Epidemiology and Etiology of Multiple Sclerosis

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The generally accepted view is that multiple sclerosis (MS) primarily is an autoimmune disease that is precipitated by undefined environmental factors in a genetically predisposed host. The author's interpretation of the epidemiologic information, however, is that the "environmental factors" include the principal cause of this illness. Epidemiologic works are concerned with the frequency of diseases, and their characteristics by race, sex, geography, and other risk factors, as well as with the severity and course of the illness. Such information is needed and should be used by all aspects of the health care system, from government to clinician. The epidemiologic unit is a person who has a given disorder. After diagnosis, the basic question is "How common is the disease?" This frequency should be described by the best count of the number of cases as the numerator within the specific populations at risk as the denominator. These ratios, with the addition of the time period to which they pertain, are referred to as rates.

The population-based rates that are in common use are the incidence rate, the mortality rate, and the prevalence "rate." The incidence or attack rate is defined as the number of new cases of the disease beginning clinically in a unit of time within the specified population. Usually, this is given as an annual incidence rate in cases per 100,000 population per year. The mortality or death rate refers to the number of deaths with the disease as the (underlying) cause of death that occur within a unit of time and population, and thus, an annual death rate per 100,000 population. The point prevalence "rate" more properly is called a prevalence ratio, and it refers to the number of the affected within the community at one point in time, again expressed per unit of population.

The Association for Research in Nervous and Mental Disease meets annually in New York to present a symposium on one specific topic. Their

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first session in 1920 dealt with von Economo's encephalitis. The second was on MS; this was the first comprehensive assessment of MS in the United States (references to this and other uncited works are in [1]). The Commission concluded that MS affected chiefly young adults and men more than women. Duration averaged 8 years, and it seemed to affect skilled manual workers more often. Geographically, in the United States it was most common near the Great Lakes, whereas in Europe is was more common in the north than in the south. The male excess was found for most of the European studies and all those from the United States, with an overall average of 3:2 (male:female).

Male preponderance also was seen for MS death rates near 1960 in the United States, but only among those of older age. White women were clearly in excess at younger ages (Fig. 1) [2]. Incidence and prevalence rates in Denmark near 1950 had a similar pattern, with higher rates for women among the younger patients and equal rates by sex in the older ones. An increasing excess of women in Denmark has characterized the incidence rates for more than 50 years, however. Two regions of Norway also demonstrated a growing female excess over time. Sweden also has shown an increasingly higher majority among women [3]. By 1980, white women had the highest death rates in the United States at all ages (Fig. 2). Young black women seemed then to have rates similar to the whites.

We studied MS in the United States among some 5300 veterans of World War II or the Korean Conflict, who were service connected by the Department of Veterans Affairs (VA) for MS. They were matched with preillness peers from the military. White women had nearly twice the risk of MS as the white men, with a relative risk ratio of 1.79. There seems to have been a change from a disorder that affected men more often to one that
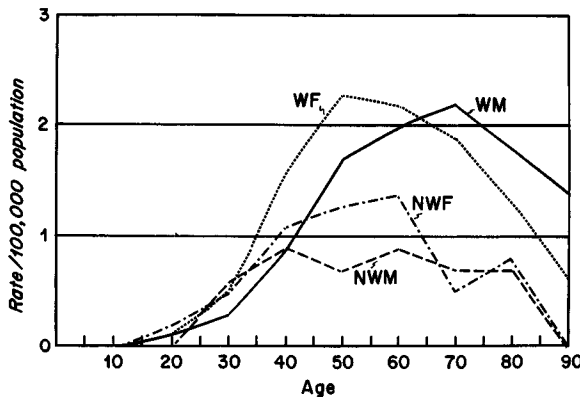

Fig. 1. Average annual age specific death rates per 100,000 population for multiple sclerosis by sex and color, United States 1959–1961. F, female; M, male; NW, nonwhite; W, white. (*Modified from* Kurland LT, Kurtzke JF, Goldberg ID. Epidemiology of neurologic and sense organ disorders. Cambridge (MA): Harvard University Press; 1973. p. 70; with permission.)
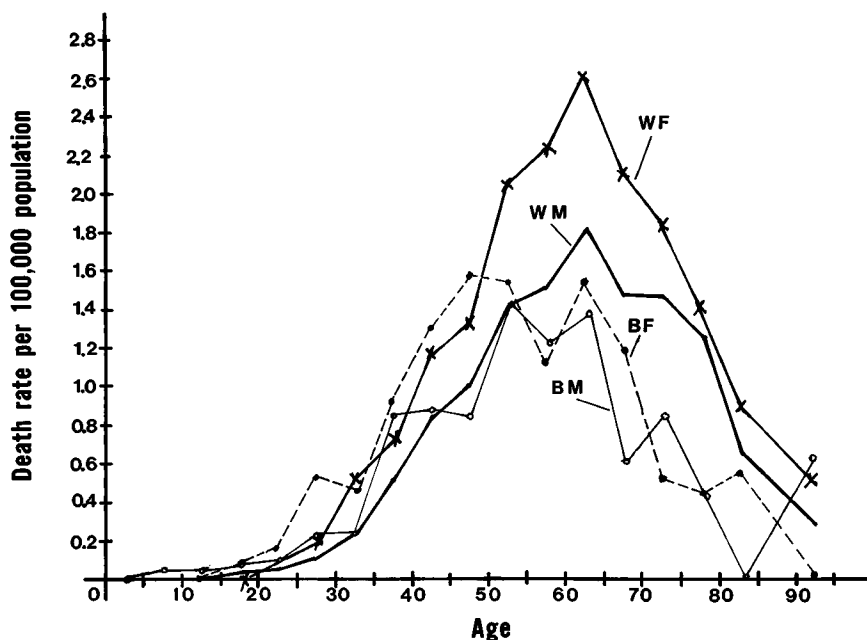
Fig. 2. Average annual age specific death rates per 100,000 population for MS by sex and race, United States 1979–1981. B, black; F, female; M, male; W, white. (*From* Kurtzke JF. Epidemiology of multiple sclerosis. Does this really point toward an etiology? Neurol Sci 2000;21:386; with permission.)

shows an increasing preponderance among women. The excess among whites versus those of other races persisted, however. Relative risk ratios were 0.44 for black males and 0.22 for other men (nonwhite, nonblack).

A more recent series is under study. This includes more than 5000 U.S. veterans with military service in the Vietnam War, or later, up to 1994, who also were service connected for MS by the VA, and who were matched on a 1:2 basis with military peers [4]. Women of all races, whether white, black, or other, now have a greater risk of MS than white men, with relative risk ratios of nearly 3 to 1. Black men have a significantly greater risk ratio of 0.67 than they showed in the World War II series, although their risk is still less than that of white men. Men of other races had little change, with a relative risk of 0.30. There has to be an environmental reason for the growing predominance of women who have MS. The changing ratios by race also suggest that these differences also are based more on environment than genes.

Geographic distributions are defined best by prevalence studies, of which there are now more than 300 for MS. Prevalence surveys from the 1960s to 1980 indicated that most of northern Europe was of high frequency, with rates of 30 or more per 100,000 population (Fig. 3) [5]. Southern Europe had a distinctly lower frequency, with rates reflecting medium frequency
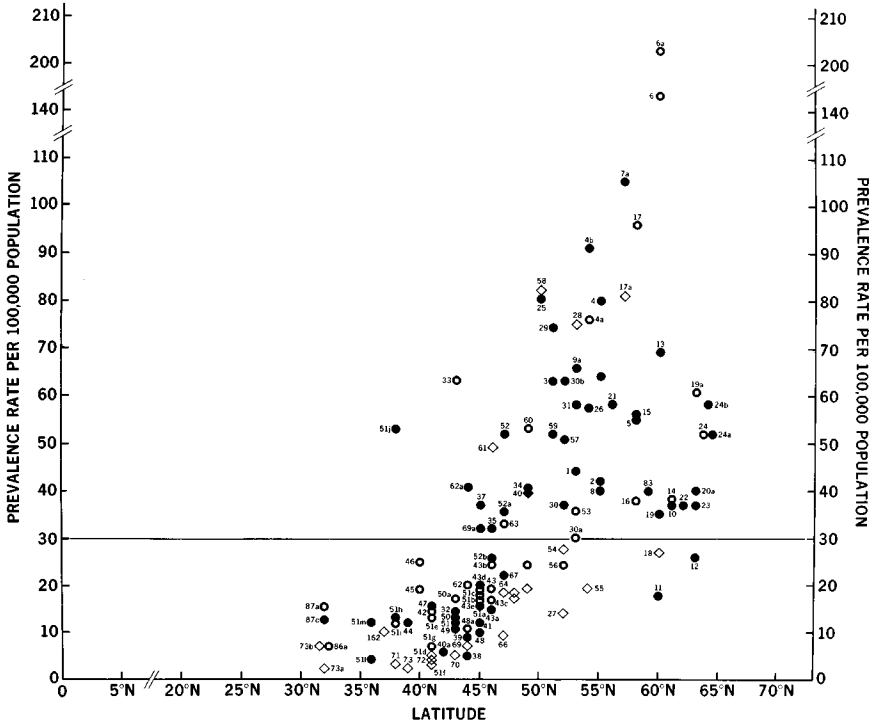
Fig. 3. Prevalence rates per 100,000 population for probable MS in Europe and the Mediterranean area as of 1980, correlated with geographic latitude. Solid circles represent class A (best) studies, open circles represent class B (good) studies, open diamonds represent class C (poor, cited only when there is no better survey for the site). Numbers identify specific surveys in the references below. (*From* Kurtzke JF. Geographic distribution of multiple sclerosis: an update with special reference to Europe and the Mediterranean region. Acta Neurol Scand 1980;62:70; and Kurtzke JF. A reassessment of the distribution of multiple sclerosis. Part One, Part Two. Acta Neurol Scand 1975;51:110–57; with permission.)

(5 to 29 per 100,000). The pattern was similar in North America, with high rates in Canada and the northern United States, whereas the southern United States had a medium frequency. Southeastern Australia had a high frequency whereas the rest of the country had a medium frequency. New Zealand also was in the high range, whereas Asia had a low frequency (prevalence less than 5 per 100,000 population).

Prevalence studies, however, are mostly "spot surveys" of small areas, and may tell little about areas that are not examined. Nationwide surveys by one team at one time permit complete geographic coverage. When such studies are repeated at a later time, we also can see if distributions have changed. The country of Denmark was surveyed twice, the old series for 1921 to 1933 disability cases, the new for 1949 prevalence. Rates were maximal across the north-central part of the Jutland peninsula on to the

island of Funen, just to the east. Switzerland also had two national estimates, the old one for 1918 to 1922, the new for 1956; both showed a strong northwestern geographic concentration. Norway also had two surveys over time; highest rates were noted in the southeast. When percentages by county of each national mean are compared between the old and the new series in each of these three countries, each are correlated highly (old versus new), but with the same regression line that shows a clear diffusion over time, with an intercept far off the 0 point on the X-axis (Fig. 4) [6].

Spread of MS may be from within this Fennoscandian focus of high frequency of MS, and from a source within the southern inland lake region of Sweden (Fig. 5). Spread from this region eastward to Finland, southward to the continent, and westward to Norway and then Denmark would provide the diffusion. Currently under investigation is whether the European spread outside of the Baltic region may have had its first dissemination with the movements of the army of King Gustav Adolf of Sweden into Germany from 1630 to 1632 during the Thirty Years War of 1618 to 1648 [7].

The long held view of a north-south gradient for MS may be little more than a reflection of this spread from Sweden—a different type of big bang theory. Compatible with this view is the finding that the high-frequency regions of France are mostly in the northeast and those of Switzerland are in the northwest. But this spread takes years. The prevalence rates (see Fig. 3) for Europe in 1980 were similar to those that were seen earlier. By 1994, however, there were major differences. Fig. 6 shows that the entire northern Mediterranean basin is now an area of high frequency; Portugal and Greece also now exhibit high frequency of MS, with prevalence rates per 100,000 population in the 40s. Diffusion is a hallmark of this disease.

The spread is not limited to Europe. In the United States, the World War II series showed a marked excess for residents in the north (Fig. 7). This was seen for both sexes among whites and for black men, with a north to south difference of almost 3 to 1. The Vietnam War and later service veterans still showed a gradient, but it was much less. All southern states were calculated to lie within the high-frequency zone, with prevalence rates that were estimated at well more than 30 per 100,000 population. For all races and sexes, the north to south difference was only 2 to 1.

In Asia and Africa, earlier assessments provided low prevalence rates—less than 5 per 100,000—except for English-speaking whites of South Africa, who had a medium prevalence. This distribution is now more complex. Rates are still low in the few surveys from Korea, China, and southeast Asia, but not in the former Soviet Union or in Japan. For the latter, two recent studies reported rates of 9 [8] and 10 [9] per 100,000, respectively. Boiko [10] of Moscow summarized prevalence studies from Russia and other parts of the former Soviet Union. In the southern region of the Ukraine, the Volga area, the Caucasus, and into Novosibirsk and
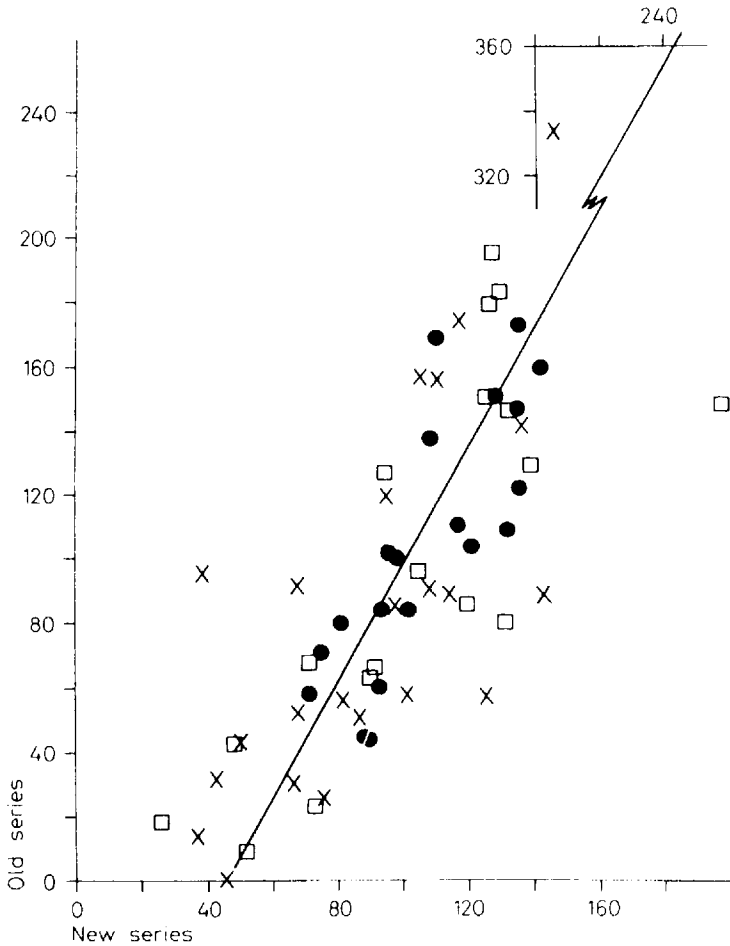
Fig. 4. Correlation of the distributions of MS by county between old series and new series of nationwide prevalence studies of three countries, each covering different generations of patients. Each county rate is expressed as the percentage of its respective national (mean) rates. ●, Denmark; □, Norway; X, Switzerland. (*From* Kurtzke JF. Further features of the Fenno-scandian focus of multiple sclerosis. Acta Neurol Scand 1974;50:490; with permission.)

Kazakhstan, rates generally were in the medium prevalence range, whereas more easterly lands had a low prevalence. In easternmost Russia, medium rates reappeared, with high rates in parts of the Amur region near the Pacific Ocean north of China.

Now the southern littoral region of the Mediterranean has a medium prevalence, and the Canary Islands, Cyprus, and Israel have a high prevalence. In Latin America, the Caribbean region, including Mexico, also may have a medium frequency now, as well as Argentina, Brazil, Chile, Uruguay, and Peru, whereas Venezuela and Colombia may have a low

Fig. 5. Distribution of MS in Fennoscandia from nationwide surveys. Areas whose frequency of MS is significantly greater than their respective national means are in solid black; areas whose frequency of MS is increased, but of dubious statistical significance are cross-hatched; areas whose frequency of MS is insignificantly increased are diagonal-lined; and areas whose frequency of MS is less than the national mean are unshaded. Unit boundaries are omitted. Fine horizontal shading represents lakes in Sweden and Finland. (*From* Kurtzke JF. Further features of the Fennoscandian focus of multiple sclerosis. Acta Neurol Scand 1974;50:491; with permission.)
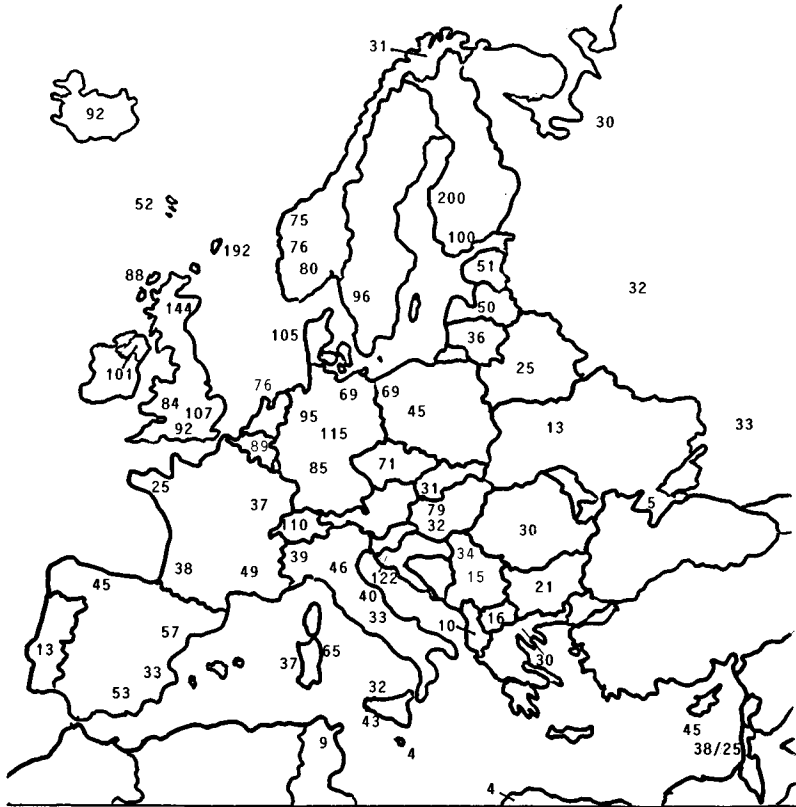
Fig. 6. Prevalence rates per 100,000 population for MS in Europe and the Mediterranean basin from publications 1980–1994. (*Modified from* Lauer K. Multiple sclerosis in the old world: the new map. In: Firnhaber W, Lauer K, editors. Multiple sclerosis in Europe. An epidemiological update. Darmstadt (Germany): LTV Press; 1994. p. 18.)

frequency. Even Cuba may have a high prevalence. Many of the Latin American studies, although well-done, have not appeared in the peer-reviewed literature.

The general worldwide distribution of MS still seems to be well-described by a division into three regions: high prevalence (30+ per 100,000 population), medium prevalence (5 to 29 per 100,000 population), and low prevalence (<5 per 100,000 population) (Fig. 8). With each iteration of this map in the last quarter century, the areas in white (unstudied) have shrunk appreciably, as expected; however, progressively more of the world has been marked in black (high prevalence).

The fate of migrants who move into regions of differing risk of MS is critical to our understanding of this disease. If migrants retain the risk of their birthplace, then either the disease is innate or it is acquired early in life.
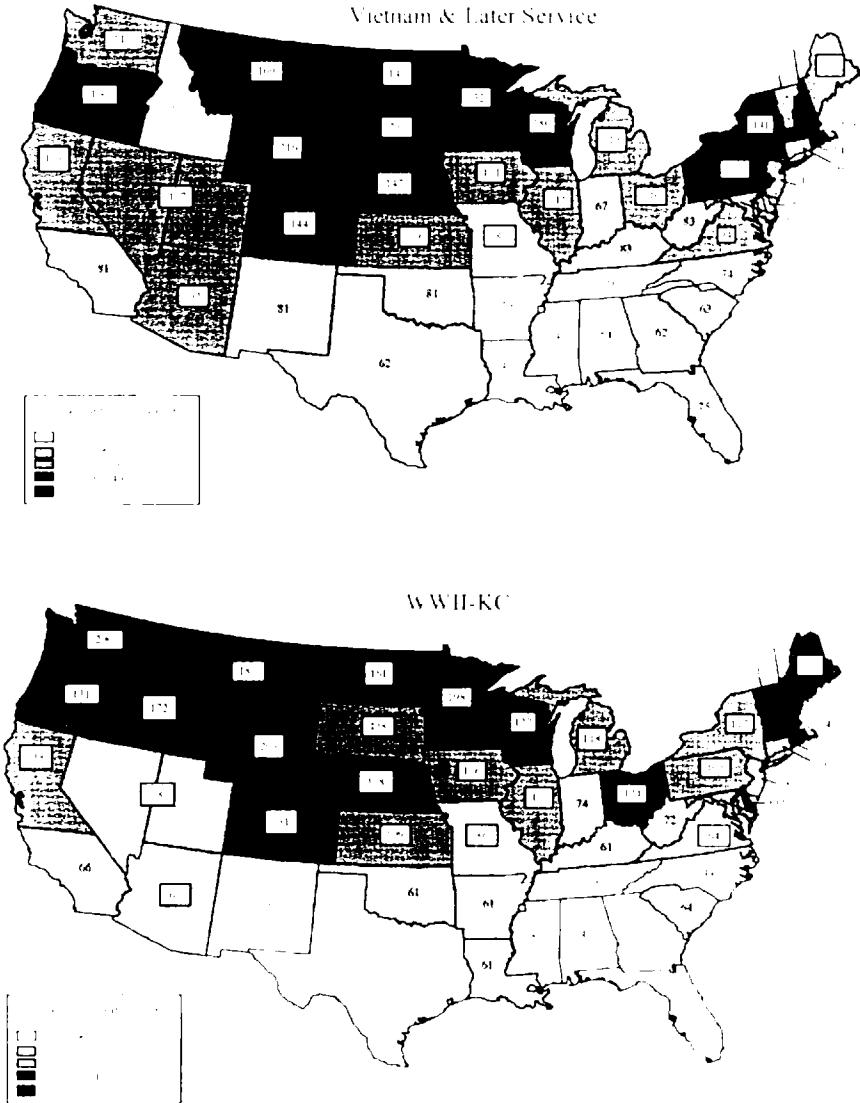
Fig. 7. Adjusted case control ratios (×100) for white male U.S. veterans service connected for MS by state of residence at entry into service. KC, Korean Conflict; WW II, World War II. (*From* Wallin MT, Page WF, Kurtzke JF. Multiple sclerosis in United States veterans of Vietnam era and later military service. 1. Race, sex and geography. Ann Neurol 2004;55:68; with permission.)

If they do change their risk upon moving, a major environmental cause or precipitant is active in their disorder well after birth.

MS-control ratios for birthplace and for preillness residence at service entry were compared for the white male veterans of World War II or

Korean service to assess migration. Ratios where these are the same locations (north-north, middle-middle, south-south tiers of residence) give MS:control ratios for nonmigrants; cells off this diagonal define the ratios for migrants. These nonmigrant ratios are 1.48 (north), 1.03 (middle), and 0.56 (south). For migrants, those who were born in the north and entered service from the middle tier have a ratio of 1.27. If they entered from the south, their ratio is 0.74, only half that of the nonmigrants. Birth in the middle tier is marked by an increase in the MS:control ratio for northern entrants to 1.40, and a decrease to 0.73 for the southern ones. Migration after birth in the south seems to increase the ratios to 0.65 (middle) and 0.70 (north). All of these changes except the last are statistically significant. The southern-born migrants were really too few to calculate valid ratios.

In a study of European immigrants to South Africa, the MS prevalence rate, adjusted to a population of all ages, was 13 per 100,000 for immigration under age 15; this was the same medium prevalence rate as native-born, English-speaking, white South Africans. For age groups that were older at immigration, the prevalence was 30 to 80 per 100,000, the same as expected from their high-risk homelands. This change was sharp and occurred at age 15 (Fig. 9). Each patient is represented by a bar, whose location on the Y-axis denotes age at immigration, and whose length on the X-axis shows the number of years between immigration and clinical onset. This also indicates that natives of high-risk areas are not susceptible to MS acquisition much before age 15, and that there is a long incubation period between acquisition and onset of symptoms.

Inferences as to the opposite migration (low-frequency areas to high-frequency areas), were afforded by the mostly white northern African migrants to France who came from Morocco, Tunisia, and especially Algeria. The migrants who had an onset of MS more than 1 year after immigration provided an age-adjusted MS prevalence rate that was 1.5 times greater than for all of France. If the rate for France is taken at 50 per 100,000 population, their adjusted rate is 77. The others who had presumed acquisition in northern Africa gave the same rate of 17 per 100,000 as expected for residents of those lands. For migrants who acquired MS in France, at each single year of age at migration there was a mean interval of 13 years between immigration or age 11 and clinical onset, with a minimum of 3 years. Only one of the four patients who had migrated after age 40 had had onset (at age 48) in France (Fig. 10). Note the solitary patient who migrated at 1 year of age and had the onset of symptoms at age 9; this supports the rarity of childhood MS.

The migrant series provide further support for the theses that MS primarily is an environmental disease that is acquired after childhood, and that acquisition requires prolonged or repeated exposure, followed by a prolonged latent or incubation period between acquisition and symptom onset.

The simplest explanation is that MS is the result of a geographically-delimited persistent infectious agent with a long latency and an age-limited
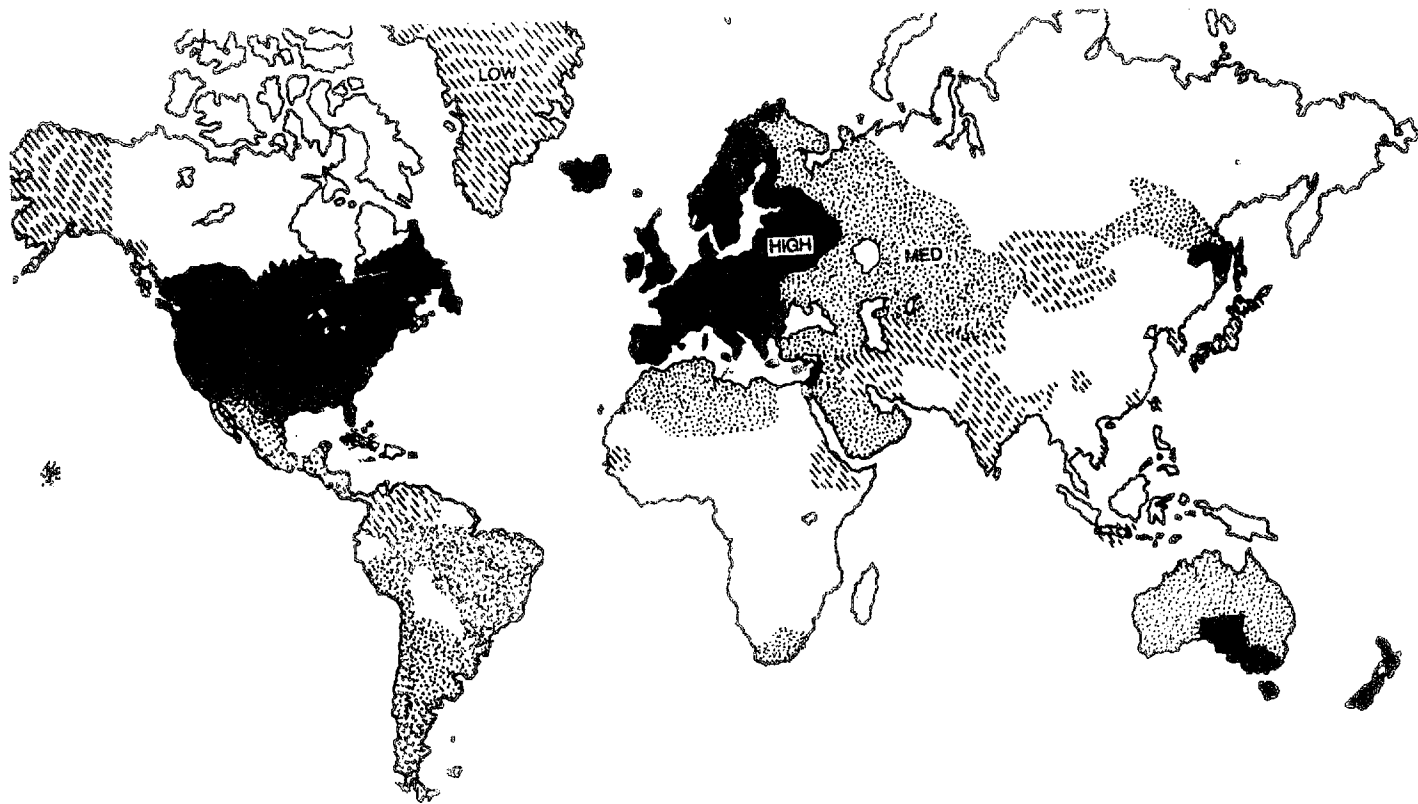
Fig. 8. Worldwide distribution of MS as of 2003 with high (prevalence 30+ per 100,000; solid), medium (prevalence 5–29; dotted), and low (prevalence 0–4; dashed) regions defined. Blank areas are regions without data, or people. (*From* Kurtzke JF. Epidemiología y esclerosis múltiple una revisión personal. Cuadernos de Esclerosis múltiple. [Epidemiology and multiple sclerosis: a personal review. Notebooks on Multiple Sclerosis.] Quarterly Journal 2003;16:17;1 [in Spanish]; with permission.)
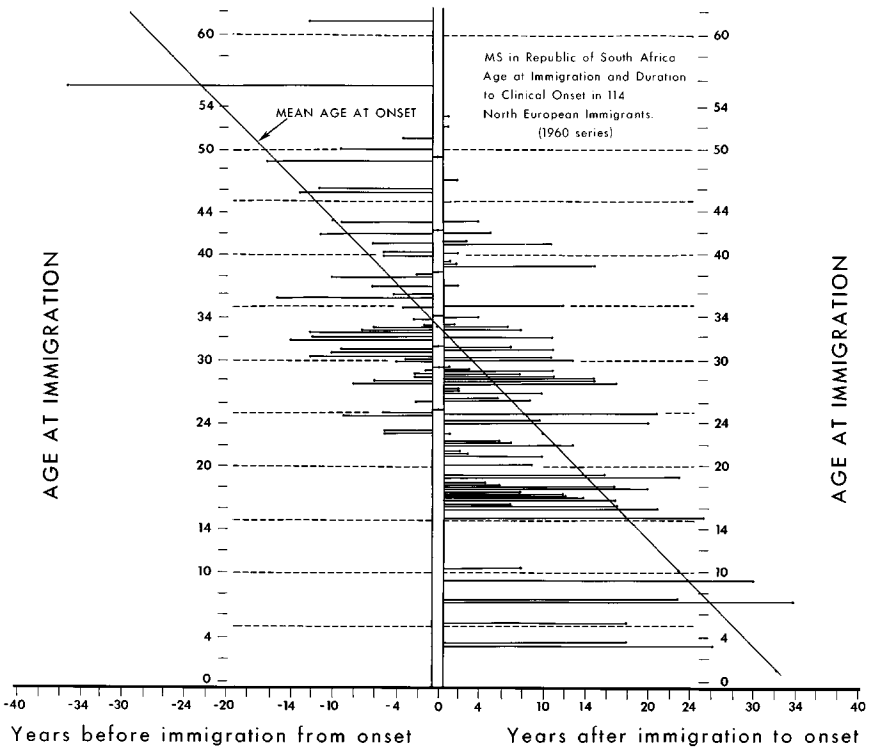
Fig. 9. MS in migrants from northern Europe to South Africa by age at immigration and years between immigration and clinical onset who were ascertained in 1960 MS prevalence survey of South Africa. (*Modified from* Kurtzke JF, Dean G, Botha DPJ. A method of estimating the age at immigration of White immigrants to South Africa, with an example of its importance. S Afr Med J 1970;44:668; with permission.)

host susceptibility. If this is true, what we call "MS" must be much more widespread than clinical cases indicate, or there must be a nonhuman reservoir. This hypothesis would have much stronger support if it could be shown that there epidemics of MS have occurred. An epidemic has been defined as disease occurrence that clearly is in excess of normal expectancy and is derived from a common or propagated source. Epidemics are divisible into two types; type 1 epidemics occur in susceptible populations who are exposed for the first time to a virulent infectious agent. Type 2 epidemics occur in populations within which the organism already is established. If the entire populace is exposed to a type 1 epidemic, the ages of those who are affected clinically will define the age range of susceptibility to the infection. Type 2 epidemics tend to have a young age at onset, because the effective exposure of the patients will be greatest for those who first reach the age of susceptibility.

Epidemics of MS seem to have occurred in the ethnically similar populations of several groups of islands in the North Atlantic Ocean: Iceland, the Shetland-Orkneys, and the Faroe Islands.

Data about all known patients in Iceland who had an onset of MS between 1900 and 1975 were collected in 1980. Annual incidence rates reveal that there seems to have been at least one definite type 2 epidemic of MS in Iceland which began in 1945. The average annual incidence rate from 1923 to 1944 was 1.6 per 100,000. For 1945 to 1954, it was significantly greater (3.2 per 100,000), and then it declined significantly to 1.9 per 100,000 for 1955 to 1974. Age at clinical onset in the 1945 to 1949 interval (23 years) was significantly younger than for any other 5-year period from 1935 to 1969.

For Shetland and the Orkneys for 1911 to 1985, the average annual incidence rates indicated that the occurrence after 1970 was significantly less than for the previous 30 or 35 years. With the small populations of these islands, the incidence rates showed considerable fluctuations and apparently differed in peaks and valleys between the islands. The overall impression of at least one epidemic between 1941 and 1970 seems to be valid, as does the clear decline after 1970.

The Faroe Islands are a semi-independent part of the Kingdom of Denmark that lies in the North Atlantic at 62°N latitude and 7°W longitude. Population numbered more than 44,000 in 1998. The Faroe Islands include 17 major volcanic islands that are made of basaltic rock, all with steep hills that reach the shore or bays and fjords. Almost all of the villages are in such inlets. Travel between many islands and even between a few villages on the same island is by boat.

The author has worked with the late Kay Hyllested and Anne Heltberg—both neurologists of Denmark—to investigate MS on the Faroe Islands since the early 1970s. At least one of the investigators examined every person on the Faroe Islands in whom MS was suspected between 1960 and June 1999. To find all possible cases of MS from 1900 on, every conceivable resource of medical information was used. Denmark, including the Faroe Islands, has had state-provided health care since the 1920s; Danish medical and health records are unsurpassed. All medical records for each suspected case was obtained and independently reviewed by each investigator.

There is no evidence that MS occurred in this century, before 1943, among native-born resident Faroese who had not lived off the islands for 3 or more years before clinical onset. July 1943 is the earliest date when symptom-onset was discovered to have taken place in such residents. There were 21 patients among the 26,000 Faroese who constituted a point source type 1 epidemic of MS on the Faroe Islands, beginning in 1943.

Inclusion of patients for this epidemic—and later ones—was dependent on two criteria: age of at least 11 years at "exposure" and "exposure" for 2 years. Thus, the "exposure" period here was 1941 to 1942 (2 years before
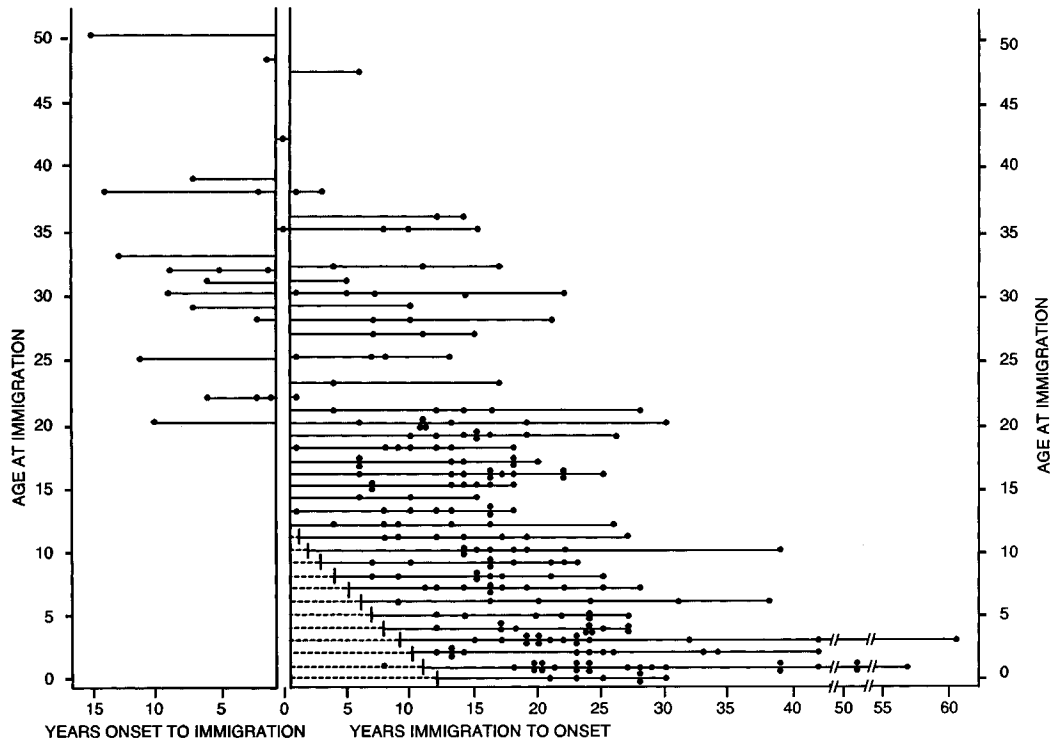
Fig. 10. MS in migrants from French north Africa (2/3 from Algeria) by age at immigration and years between immigration and clinical onset of MS. (*From* Kurtzke JF, Delasnerie-Lauprêtre N, Wallin MT. Multiple sclerosis in North African migrants to France. Acta Neurol Scand 1998;98:306; with permission.)

earliest onset) for 20 patients, and 1943 to 1944 for the last patient. What the Faroese must have been "exposed" to had to be an exogenous agent that was brought into the Faroe Islands in 1941 to 1944. We believe that this agent is a specific infection that we call the primary MS affection (PMSA). Age at first exposure to PMSA extended from 11 to 45 years. Thus, susceptibility to PMSA in this populace is limited to Faroese who were aged 11 to 45. Older and younger Faroese were not susceptible. Annual incidence rates show the striking appearance—and disappearance—of this epidemic, which peaked at annual incidence rates of 10 per 100,000 population for 1945 and 1946 (Fig. 11). Residence at the time of exposure indicates the wide scattering of these cases throughout the islands (see later discussion).

The Faroe Islands were occupied by British military forces for 5 years during World War II, from April 1940 to September 1945. Army troops were the main force, although Navy and Air Force units were present as well. The War Diaries identified the units by type, time, manning, and location. Local sources were used to confirm or deny the recorded British occupation sites.

By 1941, 1500 troops were stationed in the Faroe Islands. In 1942, the numbers increased to 7000, exceeded 4000 between June 1942 and August 1943, and were still near 1000 or so through 1944 (Fig. 12). It is clear that troop locations match the residences of the patients who had MS (Fig. 13). We concluded that the British troops brought MS to the Faroese in the Faroe Islands in 1941 to 1944.

Therefore, the troops brought something to the Faroe Islands that later resulted in an epidemic of clinical MS. This had to be an infection or a toxin, with either one geographically widespread on the islands from 1941. A toxin could not be responsible for later epidemics. Therefore, if there are later ones (and there are), then there must have been an infection that was carried by a large proportion of British troops (because of its wide distribution) in an asymptomatic fashion (because they were healthy troops). This must be a persistent infection that takes time (here 2 years) to be transmitted to a naïve populace, the Faroese. We call this agent the PMSA, which we have defined as a specific, but unknown, widespread, persistent infection that only rarely leads to clinical neurologic MS years after its acquisition.

Fig. 14 provides a model of transmission of PMSA from the British troops to that population cohort of Faroese of all ages which was first exposed geographically to this agent in 1941. Proportions of exposed persons who actually were affected are unknown, but must have been high.

After the British left, any further disease would have to be the result of transmission from F1 A to the next cohort of Faroese. If all of the F1 A persons were able to transmit PMSA lifelong, there would have been a steady input for new cases into the twenty-first century, and no further epidemics. Now, clinical MS patients do not transmit any disease. Thus, if this concept is valid, if there were later epidemics, transmissibility should have ended by the usual age of clinical onset—which we have taken as age
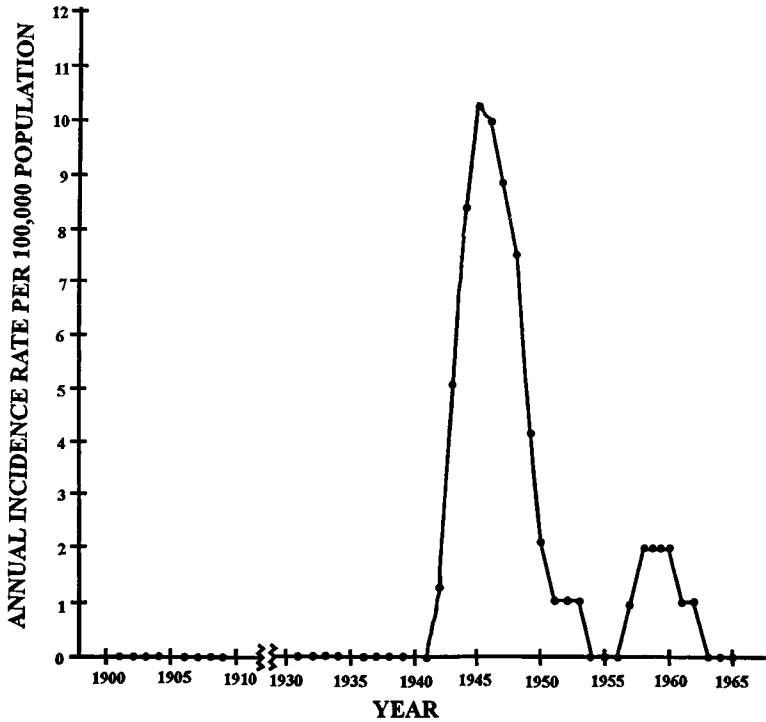
Fig. 11. MS in native resident Faroese. Annual incidence rates per 100,000 population calculated as 3-year centered moving averages for the 21 subjects of epidemic I. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001; 54:7; with permission.)

27. This F1 affected and transmissible (A + T) cohort would contain three times as many Faroese in the first 7 years (1945–51) as in the next 6 years (1952–57). On the basis that the number of persons that is available to transmit determines the frequency of acquisition for the newly exposed next cohort of exposed and susceptible Faroese (F2 E + S) as they reach age 11 each year in essentially equal numbers, this would provide three times as many PMSA-affected persons in the first 7 years as in the next 6 years; this high-low pattern would repeat itself over time. If, in turn, there is a fixed ratio between PMSA and clinical neurologic MS (CNMS), such a model could explain the later occurrence of consecutive type 2 epidemics with peaks at 13-year intervals, as illustrated in the upper part of Fig. 15.

   After epidemic I there were three later epidemics of clinical disease. The occurrence of epidemic IV was predicted by this transmission model. Membership in the epidemics has been defined by the time of exposure to PMSA for each patient (see lower part of Fig. 15). The 10 patients in epidemic II were exposed in 1945 to 1957; the 10 patients of epidemic III
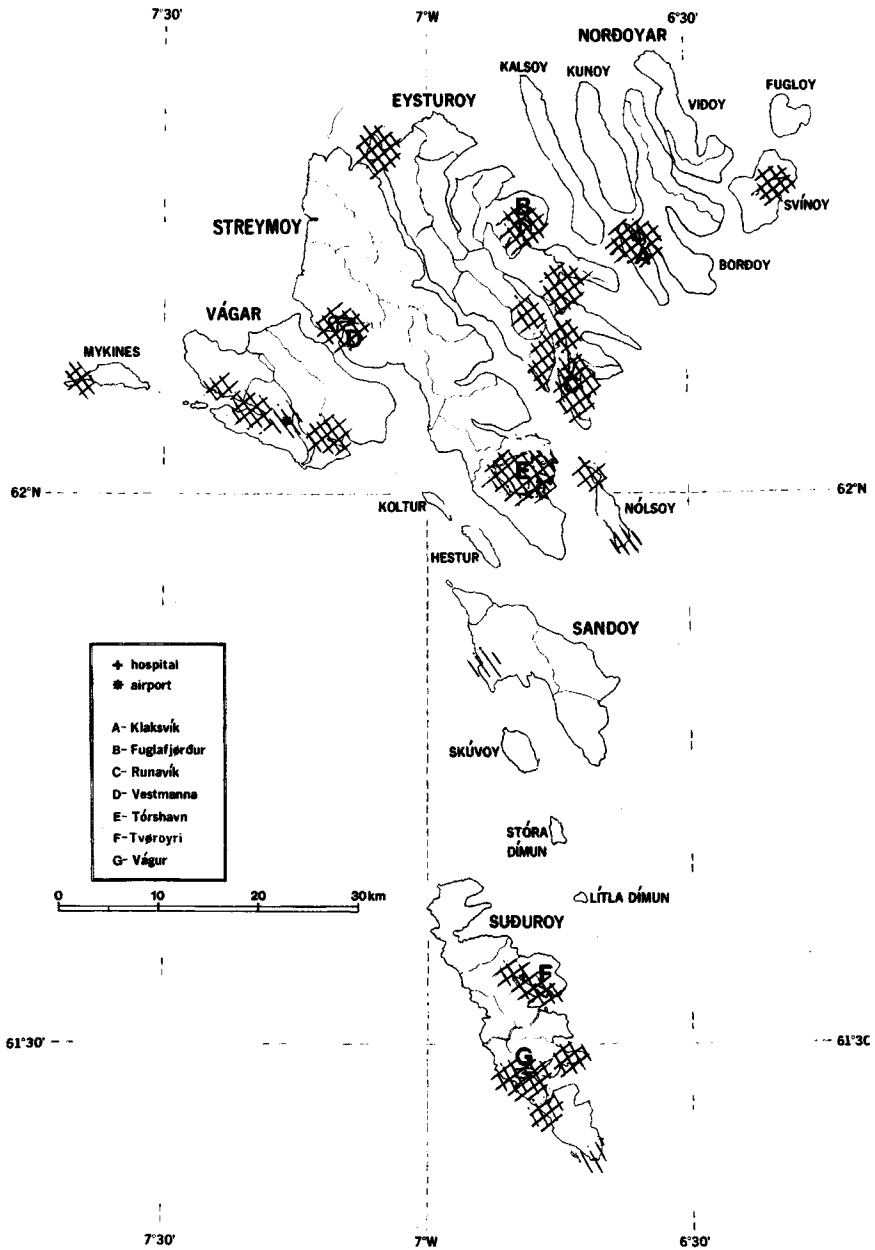
Fig. 12. British troop encampments on the Faroe Islands in World War II. Camps within Faroese villages are cross-hatched, those where no Faroese lived are diagonal-lined. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:10; with permission.)
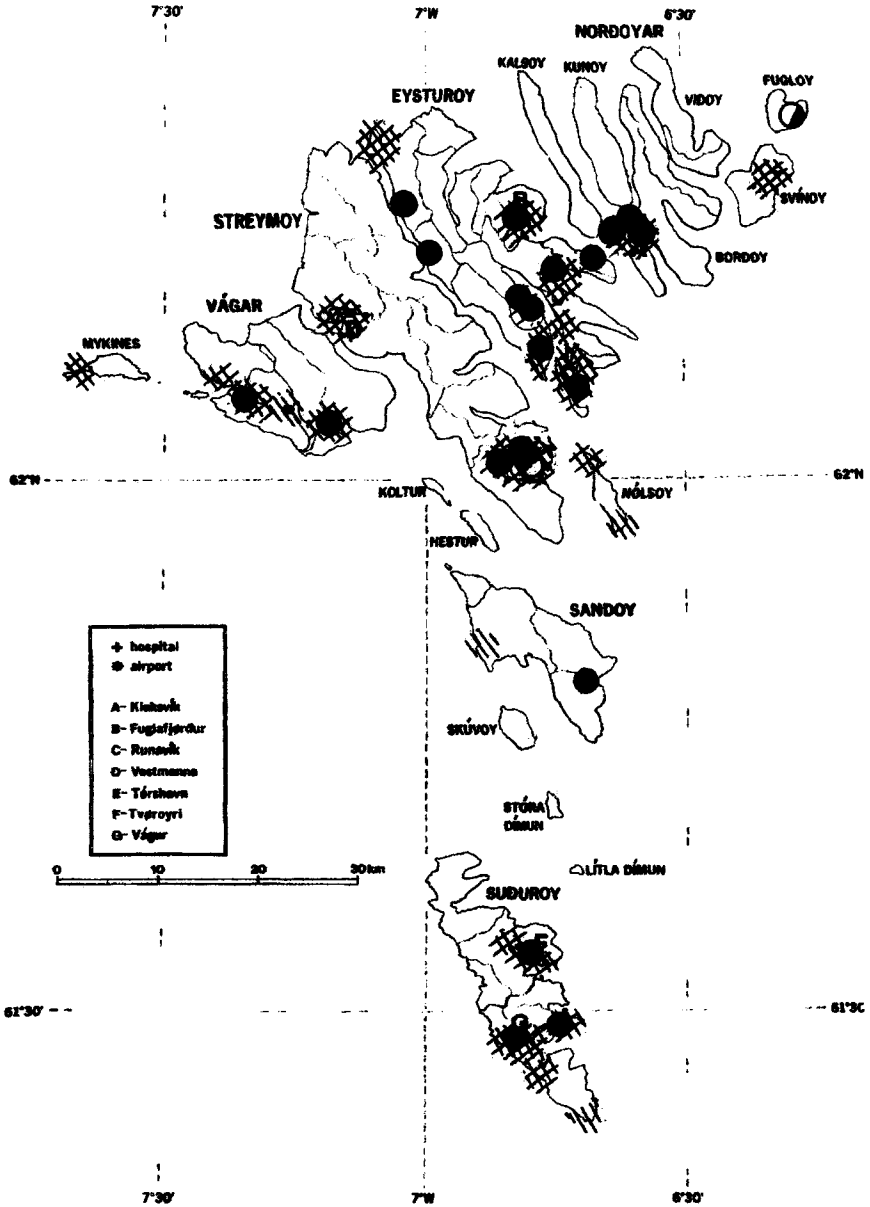
Fig. 13. Residence of patients of epidemic I (•) superimposed on British occupation sites. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:16; with permission.)
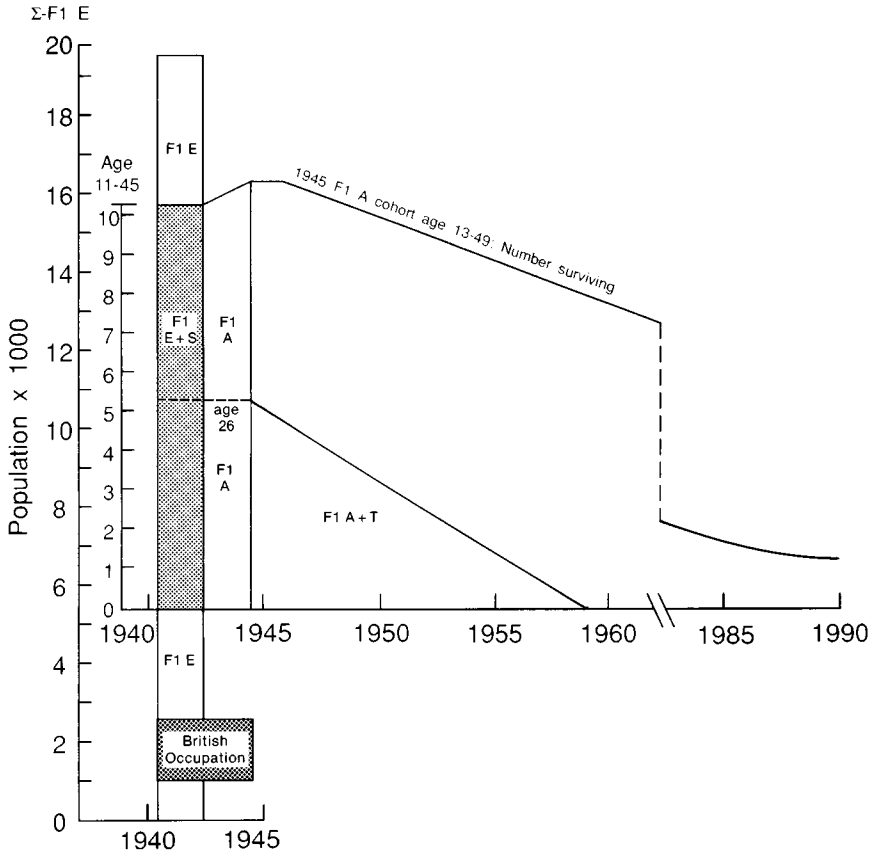
Fig. 14. Transmission model for the first population cohort of Faroese (F1) who were exposed to PMSA. Rectangle at lower left represents British occupation 1941–1944 when at least 1500 troops were stationed on the Faroe Islands. Long vertical bar represents the entire 1941 Faroese population, all ages, who were geographically at risk of PMSA (the F1 E [exposed] cohort). Only those who were 11 to 45 years of age in 1941 were susceptible to PMSA (F1 E + S) based upon the ages of the patients who had MS in epidemic I (shaded part of bar). After 2 years, the F1 E + S cohort became the F1 A (affected) cohort. If transmissibility ceases by age 27, then only that part of the F1 A cohort that was aged 13 to 26 would make up the F1 A + T cohort (affected and transmissible), which would decline to 0 in 1958 as its members attain age 27. (*From* Kurtzke JF, Hyllested K, Heltberg A. Multiple sclerosis in the Faroes: transmission across four epidemics. Acta Neurol Scand 1995;91:321–5; with permission.)

were exposed in 1958 to 1970. Open boxes indicate first exposure beyond age 11 (because of residence), as found for 4 of the 13 patients of epidemic IV whose exposure period was 1971 to 1983. Annual incidence rates per 100,000 population do show four epidemic peaks (Fig. 16). Furthermore, the male excess of epidemic I has changed to an increasing female preponderance for each later epidemic.
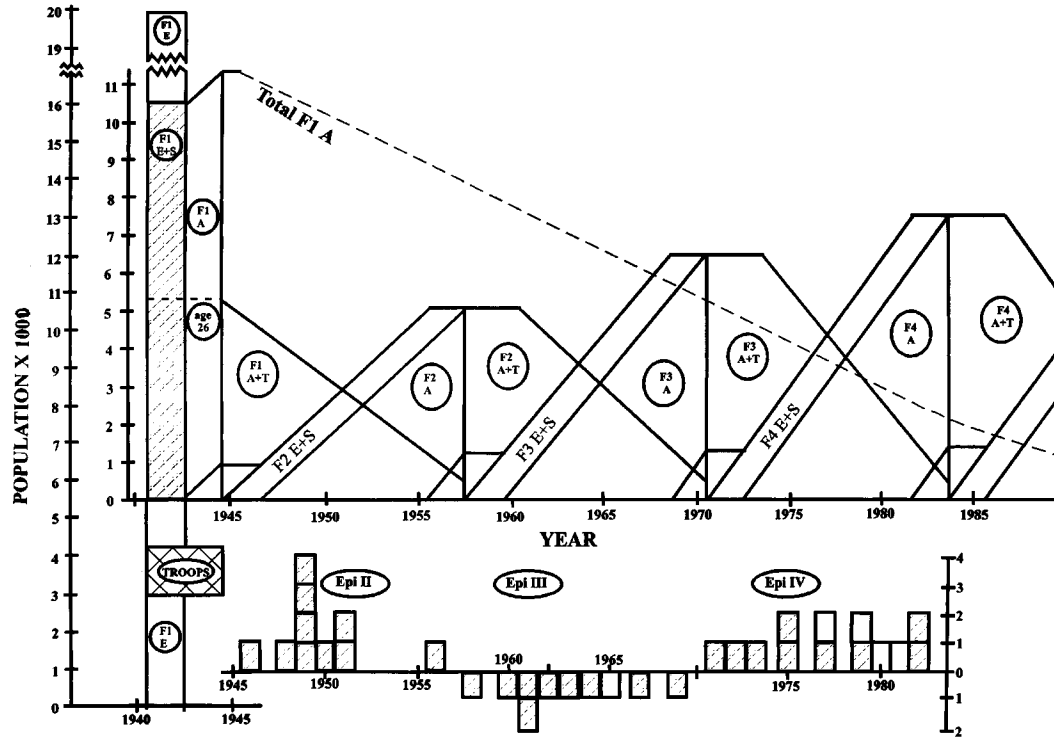
Fig. 15. Summation of PMSA transmission with actual population numbers for British, and for Faroese geographically at risk, F1 through F4 cohorts, with time of exposure of patients of epidemics II through IV (*lower portion*); each rectangle represents one patient at age 11 (*dotted*) or at older age of first exposure (*open*), by calendar time. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:15; with permission.)
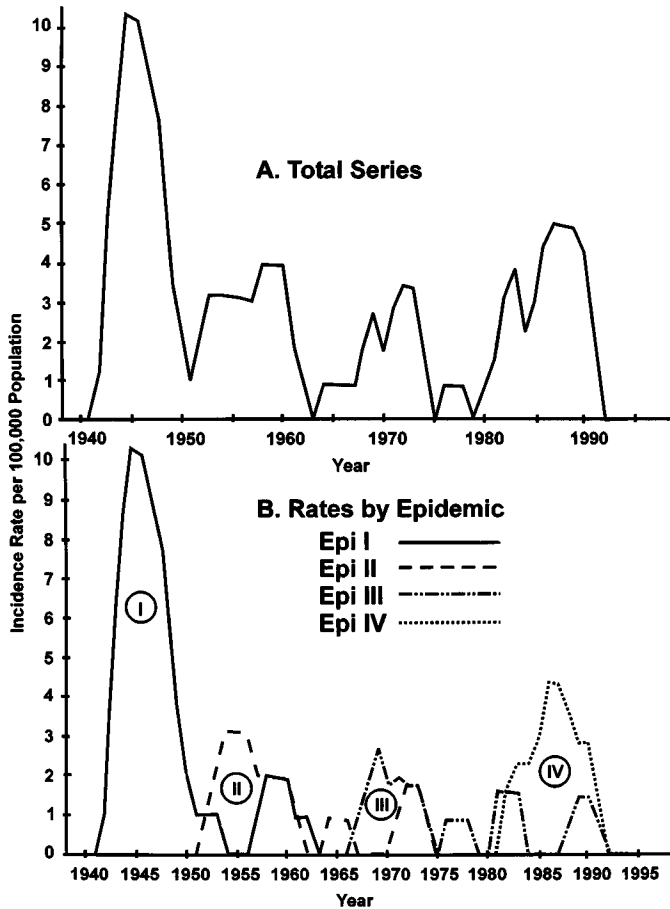
Fig. 16. Annual incidence rates per 100,000 population for clinical MS in native resident Faroese, calculated as 3-year centered moving averages, 1998. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:17; with permission.)

Most of the patients who had MS in epidemics II through IV lived in the same villages, which also were much the same as for patients in epidemic I and for the locations of British troops in World War II (Fig. 17). All patients of epidemics II though IV lived during the time of PMSA exposure in a location in which patients from epidemic I or occupying troops had lived. The disease has remained geographically stable for more than half a century on the Faroe Islands which makes it the ideal location to search for this agent. We must leave this task for other investigators. Because we could not receive permission from the Faroese authorities to draw the necessary samples, our work on the Faroe Islands has come to an end.
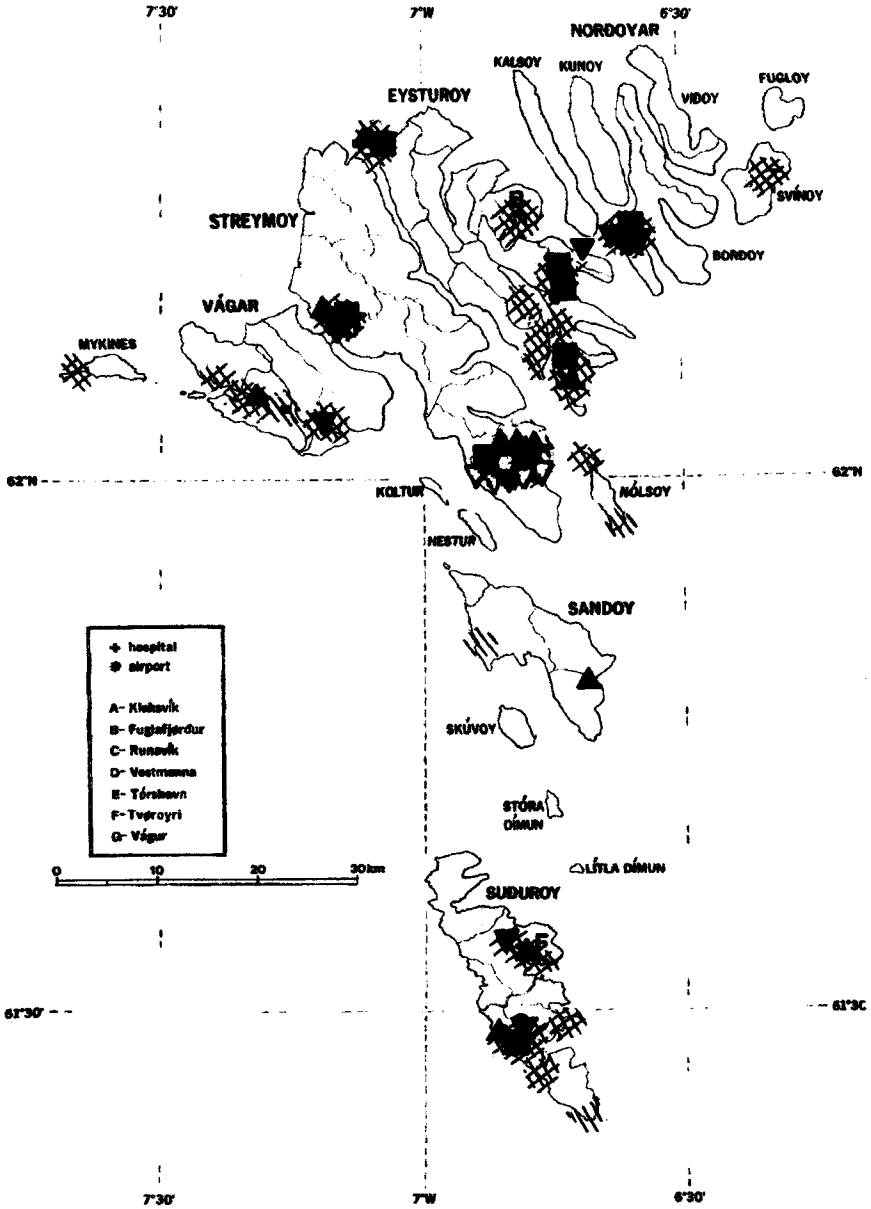
Fig. 17. Residence of patients of epidemics II through IV superimposed on British occupation sites of World War II. ▲, epidemic II; ■, epidemic III; ▼, epidemic IV. (*From* Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. J Clin Epidemiol 2001;54:20; with permission.)

Summary

The author believes that the Faroese saga provides major insight into what seems to him to be the essential nature of MS:

- There is a specific, widespread, but unidentified, infection that we call the primary multiple sclerosis affection (PMSA).
- PMSA is a persistent infection that is transmitted from person to person.
- A small proportion of persons who has PMSA will develop clinical neurologic multiple sclerosis (CNMS) years later.
- Prolonged exposure is needed to acquire PMSA. Acquisition follows first adequate exposure.
- Susceptibility to PMSA is limited to approximately age 11 to age 45 at start of exposure.
- CNMS is not transmissible.
- PMSA transmissibility is limited to a period that is less than the usual age of onset of CNMS. On the Faroe Islands, this period is approximately from age 13 to age 26.
- The existence of PMSA now must be inferred from the presence of CNMS.

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