Epidemiology and multiple sclerosis
a personal review

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Abstract

Epidemiology is the study of the natural history of disease. The proper measures of disease frecuency require a numerator (cases) and a denominator (population at risk). Incidence and death rates refer to new cases and to deaths per unit time and population; prevalence rates to cases present at one time per unit population. Incidence and prevalence rates arise from specific surveys for the disease within circumscribed populations. Death rates come from standard published governmental sources.

The geographic distribution of multiple sclerosis is best defined from prevalence studies, of which there are now over 300. These works indicate that the worldwide distribution may be divided into three zones of high, medium, and low frecuency. High frecuency areas, with prevalence rates of 30 and above per 100,000 population, now comprise almost all of Europe into former USSR, Cyprus, Israel, Canada and all the coterminous United States, as well as New Zealand and south-eastern Australia. They also seem to include the easternmost part of Russia. These high regions are bounded by areas of medium frecuency with prevalence rates of 5-29 and now mostly 15-25 per 100,000, which then include most of Australia, the southern Mediterranean basin, probably Russia from the Urals into Siberia as well as the Ukraine, South Africa, and perhaps much of the Caribbean region and South America. All other known areas of Asia and Africa and possibly Venezuela and Colombia are low, with the prevalence rates under 5 per 100,000 population. A number of nationwide surveys in Europe give evidence for geographic clustering of the disease, which is stable over time, but with diffusion over time. This last is also found in the US.

In MS there is now a female preponderance which appears to be increasing. In the US there has been a clear predilection for whites, but other racial groups have shared their geographic distribution though at lower levels. This deficit no longer holds for black women or women of other races in our latest series of MS veterans.

Studies of MS in migrants from high to lower risk areas indicate the age of adolescence to be critical for risk retention: those migrating at age 15 or older retain the MS risk of their birthplace; those migrating at younger ages acquire the lower risk of their new residence. Several low-to-high studies show that those migrating in childhood or adolescence do in fact increase their risk of MS. In one such the prevalence among the migrants exceeded that for the native-born, and suggested a susceptible period from about age 11 to age 40 or so with a three-year exposure period required. The migrant data support the idea that MS is ordinarily acquired in early adolescence, with a lengthy

“incubation” or “latent” period between disease onset and symptom onset, and with young children rarely susceptible to this illness. But susceptibility extends to about age 45 years.

Epidemic of MS have been described for the Faroe Islands, and with less certainty for Iceland and the Shetland-Orkneys. To 1999 we have been able to identify on the Faroes 55 cases of multiple sclerosis among native-born resident Faroese. They comprised four successive epidemics with peaks at 13-year intervals and the first case with symptom onset in 1943. The 21 cases constituting the first epidemic met all criteria for type 1 point-source epidemic. We believe the source of this epidemic was the British troops who occupied the Faroes in large numbers for five years from April 1940, and who were stationed where the MS patients lived. The later epidemics were presumed to be result of transmission from and to successive cohorts of the Faroese population, with all such cases occuring in residents of the same locations as the British and the first epidemic patients.

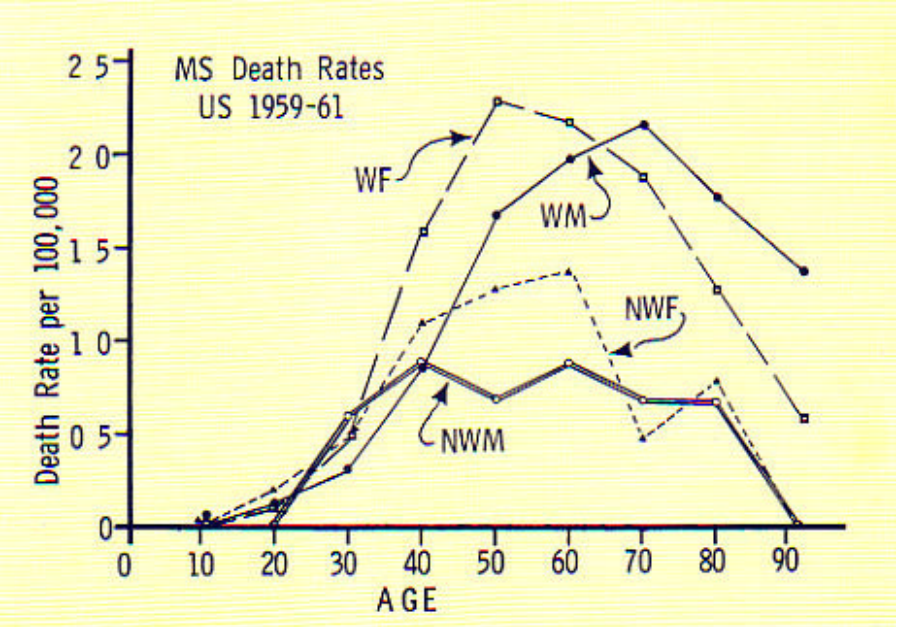
If these findings are valid, these studies would indicate the definition of MS as not only an acquired disease, but also a transmissible one. What we believe is transmissible is a widespread specific (but unknown) persistent infection of adolescents and young adults, which we call PMSA (the primary multiple sclerosis affection), and which only rarely leads to clinical neurologic MS (CNMS) after years of incubation. In this context PMSA is transmissible, CNMS is not. Further, prolonged exposure (at least two years) is required to acquire PMSA. Our best guess as to its nature at this time is an undefined (retro) virus, for which the best place to seek it is the Faroe Islands, since there is in those islands a unique control group: there are parts of the Faroes which are still free of CNMS, even after 50 years of disease.
Epidemiology works are concerned with the frecuency of diseases, and their characteristics by race, sex, geography, and other factors, as well as teh 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 with a given disorder. After diagnosis, the basic question is how common is the disease. This frecuency should be described by the best count of number of cases as numerator within defined populations as denominator. These ratios, with the addition of the time period to which they pertain, are referred to as rates.

The population-based rates in common use are the incidence rate, the morality 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. This is usually 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 occuring within a unit of time and population, and thus an annual death rate per 100,000 population. The point prevalence “rate” is more properly called a prevalence ratio, and refers to the number of affected within the community at one point in time, again expressed per unit of population.

The Association of Research in Nervous and Mental Disease meets annually in New York to present a symposium on one specific topic. Their first session in 1920 dealt with von Economo's encephalitis. The second was on multiple sclerosis. This was the first comprehensive assessment of MS in the United States. (References to this and other uncited works are in Kurtzke 2000 [1].) The Commission then concluded that MS affected chiefly young adults and men more than women. Duration avereged eight years, and it seemed to affect skilled manual workers more often. Geographically, in the United States it was most common near the Great Lakes, an in Europe more in the north than the south. The male excess was found for most of the European studies and all those from the US.

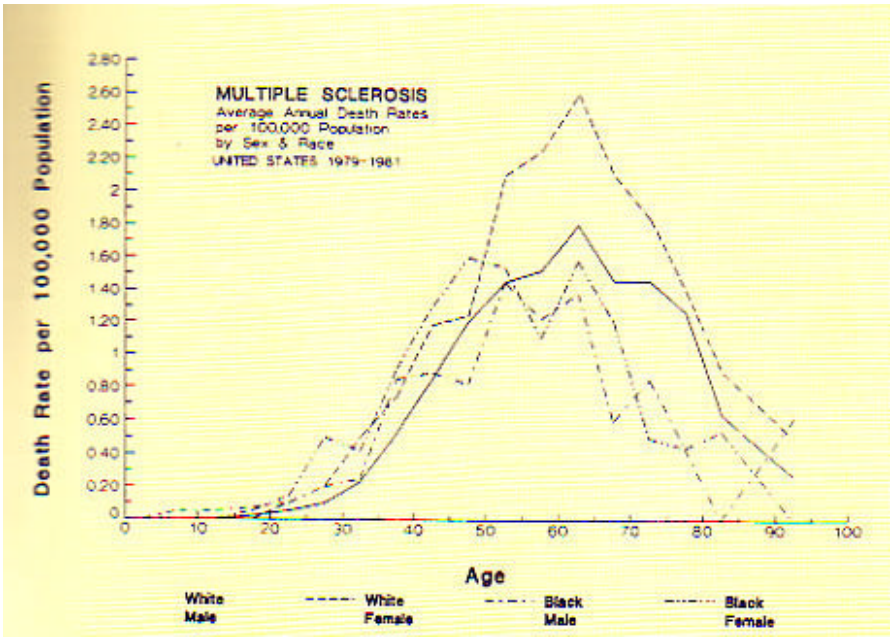
Male preponderance was also seen for MS death rates near 1960 in the US but only among those of higher age. White women were clearly in excess at younger ages (Figure 1). Incidence and prevalence rates in Denmark near 1050 had similar pattern, with higher rates for women among the younger patients and equal rates by sex in the older ones.

Prevalence rates in Ireland in 1971 had an equal sex ratio at the oldest ages. An increasing excess of women in Denmark has characterized the incidence of this disease over 50 years. Two regions of Norway also demonstrated a growing female excess over time. Sweden too showed an increasingly higher majority among women [3]. By 1980 white women had the highest death rates in the US at all ages (Figure 2). Note that young black women seemed to have rates similar to the whites.



Average annual age specific death rates per 100,000 population for multiple sclerosis by sex (M,F) and color (white, non-white), United States 1959-1961. Modified from Kurland et al 1973 [2].

We have been studying MS in the United States among some 5,300 veterans of World War II or the Korean Conflict, who were service connected by the VA for MS. They were matched with pre-illness 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 does then seem to have been a change from a disorder more often affecting men to one that shows an increasing preponderance among women. The excess among whites versus those of other races had persisted, however. Relative risk ratios were 0.44 for black males and 0.22 for other males (non-white, non-black).



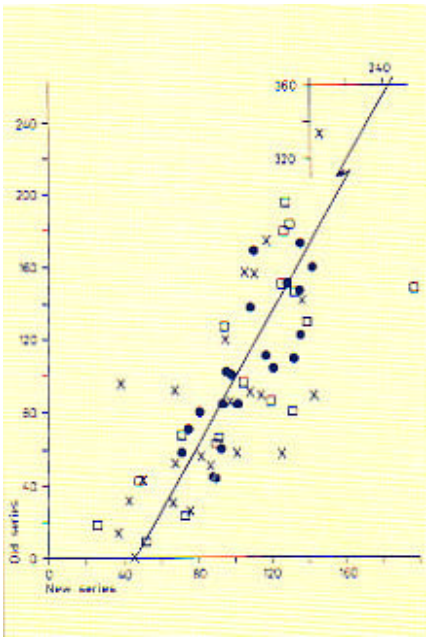
Average annual age specific death rate per 100,000 population by sex and race, United States 1979-1981. From Kurtzke 2000 [1].

A more recent series is under study. This comprises over 5,000 US veterans with military service in 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 [Wallin MT, Page WF, Kurtzke JF, submitted for publication June 2003]. Women of all races, whether white, black or other, now have a greater risk of MS than the white men, with relative risk ratios each nearly 3 to 1. Black men, though still below the whites, have a significantly higher risk ratio of 0.67 than they showed in the World War II series. Men of other races had little change, with relative risk of 0.30. There has to be an environmental reason for the growing predominance of women from an earlier male excess. The changing ratios by race also suggest that these differences too are also based more on environmental than genes.

Geographic distributions are best defined by prevalence studies, of which there are now more than 300 for MS. Prevalence rates from 1960s into 1980 indicated that most of northern Europe was of high frecuency, with rates of 30 or more per 100,000 population.

Southern Europe then appeared distinctly lower, with rates reflecting medium frecuency (5 to 29 per 100,000), a difference that has dissapeared, as we shall see below.

Prevalence studies are mostly “spot surveys” of small areas, and may tell little about areas not examined. Nationwide surveys by one team at one time permit complete geographic coverage. When such studies are repeated at a later time, we can also see if distributions have changed. Denmark was surveyed twice, the old series for 1921-1933 disability cases, the new for 1949 prevalence. Switzerland also had two national estimates, the old one for 1918-1922, the new for 1956, both showing a strong northern geographic concentration. Norway too had surveys over time. When percentages by county of each national mean are compared for the old and the new series in each of these three countries, we see they are each highly correlated, old vs. 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 (Figure 3).

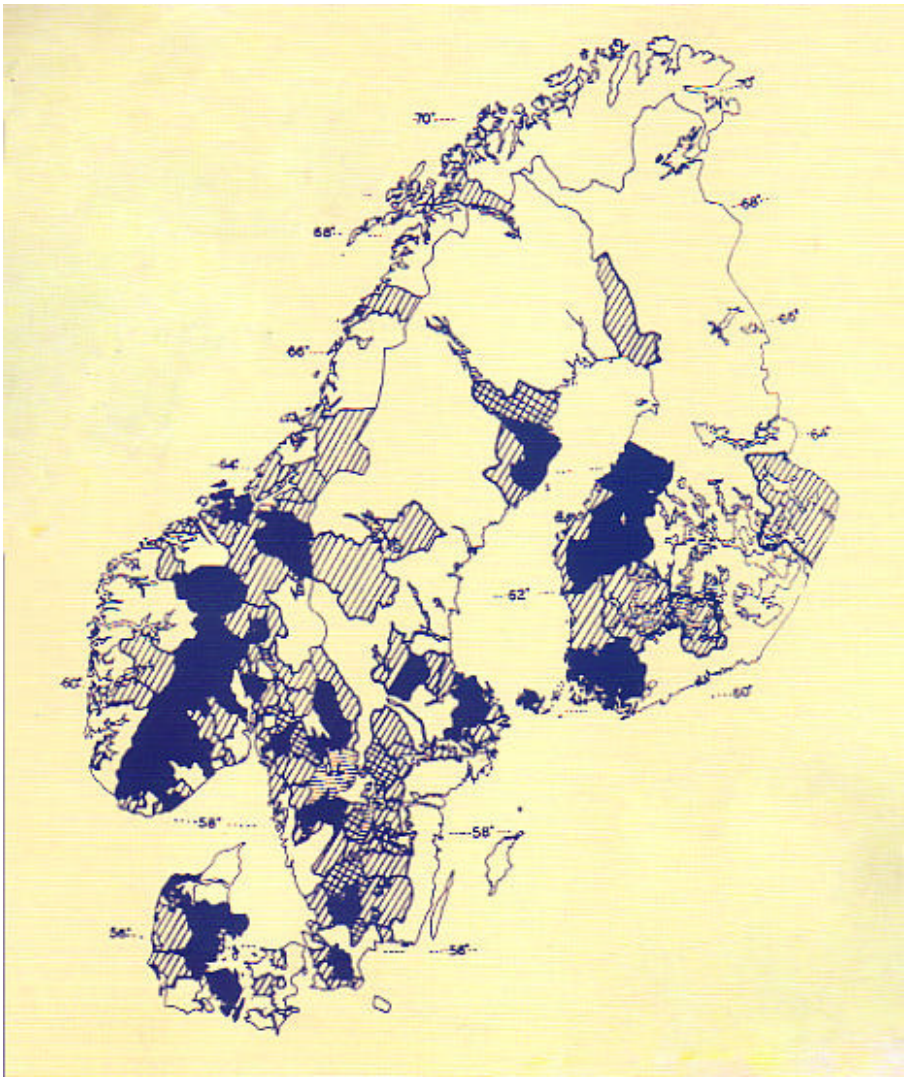


Correlation of the distributions of multiple sclerosis by county between old series and new series of nationwide prevalence studies of three countries, each covering different generations of patients: Denmark (solid circles), Switzerland (Xs), Norway (open squares). Each country rate is expressed as the percentage of its respective national (mean) rates. From Kurtzke 1974 [4].

Spread of MS may be from within Fennoscandian focus of high frecuency MS, and indeed from a source within the southern inland lake region of Sweden (Figure 4). Spread from this region eastward to Finland, southward to the continent, and westward to Norway and then Denmark provide the diffusion. Currently under investigation is whether the European spread outside 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 during the Thirty Years War of 1618 to 1648.

The long held view of a north-south gradient fro MS may then be little more than a reflection of this spread from Sweden - different type of big bang theory. Compatible with this view is the finding that the high frecuency regions of France are mostly in the northeast, and those of Switzerland in the northwest. But this spread take years. Prevalence rates throughout Europe were similar in 1980 to those seen earlier, as noted above. However, by 1994 there were major differences. This figure (Figure 5) from Lauer [5] shows that the entire northern Mediterranean basin is now an area of high frecuency, and both Portugal and Greece are now also high, with prevalence rates in the 1940s. Diffusion is a hallmark of this disease.



Distribution of multiple sclerosis in Fennoscandia from nationwide surveys.A reas significantly above their respective national means are in solid black, those high but of dubious statistical significance are cross-

hatched, those insignificantly high are diagonal-lined, and those below the national means are unshaded, Unit boundaries are omitted. Fine horizontal shading represents lakes in Sweden and Finland. Fron Kurtzke 1974 [4].

And the spread is not limited to Europe. In the US, the World War II series showed a marked excess for residence in the north (Figure 6). This was seen for both sexes among whites and for black males, with a north to south difference for almost 3 to 1. The Vietnam and later service veterans still showed a gradient, but it was much less. All southern states were now calculated to be with the high frequency zone, with prevalence rates estimated at well over 30 per 100,000 population. For all races and sexes, the north to south difference was now some 2 to 1.

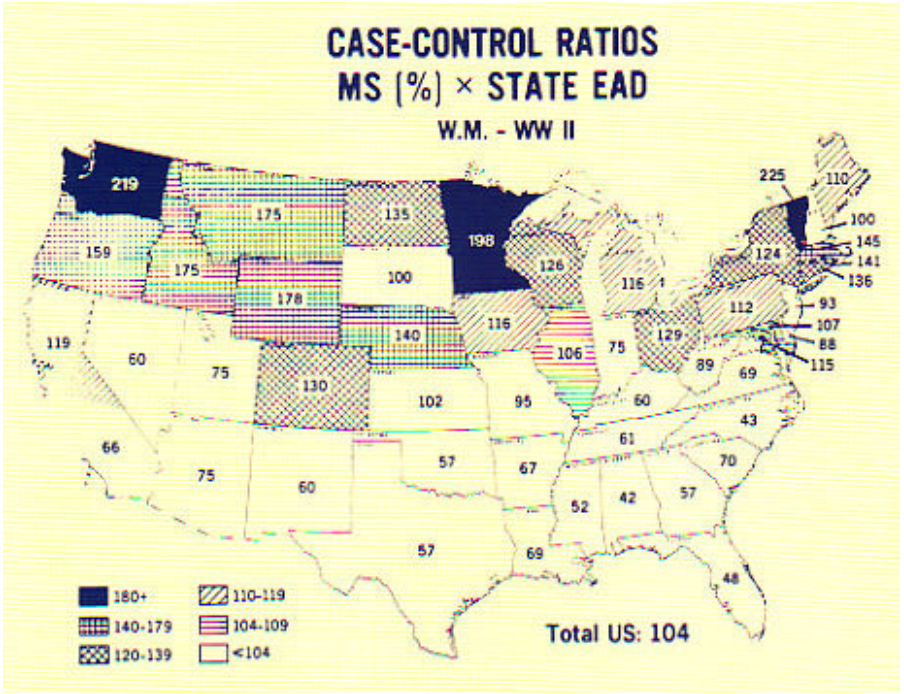
In Asia and Africa earlier assessments provided low prevalence rates, less than 5 per 100,000, except for English-speaking whites of South Africa. This distribution is now more complex. Rates are still low in Japan, Korea, China and southeast Asia, but not in the former USSR. Boiko of Moscow has summarized prevalence studies from Russia and other parts of the former Soviet Union. In the southern region of Ukraine, the Volga area, the Caucasus, and into Novosibirsk and Kazakhstan, rates were generally medium prevalence range, while more easterly lands were low. In easternmost Russia medium rates reappeared, with high rates in parts of the Amur region near Pacific Ocean above China.

And its now the southern littoral of the Mediterranean that is of medium prevalence, and Cyprus and Israel are high. In Latin America, the Carribean region including Mexico may also be of medium frecuency now, as well as Argentina, Brazil, Uruguay, and Peru, while Venezuela and Colombia may be low. But much of that American material has not yet been published as formal prevalence studies.

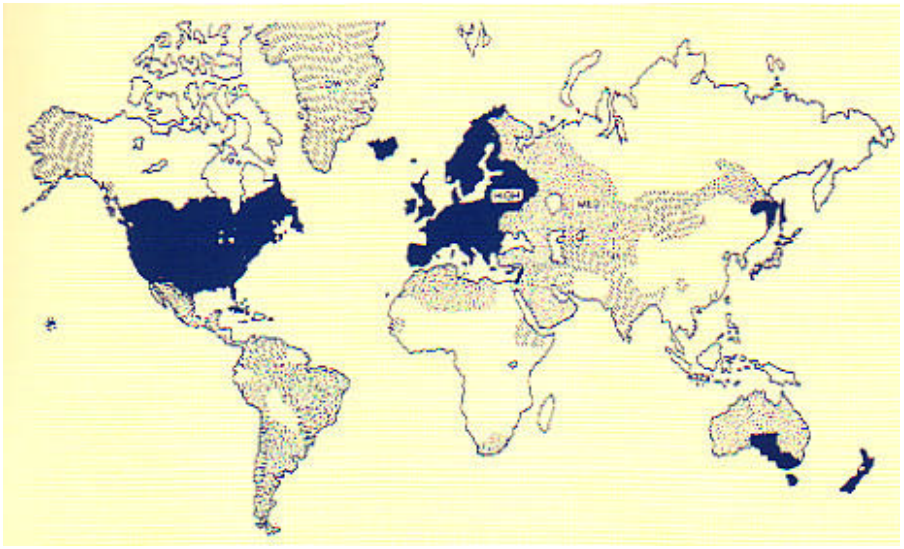
Prevalence rates per 100,000 population for MS in Europe and Mediterranean basin from publications 1980-1994, modified from Lauer 1994 [5], with permission.

The general worlwide distribution of MS still seems well described by this division into three regions, of high prevalence at 30+ per 100,000 population, medium prevalence of 5-29 per 100,000, and low prevalence, under 5 per 100,000 population (Figure 7).

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. However, if upon moving they do change their risk, then clearly there is a major environmental cause of precipitant active in their disorder well after birth.



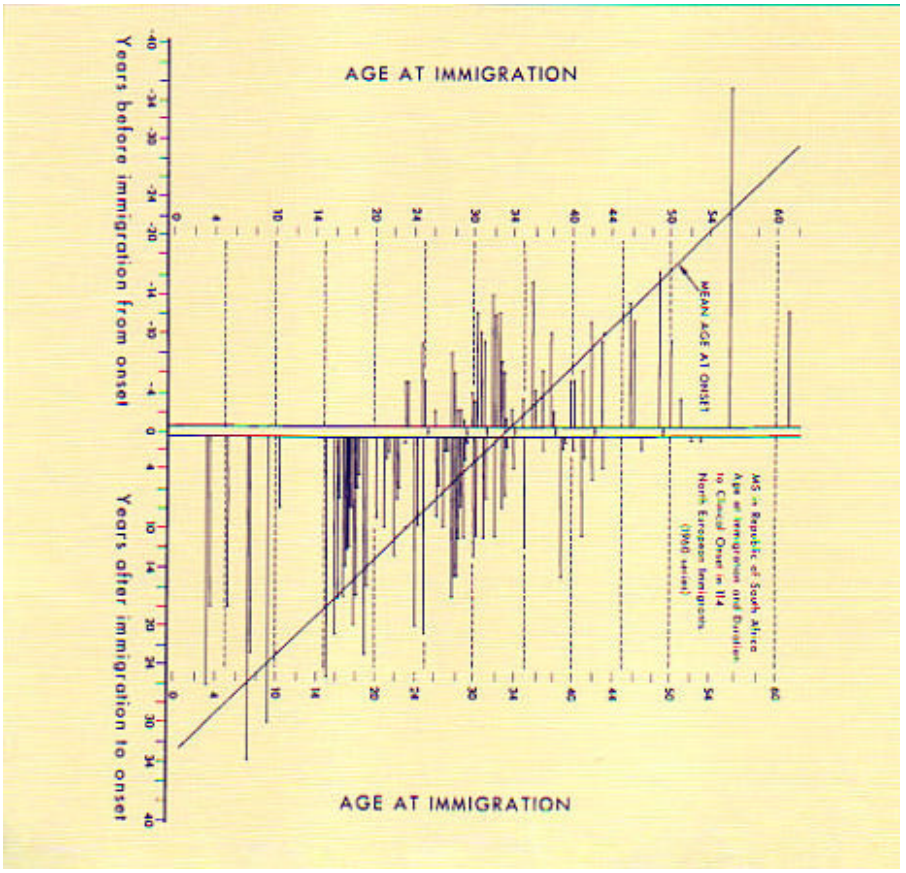
Case control ratios for multiple sclerosis in US white male veterans of World War II by state of residence at entry into military service. Modified from Kurtzke 1978 [6].



Worldwide distribution of MS as of 2002 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.

MS-control ratios for birthplace and for pre-illness 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, middlee-middle, south-south tiers of residence) give MS-control ratios for non-migrants, and cells off this diagonal define the ratios for migrants. All ratios decrease as we go from north to south. The non-migrant ratios are 1.48 north, 1.03 middle, and .56 south. For the migrants, those born north and entering service from the middle tier have a ratio of 1.27. If they enter from the south their ratio is .74, only half that of the non-migrants. Birth in the middle tier is marked by an increase in the MS/C Ratio for northern entrants to 1.40, and a decrease to .73 for the southern ones. Migration after birth in the south seems to raise the ratios to .65 (middle) and .70 (north).

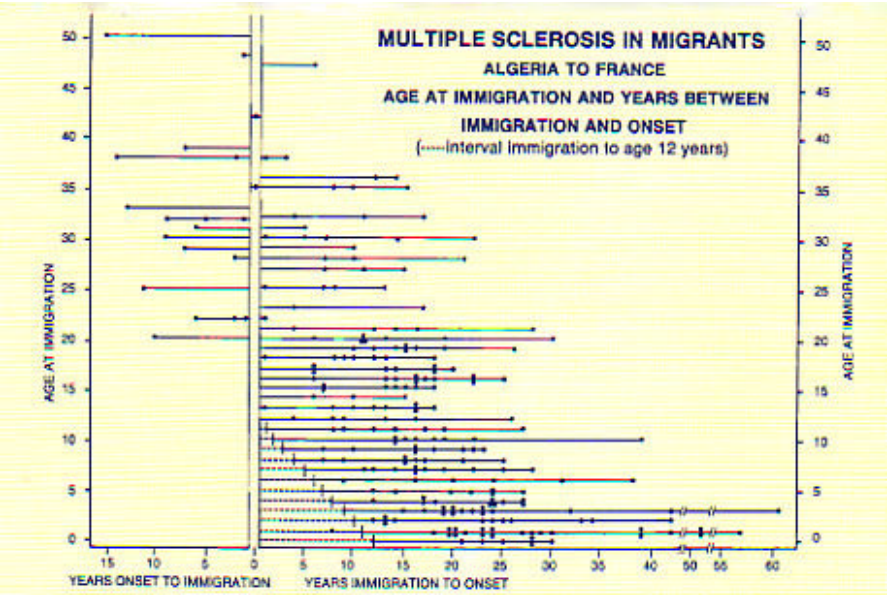


Multiple sclerosis in migrants from northern Europe to South Africa by age at immigration (Y axis) and years between immigration and clinical onset (X axis) who were ascertained in 1960 MS prevalence survey of South Africa. Each patient is represented by a bar whose locus on Y axis ± years from immigration on X axis indicates age at clinical onset. Diagonal reflects mean age onset for this series. Modified from Kurtzke et al 1970 [7].

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, which is the same medium prevalence rate as for the native-born English-speaking white South Africans. But for age groups older at immigration, the prevalence was some 30 to 80 per

100,000, the same as expected from their high-risk homelands. This change was sharp and occured exactly at age 15 (Figure 8). Here 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 to high, were afforded by the mostly white North African migrants to France. They came from Morocco, Tunisia, and specially Algeria. The migrants with onset more than one year after immigration provided an age-adjusted MS prevalence rate 1.5 times that for all France. If the latter is taken at 50 per 100,000 population, their adjusted rate is 77. The others with presumed acquisition in North Africa gave same rate of 17 per 100,000 as expected for residents of those lands. For those migrants with acquisition in France there was at each age a mean interval of 13 years between immigration or age 11 and clinical onset, with a minimum of 3 years. The oldest patient at immigration(age 48) was only one to enter France before onset in the fifth decade fo life. In this figure each patient is represented as a solid circle on the line reflecting age at immigration on the Y axis, and whose location on the X axis shows years between immmigration and onset of symptoms (Figure 9). Note the solitary patient who migrated at 1 year of age and had onset of symptoms at age 9, supporting again the rarity of childhood MS.



Multiple sclerosis in migrants from French North Africa (2/3 from Algeria) by age at immigration (Y axis) and years between immigration and clinical onset of MS (X axis). Each patient is represented by a solid circle whose locus reflects age at onset as the algebraic sum of age at immigration and years from immigration to onset. Fron Kurtzke et al 1998 [8].

The migrant series provide further support for the theses that multiple sclerosis is primarily an environmental disease 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 host suceptibility. If this is true, then what we call "MS" must be much more widespread than clinical cases indicate, or there must be a non-human reservoir. This hypothesis would have much stronger support if it could be shown that there have occured epidemics of MS. An epidemic may be defined as disease occurence early in excess of normal expectancy and derived from a common or propagated source. Epidemics are divisible into two types: Type 1 epidemics occur in susceptible populations, exposed for the first time to a virulent infectious agent. Type 2 epidemics occur in populations within the organism is already established. If the entire populace is exposed to a type 1 epidemic, the ages of those affected clinically will define the age range of susceptibility to the infection. Type 2 epidemics will tend to have a young age at onset, as the effective exposure of the patients will be greatest for those then first reaching the age of susceptibility.

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

All known MS patients in Iceland with onset 1900-1975 were collected in 1980. Annual incidence rates several that there does seem to have been at least one definite Type 2 epidemic of MS in Iceland beginning in 1945. The average annual incidence rato from 1923 tp 1944 was 1.6 per 100,000. For 1945-54 it was significantly higher at 3.2, and then it declined significantly to 1.9 for 1955-74. Age at onset in the 1945 to 1949 interval (23 years) was siginificantly lower than for any other 5-year period from 1935 to 1969.

For each of Shetland and the Orkneys for 1911-1985 average annual incidence rates indicated that the occurence after 1970 was siginificantly lower than that for the prior 30 or 35 years. The incidence rates showed considerable fluctuations, and did apparentely differ in peaks and valleys between the islands. But the overall impression of at least one epidemic between 1941 and 1970 seems valid, as does clear decline after 1970.

The Faroe Islands are a semi-independent part of the Kingdom of Denmark. Population numbered over 44,000 in 1998. They comprise 17 major volcanic islands made of basaltic rock, all with steep hills reaching the shore of the bays and fjords. Almost all the villages are in such inlets. Travel between many islands and even between a few villages on the same island is still by boat.

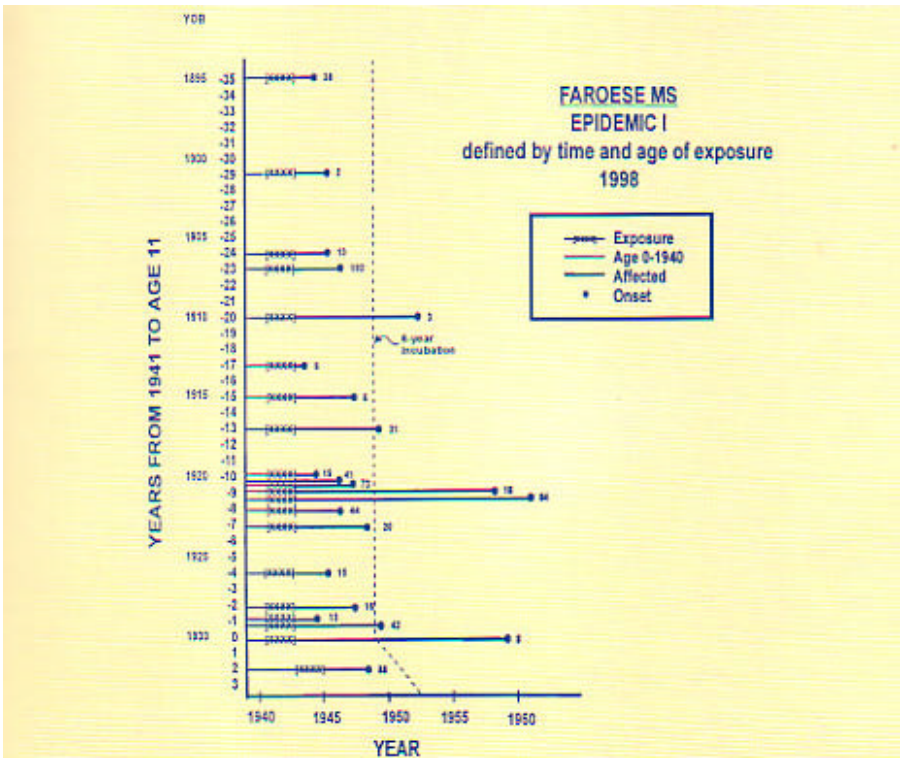
I have been working with the late Kay Hyllested and Anne Heltberg, both neurologists of Denmark, investigating MS on the Faroes since early 1970s. At least one of us has examined every person alive on the Faroes in whon MS was suspected since 1960. To find all possible cases from 1900 on, we used every conceivable resource of medical

information. Denmark, including the Faroes, has had state-provided healt care since 1920s, and Danish medical and health records are unsurpassed. All medical records for all suspected cases were obtained and reviewed by each of us.

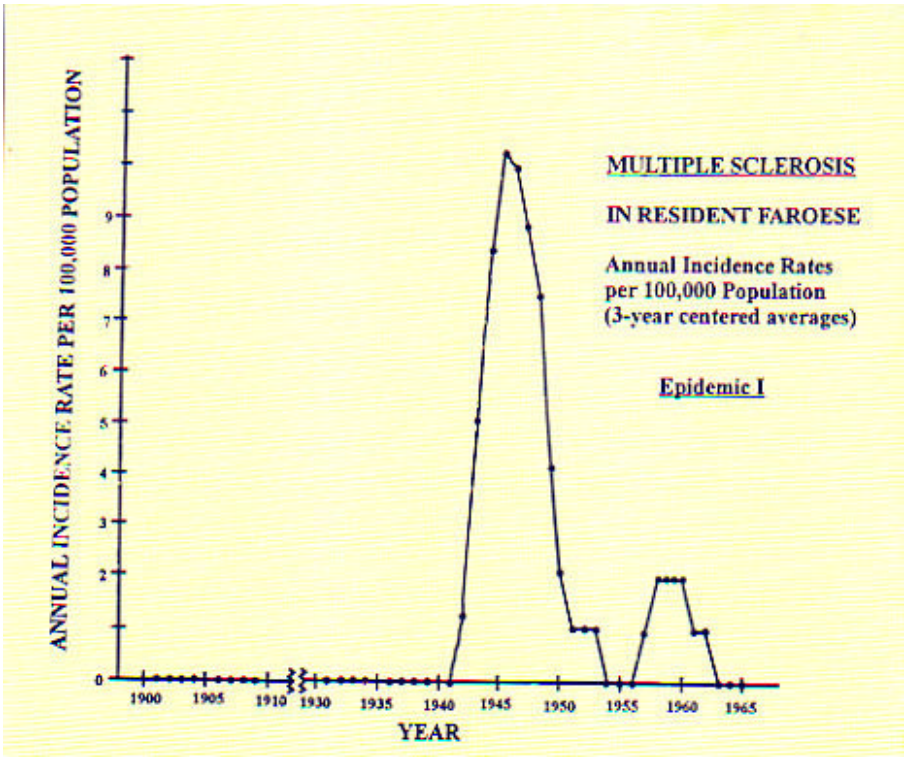
There is no evidence, despite all our efforts to find any, that MS occured in this century before 1943 among native-born resident Faroese who had not lived off islands for 3 or more years before clinical onset. July 1943 is the earliest date when symptom-onset was discovered to have taken place in such residents. This figure summarize the 21 patients among the 26,000 Faroese who constitute a point source type 1 epidemic of MS on the Faroes, beginning in t 1943 (Figure 10).

Inclusion of patients for this epidemic - and later ones - was dependent on two criteria: ahe 11+years at "exposure", and "exposure" for two years. The "exposure" period here was thus 1941-1942 (two years before earliest onset) for 20 patients, and 1943-1944 for the last. What the Faroese must have been "exposed" to had to be an exogenous agent brought into the Faroe Islans in 1941-44. We believe this agent is a specific infection we call the primary multiple sclerosis affection (PMSA). Age at first exposure to PMSA extended from age 11 to age 45. Thus susceptibility to PMSA in this populace is limited to Faroese age 11 to 45. Older and younger Faroese were not then susceptible. Annual incidence rates show the striking appearence - and dissapearence - of this epidemic (Figure 11). Residence at time of exposure indicates the wide scattering of these cases throughout the islands (see below).

The Faroe Islands were occupied by British military forces for five years during World War II, from April 1940 to September 145. Army troops were the main force, although there were Navy and Air Force units 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.

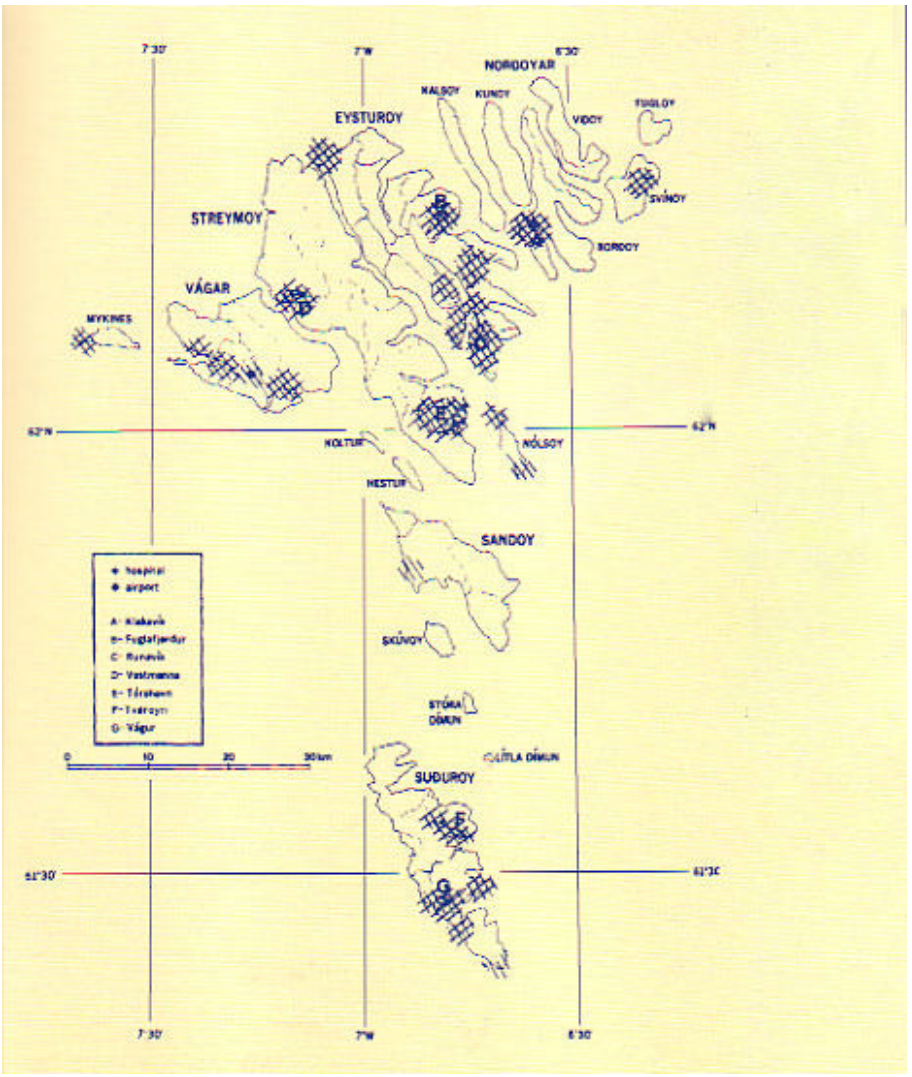


Clinical MS in the total of 21 native Faroese who comprised the first epidemic as defined by time (1941-1944), duration (2 years) and age (11+ years) of exposure to the primary MS affection (PMSA). Each patient is represented by a bar on the X axis whose location on the Y axis is determined by the number of years between 1941 and age 11. time of exposure to PMSA is cross-hatched; heavy part of the bar after exposure shows latent or incubation period to clinical onset (solid circles).C alendar year of birth (YOB) is also noted. Numbers at the end of each bar identify the patients in tables in Kurtzke and Heltberg 2001 [9].

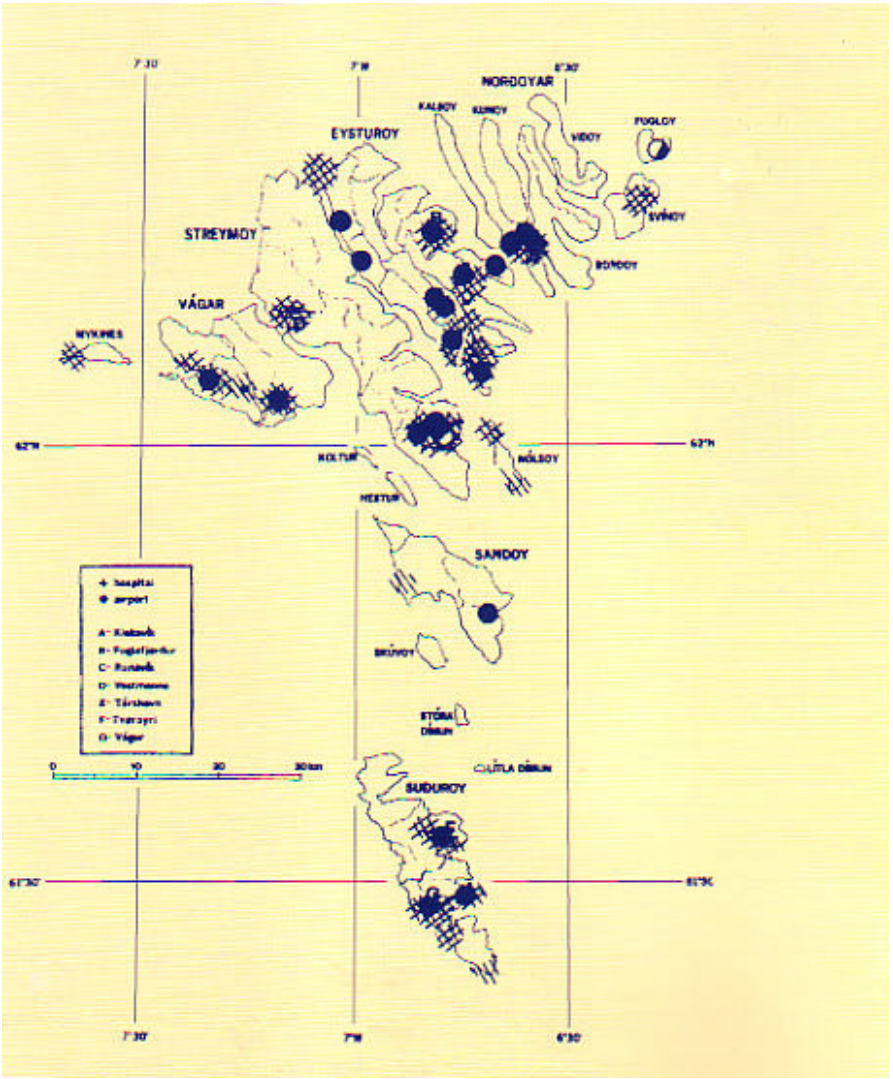


MS native resident Faroese. Annual incidence rates per 100,000 population calculated as 3-year centered moving averages for the 21 subjects of epidemic I. From Kurtzke and Heltberg 2001 [9].

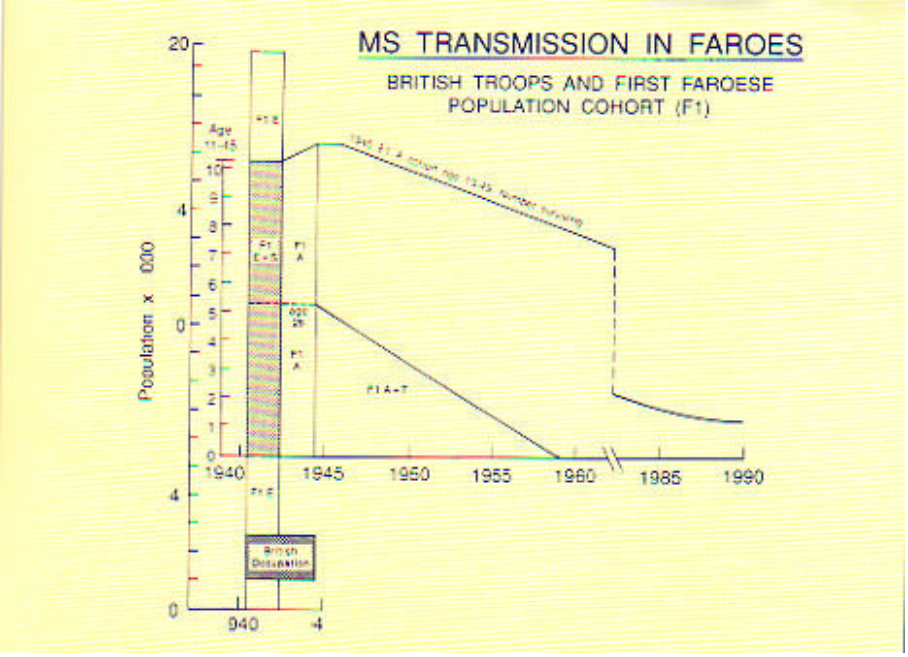
Through 1941, there were some 1500 troops stationed there. In 1942 the numbers rose to 7000, exceeded 4000 between June 1942 and August 1943, and they were still near 1000 or so through 1944. Locations of troops encampments within Faroese villages are shown here as cross-hatched areas. Camps outside villages are diagonal-lined (Figure 12). It is clear that troop locations match very well the residences of the MS patients, drawn here as clack circles (Figure 13). We concluded that the British troops brought MS to the Faroese in the Faroe Islands in 1941-1944.



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 and Heltberg 2001 [9].



Residence of patients of epidemic I (circles) superimposed on British occupation sites. From Kurtzke and Heltberg 2001 [9].



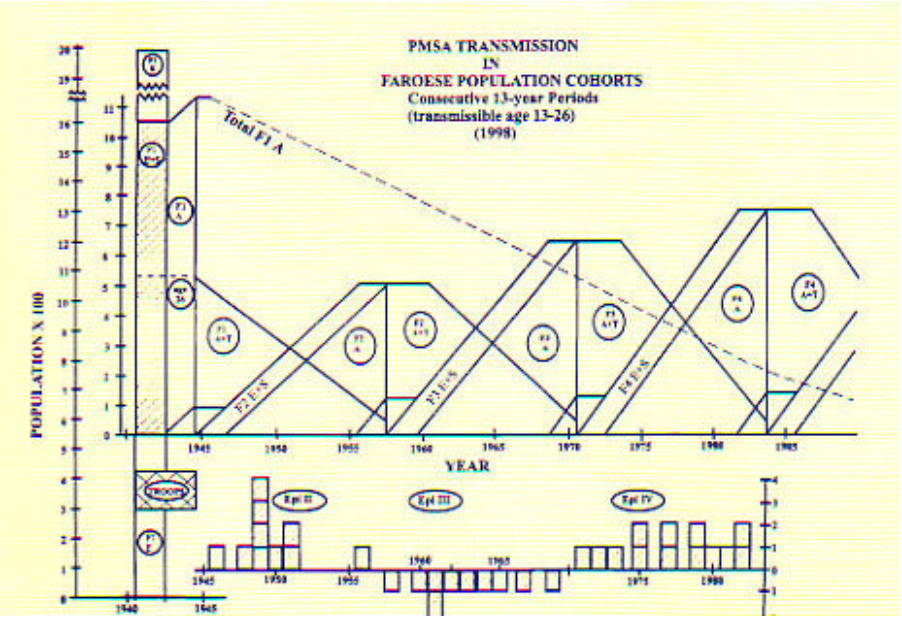
Transmission model fro the first population chort of Faroese (F1) exposed to PMSA. Rectangle at lower left represents British occupation 1941-1944 when at least 1,500 troops were stationed on the Faroes. Long vertical bar represents the entire 1941 Faroese population, all ages, geographically at risk of PMSA: the F1 E (exposed) cohort. Only those age 11-45 in 1941 were susceptible to PMSA (F1 E+S) based upon ages of the epidemic I MS patients (shaded part bar). After two years the F1 E+S cohort became the F1 A (affected) cohort. Were the entire F1 A cohort able to transmit PMSA, transmissibility would have persisted from 1945 into the 21st century ("number surviving" curve). If transmissibility ceases by age 27, then only that part of the F1 A cohort age 13 to 26 would comprise the F1 A+T cohort (affected and transmissible), which would decline to 0 in 1958 as its members attain age 27. From Kurtzke et al 1995 [10].

The troops therefore brought something to the Faroes which later resulted in an epidemic of clinical MS. This had to be either an infection or toxin, with either one geographically widespread on the islands from 1941. Now a toxin could not be responsible for later epidemics. Therefore, if there are such (and there are), then there must have been an infection carried by a large proportion of British troops (because of its wide distributio n) in an asymptomatic fashion (because they were healthy troops). This must be a persistent infection which takes time (here two years) to be transmitted to a naïve populace, the Faroese. As noted, we call this agent the primary multiple sclerosis affectio n, which have defined as a specific, but unkown, widespread, persistent infection that will only rarley lead to clinical neurologic MS years after its acquisition.

This figure provides a model of transmission of PMSA from the British troops to that populat ion cohort of Faroese of all ages, which was first geographically exposed to this

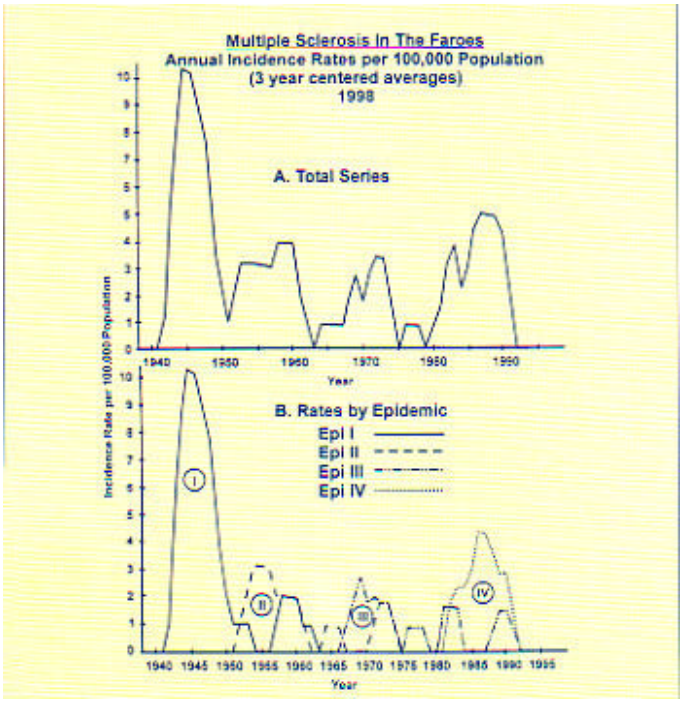
agent in 1941 (Figure 14). This is call the F1 E cohort, i.e the first cohort of the Faroese population exposed. The age range of the epidemic I MS patients in 1944 (age 11-45) defines the portion of the F1 E cohort that was susceptible to PMSA (F1 E+S), which portion becomes the affected part of this cohort (F1 A) after two years of exposure. Proportions of exposed actually affected are unknown, but must be 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 the F1 A persons were able to transmit PMSA lifelong, there would have been a steady input for new cases into the 21st century, and no further epidemics. Now, clinical MS patients do not transmit any disease. This, if this concept is valid, then, if there were later epidemics, transmissibility should have ended by the usual age of clinical onset - which we have taken as age 27.



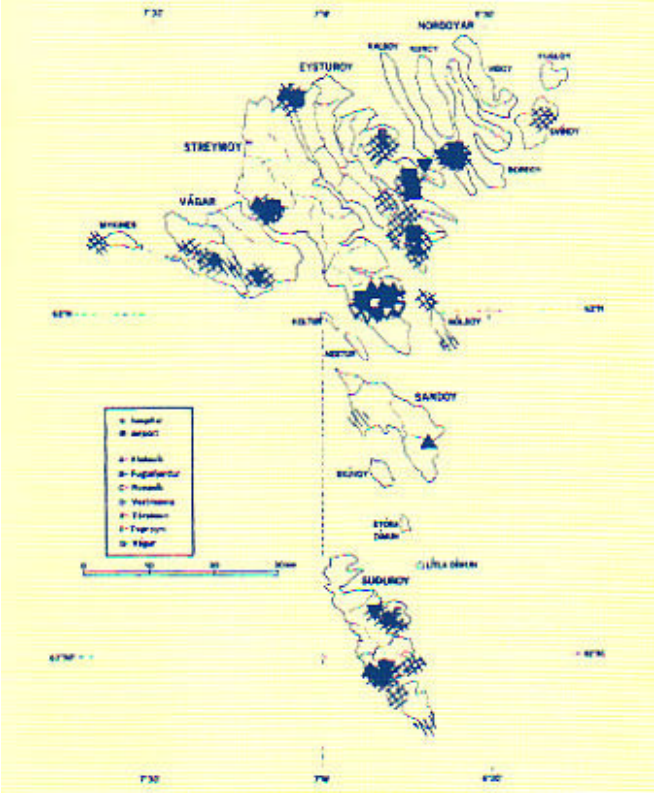
Summation of PMSA transmission with actual population numbers for British, and for Faroese geographically at risk, F1 through F4 cohorts, with time of exposure of patients of epidemics II-IV (lower portion); each rectangle there represents one patient at age 11 (dotted) or at older age of first exposure (open), by calendar time. From Kurtzke and Heltberg 2001 [9].

And in fact, after epidemic I there have been three later epidemics of clinical disease. Membership in the epidemics has been defined by the time of exposure to PMSA for each patient, as seen in the lower part of this figure. The 10 epidemic II patients were exposed in 1945-57; the 10 of epidemic III in 1958-70. Open boxes indicate first exposure after age 11, as found for 4 of the 13 epidemic IV patients who were exposed in 1971-83 (Figure 15). Annual incidence rates per 100,000 population do show four epidemic peaks. The top panel provides tha rates fro the total series, the lower panel the rates for the individual epidemics (Figure 16). Furthermore, the male excess of epidemic I has changed to an increasing female preponderance for each later epidemic.



Annual incidences rates per 100,000 population for clinical MS in native resident Faroese, calculated as 3-year centered moving averages, 1998. Upper panel: total series, lower panel: rates for each of the four epidemics. From Kurtzke and Heltberg 2001 [9].

The MS patients of epidemic II-IV lived mostly in the same villages, which also were very much the same as for epidemic I patients, and for the British troop locations of World War II (Figure 17). No patient of epidemic II-IV lived at time of PMSA exposure in any location where there had not lived epidemic I patients or occupying troops. The disease has remained geographically stable for over half a century on the Faroes. Unfortunately, this is the end of our work on the Faroe Islands. The Faroese authorities have not given us permission to pursue the obvious virologic and immunologic questions to define PMSA. I sincerely home someone will be able to do so with this unique experiment of nature. Here may well lie the solution of the riddle which is multiple sclerosis.



Residence of patients of epidemics II-IV superimposed on British occupation site of World War II. Triangles are for epidemic II patients, squares epidemic III, inverted triangles epidemic IV. From Kurtzke and Heltberg 2001 [9].

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