

**How Far Can Epidemiology Take Us  
in Finding the Cause of Multiple Sclerosis?**

John F Kurtzke MD, FACP, FAAN

Department of Veterans Affairs Multiple Sclerosis Center of Excellence-East

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Parts A and B

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10 North Greene Street

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## Preface to the 2013 John Whitaker Memorial Lecture Monograph

Christopher Bever, MD, MBA  
Director

### How Far Can Epidemiology Take Us in Finding the Cause of Multiple Sclerosis?

Walter Royal, III, MD  
Associate Director, Research

Mitchell Wallin, MD, MPH  
Associate Director, Clinical Care

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We are pleased to present this monograph as part of our annual Whitaker Memorial Lecture series. The 2013 lecture entitled “How Far Can Epidemiology Take Us in Finding the Cause for Multiple Sclerosis?” was given by John Kurtzke on August 29, at the PVA Summit and Exposition in Orlando, FL. This presentation summarizes the major findings on the epidemiology of multiple sclerosis (MS) over the last century with a focus on the work from John’s long and distinguished research career. To name but a few highlights, he developed the most widely used disability scale in MS, the Expanded Disability Status Scale (EDSS), initiated the first randomized controlled trial of MS, and has taken the lead on the development of large population-based military cohorts to describe seminal epidemiological trends in MS. John continues to be a pioneer in MS and largely started the field of neuroepidemiology in the 1950s-1960s. In the text and slides that follow, John meticulously leads us through the population-based studies that point to an infection as the underlying cause for MS.

Epidemiology can be a helpful starting point to understand risk factors and eventually causation for disease. We would point out that over the 20<sup>th</sup> century, epidemiological studies have been critical in unraveling the causes of the HIV epidemic and pellagra, and of infectious agents associated with Guillain-Barré. While the lessons from epidemiology are not always embraced by the research community, they should be assessed and integrated into the work by clinical and lab-based investigators, especially where there is consistency in the findings.

We are grateful to be the recipients of this important lecture and John is to be congratulated for his hard work and thoughtful synthesis of ideas. We trust that this lecture will stimulate the MS community toward new studies to better clarify the infectious etiology of MS.

Sincerely,



Christopher Bever, MD, MBA  
Director, VA MS Center of Excellence-East  
Professor of Neurology, University of Maryland School of Medicine



Mitchell T. Wallin, MD, MPH  
Clinical Associate Director, VA MS Center of Excellence-East  
Associate Professor of Neurology, Georgetown University School of Medicine



How Far Can Epidemiology Take Us in Finding the Cause of Multiple Sclerosis

John F Kurtzke MD, FACP, FAAN

Professor Emeritus of Neurology, Georgetown University

Consultant in Neurology and Neuroepidemiology

Veterans Affairs Medical Center, Washington, DC

Address for correspondence:

John F Kurtzke MD

Neurology Service (127)

VA Medical Center

Washington, DC 20422

Fax: 703-560-6490

e-mail: [kurtzke2@aol.com](mailto:kurtzke2@aol.com)

address for editor:

John F Kurtzke MD

7509 Salem Road

Falls Church, VA 22043

phone: 703-560-6016

Fax: 703-560-6490

e-mail: [kurtzke2@aol.com](mailto:kurtzke2@aol.com)

Part A

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## **ABSTRACT**

While still a resident I became intrigued with this disease. To seek clues to its cause I turned to its epidemiology, of which little was then known. This began with detailed analysis of all population-based measures of frequency. Community surveys divided the world into three regions of high (30+ per 100,000), medium (5-29) and low (<5) prevalence rates. At first review high regions comprised northwestern Europe, southern Canada, northern US, New Zealand, and southeastern Australia. Since then more and more of the world have fallen into the first two classes.

Nationwide surveys of each country of Fennoscandinavia and of Switzerland showed high rates in single contiguous regions in each land. These suggested an origin of MS itself in south-central Sweden with spread to its neighbors and southward on to the continent. Emigrants from the high areas of Norway and Sweden seem to have introduced MS into Wisconsin and Minnesota in the latter 19th century, followed by diffusion of high areas across all the northern states and later into the southern ones as well.

Migration of patients from high to lower areas indicated acquisition by about age 15 with prolonged latency before clinical onset. Reverse migrations showed susceptibility limited to a period from age 11 to 45 or so. Variations in herd immunity would explain such differences in times of acquisition and latency, from 4 and 15-20 years in high areas, to 3 and 10 years for migrants from medium to high, and to 2 and 5 years in virgin populations, where its first appearance in some lands occurred as epidemics.

We spent a quarter century investigating MS in the Faroe islands, where there were no cases in the 20th century among native resident Faroese until 1943, when symptoms began in the first of 21 cases defining a Type 1 epidemic with incidence rates over 10 per 100,000 in 1945 and 1946. We concluded this was introduced into the islands by British military forces stationed there from April 1940 to September 1945. We further concluded that they had brought a previously unknown, widespread, asymptomatic, persistent infection we call the primary multiple sclerosis affection (PMSA). We believe that its precursor onset stage was a newly-acquired acute infectious gastroenteritis affecting Faroese of all ages, and that among those infected at age 11 to 45, the PMSA cases, this persisted for years in the gut up to about age 25-30, with early spread to intestinal lymph nodes and, in a few of the affected, with further (lifelong?) spread into the CNS via blood and cerebrospinal fluid. These cases resulted in the cases of clinical MS whose onset defined this epidemic.

Since Faroese MS seems then to be British MS, I believe this to be a model for MS elsewhere. Search for such a presumed persistent neurotropic enterovirus in current patients would provide a test of this somewhat involved hypothesis for the cause of MS.

Keywords: multiple sclerosis, epidemiology, focal concentrations, diffusion, epidemics, ages of susceptibility and acquisition, neurotropic enterovirus

Good morning. As with many of your presenters, I have no conflicts of interest to declare, but much to say.

The objectives of my talk this morning are: first, to summarize the geographic distribution of multiple sclerosis in time and space; then, to demonstrate the effects of migration of patients on its frequency by age and place; next, to indicate how the migration or spread of high risk populations led to its introduction in different lands, including the occurrence of epidemics; and last, to offer an integration of all these quite complex findings into a testable hypothesis of the cause of this disease.

[slide 2] I am deeply honored to have been asked to give this year's Whitaker Lecture. I knew John primarily from his involvement in multiple sclerosis, where he was indeed a leader in studying the clinical, immunologic, and therapeutic aspects of this disease. His tragic death at the young age of 61 was a major loss to the field.

[3] It was Harold Wolff who decided my fate in medicine. Unique was his four-week obligatory course in Neurological Diagnosis in second year, distinct from the Physical Diagnosis course of the internists. Each examination was organized by body part, listing all positive and negative findings to provide a 20-page hand written report. In third year there was a required four-week clinical clerkship in neurology given at one of the teaching hospitals of Cornell, which included the Veterans Administration Hospital in the Bronx where I was assigned.

[4] I took my residency at the Bronx VA with Wolff as director of training. It was there that my interest in multiple sclerosis really crystallized. Then and now this remains a disease of unknown cause. Among the disciplines used to try to find a solution, the least explored at that time was epidemiology.

[5] Epidemiology has been called by some the basic science of clinical medicine, providing information about disease of importance to all aspects of the health care system. The main question for the field is the distribution of a disease in time, place and person. Real differences in distributions must have their causes, which may be multiple, but among them will be its etiology.

[6] Just as the clinician needs the history and physical to point to the diagnosis, so too does the epidemiologist need the distributions to point to the cause. The principles of practice for the epidemiologist are the same as for the neurologist, except that localization is in the environment rather than in the patient. The anatomic lesions are located where their cause will be found, just as the cases are located where their cause will be found.

There is though one major difference between the two, reflecting perhaps the MD: PhD dichotomy. The physician has to treat his patient now with the best information he has. The

epidemiologist can become so involved with caveats and possible exceptions that major conclusions may be obfuscated.

Disease distributions are best defined from population-based rates. The *incidence* or *attack rate* is the number of new cases of a disease occurring in a unit of time and population, usually given as an annual incidence rate in cases per 100,000 population per year. The *point prevalence* “rate” refers to the number of the affected at one time, again expressed per unit of population. These are the main measures of morbidity.

There are other indirect measures of frequency, where the cases are provided from records in administrative files without clinical validation. The oldest examples of these are *mortality* or *death rates* by cause of death, which are routinely gathered by most countries. Similar administrative files may provide data on some diseases in some locations that can be used to estimate morbidity rates.

[7] Between 1956 and 1974, I had twice reviewed in detail all population-based studies of multiple sclerosis that I could find. All conclusions were my own based on my analysis of the data presented or obtained from the authors, with no preconceived notions as to what they should be, an approach I continued to use to the present.

By the 1970s there were almost 200 surveys of individual communities, only one of which had been published before 1948. Together with their confidence intervals, the rates at that time provided two separate clusters of frequency in Western Europe. Most of northern Europe was of high frequency, defined as prevalence rates of 30 or more per 100,000 population, while southern Europe was distinctly lower, with medium rates of 5 to 29. Rates classed as low were those of less than 5 per 100,000.

[8] By 1980 the world wide prevalence rates, divided into the same three ranges, indicated that southern Canada and northern US were high, as were much of north central Europe, southeastern Australia and New Zealand. Medium areas were southern and eastern Europe, southern US, the rest of Australia, South Africa, and parts of Latin America, with the remainder of the surveyed world of low frequency.

[9] By 2011 all the Canadian provinces and the coterminous US were high, as were most of Europe extending into the Near East, and more of southeastern Australia. Medium frequency areas included still some of eastern Europe, the rest of Australia, and more of Latin America, Africa, and Asia – now including Japan. Diffusion *is* a hallmark of this disease.

However, this trifold division is based on such scattered data that the patterns are open to varied interpretations.

[10] There were also several well-done surveys of MS covering entire countries of northern Europe, which do permit more specific inferences about this disease.

Sällström in 1942 provided an extensive report on MS throughout Sweden for 1925 to 1934, with a 1933 prevalence rate for the definite cases of 21 per 100,000 population. Their residences were plotted by county and by the smallest units permitted by the method of analysis. The high rate for Västerbotten (# 23) in the north was limited to the region of Umeå on the coast. Otherwise, both distributions describe essentially the same largely contiguous and highly significant focus of high frequency MS centered in the inland lake region of south central Sweden.

[11] Repeated surveys of successive generations of patients in Denmark were carried out by Gram and by Hyllested. Respective prevalence rates were 45 per 100,000 in 1933 and 58 in 1949. The former, with rate percentages by county cited in the first column, was more accurately a cumulative incidence rate, as he reported (in translation) that this was his “investigation concerning 689 cases of disseminated sclerosis among persons who had sought pensions since the foundation [1921] of Disablement Insurance.”

In his thesis “for den medicinske doktorgrad,” Hyllested had uniquely described the cases by their “main domicile” in four life-periods: at birth; at age 0-15; at 15-onset; and at onset – though not at prevalence day. As seen in the remaining columns, each one showed similar monofocal distributions, but the deviations from homogeneity were significantly by far the greatest at age 0-15. To me, this raised the possibility that MS in Denmark was actually acquired at about age 10-15 or so, since maximal spatial concentrations of a focal illness are found at the time of onset.

[12] County of residence in the old series of Gram was compared with Hyllested’s cases at age 0-15 in 1921. Both distributions are very highly correlated, with a Spearman coefficient of 0.88. The highest rates extended across the Jutland peninsula from Thisted (# 17) on the Atlantic coast, southeast on to the island counties of Odense (#10) and Svendborg (#9).

[13] The later study also showed a clear spread or diffusion of this focus of 1921, (A) on the left, to the time of onset, (B) on the right, but still with a strong correlation (0.77) between them.

[14] The same findings of a single focus of high statistical significance were seen for two nationwide surveys of Switzerland. The early one on the left, with a prevalence of 22 per 100,000 for 1922, was published in part in 1926 by Bing and Reese, the rest in 1931 by Ackermann. Maximal rates were in the contiguous cantons of Basel Stadt (k), Baselland (l), Aargau (q), and Zurich (a). This too showed a strong correlation with a later series, on the right, with a prevalence rate of 51 in 1956-57

reported in 1960 by Georgi and Hall. And again, there was diffusion between the early and later surveys.

To me, these nationwide data indicated 50 years ago that MS was an acquired, place-related and spreading, exogenous disease warranting search for an environmental cause. But MS is limited to humans, and this kind of distribution is what one might expect for a human disease that is transmitted from one person to another.

However, if there is anything that we do know about this disorder, it is that neurologically affected persons do not transmit anything to anyone. Further, clinical cases of MS are far too few to maintain any infection in a population. And certainly, to this date no such causative infection has been identified.

One possibility to counter these points is that the disease might be transmissible only in a pre-neurologic phase, as suggested by the Danish maximal concentrations under age 15. Another is that MS could be a far more widespread illness than clinical cases indicate - like poliomyelitis, where perhaps only one in a thousand affected shows any neurologic signs.

The joint hypothesis would then be that clinical MS could be the late and rare result of a widespread infection, mainly acquired in adolescence, which might be completely asymptomatic in endemic, high risk areas. It would take much more evidence, though, before credence could be given to any part of this explanation.

[15] An extensive study of MS throughout Norway was reported by Westlund in 1970, with distributions by county and small administrative units. Cumulative death rates 1951 to 1965 gave a nationwide rate of 28 per 100,000. The disability prevalence rate for 1966 was 37. Both sets of data demonstrated essentially the same single foci of contiguous high frequency regions, extending from the Atlantic coast across the waist of the country and southward into the eastern mountain plains, to join the Swedish focus to the east.

Combining the distributions for Norway, Sweden, Finland, and Denmark provides evidence for one single Fennoscandian focus of high frequency MS. One possibility is that MS might actually have originated in the inland lake region of south-central Sweden, with spread eastward to Finland and westward to Norway.

[16] Its first dissemination on to the continent may have been the result of the 30 Years War of the 17<sup>th</sup> century. The armies of Gustav Adolf of Sweden occupied much of what is now central Germany, including Frankfurt and Nürnberg, and extending down almost to the Swiss Confederation.

[17] On this map of MS autopsy rates in Germany for 1906 to 1950, Frankfurt is IV-C and Nürnberg is III-D. Comparison of the two shows considerable concordance between Swedish occupation sites and centers with high MS frequencies 300 years later. The high prevalence areas for MS in Switzerland included Basel and Zurich, just south of the Swedish army encampments. [18] And the highest prevalence rates for France are in the northeastern regions of the country, which were the nearest to Gustav Adolf's zone of occupation.

This spread from Sweden seems to me to be a likely explanation for the north-south gradient of MS in Europe that has been so often noted in the past – and that has now almost disappeared.

[19] the Swedish occupations may also be responsible for the occurrence of MS in Denmark. Up to the 16<sup>th</sup> century, Sweden was a largely rural, landlocked country whose southernmost counties belonged to Denmark, often at war with Sweden, and the southwestern coastal ones to Norway-Denmark.

It was the Vasa kings, starting with Gustav Vasa who ruled from 1523 to 1560, and especially his grandson, Gustav II Adolf, king from 1611 to 1632, who turned Sweden into a northern power in the 17<sup>th</sup> century. Swedish Pomerania, shown on the map as the shaded part of the German states on the coast of the Baltic sea, was from 1630 a Dominion under the Swedish crown. It lay just below the high MS counties of Svendborg (#9) and Odense (#10) of Denmark.

[20] Since 1920, the Association for Research in Nervous and Mental Diseases has met annually in New York to present a symposium on one specific topic. Their second session was on MS.

The geographic distribution in the US, conclusion number 5 of the commission, relied on the presentation of Davenport's paper at that meeting. [21] He had reported prevalence rates by state for World War I draftees rejected because of MS. [22] The data for his figure came from a 1700-page publication of the War Department in 1920. The MS rates, though, were based on only 255 men, far too few to provide valid distributions by state.

[23] However, we had earlier devised a method to evaluate distributions for small numbers of cases by combining some adjacent states to provide 23 units with populations large enough for statistical testing. There was then a striking and significantly high prevalence rate for MS in area **P**, comprising the two states of Wisconsin, just west of Lake Michigan, and Minnesota to its west. They had achieved statehood in 1848 and 1858, and immigrants from Sweden and Norway had provided most of their early residents. [24] The original homes of these immigrants were located in the high frequency MS regions of both Norway and Sweden that we have just shown.

[25] It does seem likely that MS had been introduced into this country by the Scandinavian immigrants to Minnesota and Wisconsin in the latter half of the 19<sup>th</sup> century. By World War I, the high rate areas had diffused from this original focus eastward to the northern Atlantic coast [23]. Note that this distribution does not support an earlier importation from Europe into the original 13 colonies, which lay along the Atlantic seaboard. This suggests that MS was not a widespread disease in Great Britain in the 17<sup>th</sup> and 18<sup>th</sup> centuries.

[26] This map shows, for the same 23 areas, percentages of case control ratios for residence at service entry in an MS cohort of some 4000 white male veterans of World War II, compared to their matched, pre-illness, military controls. The high ratios then extended in the north from ocean to ocean. [27] A more recent series consists of almost 3800 white male veterans with MS who had entered the military between 1960 and 1994, again matched with their military peers. Their distribution indicates even further diffusion. MS is clearly a spreading disease in the United States as well as in Europe.

The fate of migrants who move into regions of differing risk is critical to our understanding of this disease. If migrants change their risk after moving, then there *must* be an environmental cause or essential precipitant active in this disorder well after birth.

[28] Residence at service entry was compared with birthplace for the 5000 white veterans of WWII or the Korean Conflict. Non-migrants are on the main diagonal, north-north, middle-middle, south-south tiers of states. Migrants born north and entering in the south had reduced their risk of MS by half, from 1.48 to 0.74. This could be explained if they comprised two groups: an older one who had already acquired their disease at the northern ratio of 1.48 before leaving the north, and a younger one who acquired their disease at the southern ratio of 0.56 after they had moved south. These data support the Danish findings that MS may be acquired in high risk areas near age 10 to 15 or so, a range that here is midway between birth and age 29, the average age at service entry. Moves northward by the other veterans showed increased MS risk, but its potential extent is truncated by their young age at entry into service.

[29] The British victory in the Boer War at the end of the 19<sup>th</sup> century opened South Africa to immigration. In 1960, the prevalence rate for MS in immigrants entering under age 15 was 13 per 100,000, about the same as for native-born whites. But for older ages, their prevalence was some 30 to 80 per 100,000, the same range as in their homelands. [30] This change was sharp and occurred exactly at age 15. Here each patient is represented by a bar on the y-axis for age at immigration, and whose length on the x-axis is the number of years between immigration and clinical onset.

[31] A similar study of MS in migrants from the United Kingdom and Ireland to Australia was previously reported to show no difference by age at immigration. However, more detailed analysis indicates otherwise. The absolute risk of MS for entry at age 0-14 was 22 per 100,000 population. All the older entrant groups had significantly higher ratios. Even for age 15 to 19 the risk was 57 per 100,000.

The South African and Australian findings, together with those for our veterans, support the inference that natives of high risk areas have already been affected with this disease by about age 15. There then follows an incubation or latent period of some 15 to 20 years before the onset of symptoms, during which time place of residence is no longer relevant to the occurrence of the disease.

[32] One opposite migration was that for North Africans into Metropolitan France. Most of them had arrived in 1962 at the end of the Algerian War for independence, when all the *pieds noirs*, the Europeans, had to leave Algeria. The migrants with MS onset more than one year after immigration, cited as rate (2) in the "A. Migrant" columns, gave an age-adjusted prevalence rate that was 1.5 times that for all France, seen in the "B. All MS" columns. The calculated rates themselves are given in the lower rows. Rates higher than those of a place into which migrants have moved are typical of first exposure to an infectious disease.

[33] The migrants with acquisition in France showed, at each year of age at migration, a minimum period of 3 years and a mean interval of 13 years before symptom onset, starting *either* from age 11, *or* from age at immigration if they were then older. These observations suggest that some 3 years of exposure are needed in order for migrants from medium to high risk areas to acquire the disease, with then a latency of about 10 years before symptom onset. They also suggest that susceptibility to MS usually extends from about age 11 to age 45 or so at first exposure.

[34] The migrant studies provide further support for the theses:

[1] that multiple sclerosis is primarily an acquired, place-related and diffusing disease whose monofocal distributions within countries raise the possibility of person-to-person spread;

[2] that it is most often acquired after early childhood; and

[3] that its acquisition requires prolonged or repeated exposure, followed by a prolonged interval between acquisition and symptom onset.

The simplest explanation would be that MS is the result of a geographically delimited persistent infection with long latency and age-limited susceptibility. If this is true, then *either* there must be a non-human reservoir – for which there is no evidence -- *or* the underlying cause of this disease *does* occur as an asymptomatic illness that is much more widespread than clinical cases of MS.

This infectious hypothesis would have stronger support if it could be shown that there have occurred *epidemics* of MS.

[35] There are two kinds of epidemics: Type 1 are found in susceptible populations exposed for the first time to a virulent infectious agent; Type 2 in populations within which the organism is already established. [36] Francis Bacon's essay "On Boldness" concerned Mahomet's reaction to his unsuccessful claim that he would make a hill come to him. Migrant studies are examples of Mahomet himself going to or from the hill of high MS. Epidemics would be instances of the MS hill actually coming to Mahomet.

[37] We think there have been epidemics of MS in several groups of North Atlantic islands, formerly members of the Kingdom of Norway: Iceland, Shetland-Orkney, and the Faroes.

[38] Cases of MS in Iceland with onset from 1900 to 1975 provided annual incidence rates that indicate at least one Type 2 epidemic beginning in 1945. [39] The average rate from 1923 to 1944 was 1.6 per 100,000. For 1945 to 1954, it was significantly higher at 3.2, and then decreased significantly to 1.9 for 1955 to 1974.

[40] Stuart Cook and the late David Poskanzer had studied MS in Shetland and Orkney, describing cases with onset 1911 to 1985. [41] When recalculated, the annual incidence rates between 1938 and 1970 showed recurrent epidemics, several times surpassing 14 per 100,000 population, among the highest rates reported anywhere to this date. They then fell steeply to some 3 per 100,000 in the 1970s.

[42] Norway with its Atlantic islands had been absorbed into Denmark in the 14<sup>th</sup> century. The Faroes became a standard county or *Amt* of Denmark until 1948, when they achieved semi-independence though still remaining part of the Kingdom of Denmark with the same Danish medical care. [43] Despite that governance, through all these centuries the Faroese people have retained their old Norse language and culture, even to the present day.

[44] The Faroes lie in the North Atlantic Ocean at 62 degrees north latitude and 7 degrees west longitude. They comprise 18 major volcanic islands made of basaltic rock, all with steep hills reaching the ocean or the bays, calderas, and fjords. Almost all the 120-odd villages are in such inlets. [45] The population exceeded 44,000 in 1998. On the main island of Streymoy is Tórshavn, the capital. [46] The city had a population of 14,000 and is the site of the National Hospital. There has been a hospital in Tórshavn since 1829. Two more hospitals were established in 1905, [47] one in Klaksvík on the northern island of Borðoy, the other in Tvøroyri [48] in the southern island of Suðuroy.

I have been working with the late Kay Hyllested and Anne Heltberg, [49] investigating MS on the Faroes since the early 1970s. We have already met Hyllested with his 1956 survey of MS in Denmark. He was the founding Director of the nationwide Danish DS Registret from 1948 until 1992, and he continued with our Faroese project until shortly before his death in 1998. Anne Heltberg had in the 1980s taken over his position as Chief of the Neurology Department of the Roskilde Hospital outside Copenhagen.

[50] Between 1974 and June 1999, we all had personally examined every person alive on the Faroes in whom we suspected MS. We used every conceivable source of medical information to find all possible cases from 1900 on. The medical records of all cases were obtained and independently reviewed. I still have my copies, which, fortunately, are written in Danish rather than Faroese. We also interviewed relatives of all the suspects who had already died.

As of 1999, we had found 189 suspected cases, and we had agreed that 83 of them were MS. They were then classified according to birthplace and any residence off the islands. We first excluded 13 non-Faroese MS living in the Faroes.

[51] There were 15 Faroese, called Group **C**, with long periods of foreign residence before onset. They were also excluded, since their disease might well have been acquired off the islands. The included series then consisted of 14 Faroese of group **B**, those with short periods of overseas residence, and 41 of Group **A**, those who never lived off the islands for more than 6 months before onset. The Group **B** cases were accepted since their age of overseas residence did not correlate at all with age of MS onset.

[52] There is no evidence that MS occurred in the 20th century among native-born resident Faroese before July 1943, when symptoms began in one patient. Note that Groups **A** and **B** both follow the same time course.

[53] Among them, there were 21 MS who had been age 11 or older in 1941, meeting our criteria of susceptibility from age 11 and exposure for at least two years. These 21 Faroese in the 26,000 population do constitute a point source, Type 1 epidemic of MS.

[54] The annual incidence rates show the striking appearance – and disappearance – of this epidemic. An apparent secondary peak actually reflects a later onset at older ages [55] for four patients with the same time of exposure as the others.

The abrupt onset indicates that the disorder had to have been introduced into the islands essentially at a single time, and as recently as possible before 1941. [56] Its widespread occurrence throughout the islands, even then, is seen by the scatter of the villages in which the patients then lived.

They are shown here as solid black circles. What was introduced into the Faroes **had** to be a new exogenous agent, carried in Mahomet's hill into the islands between 1940 and 1944.

[57] Denmark and Norway were both invaded by Germany on 9 April 1940. [58] On 13 April a detachment of Royal Marines landed in Tórshavn. Ten days later they took part in an air raid drill conducted by the Faroese. The next month they were replaced by Army troops. Later came Air Force units, and the entire operation was under the Royal Navy. [59] The Naval Officer-in-Charge was the Fortress Commander. His headquarters in Tórshavn flew the White Ensign of a commissioned vessel, together with the Danish flag.

[60] This was the first occasion for the legal display of the **Faroese** flag, but only at sea, and only after request by the British. The original flag was designed by Faroese university students in Copenhagen after World War I. [61] It lies in the village church where one of its inventors is buried. In 1948 this became the official national emblem of the Faroe Islands.

[62] We obtained a half kilometer of 35 mm microfilm recording the War Diaries of the occupying forces on the Faroes. This table shows Arms, the combatant units, with dates of occupation. For much of the time, there were a full battalion of infantry and two regiments of artillery stationed on the islands. [63] Data listed here for Services, the support forces, actually include units of two Arms, the Corps of Royal Engineers, and the Pioneer Corps. The latter had an entire Group deployed, the 309<sup>th</sup>.

[64] By late 1940, the troops numbered 1000 or so, and by 1941, there were some 1500 stationed on the Faroes. In 1942 the numbers rose to 7000, exceeding 4000 between June 1942 and August 1943. They were still over 3000 into March 1944, and the last troops left in September 1945.

[65] Locations of troop encampments *within* Faroese villages are drawn here on the left as cross-hatched areas. Camps *outside* villages, where no Faroese lived, are diagonal-lined. It is clear that troop locations match nicely the superimposed residences of the patients, shown again as solid circles on the right.

We concluded that the troops had introduced something into the Faroe islands which resulted in an epidemic of clinical MS. [66] This had to be a persistent infection, and one 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 infection would take time (here two years) to be transmitted to **and then persist** in a naïve populace, the Faroese. We call this infection the primary multiple sclerosis affection (**PMSA**).

[67] This figure provides a *model* of transmission of **PMSA** from the British troops, indicated by the lower box, to that population cohort of Faroese of all ages, shown as the long bar, who were first

*exposed* to the PMSA agent at least by 1941. This is called **F1 E**, for the exposed first cohort of Faroese. In 1941 the patients of Epidemic I were all age 11 to 45, the same ages of susceptibility as we saw for the Africans migrating to France. That age range then is also the range for Faroese susceptible to PMSA (**F1 E+S**): the shaded part of the bar, even though Faroese of all ages were exposed. This may then be the typical range of susceptibility to MS elsewhere. This portion becomes the *affected* part of the cohort (**F1 A**) after some two years of exposure.

Since there was no MS among Faroese before the war, after the British left any cases following Epidemic I would have to be the result of transmission from a persistently infected **F1 A** cohort to later susceptible cohorts of Faroese. Now, as we noted earlier, clinical MS patients do not transmit any disease. Therefore, any transmissibility by these Faroese should have ended by the usual age of clinical onset, taken here as age 27. This **F1 A+T** (transmissible) cohort, shown as the lower triangle, would therefore decrease each year by the number of Faroese then reaching age 27, and it would disappear by 1958. This transmissible cohort would contain some three times as many Faroese in the first seven years as in the next six.

[68] This same model is drawn here as the left part of the upper figure, which shows the *actual* Faroese population at risk of PMSA at age 11 to 26 across four transmission cohorts. At the bottom are boxes showing time of exposure for each PMSA-affected adolescent who will become one case of MS within later epidemics.

[69] Age at clinical onset versus calendar year of exposure for each of four epidemics indicates that there was no overlap at all among them. And after Epidemic I most patients did have their exposure years in the first part of each period, the time when there were three times the number of transmissible Faroese as in the later years. This suggests a dose-response curve for transmission.

[70] Age at onset versus calendar year of onset showed overlap, but each onset year rhombus contained all the cases of its epidemic – a population cohort effect with older onsets in later years. This supports a common *time* of disease acquisition for all members of each epidemic. Despite this overlap, the annual incidence rates do still show four epidemic peaks [71].

Does this experiment of nature and history tell us anything at all about MS outside these small islands? If we are correct, Faroese MS is British MS, and there is no reason to think that MS in Britain is any different from MS elsewhere in Europe or in the Americas.

[72] I think the epidemics of MS in Iceland and Shetland-Orkney were also the result of their military occupations during World War II. Iceland was occupied by large numbers of British troops from May 1940 and of US forces from July 1941. Scapa Flow in Orkney had been the main northern

base for the Royal Navy in World War I, and it was rebuilt as such for World War II from the mid-1930s. In fact, British forces outnumbered the residents of both Orkney and Shetland from then until well after the war.

[73] I believe these findings do provide major insight into this disease:

- I think there is a widespread and specific - but unidentified - persistent infection called the primary multiple sclerosis affection
  - only a small proportion of persons with **PMSA** will years later develop clinical neurologic MS
  - up to 1999, the existence of this infection could only be inferred from the presence of symptomatic MS.

But perhaps we finally **do** have a lead to its nature. To rephrase the thesis, we think the British troops brought with them an asymptomatic persistent infection previously unknown to the Faroe Islands. After repeated exposure this caused a type 1 epidemic *of persistent **PMSA*** in a **large** proportion of Faroese, leading to a later Type 1 Epidemic *of clinical MS* in a **small** number among those affected. Now Type 1 Epidemics are marked by greater severity and shorter incubation than the agent produces in endemic areas. It is **possible**, then, that clinical signs of this infection might have occurred at the initial stage of exposure in at least some affected Faroese.

[74] We therefore assessed the Danish records of all notifiable diseases in the Faroes for 1900 to 1977 as to whether any of the 38 acute disorders that had occurred more than occasionally were significantly in excess in the World War II period, and in particular, whether any showed excesses shortly after the arrival of the troops in April 1940, perhaps with similar changes with their surge from mid-1942 through 1943. There were only seven infectious diseases with highly significant excesses during the war: acute infectious gastroenteritis (AIGE); paradysentery; syphilis; gonorrhoea; mumps; scarlatina; and rubella. All but the first two of them showed single peaks in 1941, with or without extension into 1942 – not the time of interest. However, AIGE *did* show a sharp peak in the 4<sup>th</sup> quarter of 1940, and a lesser one in the 2<sup>nd</sup> to 4<sup>th</sup> quarters of 1943. Paradysentery had significant excess in the second half of 1940 and in the second half of 1943.

Now paradysentery is clearly not **PMSA**. [75] But its epidemics - **and** those of AIGE – could indicate the *mode of transmission* for **PMSA** as being the *fecal-oral route*. AIGE may be more germane. In 1940 and in 1943, cases of AIGE had been diagnosed in over 1 percent of the population.

[76] There was also a marked change from what had earlier been mainly a disease of infancy and very early childhood. In those two years, far more cases occurred at **all** ages than previously, an age change seen to some degree in the other war years as well. This suggests that there had occurred Type

1 epidemics of a new enteric illness to which persons of all ages were susceptible, and which seems to have persisted as such, at least throughout the war.

[77] I think that the agent responsible for these wartime epidemics of AIGE *could* well be persistent PMSA. This concept does seem to fit the epidemiologic data, with an overall age range of susceptibility of 11 to 45 or so, and with other features varying with levels of herd immunity:

in endemic high risk areas, acquisition would take a period of some 4 years from age 11 with a 15 to 20 year latency before clinical onset;

in immigrants from medium risk areas to high, 3 years for acquisition from age 11 with a 10 year latency;

and for first exposure in virgin lands, 2 years for acquisition from age 11 with a 5 year latency. Clinical multiple sclerosis could then possibly be the rare result of a single persistent infection caused perhaps by a novel neurotropic enterovirus, like a chronic form of paralytic poliomyelitis. This is today a testable hypothesis.

This seems about as far as epidemiology could be expected to go in seeking a specific cause, and I would now pass that torch to our virology colleagues, with the strong hope that someone will pick it up. For even if everything I have presented is completely correct, without laboratory proof the best I can do is to join Churchill in his well-known comment after the 1942 victory at El Alamein:

[78] *Now this is not the end.*

*It is not even the beginning of the end.*

*But it is, perhaps, the end of the beginning.*

Thank you

## ACKNOWLEDGEMENT

It was in the fall of 2012 when Alastair Compston, Editor of *Brain*, invited me to submit an Occasional Paper summarizing my career in neurology and neuroepidemiology. We settled on a title of “Epidemiology in multiple sclerosis: a pilgrims’s progress”, and I sent him in due course a preliminary draft that included listing of a goodly number of slides to document my statements. It was then made clear that *Brain* would not be at all interested in a review of my prior works, and that only a minimum number of such tables and figures that were essential to the presentation would be looked on with favor, though of course all relevant references were to be cited. When in the winter of 2012 I tried submit it I found I was not able to use the requisite format, at which point both Professors Compston and Eleanor Riches, Managing Editor, came to my rescue by transferring my typescript and power point slides into a formal submission. Submitted in January, this was returned for revision after a set of most thorough and cogent comments by the reviewers. The same course followed my second and third revisions, having by this point added Joanne Bell, Scientific Editor, and Siobhán Fogarty, Production Editor, to the team of my active helpers at the journal - all resulting finally in its acceptance June 9, 2013 (Kurtzke, 2013).

In the spring of 2013 I was asked if I would present this year’s Whitaker Lecture at the Paralyzed Veterans of America’s Summit 2013 + Expo that was to be given on 29 August in Orlando, Florida. Since I was actively involved in the Pilgrim paper, this provided an opportunity for me to present all the materials underlying that paper. My proposed title of “How far can epidemiology take us in finding the cause of multiple sclerosis?” was accepted and duly presented as a 70-minute talk involving 85 power point slides. Surprisingly, this was quite enthusiastically received, and a number of the audience then and since have asked whether this would be published.

I have also taken the opportunity here to correct a misleading figure presented in my *Brain* article, whose legend read: “Figure 7. Distribution of multiple sclerosis by county (*Amt*) in Denmark, expressed as significance levels for rates at/above the respective national mean prevalence rates per 100,000 population. (A) Old series, 1933, rate 45.0; (B) new series, 1949, rate 74.2.... From Gram, 1934 (A) and Hyllested, 1956 (B).” This figure and legend had also been used in several prior oral presentations over the years, and I had completely forgotten until after the *Brain* paper was set in print that this had been an approximation of the Danish results that condensed the findings for the two series into a single slide in order to minimize data presentations: **A** was actually Hyllested’s series for cases age 0-15 vs 1921 population, and **B** the same for his cases at onset vs 1940 population, as shown above as slide 13. Justification for using the former as Gram’s results was the high correlation (0.88) with Hyllested’s childhood distribution, and for the latter that no prevalence day distribution existed and

onset distributions are almost never reported. More recently I finally found the paper in which that figure first appeared (Kurtzke, 1967): this was a comparison of age specific rates with rates all ages for distributions in several surveys. Slide 12 here was my original figure in Brain that this one had replaced, and slide 11 shows the data by time and county for these two important studies in the history of the epidemiology of this disease.

This incorrect figure in Brain, which I had exchanged at the last minute before publication for the simple reason that it did not show the diffusion over time that was present there as well as in Switzerland, also resulted in presenting what had therefore become a quite erroneous passage in the text pertaining to the Danish results. I apologize most sincerely to those who may have been confused or misled by these inexplicable errors – and deeply so to all the editors of Brain who have been so instrumental in having my views on the epidemiology of this disease and their background see the light of day - or at least print.

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How Far Can Epidemiology Take Us in Finding the Cause of Multiple Sclerosis

John F Kurtzke MD, FACP, FAAN

Professor Emeritus of Neurology, Georgetown University  
Consultant in Neurology and Neuroepidemiology  
Veterans Affairs Medical Center, Washington, DC

Address for correspondence:

John F Kurtzke MD

Neurology Service (127)

VA Medical Center

Washington, DC 20422

Fax: 703-560-6490

e-mail: [kurtzke2@aol.com](mailto:kurtzke2@aol.com)

address for editor:

John F Kurtzke MD

7509 Salem Road

Falls Church, VA 22043

phone: 703-560-6016

Fax: 703-560-6490

e-mail: [kurtzke2@aol.com](mailto:kurtzke2@aol.com)

Part B

Whitaker Lecture presented at Paralyzed Veterans of America's Summit 2013 + Expo,

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