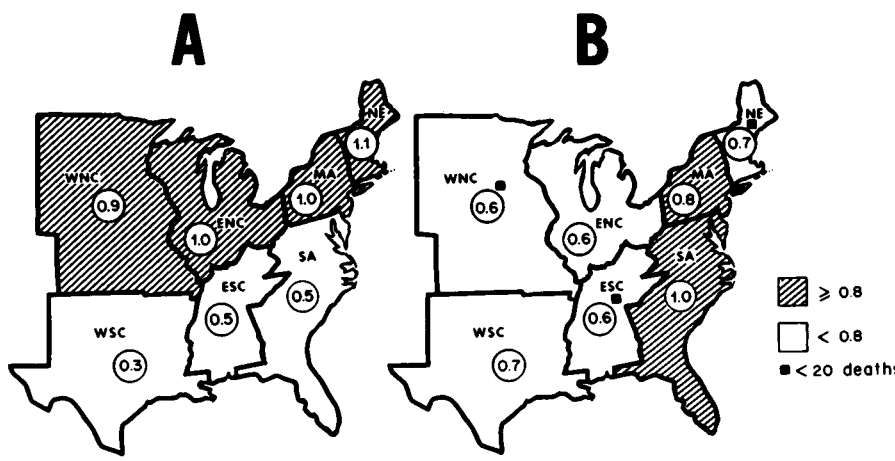


FIG. 16. Average annual death rates for MS per 100,000 population by residence by census region in the eastern two-thirds of the United States for 1959 to 1961. (A) Birth region residence = death region residence. (B) Birth and death region residences in opposite tiers, i.e., born in the north but died in the south versus born in the south but died in the north. The northern tier includes northeast (NE), middle Atlantic (MA), east north central (ENC), and west north central (WNC) census regions; the southern tier includes south Atlantic (SA), east south central (ESC), and west south central (WSC) census regions. Adapted and reprinted with permission from the publisher (170).

TABLE 10. MS case/control ratios for all white veterans of World War II or the Korean Conflict by tier of residence at birth and at EAD for the coterminous United States only[a]

Birth tier	MS case/control ratio (no. of MS cases/no. of controls) by the indicated tier at EAD:			
	North	Middle	South	Birth total
North	1.48 (2,033/1,377)	1.27 (133/105)	0.74 (39/53)	1.44 (2,205/1,535)
Middle	1.40 (160/114)	1.03 (1,899/1,836)	0.73 (80/110)	1.04 (2,139/2,060)
South	0.70 (21/30)	0.65– (50/77)	0.56 (565/1,007)	0.57 (636/1,114)
EAD total	1.46 (2,214/1,521)	1.03 (2,082/2,018)	0.58 (684/1,170)	1.06 (4,980/4,709)

[a] Modified and reprinted with permission from the publisher (156).

tier, and a southern tier below 37°, including California from Fresno southward. Migrants would be those who were born in one tier and entered service from another. The marginal totals in Table 10 provide the ratios for birthplace and for residence at service entry within the three tiers for all white veterans of World War II or the Korean Conflict. The major diagonal (north-north, middle-middle, south-south) provides the case/control ratios for nonmigrants, and cells off this diagonal define the ratios for migrants (156).

All ratios decreased from north to south. The ratio for migrants born in the north tier and entering service from the middle tier decreased from 1.48 to 1.27; for those entering service from the southern tier, the ratio was 0.74. Birth in the middle tier was marked by a significant increase in the MS case/control ratio to 1.40 for northern entrants and a significant decrease to 0.73 for southern ones. Migration after birth in the south provided ratios of 0.65 (middle) and 0.70 (north). This entire distribution showed a highly significant difference from the null hypothesis of no change in birthplace risk: χ^2_6 was 25.150, and P was 0.0003. For all white males only or those of World War II service alone, the differences were still highly significant, while for black males and white females, with their small number of migrants, the trends were similar, although statistical significance was not attained (156).

Nevertheless, opposing viewpoints regarding an increased risk for moves to high-risk areas have been propounded. Detels et al. (61, 63) found no significant increase in either death or prevalence rates for southern-born migrants to Washington. Numbers were so small, though, that a true increase could not be ruled out. Detels et al. (63) did record an increasing prevalence of MS with increasing age at migration for both northern and southern immigrants, with preservation of the north-south differential, which was maximal for the youngest immigrants. Dean et al. (51, 55) described a marked paucity of MS in England among immigrants from low-risk areas. However, it seems that the calculated numbers of the cases expected for such immigrants were markedly inflated, primarily because of the very rapidly expanding immigrant population during the study period and the short length of residence of the immigrants in the new country (139, 148). Of great interest is the finding of Elian and Dean (68) that children of these immigrants had a prevalence rate very much higher than that which Dean et al. (51, 55) recorded for their parents and indeed about what was expected in London (286).

Age at Migration

The veteran series provides the best evidence of an increase in the risk of MS with migration from low- to high-risk areas—and it also indicates that the time at which such moves are critical in defining MS risk is well before clinical onset, since the north/south and south/north migrant ratios were equivalent, as too were the overall birth and EAD tier ratios (see also Fig. 16 and the discussion above). In an early Army study, case/control ratios were similar for the same three tiers for residence at birth and at EAD; however, this risk gradient had totally disappeared for residence during military service but before clinical onset, with all ratios then near unity (26). This result further supports an effect of age on MS risk. The inference is that the critical age for the acquisition of MS in these series is either midway between birth and age at service entry (24 years)—or at about age 12—or equally distributed for some interval above and below age 12.

Other evidence suggesting the acquisition of MS at between approximately ages 10 and 15 years, based largely on ages when patients were most concentrated geographically, has been presented elsewhere (130, 136, 140). Riise et al. (232) found maximal clustering at ages 13 to 20 in Hordaland, Norway, and indicated that a high degree of clustering in adolescence correlated with a young age at onset (233). Schapira et al. (247) also concluded that MS was acquired in early adolescence, on the basis of the ages during common residence for siblings who both had MS. All of these inferences arose from surveys in high-risk areas.

Bulman et al. (38) disputed the analysis of Shapira et al. (247) and presented their own materials on twins and siblings concordant for MS in Canada. They found a tendency for age at onset to be more closely related than year of onset, especially for their MZ twins, and concluded "that age of onset is partly under genetic control. . . ." (38) However, if Canada is a high-risk area of endemicity (as it is), if MS is an acquired exogenous disease, and if susceptibility begins at a mean age of 11 or 12 years, then there would be a tendency for age at onset to be more similar than year of onset in these related patients, even in the total absence of any genetic influence.

Migrants moving from high- to low-risk areas. Aside from the veteran series, there are other prevalence studies for migrants moving from high- to low-risk areas that also suggested that adolescent age is critical for risk retention: those migrating over age 15 retained the MS risk of their birthplace, and those migrating under age 15 acquired the lower MS risk of their new residence (14, 16, 17, 54, 63). These studies considered immigrants to Israel, Hawaii, Los Angeles, and South Africa. The South African study is particularly pertinent. For the 114 northern European immigrants with MS who were resident in South Africa by 1960, there was a very sharp change in frequency and in adjusted prevalence rates for migration at exactly age 15 (Fig. 17) (54, 158). The adjusted prevalence rates for persons aged 15 to 19 at immigration were 66 per 100,000 for United Kingdom immigrants and 81 for all northern European immigrants; the prevalence rate was 13 per 100,000 for either group at ages 0

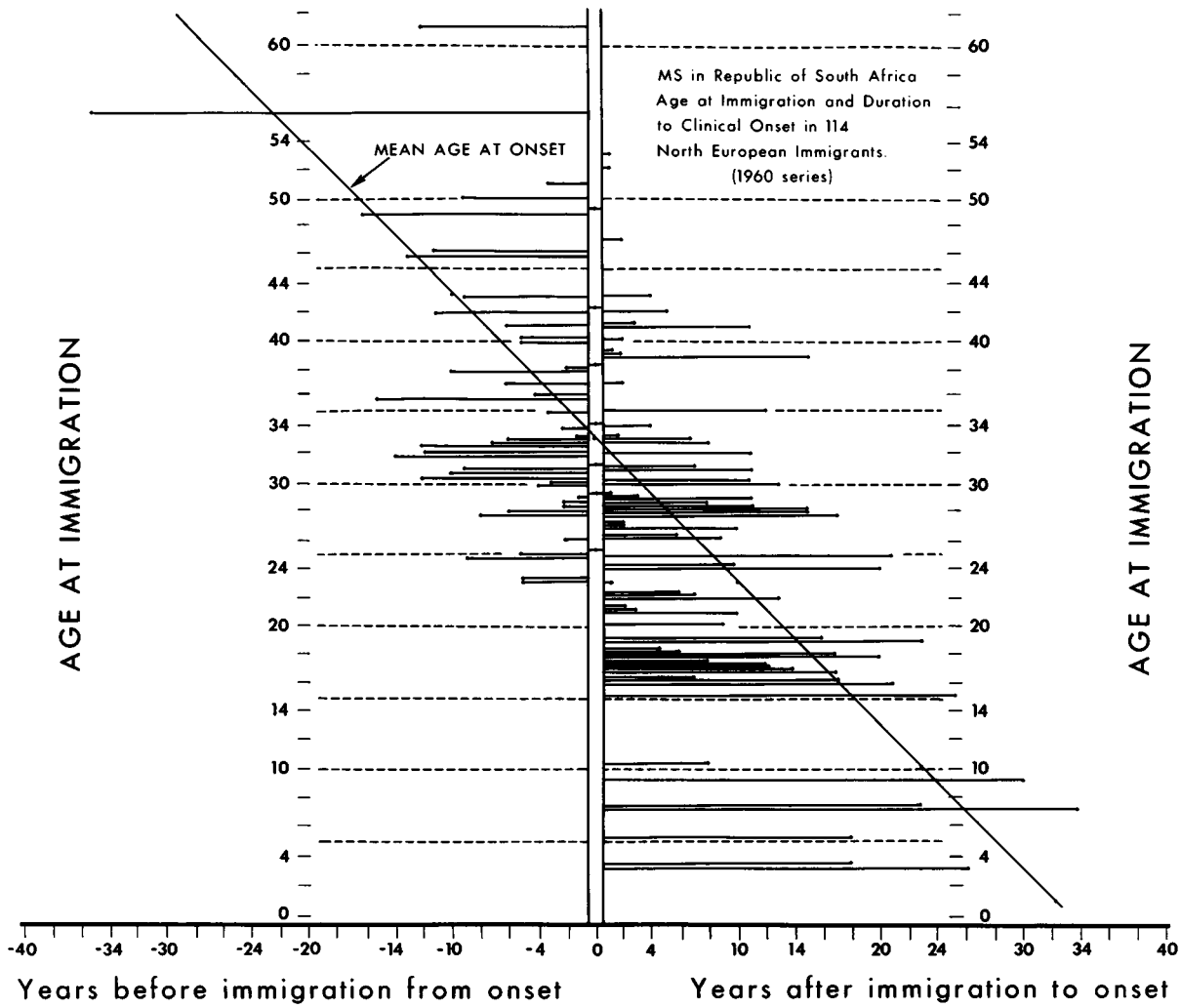


FIG. 17. MS in northern European immigrants to South Africa as of 1960, according to age at immigration and length of time between immigration and clinical onset. Each patient is represented by a bar whose locus on the *y* axis denotes age at immigration and whose length denotes the number of years between immigration and clinical onset. The diagonal line represents mean age at onset for the entire series. Modified and reprinted with permission from the publisher (158).

to 14 at immigration. The inference is that older immigrants had acquired MS by exactly age 15 in their high-risk European homelands, while younger immigrants acquired the disease after migration to medium-risk South Africa. Both groups thereby reflected the prevalence rates typical of the respective geographic locales. This result suggests not only a prolonged incubation period between acquisition and clinical onset but also a lack of susceptibility in young children, even in a high-risk area.

Migrants moving from low- to high-risk areas. All the population-based material available is in Table 9. However, there are several unique numerator-only series that address ages of susceptibility and latency intervals between exposure and clinical onset of MS.

Below I discuss MS in the Faroe Islands. In that study, patients were allocated on the basis of whether they had lived off the Faroes in a high-risk area (almost all in Denmark). This was done to exclude from the Faroese resident MS series those who had lived "too long" off the islands for their MS to be definitely attributed to events on the Faroes. In 1974, the exclusion period was arbitrarily defined as 3+ years before onset; such patients were called group C. Patients living overseas for less than 2 years were classed as group B, and those never living away were classed as group A. Group B patients were accepted in the resident series. By 1986, it was realized that the group C patients not only should have been excluded but also constituted a series of migrants moving from a low- to a high-risk area, so nine group C patients were then contrasted with seven group B patients as to timing (age) and duration of foreign residence (162).

In an update of the Faroese MS study to 1991, it was necessary to make the exclusion criteria more stringent: group C′ was defined as 4+ years for patients living overseas in early adolescence or 6+ years before clinical onset. Group B′ (accepted in the resident series) included all others with a foreign residence (167). Further details are given below.

In Fig. 18, groups C and C′ (n = 12) are compared with groups B and B′ (n = 10) as to ages and durations of overseas residence. With short childhood visits being ignored for one of them, all group C and C′ patients had at least 2 years of

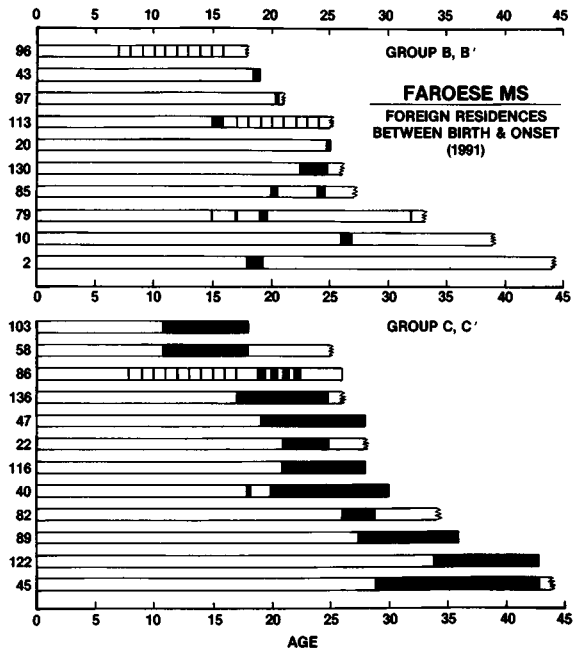


FIG. 18. Ages and durations of foreign residences (black bars) for groups B and B' and group C and C' Faroese MS patients as of 1991. MS onset is the terminus of each bar; the origin of each bar is birth; a straight terminal line indicates onset of MS while overseas, and a jagged terminal line indicates onset of MS while in the Faroes. Numbers at left identify the patients in the studies of Kurtzke and Hyllested (162) or Kurtzke et al. (167).

their stay off the Faroes between ages 11 and 43, and 2 years was the minimum period for such stays.

The foreign residences for groups B and B' not only were short but also showed little consistency in time to MS onset. On the other hand, the group C residences clustered within about 10 years before clinical onset, and the mean duration from start of foreign residence to MS onset was 9.3 years. There was a quite regular progression in age at start of overseas residence that matched well the progression in age at clinical onset (Fig. 18). Subtraction of the 2 years of "exposure" (foreign residence common to all) resulted in an "incubation" period of 7.2 years (range, 3 to 13). The 2-year exposure period was continuous in all patients but one.

From the group C and C' cases it was concluded that residence in a high-risk area by a susceptible but "virgin" (as to MS) population for a period of 2 years from age 11 could result in clinical MS beginning after a further period of about 7 years. Additionally, residence need not have been maintained in the area of endemicity for that entire interval (Fig. 18, patients 22, 45, 58, 82, and 136). In other words, 6 (162) or 7 (167) years is a true incubation or latency interval between disease acquisition and symptom onset in these Faroese patients.

Dassel (47) reported three instances of MS among a probably small group of white immigrants who migrated from Indonesia to The Netherlands. They arrived at ages 10, 14, and 17 years, and their MS onsets occurred, respectively, 7, 9, and 8 years later. Subtraction from these intervals of 2 years for exposure again results in an average incubation period of 6 years. Mentioned above were children who had emigrated from Vietnam to France (157), among whom were three with MS onset at ages 17, 22, and 16. For the period in France from age 10 (as in The Netherlands series) or age 11 (as in the Faroe Island series), the interval to onset also averaged close to 8 years, with 2 for exposure and 6 for incubation.

TABLE 11. Latency period between migration and MS onset by age at migration from North Africa to France for patients ascertained in 1986 and with onset after migration in 1960 to 1965[a]

Age at migration (yr)[b]	No. of patients	Mean age at onset (yr)	Latency period (yr)[c]	Mean age at time of study (yr)
2	37	24.7	(22.4 − 10) = 12.4	33.9
7	43	25.1	(18.0 − 5) = 13.0	35.3
12	40	26.0	14.3	39.0
17	40	30.4	13.3	42.5
22	20	32.2	10.2	47.1
27	12	36.3	9.5	52.5
32	15	42.0	10.8	54.1
37	12	45.4	8.2	61.3
Total	219	29.7	12.3	41.8

[a] Data are from reference 58.
[b] Middle year of 5-year age groups.
[c] The hypothesis is that susceptibility begins at age 12; the latency period is the interval between immigration or age 12 and clinical onset.

In this respect, an interesting paper is that of Delasnerie-Lauprêtre and Alpérovich (58), from the French Collaborative Group on Multiple Sclerosis, Institut National de la Santé et de la Recherche Médicale. This group provided the data on MS in twins reviewed above. From among the approximately 8,000 cases ascertained in France in 1986, they identified 246 persons who had immigrated from North Africa between 1960 and 1965 consequent to the Algerian war for independence. Of these 246, 86% were of European origin, with the remainder being Arab or Berber. There were 24 patients with MS onset before migration and 3 with onset at the time of migration, leaving 219 with onset of MS after migration to metropolitan France.

When matching was done for sex and age at the time of study with mainland French MS cases (3:1), these workers (58) "found no differences in mean age at MS onset between the two groups. Therefore, it is likely that MS was acquired by the same age in migrants as in French-born patients . . . [and] that the unknown causative factors of MS are equally frequent, whatever the latitude of origin." The problem with this analysis is that by matching by age at the time of study, these researchers also matched by age at the time of onset. Patients whose mean age at the time of study is 34 years must have a younger mean age at onset than those who are then about 50 years old.

Table 11 shows the essential data from the Northern African migrant study. It is clear that there is indeed a relatively fixed interval between immigration and clinical onset, regardless of age. Furthermore, if one assumes that susceptibility begins (on average) at age 12 years, then the latency period from immigration to onset averages about 12 years. This study provides evidence as well that susceptibility extends to the 35+ age group, which was an average of 37.2 years old at immigration. It is perhaps not an accident that individuals well beyond about age 40 did not appear in this series. In other words, there may well be an upper limit to age of susceptibility, in the 40s, as well as a lower limit, close to ages 10 to 12.

The data in Table 11 show that the total latency period from immigration to onset averaged 12 years, as opposed to the approximately 8 years for Faroese, Indonesians, or (as

calculated above) half-Vietnamese. Algeria may be a medium-risk area for MS, as suggested by the surveys of Libya (229) and Tunisia (28), previously noted. Furthermore, 27 of 246 (11%) patients in this French series had onset at or before immigration (58). On the other hand, MS was rare in Indonesia and Vietnam and absent in the Faroes before 1943 (see below); in addition, a short latency or incubation period for virgin populations has considerable support in infectious diseases (see below).

EPIDEMICS OF MS

The occurrence of MS in the Faroe Islands was described preliminarily as an epidemic in 1975 (160); the complete report appeared in 1979 (161). For over 20 years, my colleagues and I have been actively investigating MS on these islands (161–167). However, other possibly pertinent materials, starting with another Nordic land, are discussed here first.

Iceland

After the earlier work in the Faroe Islands, an obvious next question was what had happened with MS in Iceland? The same Norse Vikings had settled Iceland at about the same time as the Faroes. Like the Faroes, Iceland had been a county of Denmark but attained semiindependence in 1918 and later became fully independent during World War II.

In Iceland, there were 168 cases of MS with onset between 1900 and 1975 (159). The annual incidence rates showed an abrupt rise in 1922, a plateau until another abrupt rise in 1945, and then a sharp decline about 10 years later. The average annual incidence rate for 1923 to 1944 was 1.6 per 100,000 population. The rate for 1945 to 1954 was 3.2, significantly higher than the rate of 1.6 for the preceding intervals and the rate of 1.9 for 1955 to 1974 (Fig. 19). In fact, almost all of the individual 5-year intervals from 1900 on had incidence rates significantly below those for 1945 to 1949 or 1950 to 1954. Furthermore, age at onset for the interval from 1945 to 1949 (23 years) was significantly lower than that for any other quinquennium from 1900 to 1974. Thus, there appeared to be a postwar epidemic of MS on Iceland. Cook et al. (45) had independently come to the same conclusion. Conversely, Benedikz et al. (27) and Poser et al. (216) concluded that there was never any significant variation in incidence in Iceland, attributing any prewar deficit to incomplete ascertainment.

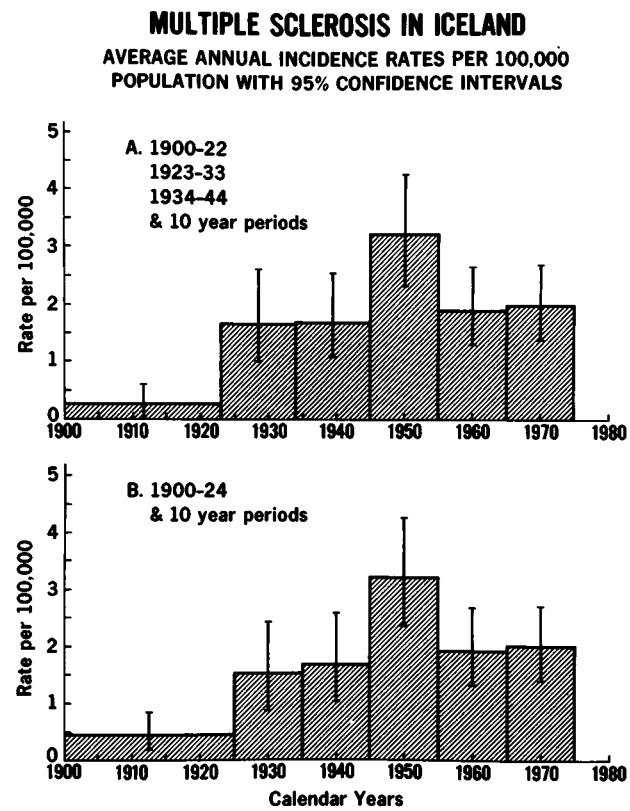


FIG. 19. Average annual incidence rates per 100,000 population for MS in Iceland, at 10-year intervals, with 95% confidence intervals for the rates. Reprinted with permission from the publisher (159).

Other Areas

Shetland and Orkney Islands. Cook et al. (43) observed that MS on the Orkney Islands seemed to have shown a marked decline in the annual incidence between 1965 and 1973, with no cases thereafter to 1983, when survey input ended. They concluded that the Orkney experience was compatible with a post-World War II epidemic but attributed the increase and decrease in incidence to the occurrence of canine distemper on those islands. A similar decline was found for the Shetland Islands (46) up to 1986, "beginning between 1951 and 1968." Actual data were not provided, but it appears from Fig. 1 in reference 46 that there were seven cases from 1971 to 1985 in a population of about 23,000, yielding an average annual incidence rate of 2.0 per 100,000—certainly no longer a high rate. Note that these islands had the highest prevalence rates in the world in the 1950s. Thus, there seems clearly to have been a postwar epidemic of MS in the Shetland-Orkney Islands. Martin (181) has raised the question of whether this epidemic was attributable to British troop concentrations there during the war—as was the situation with the Faroes (see below).

North America. The purported Key West epidemic reported by Sheremata et al. (252) was discussed above, as were the later reports of Bigler (30) and Helmick et al. (94). Other MS clusters have been reported for the Americas, such as the 6 cases occurring in the 500-person population of Mossyrock, Wash. (114), and the 13 cases occurring in the 10,000-person population of Mansfield, Mass. (64); the 10 cases in the 150-person population of a farming area in Colchester County, Nova Scotia (199), seem less well documented. No satisfactory explanation has arisen for these clusters, and no follow-up studies have been reported for either the cases or their communities.

The Faroe Islands

The Faroe Islands are a group of 18 major volcanic islands, 17 of which are inhabited, lying between Iceland and Norway in the North Atlantic Ocean at 7° west longitude and 62° north latitude. Until 1948, Færø Amt was a standard county (amt) of Denmark. As Føroyar, it achieved semiindependent status, although it remains part of the Kingdom of Denmark both for international affairs and for a great part of its health and welfare services.

Because the "Faroese Saga" has aroused considerable interest—and contention—and because it is the primary basis for my conclusions as to the nature of MS, more

documentation will be provided here than has been offered for other aspects of this paper.

Background of the study. In 1956, John Sutherland published the results of his survey as to the prevalence of MS in northern Scotland. As mentioned above, the rates in the Shetland-Orkney Islands were then by far the highest in the world (262). At that time, MS was considered rare on the Faroe Islands, and this fact was curious because of their similarities to the Shetland-Orkney Islands in geography, climate, and origin—both having been settled or occupied by Norse Vikings around the ninth century. For these reasons, a cooperative study of MS in the Faroes and the Shetland-Orkneys was undertaken by Mogens Fog of Denmark and Allison of Northern Ireland. This intensive work was never reported in detail; it was included in Allison's presidential address to the Royal Society (7), and a summary was presented by Fog and Hyllested in 1963 (73). Intriguing with regard to the Faroese MS patients was what appeared to be their young age at prevalence day. However, nothing further was done until the original Faroese case abstracts of Hyllested were reviewed in 1972 to 1974. It then became obvious that there were no patients on the list who were calculated to have had a clinical onset of MS before 1945. Hyllested concurred; therefore, we both initiated the study that continues to date, having been joined by Anne Heltberg a few years ago. As noted above, in the first presentation of our findings, we had indeed called the occurrence of MS on the Faroes an epidemic (160).

Description of the Faroe Islands. The Faroes were a regular county (amt) of Denmark proper until 1948, and the official language was Danish. Now the primary language is Faroese, a development of Old Norse similar to Icelandic. The Faroese also have their own literature, art, currency, stamps, parliament, and laws. The principal industries have been fishing and sheep raising (the most accepted translation of Føroyar is "sheep islands"). Only about 3% of the total land area is habitable or arable. The terrain is that of steep hills and fjords covered with only a thin layer of soil. Virtually all of the villages (bygdir) are clustered along the shores of the bays, fjords, and inlets. In 1986, the Faroes consisted of 120 bygdir within 50 parishes (kommunur) making up 7 districts (sýslur)—plus the capital, Tórshavn (Fig. 20); there has since been some change in kommunur.

Tórshavn on the island of Streymoy now has a population of over 14,000, while the next largest town, Klaksvík, on the northern island of Borðoy, has about 5,000 inhabitants. In the Middle Ages, the population of the Faroes did not exceed about 4,000, but by 1900, this number had risen to 15,000 and continued to grow, reaching about 48,000 in 1990.

(i) Medical facilities. Færø amt has, of course, been part of the Danish medical system. Its first hospital opened at Tórshavn in 1829. Klaksvík Hospital and Tvøroyri Hospital, in the south, were established in 1904; there was a tuberculosis hospital near Tórshavn from 1908 to 1962. The State Psychiatric Hospital was opened in 1963 at Tórshavn. The first physician was assigned to the Faroes in 1584; the first official government surgeon (Landkirurgen) was assigned in 1842. In 1943, there were 17 physicians, 1 per 1,500 population, including 1 government physician (Landslæge), 8 hospital physicians, and 8 practitioners. In 1980, these numbers were 1, 40, and 20, respectively, or 1 per 700 population (161, 162, 165).

Since medieval times, medical care on the Faroes has been a charge of the Danish government. Danish medical statistics have been perhaps the most accurate and complete of any nation. Their routine hospital recordkeeping has long been outstanding, with each hospital, including those on the Faroes, reporting annual discharges by name and diagnosis to the (National) Health Service (Sundhedsstyrelsen). The country has had nationwide medical coverage provided by the entire state or individual counties since 1921, and there has been a national MS Registry since 1947.

Faroese patients in need of specialized diagnosis and treatment have long been sent to the National (Royal) Hospital (Rigshospitalet) in Copenhagen. Since 1929, this hospital has had a separate neuromedical department, while neurologic care beforehand was provided under the medical departments. Faroese are treated there under the "Greenland Rules," which require complete assessment of all medical problems regardless of admitting diagnosis (161, 162, 165).

Case ascertainment. Critical to the findings and interpretations of my colleagues and me is the requirement that we have found all cases of MS that have occurred among the Faroese in the 20th century. Obviously, we are constrained by the fact that the person must have been seen medically and neurologic symptoms must have been recorded. However, two points argue for completeness: MS clinically is a disorder with repeated or progressive symptomatology over a considerable time, and medical care for Faroese, not constrained by financial factors, is of high quality and is well documented. Also, MS is generally the first consideration when physicians are confronted with unexplained neurologic symptoms in young adults.

As summarized in Table 12, every conceivable resource has been used to identify potential cases of MS among Faroese. Copies of death certificates for all Faroese were reviewed for any mention of MS or any possibly related disorder in any location on the certificate, not merely the underlying cause. Records of the Faroese hospitals and Rigshospitalet were searched several times for diagnoses of MS and once for alternative diagnoses. Haslev Hospital, an MS rehabilitation facility outside Copenhagen, was also the target of a record review. Furthermore, the complete hospital diagnosis files of Sundhedsstyrelsen were also surveyed, as were the National Disability Compensation files from 1921 to 1977, when this resource ceased and each county began to maintain its own proceedings.

In the 1940s, Hyllested (99) performed an extensive nationwide survey of MS in Denmark, including the Faroes, with questionnaires to all physicians and hospitals, starting with lists from a prior nationwide MS survey of compensated cases from 1921 to 1933. Hyllested's survey led to the formation in 1947 of the Danish MS Registry, of which he is still head. All Danish neurologic departments report any MS suspects to the Registry, at which the hospital records are critically reviewed and abstracted by a neurologist. The Registry also uses the National Patient and Death Registries. These files were repeatedly scanned for Faroese cases. In addition, Hyllested studied MS on the Faroes themselves in 1957 and was part of the Faroes-Shetland-Orkney project of 1961 to 1962 (73).

Furthermore, a special search of all 1960 to 1976 admissions to the three Faroese hospitals was made by a Faroese neurology resident for all patients with any neurologic signs or symptoms that could possibly reflect MS, regardless of actual diagnosis. This was done to determine whether MS was not considered by physicians on the Faroes when it should have been. This review yielded no cases even remotely suspicious of MS.

All neurologists at Rigshospitalet and other Danish hospitals as well have continued since 1975 to alert my colleagues

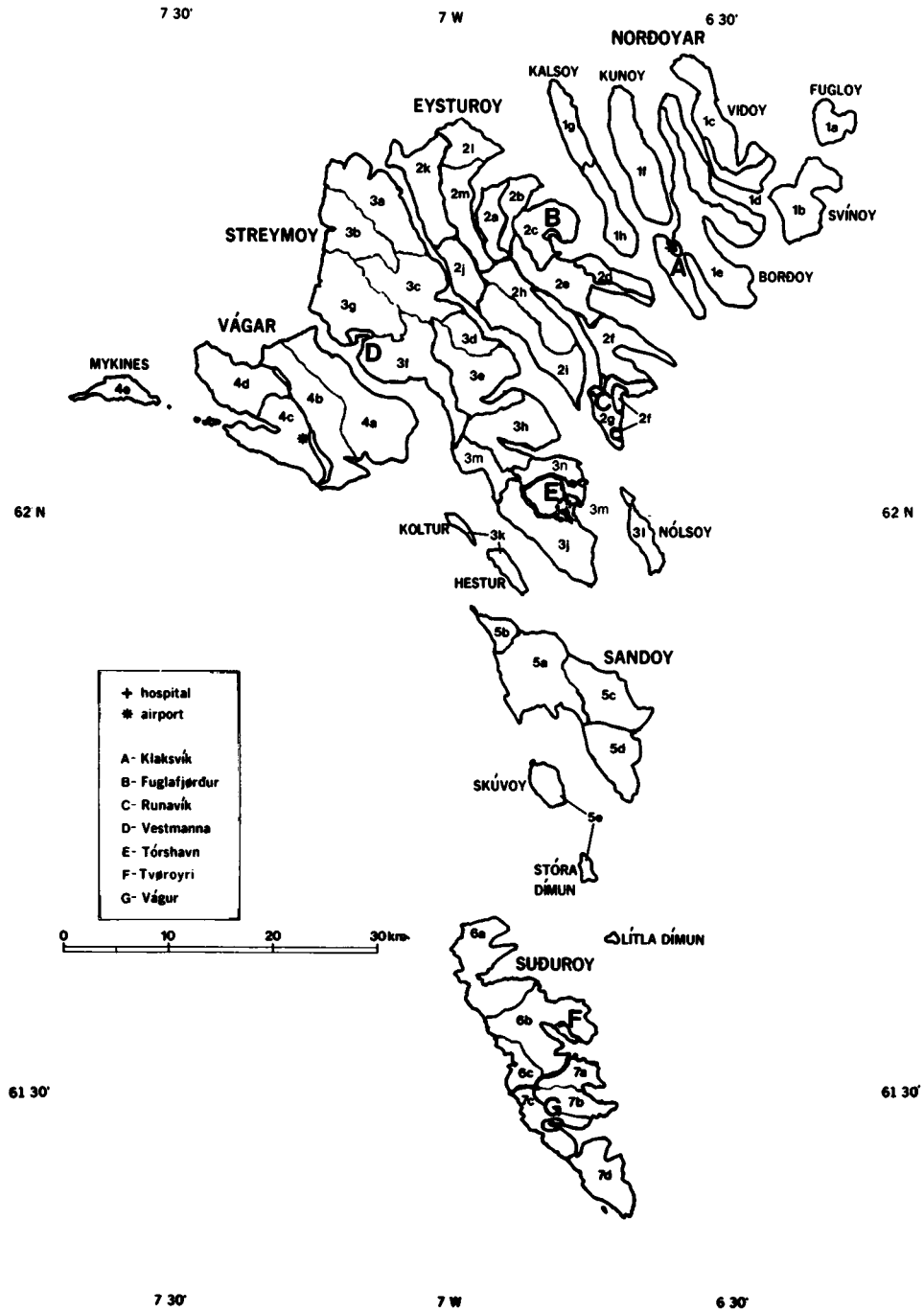


FIG. 20. The Faroe Islands as of 1986 by districts (sýslur) and parishes (kommunur), the latter containing one or more villages (bygdir). Parishes are identified by Kurtzke and Hyllested (162). Reprinted with permission from the publisher (162).

and me to possible cases. On the Faroes, all physicians and the general public as well have been aware of our efforts as a result of presentations, radio and television broadcasts, and newspaper reports. The MS Club was founded on the Faroes in 1977, and we remain in close contact with its members. We have been on the Faroes to examine patients and review resources every year but one since 1974, the last such visit being in May 1993.

(i) **Case definition.** For whatever source from which a prospective case was ascertained, we then obtained all medical records from the Faroes and Denmark. We separately read all the charts, of which we each have complete copies. We then jointly examined neurologically each living patient, with special attention to onset dates and symptoms. If patients had died before our review, relatives were jointly interviewed for the neurologic history. Only after the diag-

TABLE 12. Case ascertainment for Faroese MS patients

Resource	Yr
Faroese death certificates	1900–1977
Faroese hospital (n = 3) records	1900–[a]
Rigshospitalet records	1900–1983
Sundhedsstyrelsen National Patient Registry	1921–[a]
Disability Compensation Board records	1921–1977
Neuromedical department (Rigshospitalet) records	1929–[a]
All physicians and hospitals in Denmark	1944–1949
Danish MS Registry files	1947–[a]
Faroes survey (KH[c])	1957
Faroes-Shetland survey (KH)	1960–1962
Neurologic symptoms in Faroese hospitals	1960–1976
Haslev Hospital records	1965–[b]
Faroese patients, relatives, and friends	1974–[b]
Danish neurologists	1975–[b]
Faroese physicians	1975–[b]
Faroese MS Club	1977–[a]
National Registry Causes of Death	1978–[b]

[a] Principal ongoing resources.
[b] Other ongoing resources.
[c] KH, Kay Hyllested.

nosis was established to our satisfaction following our case review and examination did we then seek family, travel, and other historic data.

Diagnoses were uniformly concurred upon by all of us. When a definitive answer, positive or negative as to MS, could not be given, we reexamined the patient one or more times in succeeding years until the questions could be clarified. We used the diagnostic criteria of the Schumacher Panel (249) for (clinically definite) MS, except that age at onset was not an obstacle to inclusion. All patients but two had also been seen and diagnosed as having MS independently by other neurologists, and most of them had been seen by some of the most senior neurologists of Denmark. Almost every patient was seen at Rigshospitalet and subjected to diagnostic tests appropriate to the time of examination, including CSF (oligoclonal bands, immunoglobulin G), evoked potentials, contrast computerized tomography, and recently, for some, magnetic resonance imaging. Spinal fluid examinations and, for about 10 years, CT examinations were done on the Faroes as well. In most instances, the appropriate abnormalities were found, although we did not rely on laboratory findings for our clinical diagnoses. So far, we have autopsy confirmation in two cases: one negative among our "not-MS" suspects and one positive among the MS cases.

(ii) MS grouping and inclusion criteria. Throughout this century, many Faroese have spent variable periods living overseas, mostly in Denmark, for educational or occupational purposes. Since we wished to investigate the occurrence of MS on the Faroe Islands among Faroese, we then had to exclude those who had been living too long off the islands. The reason was so that we could avoid attributing their disease to events on the Faroes when in actuality they had acquired the illness elsewhere. Since we already knew that MS rarely occurred in the Faroes before the 1940s, we could properly conclude that short periods overseas were irrelevant to the development of MS.

The question then was what was "short" and "long." For the former, we had decided in 1974 that a total of less than 2 years overseas before clinical onset was highly unlikely to be relevant to the development of MS. We called those patients group B, having defined group A as those never living off the Faroes.

Our original 1974 criterion for long residence was a total of 3 years or more overseas in a high-risk area before clinical onset. From our findings (see below), there later arose two corollaries: only residence intervals from age 11 to onset were relevant, and for inclusion in group C (excluded from the study), the long intervals should have included about 2 years of nearly continuous overseas residence.

Because MS has been established on the islands, we have recently modified the criteria to create new groups B′ (included) and C′ (excluded), for those exposed to the Faroes MS environment (167). We thought it necessary in this instance to be more restrictive in our exclusions than we were previously. This decision of 1990 led to our reclassification of all Faroese MS cases; however, no prior group C patient needed reassignment on this basis.

Faroese MS as of 1986. By 1986, we had ascertained 41 cases of MS from 102 suspected cases among Faroese who had had clinical onset in this century: 32 resident cases (25 group A and 7 group B) and 9 (excluded) cases in group C (161–163).

By that time, we had realized that the group C cases were not merely persons who should be excluded but in fact made up a group of migrants from a low-risk area (Faroes) to a high-risk area (Denmark). This was also true for the group B patients, and comparison of the two groups gave us a twofold opportunity: to test whether our inclusion and exclusion criteria were correct and, should that be the case, to define the characteristics of the acquisition of MS by yet another migrant series (migration from low- to high-risk areas). The latter information was presented above in the section on migration in MS.

(i) 1986 resident series. There was not one single native resident Faroese with the clinical onset of MS in this century until July 1943. Then there were 16 patients with onset between 1943 and 1949 and another 16 with onset from 1950 to 1973 (Fig. 21). To 1987, no further MS patients were identified among the native resident Faroese, a period of 14 years in which the population had increased from about 40,000 to over 45,000.

Sixteen cases occurring in a 7-year period in a populace of less than 30,000—and none before—does not require a statistical test to meet anyone's criteria for an epidemic. Formal testing did demonstrate that the appearance of MS during that time was of very high statistical significance (165). The annual incidence rate per 100,000 population showed an early and dramatic rise and fall, followed by two irregular and lower secondary peaks (Fig. 22, top). The rate exceeded 10 per 100,000 in 1945. The first question was whether the incidence rate curve in fact reflected separate epidemics.

Our first approach to that query was to divide the series into two parts, based on whether in 1943 patients were prepubertal or postpubertal. The reason was the evidence considered above, that elsewhere MS is acquired between ages 10 and 15, and puberty is one datable event in that interval (Fig. 22, middle).

When this was done, it was clear not only that the first incidence rate peak (epidemic I) was attributable to the patients postpubertal in 1943 but also that there still appeared to be two later, discrete peaks (epidemics II and III) for the prepubertal patients (162).

We then referred to the group C (migrant) experience, for which 2 years of exposure from age 11 was shown to be required to acquire the disease (see above). For the postpubertal (epidemic I) resident patients, the age at clinical onset averaged 31; for the migrants, that age was 30. Incubation

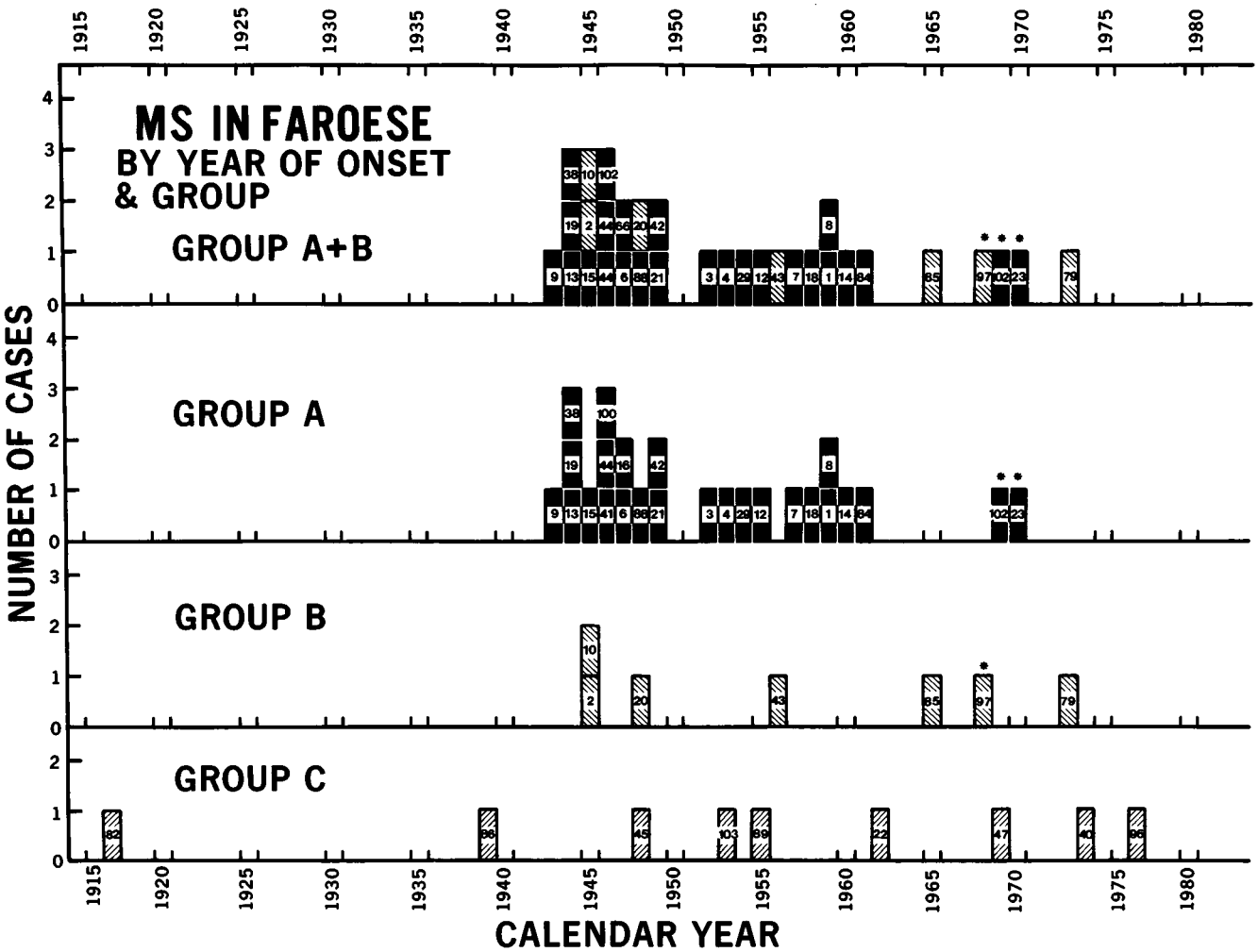


FIG. 21. MS in native-born Faroese according to calendar year of clinical onset as of 1986. Group A (never off the Faroes before onset) and group B (off the Faroes for less than 2 years [total] before onset) comprise the resident Faroese MS series. Group C (off the Faroes for 3 or more years [total] before onset) cases comprise the nonresident series. Numbers identify the patients listed in tables presented in references 161 and 162. Asterisks identify three patients of postwar birth. Reprinted with permission from the publisher (165).

for those residents averaged 5 years from 1943; that for migrants as of 1986 was 6 years. Therefore, we concluded that the residents also required 2 years of exposure before 1943, so this exposure would have occurred in 1941 to 1942. In addition, this exposure would then have begun when the patients were at least 11 years of age—also like the migrants.

We then asked whether in actuality MS was acquired by all Faroese only if they were at least 11 years of age at first exposure and only if the exposure was then for at least 2 years. Hence, we reassessed the Faroese experience by reclassifying the resident series according to the calendar time at which the patients had attained age 11. For the reasons discussed below, we extended this time from 1941 to 1943 for acceptance as epidemic I patients, but from that point on, time at which age 11 had been attained was to determine membership in any later epidemics.

Figure 23 represents the native resident Faroese MS series as of 1986, showing each patient's life experiences relative to MS from calendar year of birth (y axis) to calendar year of clinical onset (x axis). Each patient is represented by a horizontal line, with the 2-year exposure period cross-hatched; the incubation period is indicated by the heavy line; and the time of clinical onset is indicated by the closed circle. It is clear that the series is divided into three parts on the basis of the time at which the patients had attained age 11: by 1941 (1943) for the first, or later for the other two. Definition either by the pubertal separation or by age 11 was very highly significant ($P < 0.001$) in terms of the existence of three discrete groups or epidemics (163, 165).

Epidemic I then comprised all patients aged 11 or more in 1941 plus those aged 11 by 1943 ($n = 20$). Epidemic I accounted for all cases contributing to the first MS incidence rate peak (Fig. 22, bottom). Epidemic II comprised patients aged 11 in 1946 to 1951 and accounted for the second MS incidence rate peak ($n = 9$). Epidemic III comprised patients aged 11 in 1958 to 1963 and accounted for the third MS incidence rate peak ($n = 3$). This last figure needs updating; there are now six patients for epidemic III, as of June 1991 (see below).

Age at clinical onset was similar, close to age 21, for epidemic II and III patients, but both were significantly lower than age at onset for epidemic I, age 30. Incubation

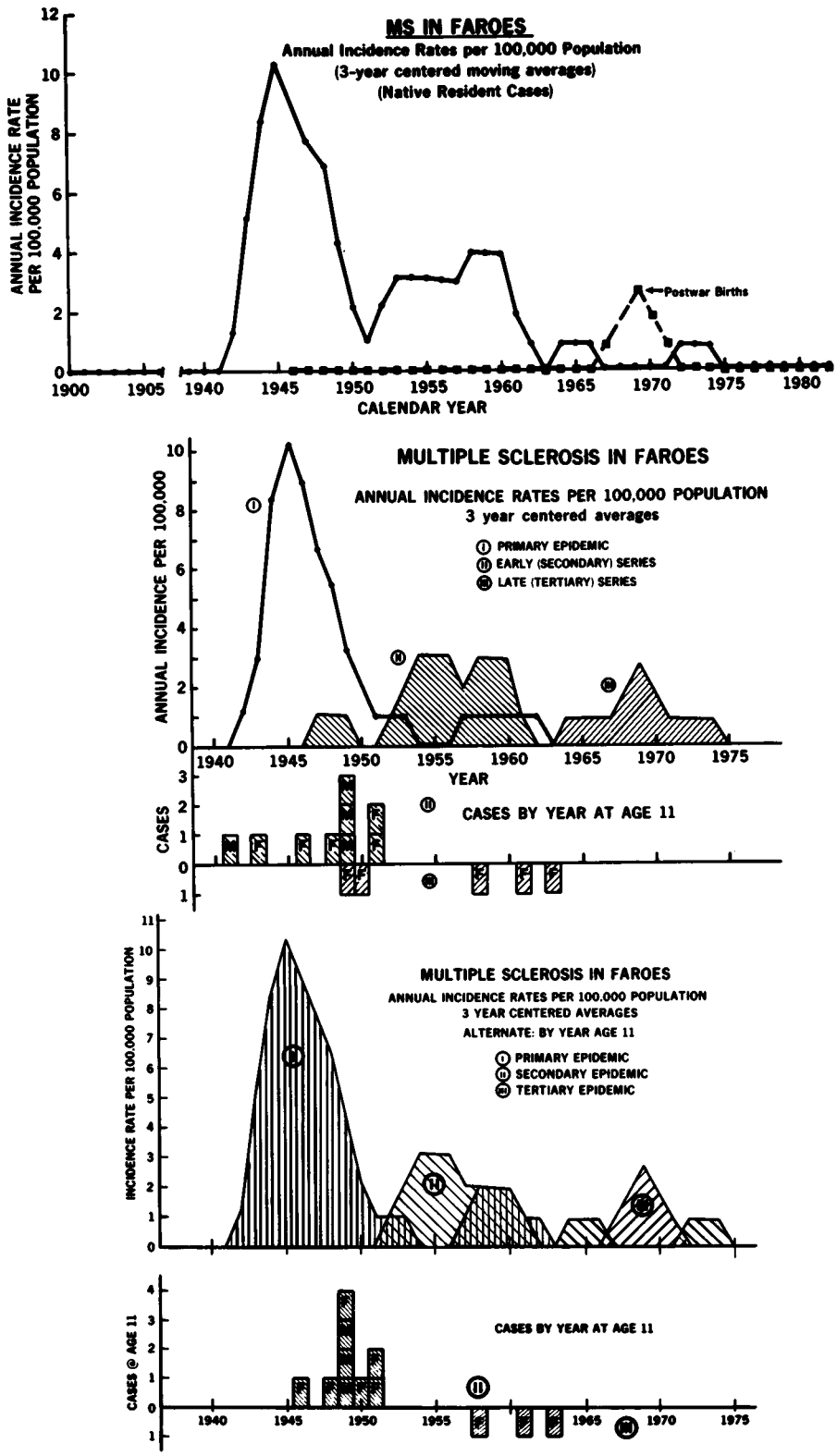


FIG. 22. MS in native resident Faroese as of 1986. Annual incidence rates per 100,000 population were calculated as 3-year centered moving averages. (Top) Rates for patients born after World War II (broken line), separated the from remainder. (Middle) Rates for patients postpubertal in 1943 (epidemic I) versus those prepubertal or unborn (epidemics II and III). (Bottom) Rates for three epidemics defined by calendar year in which patients attained age 11—by 1943 (epidemic I) or later (epidemics II and III). The sex and calendar year in which patients of epidemics II and III were aged 11 are noted for the middle and bottom portions. Modified and reprinted with permission from the publisher (162, 163).

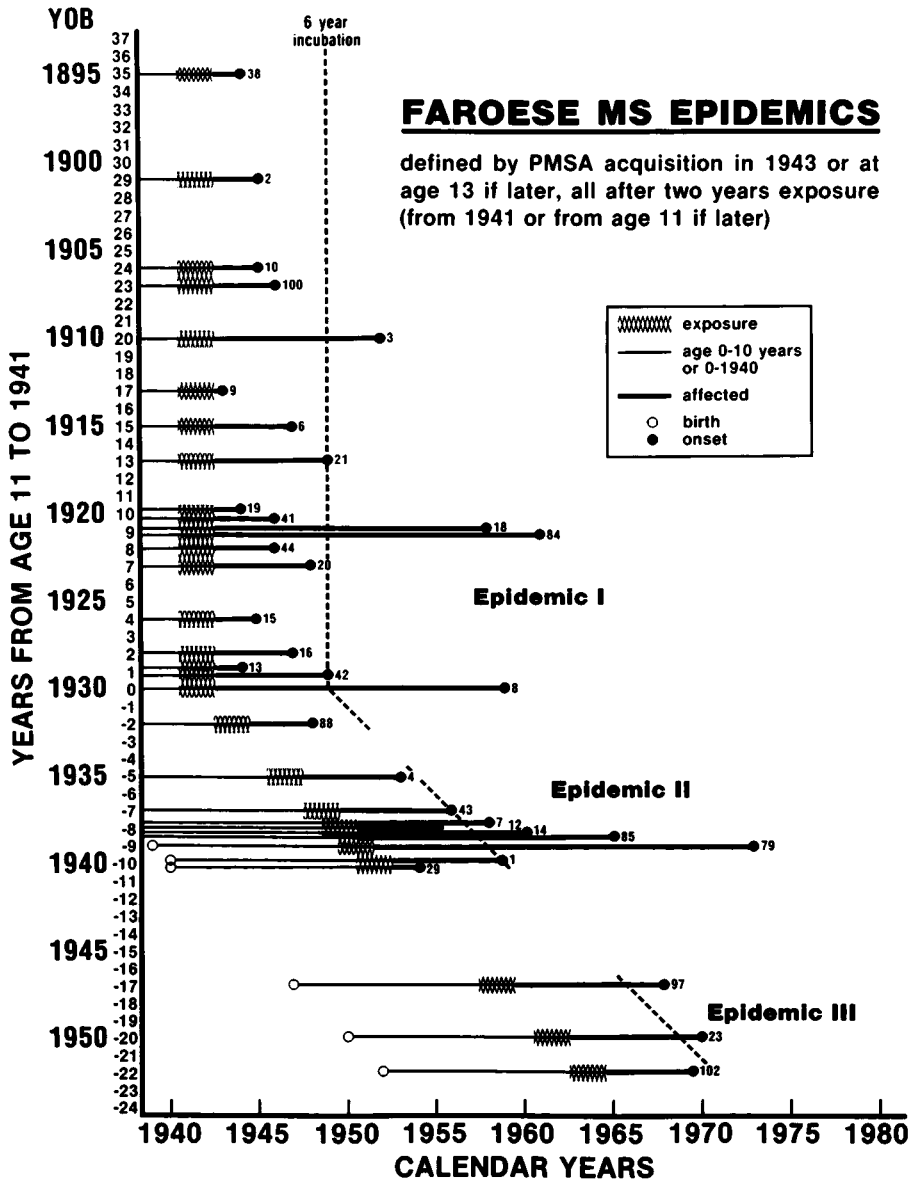


FIG. 23. Native resident Faroese MS patients as of 1986. Each patient is identified by calendar time when age 11, whether by 1941 or later, and by time of clinical onset. Each patient is represented by a horizontal line, and the number at the end of each line identifies the patient listed in references 161 to 163. The thin portion of each line represents time and ages for each patient before exposure to PMSA (see the text), and the 2 years of cross-hatching represent the period of PMSA exposure, following which (heavy portion of each line) the patient is affected but neurologically asymptomatic (the incubation period). The solid circle at the end of the line represents the time and age of clinical onset. The open circle at the origin of the lower lines represents time of birth for patients born after 1938. The y axis defines the number of years by each year from 1941 by which each patient attained age 11, with the calendar years reflecting their year of birth also identified. The broken line represents the end of a 6-year incubation period from the time of acquisition of PMSA after a 2-year exposure. Reprinted with permission from the publisher (163).

averaged about 6 years from 1943 or age 13, whichever came later (5, 8, and 6 years for epidemics I, II, and III, respectively) (163).

The existence of the epidemics on the Faroes has been contested by Poser et al. (218) and Poser and Hibberd (217); our detailed response has been published (165). Their essential points were that there must have been MS in the Faroes before 1943, since this was true of the rest of the North Atlantic lands, and that MS must begin at age 15. They also had problems with our classification—and even diagnosis—of cases and with the "biologic plausibility" of our interpretations. Their first criticism has been addressed above. As to the second, the characteristics of a point-source epidemic in a previously unexposed populace are such that susceptible persons of all ages will be affected; indeed, such an experience defines an age range of susceptibility. Further discussion is pursued below in the section on validity.

To this date, we have sought any event on the Faroe Islands that took place in 1941 to 1942 (and later) to explain

the appearance of epidemic I (and later). All that we have found is the British occupation.

(ii) British occupation. As detailed elsewhere (162, 163), British troops occupied the Faroes from April 1940 to September 1945. At the peak, there were about 7,000 troops stationed there.

There is no question that the British occupation was temporally related to the appearance of MS on the Faroes. By our criteria, the exposure period for the Faroese then aged 11 or more was the interval from 1941 to 1942. During that time, there were 1,500 or more British troops stationed on the islands. At least a similar number of troops were also present throughout 1943 and 1944, so patients attaining age 11 by 1943 would also have been subject to the British influence. In fact, this extension to 1943 added but one patient to the series defined by age in 1941.

However, the occupation not only showed this strong temporal relationship with MS but also demonstrated a very strong spatial relationship—for all the patients, regardless of epidemic (Fig. 24). In most instance, troops were billeted within the Faroese villages. In the major occupation sites, enlisted men (Other Ranks) were quartered in Nissen huts constructed in the "inmark"—the land area just inshore of the houses—and thus within meters of Faroese homes. Elsewhere, enlisted men were billeted in Faroese houses themselves, as were in general all officers at most occupation sites.

Therefore, we took as the most stringent—and unbiased—measure of contact with British troops the answer to the question of whether villages with MS patients were the villages with troops quartered there. The answer was clearly in the affirmative, with high statistical significance—not only for the patients of epidemic I but also for those of epidemics II and III (163).

An overview of the populations of the places in which patients lived versus those in which troops were stationed is provided in Table 13. The odds ratio of 41 (nearly twice as strong as the relationship between heavy cigarette smoking and bronchogenic carcinoma) has a χ^2 value of over 14,000. In 1943, the Faroes comprised 44 parishes, including Tórshavn. There were 16 parishes in which any patient with MS lived, containing two-thirds of the 1943 Faroese population, and 96% of the residents of those 16 parishes were living in areas where troops were billeted. Conversely, for the 20 parishes with occupation troops during the war, containing three-quarters of the Faroese population, 85% of the Faroese in these 20 parishes were living in areas where MS patients, of any epidemic, resided. There was, however, one-quarter of the population living in 21 parishes with neither troops nor MS; we concluded that this proportion of the resident Faroese was not exposed to—and did not acquire—any illness from the British troops and thus was not at risk for MS then or later.

(iii) Transmission of MS. We believe that there is no question that the British troops introduced MS into the Faroe Islands during the occupation of World War II. As discussed above, 1,500 asymptomatic British troops, the number present in 1941, must have been sufficient to introduce the disease. Furthermore, even though the occupation ended in 1945, because of the residence correlation between troops and the later epidemic cases as well as that between patients of epidemic I and those of the later epidemics, the occupation must have been responsible for all the epidemics. The only possible explanations are that the British brought either a persistent toxin or a transmissible infection. A toxin cannot explain successive epidemics. Therefore, the cause of MS in the Faroes is a transmissible infection.

Since the cumulative risk of MS is such that there would occur only three clinical cases over the lifetimes of 2,000 healthy British troops (142) and since a much larger proportion than 3 of 2,000 must have been affected to transmit the disease so widely and simultaneously to Faroese, we concluded that MS exists in a widespread, transmissible, but neurologically asymptomatic form. It is this state that we have defined as the primary MS affection (PMSA). Like asymptomatic poliomyelitis, PMSA must be common within a population in which clinical MS occurs but must only rarely ever produce the neurologic symptoms to which we affix the label of clinical neurologic MS (CNMS). The same observation holds true for the Faroese: many more must have been affected (and able to transmit MS) than is evident from the cases in the epidemics. The cases in each successive separate Faroese epidemic must then be the numerator for a ratio whose denominator is a successive separate population cohort of Faroese at risk of PMSA. How, though, can there be separate population cohorts over time within the continuum that comprises the total resident population? It seems to be our transmission modeling that troubles critics most (183, 216–218).

(iv) Transmission models. Any epidemic is terminated when the pool of the susceptible individuals among the population at risk is exhausted. This fact explains the end of epidemic I but not the appearance and disappearance of later epidemics. How the transmission of PMSA from the British to the Faroese as consecutive epidemics could occur therefore requires the construction of models that would provide for each epidemic its own necessary population at risk to explain the sequence of British to epidemic I to epidemic II to epidemic III. Therefore, there must be over time separate consecutive cohorts of the Faroese population at risk, each one rising and falling at the appropriate time. We must remember that in these models all the numbers and ages should be taken as population averages, about which individuals will doubtless vary appreciably. We also retain the thesis that 2 years of exposure from at least age 11 are required to acquire PMSA—and hence CNMS (see below).

In any population, the numbers of CNMS cases and of individuals at risk can be defined. It is, of course, unknown what proportion of the population at risk is actually affected with PMSA, but this proportion can clearly be no more than 100%. In modeling possible modes of transmission, we have taken for illustrative purposes the total Faroese population at risk as having been affected with PMSA, just as we did with the British troops. As long as the "true" rate of infection is a reasonably fixed proportion of the population at risk, this is a valid assumption.

The potential population at risk for the first CNMS epidemic is, of course, that cohort comprising the entire Faroese population alive in 1941. We noted (Table 13) that the locations that housed British troops and/or MS patients were the residences of 75.7% of the Faroese population; this number is taken as the maximal proportion of Faroese exposed to and at risk for PMSA. This is called the F1 E cohort (F for Faroese, 1 for first, E for exposed) (Fig. 25). If the age range of the CNMS patients of epidemic I reflects the limits of the age range of susceptibility to PMSA, then this Faroese population cohort would be further reduced to 75.7% of those aged 11 to 45 in 1941. This is called the F1 E+S cohort (S for susceptible). After the 2 years of exposure, F1 E+S becomes in 1943 the first Faroese cohort affected with PMSA, the F1 A cohort, then aged 13 to 47. To

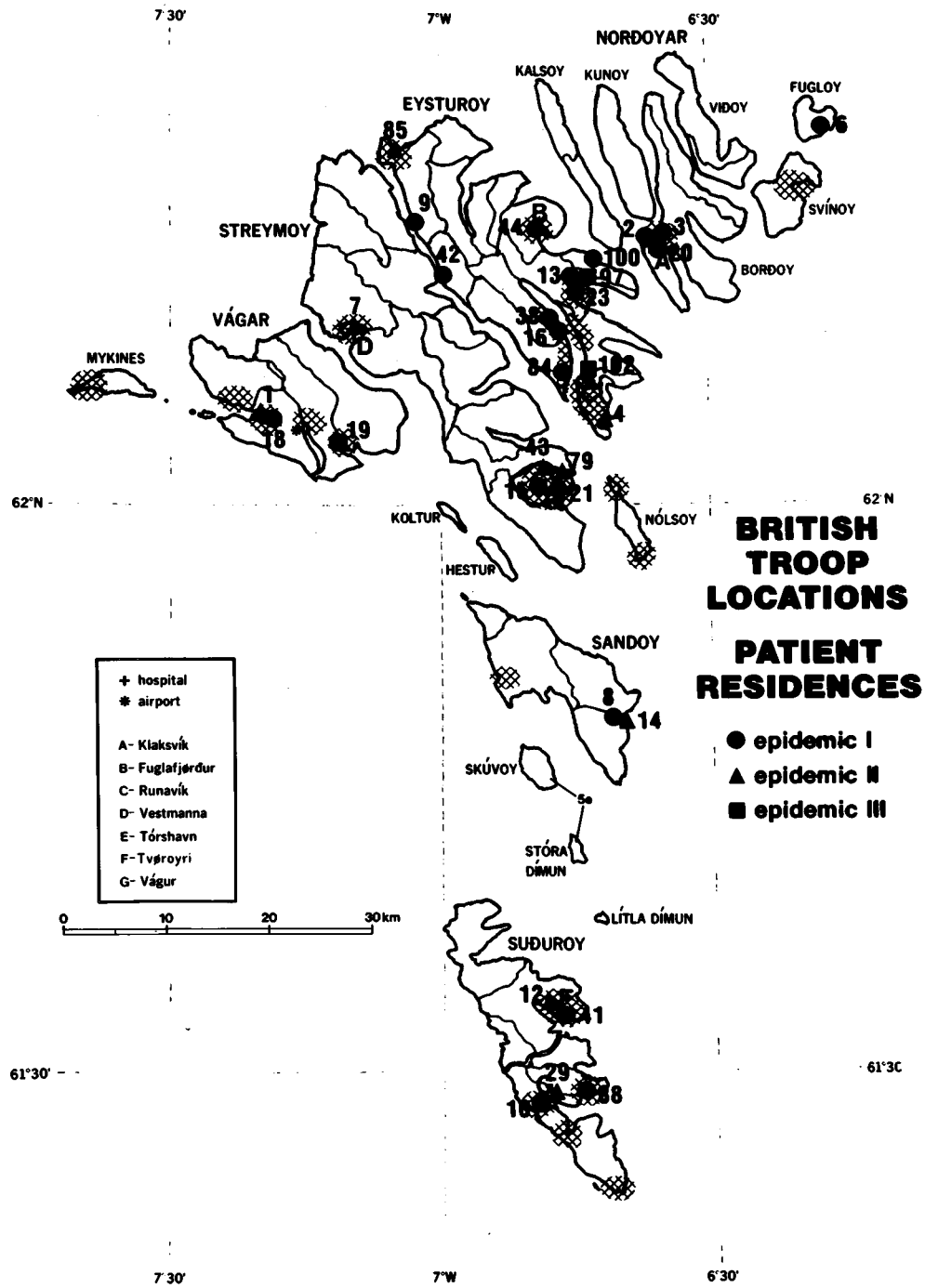


FIG. 24. British troop encampments (cross-hatched areas) and residence by village of Faroese MS patients in 1943 or at age 11 if then younger for three epidemics defined by the time at which patients attained age 11, as of 1986. Numbers identify patients listed in tables presented in references 161 to 163. Occupation sites at which no Faroese lived are the southern end of Nólsoy Island, part of the hatched area on the west coast of Vágar Island, the Vágar airport, the western coast of Sandoy Island, and the southern end of Suðuroy Island. Reprinted with permission from the publisher (163).

this cohort are added Faroese attaining age 11 by 1943, as the British were then still present. The CNMS cases constituting epidemic I are a proportion of this F1 A cohort.

With the British departure, no further input from them to the F1 E cohort was possible. Thus, the F1 A cohort was at its maximal size in 1945. The CNMS cases occurring after epidemic I must reflect the transmission of PMSA from the F1 population cohort to later population cohorts of Faroese. The first of these, the F2 population cohort, comprises 75.7% of Faroese attaining age 11 each year (F2 S) from 1945 up to the end of PMSA transmission input from the F1 A cohort. The 2 years of exposure for F2 defines F2 E (or F2

TABLE 13. 1943 Faroese population distribution by parishes with and without MS residents and with and without British troops stationed[a]

Parishes with (+) or without (−) troops	Population proportion		
	In parishes[b]		Total
	With MS	Without MS	
+	0.617	0.104	0.721
−	0.035	0.243	0.279
Total	0.652	0.348	1.000 (n = 26,232)

[a] Modified from Kurtzke and Hyllested 1987 (163). Two-thirds of the population lived in 16 parishes with MS; 96% lived where troops were stationed. Three-quarters of the population lived in 20 parishes with troops; 85% lived where any patient with MS lived. One-quarter of the population lived in 21 parishes with neither troops nor MS.

[b] Odds ratio, 41.190.

E+S), and from age 13 members of this group comprise the F2 A population cohort (with PMSA). The size of the F2 cohort will thus depend on how long the F1 A cohort can transmit illness.

If the Faroese of the F1 A cohort were able to transmit PMSA for the rest of their lives, the F1 A+T cohort would provide, well into the 21st century, a steady input of new PMSA cases within a continually growing F2 cohort, and thus a steady input of new cases of CNMS over time rather than successive epidemics (see "number surviving" curve in Fig. 25). Therefore, PMSA does not persist lifelong as a transmissible agent. All evidence indicates that CNMS is not transmissible from affected patients. If the PMSA concept is valid, then transmissibility should cease by the usual time of clinical MS onset, which we have taken as age 27 on average. Thus, PMSA is presumed transmissible by the affected only from about ages 13 to 26. The F1 A+T cohort is therefore defined as F1 A cohort members aged 13 to 26 in 1945. Each year as age 27 is reached, those members of the cohort cease to transmit PMSA, so this cohort of somewhat less than 5,300 persons disappears by 1958 (Fig. 25). Since there must be some number of persons above 0 below which the cohort is too small to transmit disease, two possible minima for transmission were proposed: 1,000 and 500 persons. The F1 A cohort reached 1,000 persons in 1956 and 500 persons in 1957. With minimum numbers of 1,000 and

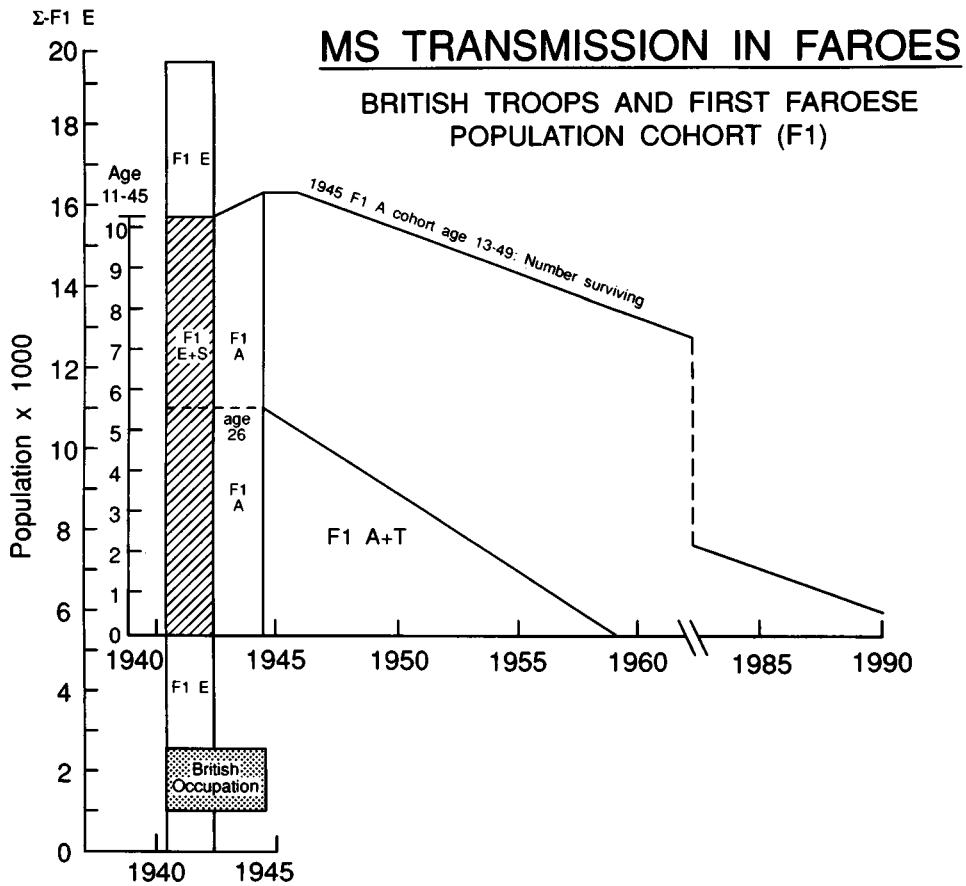


FIG. 25. Transmission model for Faroese MS, including British troops and the first Faroese cohort. The long vertical bar represents the entire Faroese population, all ages, first exposed to PMSA from British troops (box near the bottom of the bar) in 1941 (F1 E). Only that proportion aged 11 to 45 in 1941 later developed CNMS, so only those aged 11 to 45 at the start of exposure were susceptible (F1 E+S). This segment of the F1 cohort, after the 2 years of exposure, was affected with PMSA (F1 A). Subjects aged 11 by 1943 were added to this cohort. With British troop departure after 1944, the F1 A cohort was at its maximal size in 1945, comprising persons then aged 13 to 49. Survival for this total F1 A cohort is as noted. That part of the F1 A cohort under age 27 in 1945 comprised the segment of the cohort able to transmit illness (F1 A+T). Each year its size was reduced by the number attaining age 27, and it disappeared after 1958. This F1 A+T cohort transmitted PMSA to the F2 cohort, consisting of Faroese attaining age 11 while the F1 A+T cohort was of a size sufficient for transmission.

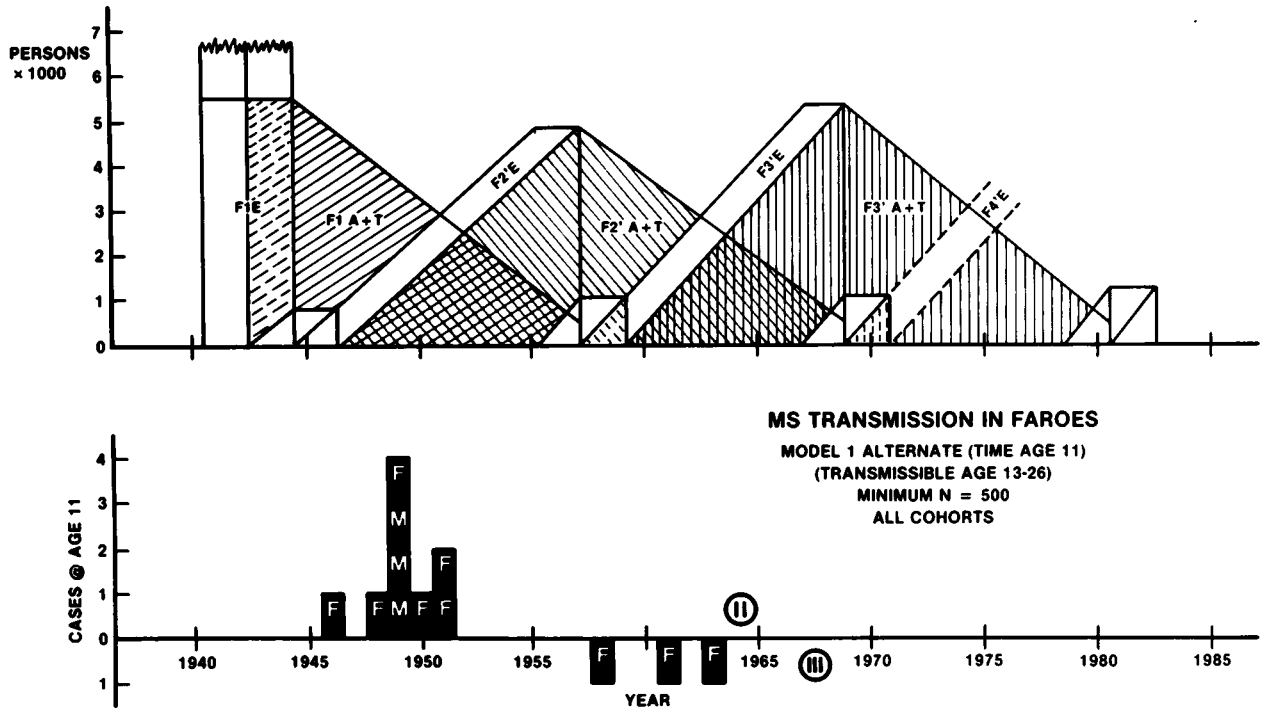


FIG. 26. Transmission model for the first three Faroese population cohorts affected with PMSA, as in Fig. 25, with a minimal number of 500 Faroese able to transmit disease. The lower graph shows patients of epidemics II and III by sex and year at which age 11 was attained, as of 1986. Reprinted with permission from the publisher (163).

500, the F1 A+T cohort would provide exposure for 2 years to an F2 E cohort accumulating from 1945 to 1954 or from 1945 to 1955. The epidemic II cases of CNMS all attained age 11 in 1946 to 1951 (Fig. 26).

Since the F2 cohort input ends in 1954 or 1955, F2 A reaches its maximum size then (and to 1956 or 1957). From this point, it comprises the F2 A+T cohort (for F3 E), and it then too starts its own decline over time to its own minima for transmission. From the point in time at which the F2 A+T cohort is at its maximum, the F3 E cohort, comprising Faroese attaining age 11 each year from 1956 or 57, begins to accumulate until the time (less than 2 years) at which the F2 A+T cohort reaches its minima. The CNMS cases of epidemic III attained age 11 during the F3 E interval. After 2 years of exposure, this cohort becomes the F3 A cohort, and from its maximum through its decline as F3 A+T, it would provide input for an F4 E cohort for a fourth epidemic of CNMS—which is what has happened.

Fourth epidemic. One point seemed apparent by 1986: the Faroes were behaving as a geographic isolate insofar as MS was concerned. Despite the markedly increasing traffic with other lands and a progressively growing influx of tourists over the years, there was no evidence whatsoever that the disease was later brought into the islands at any time after the war. The second and third epidemics could logically only be attributed to transmission, respectively, from the affected populace of the first epidemic, who had acquired the disease from the British, and then from that second cohort (including the second epidemic) to the cohort including the third epidemic.

This was the situation in 1986: MS was not endemic on the islands, but were the epidemics over, or was there to be an epidemic IV?

By 1990 we had identified several new cases of CNMS. Table 14 summarizes the total resident series as of 1991, including three additions to epidemic III and seven new patients who (so far) constitute epidemic IV (167). The average age of clinical onset for the epidemic IV patients remains age 21, the same as was found for epidemics II and III. Annual incidence rates for all four epidemics are shown in Fig. 27, and transmission modeling is summarized in Fig. 28.

(i) Geographic distribution and British troops. The residence history for patients of all four epidemics is described elsewhere (167). Correlations of parishes of residence of the patients with sites of British troop encampments are shown in Tables 15 and 16. There is a strong relationship between the British occupation and all the epidemics, even excluding epidemic I. In fact, despite the small numbers, each epidemic shows a significant relationship with the troop locations, except for epidemic IV; for that epidemic, significance is lacking solely because of one patient who lived in Leirvík, Eysturoy. This village was the site of the ferry from Eysturoy to Klaksvík, where troops were stationed, so its residents were exposed throughout the war to considerable numbers of British. It was also the residence of one patient from the first epidemic.

A highly significant relationship was also found for the correlation of residences for epidemic I patients and those from later epidemics. Odds ratios for individual epidemics II to IV were 12.43, 9.00, and 13.78, respectively (167).

(ii) Validity of the epidemics. Considerable doubt has been raised as to our interpretations because of the small number of cases. With the standard χ^2 test of homogeneity, we had earlier demonstrated a highly significant variation in year of onset for the three epidemics (165). This significance is even

TABLE 14. Faroese resident series by epidemic (revised June 1991)[a]

Epidemic and case	Sex	Yr of birth	Yr of onset	Age at onset	Yr in which age 11 was attained	Group
I (20 cases)			1943–1961		Pre-1944[b]	
II (9 cases)			1953–1973		1946–1951	
III (6 cases)			1968–1982		1956–1967	
23	F	1950	1970	20	1961	A
96	F	1953	1972	18	1964	B
97	F	1947	1968	21	1958	B
102	F	1952	1969	17	1963	A
113	F	1956	1982	25	1967	B′
121	M	1945	1972	27	1956	A
IV (7 cases)			1984–1989		1973–1980	
112	F	1966	1984	17	1977	A
123	F	1964	1986	21	1975	A
126	F	1959	1986	26	1977[b]	A
127	M	1966	1987	20	1980[b]	A
130	F	1962	1989	26	1973	B′
140	M	1964	1987	22	1975	A
141	F	1968	1986	17	1979	A

[a] Modified and reprinted with permission from the publisher (167).
[b] Year of first exposure.

more obvious when the four epidemics are considered (Table 17).

While homogeneity is clearly rejected, this analysis does not document four epidemics. However, the median years of symptom onset were 1947 for epidemic I and 1986 for epidemic IV (167). If this division into four epidemics is valid, there should be an average interval of about 13 years [(1986 − 1947 = 39)/3] between the beginning or end of each epidemic. Thirteen years is also the effective transmission period hypothesized in our models. Thus, if there were four epidemics, they should have begun about 1943, 1956, 1969, and 1982, respectively, and the few years before these respective dates should be the "valleys" of virtually no cases. Table 18 shows the data for 7 years "on" (high case expectation) and 6 years "off" (low case expectation) for each epidemic (8- and 5-year-division results were quite similar).

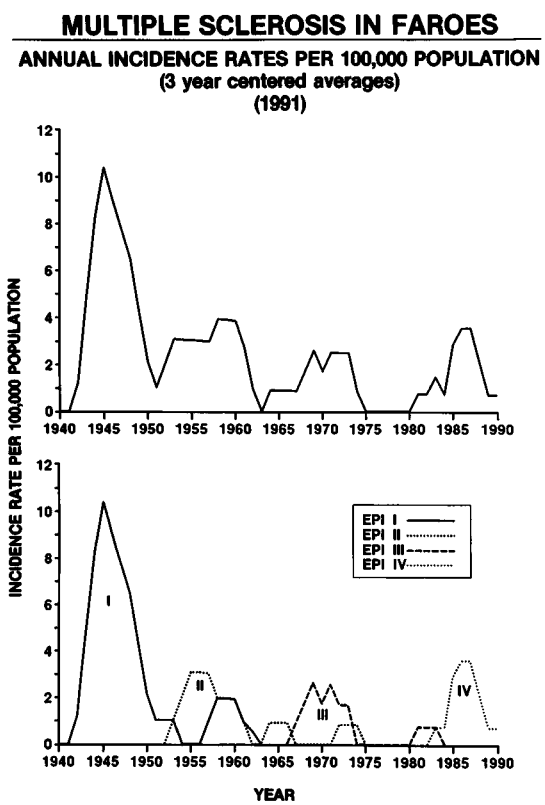


FIG. 27. MS in native Faroese as of 1991. Annual incidence rates per 100,000 population were calculated as 3-year centered moving averages. (Top) Total series. (Bottom) Incidence rates by epidemic (EPI). Reprinted with permission from the publisher (167).

Even by limiting attention to the period from 1943 and later and ignoring all earlier years, we find that there is a very highly significant rejection of homogeneity for the periods defined by the four epidemics at 13-year intervals.

The hypothesis of three epidemics after the first within population cohorts, each defined by the calendar time at which age 11 occurred, can also be tested with the same a priori division of 13-year intervals (7 on and 6 off) as that used above, beginning in 1945. Thus, if this is a valid criterion, age-11 "on" intervals should start close to 1945, 1958, and 1971. The denominator for each interval is the number of Faroese aged 11, derived from published data for Faroese aged 10 to 14, or similar intervals. Even with these very small numbers, the findings are still statistically significant (Table 19). Consolidating the three high-risk periods and comparing them with the three low-risk periods yields risk ratios of 1.21 and 0.30 per 1,000, respectively ($\chi_c^2 = 6.24$; $0.02 > P > 0.01$).

However, were there really no cases before 1943? In a prior section I detailed the methods used to ascertain possible instances of MS and the procedures used once a suspect was identified. Could my colleagues and I still have missed early cases? Given the prewar situation of the Faroes as a standard Danish county, given the national health care system and the national disability system of Denmark since 1921, and given the nature of MS, with the expectation of disease activity over many years, we are confident that the

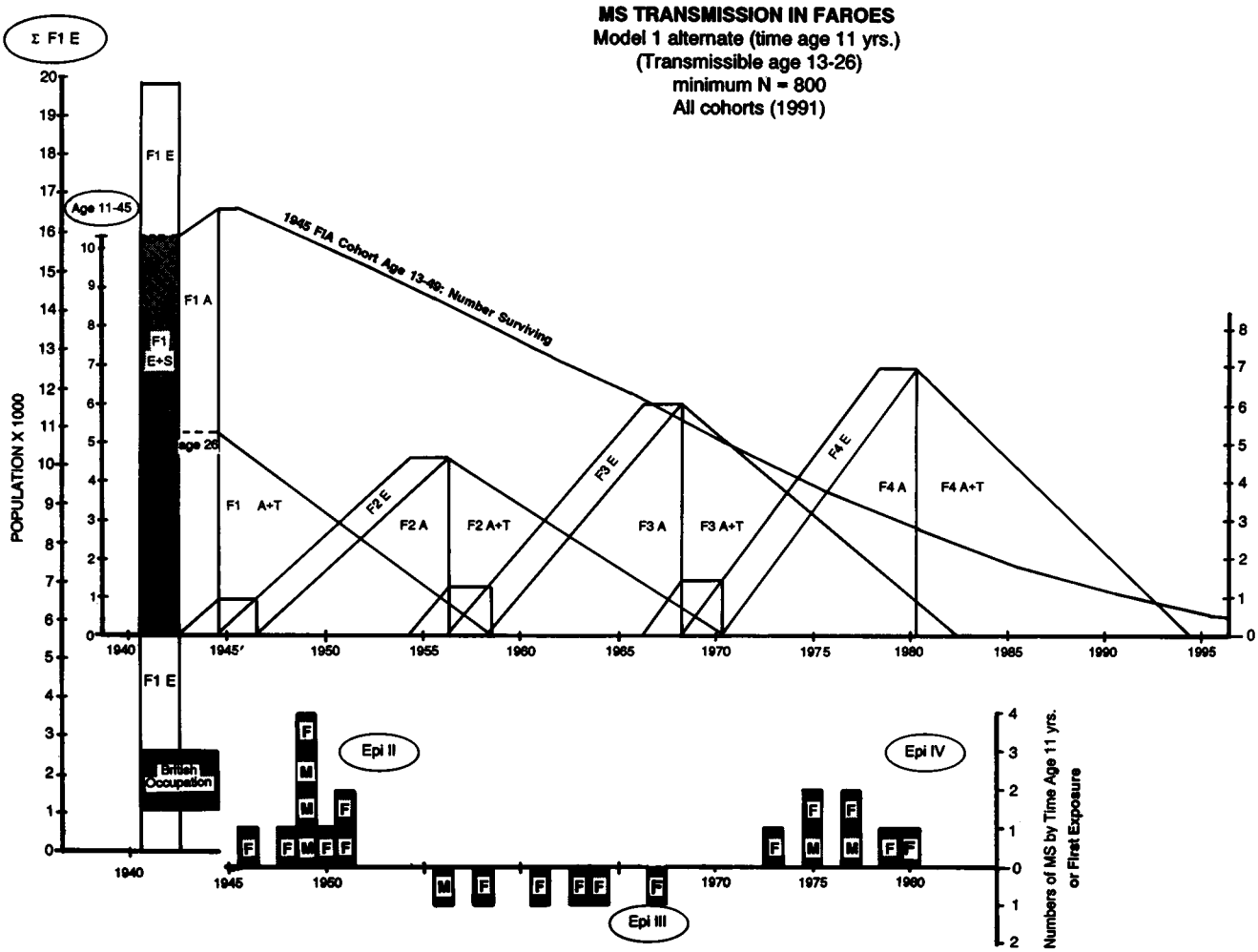


FIG. 28. Summary of the transmission of PMSA in the Faroes as of 1991. The first Faroese cohort (F1) exposed to PMSA (F1 E) from the British troops (block at lower left) comprised the entire Faroese population, all ages, geographically at risk in 1941 (long vertical bar). Only those aged 11 to 45 in 1941 were susceptible (F1 E+S) to PMSA, on the basis of the later occurrence of CNMS (shaded portion of bar). After 2 years of exposure, F1 E+S became the F1 A (affected) cohort. That part of the F1 A cohort under age 27 in 1945 defined the F1 A+T cohort (affected and able to transmit disease), which declined in number each year as those attaining age 27 were excluded (first decreasing triangle). The F1 A+T cohort transmitted PMSA to the second cohort of Faroese (F2), formed from those reaching age 11 each year while F1 A+T was of sufficient size. The 2 years of exposure for F2, resulting in F2 E (first rising parallelogram), preceded the affected stage (F2 A); when F2 E and F2 A ceased growth, it began to decline while serving as the F2 A+T cohort for the transmission of PMSA to F3 E. Similar is the transmission from F3 A+T to F4 E. Below the main graph, each patient from epidemics (Epi) II to IV is identified by time of first exposure to PMSA. The survival curve for the entire F1 A population cohort from 1945 is also drawn in the main graph. Reprinted with permission from the publisher (167).

chances of missing more than a rare patient are very low. Furthermore, it would require 22 patients with onset before 1943 to have been missed to equate with the experience from 1943 to 1989 (calculated from person-years for 1900 to 1942 and an average incidence rate of 2.38 per 100,000 person-years for 1943 to 1989). We find the likelihood of such an event to be vanishingly small.

Biologic plausibility. Among the objections raised to the Faroe experience is that our findings are biologically implausible, our incubation period is too short, and our exposure period is too long, and the concept of PMSA itself has been questioned (216, 217).

This brings up the question of what we believe PMSA to be. We believe that it is clearly the result of an infectious agent, probably an as-yet-undefined (retro)virus. The theory of an infectious cause for MS has a long history antedating this century, but all agents proposed thus far—from mycoplasmas to mycobacteria to spirochetes to rickettsiae to a host of viruses ranging from measles to HTLV-I—have been refuted by negative efforts at replication and will not be further reviewed here; see the section on antibodies above.

(i) Incubation and exposure. We are positing an average of 2 years of exposure for Faroese to acquire PMSA (at or after age 11) and then 6 years of incubation before clinical onset. In high-risk areas of endemicity, the incubation period after acquisition at age 15 would be 12 years (twice that posited for Faroese), as previously discussed.

However, it is well known that many infections have a shortened incubation period when introduced into virgin populations. Levine noted this fact for hepatitis B (178), and similar findings have been discussed (162) for measles and experimental Q fever. As to the need for prolonged exposure

TABLE 15. Odds ratios and significance levels for parishes of residence of British troops and of MS patients by epidemic[a]

Item no.	Comparison	Odds ratio	95% Confidence interval	χ_c^2	P
1	Troops vs epidemics I–IV	20.43	3.68–113.47	13.171	<0.001
2	Troops vs epidemics II–IV	9.00	1.65–49.00	6.988	<0.01
3	Troops vs epidemic I	13.44	2.47–73.19	9.282	<0.01
4	Troops vs epidemic II	12.38	1.37–112.10	5.055	<0.05
5	Troops vs epidemic III	(>6.0)		4.514	<0.05
6	Troops vs epidemic IV	4.06	0.39–42.49	0.516	>0.30
7	Epidemic I vs epidemics II–IV	32.63	5.10–208.50	16.049	<0.001

[a] Modified and reprinted with permission from the publisher (167). Data for items 1 to 6 in Table 16; those for item 7 are in reference 167.

to acquire disease, leprosy is perhaps the best example. Furthermore, Levine (178) stated, "It appears that HTLV-I is very poorly infectious—multiple exposures via breast-feeding or sexual intercourse are required to pass it from host to host." Levine also noted the prolonged incubation period between the acquisition of this persistent virus and clinical symptoms—as well as the very small proportion of affected persons who ever develop T-cell leukemia, as is also true of HTLV-I-associated tropical spastic paralysis—and poliomyelitis. Persistent viruses include not only the retroviruses (HTLV-I and HTLV-II, HIV types 1 and 2, simian immunodeficiency virus, and visna virus) but also the papovaviruses (human papillomavirus), herpesviruses (varicella-zoster virus, EBV, herpes simplex virus types 1 and 2, and cytomegalovirus), hepadnaviruses (hepatitis B) (178), and the JC virus (progressive multifocal leukoencephalopathy) (106). As to age of susceptibility beginning in adolescence, Rodriguez (237) noted this age limitation in his work on experimental Theiler's virus infection of mice, as well as other similarities with PMSA that we are exploring together.

If in areas of high endemicity PMSA requires 4 years of exposure and 12 years of incubation and unexposed persons of a virgin populace require 2 and 6 years, respectively, might one expect intermediate values for intermediate-risk areas? The findings for the Algerian French immigrants from a medium-risk area (58) described in Table 11 could be calculated as 3 years of exposure and 9 years of incubation for the 12-year average between immigration and CNMS.

If it truly takes about 4 years of exposure to acquire PMSA in high-risk areas, then the spread of the disease would be slow—perhaps measured in decades, barring an unusual introduction (as on the Faroes). Is there evidence regarding the spread of MS over time?

Origin and spread of MS. It is clear that CNMS is a place-related disorder. All the high- and medium-risk areas are found in Europe or the European colonies: Canada, the United States, Australia, New Zealand, South Africa, and probably central and southern South America. It seems likely, therefore, that MS originated in northwestern Europe and was brought to these other areas by their European settlers. In Europe itself, although the disease clearly has remained clustered in some areas, there is evidence even within these clusters of a slow diffusion over time. Note in this respect the slope of the regression line in Fig. 3. There is also the marked change in incidence and prevalence rates found for Hordaland, Norway, discussed above, so that that region is now one of high rather than medium risk (it now joins the Fennoscandian focus shown in Fig. 4), as well as the changes seen for Italy and Israel.

The following is a hypothesis as to the origin and spread of MS which requires much better documentation but which is a tenable, and partly testable, one. PMSA—and CNMS—may have originated in central Norway and the south-central Swedish lake region near the center of the Fennoscandian focus shown in Fig. 4, possibly at about the 17th or the beginning of the 18th century. With regard to high-risk areas, it then spread slowly from this nidus to form the focus depicted, and from Scandinavia it diffused across the Baltic States, Poland, Germany, and France before the start of the 19th century. Further spread into the British Isles took place in the early 19th century, and spread to the United States (and Canada) by the Scandinavians took place in the mid and latter parts of that century (270); toward the end of that century came the emplacement in Australia and New Zealand by the British. In the current century, spread came to South Africa early and Italy late, although South Africa is still of only medium prevalence.

If this hypothesis is correct, then our long-held belief in a latitude gradient for the risk of MS may be in error—we may be seeing merely the pattern of spread of PMSA from Scandinavia outward.

TABLE 16. Data for comparisons in Table 15[a]

Item no.	No. of parishes (no. of MS cases) with:				
	MS cases and troops	MS cases but no troops	No MS cases but troops	No MS cases and no troops	Total
1	13 (38)	2 (4)	7	22	44 (42)
2	9 (20)	2 (2)	11	22	44 (22)
3	11 (18)	2 (2)	9	22	44 (20)
4	7 (8)	1 (1)	13	23	44 (9)
5	5 (6)	0	15	24	44 (6)
6	3 (6)	1 (1)	17	23	44 (7)

[a] Modified and reprinted with permission from the publisher (167). Specific comparisons are identified by the same item number in Table 15.

Nature of MS

It is perhaps more clear now why I am so intrigued with the Faroese saga and why it needs further investigation. To recapitulate the story to date, two summary lists are offered.

MS in the Faroes. (i) CNMS did not exist among resident Faroese before 1943. (ii) PMSA was introduced into the Faroes by British troops in 1941 to 1944. (iii) This introduction led to a point-source epidemic of CNMS (epidemic I) within the cohort of Faroese who were affected with PMSA (F1 A) after 2 years of exposure (F1 E). (iv) Only Faroese aged 11 to 45 at onset of exposure were affected with CNMS and hence PMSA. (v) Affected Faroese aged 13 to 26 (F1

TABLE 17. Average annual incidence rates for Faroese CNMS per 100,000 person-years for 1900 to 1989 according to equal periods of expected incidence[a]

Period	Person-yr	MS-O[b]	MS-E[b]	χ^2	Rate[c]	95% Confidence interval
1900–1921	394,577	0	6.204	6.204	0.00	0–0.94
1922–1937	384,689	0	6.048	6.048	0.00	0–0.96
1938–1951	398,976	16	6.273	15.083	4.01	2.29–6.51
1952–1963	404,028	11	6.353	3.399	2.72	1.36–4.87
1964–1973	381,031	7	5.991	0.170	1.84	0.74–3.78
1974–1982	383,220	1	6.025	4.191	0.26	0.01–1.45
1983–1989	324,719	7	5.106	0.703	2.16	0.87–5.60
Total	2,671,240	42	42.000	35.798	1.57	1.13–2.13

[a] Modified and reprinted with permission from the publisher (167).
[b] MS-O/E, number of MS observed/expected on null hypothesis of homogeneity.
[c] Per 100,000 person-years ($\chi^2_6 = 35.798$; $P < 0.00001$).

A+T) transmitted PMSA to a second cohort of Faroese (F2 E), comprising those attaining age 11 while F1 A+T existed. (vi) The F2 A+T cohort included the CNMS of epidemic II and was the source of PMSA in the F3 cohort, resulting in epidemic III of CNMS. (vii) The F3 A+T cohort similarly has produced epidemic IV within the F4 cohort with PMSA.

Nature of MS from the Faroese experience. (i) There is a specific, widespread, but unidentified infection that we call PMSA. (ii) PMSA is a persistent infection transmitted from person to person. (iii) A small proportion of persons with PMSA will later develop CNMS. (iv) Prolonged exposure (about 2 years for a virgin populace and 4 years in an area of endemicity) is needed to acquire PMSA. (v) PMSA acquisition follows a first adequate exposure. (vi) Susceptibility to PMSA is limited to about ages 11 to 45 at the start of exposure. (vii) CNMS is not transmissible. (viii) Therefore, the transmissibility of PMSA is limited to a period under the usual age of CNMS onset. (ix) The existence of PMSA can now be inferred only from the existence of CNMS.

COMMENTS

The best measures of the geographic distribution of MS come from prevalence studies, of which there are now over 300. 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 of 30 or more per 100,000 population, now mostly 50 to 120 per 100,000, comprise northern and central Europe into Italy and the former USSR, Canada, the northern United States, New Zealand, and southeastern Australia. These regions are bounded by areas of medium frequency, with prevalence rates of 5 to 29 per 100,000 population and comprising much of Australia; the southern United States; southwestern Norway; northernmost Scandinavia; much of the northern Mediterranean basin and possibly its eastern and southern shores as well; probably Russia from the Urals into Siberia as well as the Ukraine; South Africa (whites); and perhaps central South America. All other studied areas of Asia, Africa, and the Caribbean region, including Mexico and possibly northern South America, are all of low frequency, with prevalence rates of less than 5 per 100,000 population. A number of nationwide prevalence studies in Europe provide evidence for geographic clustering of the disease, which is stable over time, but with, however, evidence of diffusion over time as well.

There is a female preponderance in incidence, prevalence, and mortality rates of about 1.5:1 (female/male). Annual incidence rates are about 3 to 5 per 100,000 population in high-risk areas, about 1 per 100,000 in medium-risk areas, and about 1 per 1,000,000 in low-risk areas. Age-specific incidence rates rise from 0 in childhood through adolescence to a peak close to age 27 and then return more slowly to 0 by age 60. This pattern is what one might expect for an infectious disease with a limited age range of susceptibility.

All high- and medium-risk areas are among predominantly white populations: MS is a white female burden. In the United States, blacks, Orientals, and possibly American Indians have much lower rates of MS than do whites, but

TABLE 18. Average annual incidence rates for Faroese MS cases per 100,000 population, divided into four epidemic periods of 13 years, with each period expected to comprise 7 years of high case expectation followed by 6 years of low case expectation[a]

Period	Person-yr	MS-O	MS-E	χ^2	Rate[b]	95% Confidence interval
1943–1949	205,033	16	4.888	25.261	7.80	4.46–12.67
1950–1955	192,711	4	4.594	0.077	2.08	0.57–5.31
1956–1962	239,155	7	5.702	0.295	2.93	1.17–6.03
1963–1968	221,324	2	5.276	2.034	0.90	0.11–3.26
1969–1975	277,106	5	6.606	0.390	1.80	0.58–4.21
1976–1981	257,194	0	6.132	6.132	0.00	0.00–1.43
1982–1989[c]	369,205	8	8.802	0.369	2.17	0.93–4.27
Total	1,761,728	42	42.000	34.558	2.38	1.72–3.22

[a] Modified and reprinted with permission from the publisher (167). For MS-O/E, see Table 17, footnote *b*.
[b] Per 100,000 person-years ($\chi^2_6 = 34.556$; $P < 0.00001$).
[c] Results were similar to those for 1982 to 1988.

TABLE 19. Risk of CNMS per 1,000 population at age 11 for three epidemics after epidemic I, divided into periods of 13 years, with each period expected to comprise 7 years of high case expectation followed by 6 years of low case expectation[a]

Period	Persons aged 11	Patients aged 11		χ^2	Risk[b]	95% Confidence interval
		O	E			
1945–1951	3,963.6	9	3.112	11.140	2.27	1.04–4.31
1952–1957	3,994.5	1	3.137	1.456	0.25	0.01–1.39
1958–1964	5,070.5	4	3.981	0.000	0.79	0.21–2.02
1965–1970	4,465.5	1	3.506	1.791	0.22	0.01–1.25
1971–1977	5,804.4	5	4.558	0.043	0.86	0.28–2.01
1978–1983	4,719.1	2	3.706	0.785	0.42	0.05–1.53
Total	28,017.6	22	22.000	15.215	0.79	0.49–1.19

[a] Modified and reprinted with permission from the publisher (167). For O and E, see Table 17, footnote *b*.
[b] Per 1,000 persons aged 11 ($\chi^2_5 = 15.215$; $0.02 > P > 0.01$).

each group still demonstrates the geographic gradients found for whites.

Aside from geography, age, sex, and race, risk factors for MS include high socioeconomic status and level of urbanization of preillness residence, at least in the U.S. Army series. No meteorologic correlate of geography is a risk factor for MS when latitude is controlled. In the United States, there is a strong correlation of MS risk with populations with Scandinavian, particularly Swedish, ancestry.

There is an increased familial frequency in MS. Twin studies are inconclusive in terms of a genetic component, and I believe that the familial excess reflects common environment more than common genes.

Migration studies indicate that, on the whole, migrants do not retain all of the risk of their birthplace. MS risk is clearly not defined at birth: MS death rates for migrants born in one risk area and dying in another are intermediate between those characteristic of their birthplace and their death residence, regardless of the direction of the move. Prevalence studies for migrants from high- to low-risk areas indicate age of adolescence to be critical for risk retention; those migrating above age 15 retain the MS risk of their birthplace, and those migrating below age 15 acquire the lower risk of their new residence. Thus, in high-risk areas of endemicity, MS is acquired in early adolescence, and young children are not susceptible to the disease. Several studies of migrants moving from low- to high-risk areas show that those migrating in childhood or older do in fact increase their risk of MS, with age 10 or 11 apparently being the minimum age of susceptibility and about ages 40 to 45 being the maximum. The migrant data and the geographic distributions serve to define MS as an acquired, exogenous, environmental disease with a prolonged incubation period between acquisition and clinical expression—a situation most compatible with an infectious disease with prolonged latency.

MS on the Faroe Islands has occurred as four successive epidemics beginning in 1943. The disease was introduced by British troops who occupied the islands for 5 years from 1940. What they introduced must have been an infection, which is called PMSA.

In this concept, PMSA is a single widespread systemic infectious disease (perhaps asymptomatic) that only rarely leads to CNMS after an incubation period averaging 6 years for virgin populations (and 12 years for populations in areas of endemicity). It requires 2 (for the former populations) or possibly 4 (for the latter populations) years of exposure before the disease is acquired. Susceptibility to PMSA is limited to about ages 11 to 45 at the start of exposure; transmissibility ends at about age 26.

If the PMSA agent has these characteristics of prolonged exposure, limited age of susceptibility, prolonged incubation, and rare clinical disease, then the geographic spread of this disorder would also be prolonged. In this manner, one could explain the current distribution of MS as the result of slow diffusion from an origin in the lower Scandinavian peninsula at or before the start of the 18th century, with overseas spread by migrations: Scandinavians to America in the mid-19th century and British to Australia, New Zealand, and South Africa rather later.

Thus, I believe that clinical MS is the rare late outcome of a specific but unknown infectious disease of adolescence and young adulthood and that this infection could well be caused by a thus-far-unidentified (retro)virus.

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