The long journey of John Kurtzke (1926-2015) through the world of multiple sclerosis

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ABSTRACT

John Kurtzke is a giant of contemporary neurology. He is one of the founders of international neuroepidemiology, to which he dedicated a significant part of his career, with a particular focus on the field of multiple sclerosis. He also developed scales for assessing neurological disability associated with the disease. His Disability Status Scale was created to evaluate the first therapeutic trial conducted for a neurological disease, in this case to establish the effect of isoniazid in multiple sclerosis. In 1983, he created an expanded version, the Expanded Disability Status Scale, which continues to be universally accepted for assessing the clinical status of these patients. Kurtzke developed his professional activity at Veterans' Administration hospitals in the United States, affording him the opportunity to study cohorts of army veterans with multiple sclerosis; this, along with other research, enabled him to make important discoveries about its natural history and geographical distribution, and the effects of migration and epidemics on the disease, which supported the hypothesis that its aetiology was predominantly environmental, with a possible infectious origin. Furthermore, he was a distinguished general neurologist who also stood out in the epidemiological study of other neurological diseases and as a university lecturer. His extensive professional and scientific career spanned six decades.

KEYWORDS

John Kurtzke, United States Veterans' Administration, multiple sclerosis, EDSS, neuroepidemiology, environmental factors

Introduction

> "Don't go into neurology. You'll never make a living unless you do psychiatry."[1]

John Kurtzke was a great clinical neurologist, although he is better known as the author of clinical scales for evaluating disability in multiple sclerosis (MS), the Disability Status Scale (DSS), created in 1955, and its extended form, the Expanded Disability Status Scale (EDSS), which appeared in 1983. These two sophisticated, detailed scales were intended as a useful clinical tool for assessing the clinical status of patients with MS, and enabled clinical characterisation of the disease and the performance of successive therapeutic trials.

Throughout his career, he worked within the United States Veterans' Administration (VA), where he made use of the abundant data that were available to him through the follow-up of army veterans with MS. He was one of the founders and the greatest exponent of the epidemiological study of MS and of other neurological diseases. Kurtzke was the leading researcher of the geographical distribution of MS, and defended the decisive role of underlying environmental factors in its pathogenesis, proposing that an infectious agent may

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be the cause through his research into epidemics and migration. His studies of series of army veterans over more than five decades enabled him to characterise the natural history of the disease.

John Kurtzke was a tireless worker; discreet and methodical, he remained lucid until the end of his long life. He did not hesitate to share his data, many of which were painstakingly collected before the digital age. The commemoration in 2026 of the centenary of his birth offers the opportunity to acknowledge his legacy.

Material and methods

An extensive review was conducted of the literature on the life and work of John Kurtzke, with particular emphasis on his studies of MS. Happily, his own memories and opinions are readily available through numerous publications, particularly in the last decade of his life and even in posthumously published works.

Development

The early years

John Francis Kurtzke was born in Brooklyn, New York, on 14 September 1926, into a Catholic family in which he was the eldest of five siblings. He studied at Saint John's University College, Brooklyn, between 1943 and 1948, obtaining a bachelor's degree in sciences with the classification *summa cum laude*. Still a student, he enlisted in the Navy in 1944, serving as a pharmacist's mate, second-class, until he received his degree in 1946, although he remained in the Naval Reserve. Thanks to the GI Bill, he was able to continue studying medicine after completing his undergraduate degree. The GI Bill, or Servicemen's Readjustment Act, was a law approved by Congress in 1944 that provided army veterans with a series of benefits for reintegration into civilian life, with higher education grants, assistance for buying homes, and unemployment benefits. Thus, training programmes were created to take up the great number of young men who wished to begin or continue their medical training after completing their military service. In 1947, nearly half of American college students were war veterans.[2-4]

In 1948, Kurtzke enrolled at Cornell University Medical College in New York, where he obtained the degree of doctor of medicine in 1952. During his medical studies, he attracted the attention of the neurologist Harold G. Wolff (1898-1962), and trained under him in this specialty. Wolff had been head of neurology at New York Hospital Cornell Medical Center since its inauguration in 1932, and was professor of neurology at the university.[2,3,5] Under Wolff, more instruction in neurology was available at the university than at almost any other centre in the country at the time that Kurtzke began his training, despite a widespread negative attitude towards the discipline.[1,6]

In the second year of the degree programme, Wolff directed an obligatory course on neurological diagnosis, which was taught by neurologists at the VA Hospital in the Bronx. Neurological examination was based on a 54-page typed document encompassing all positive and negative findings, organised by body part, including measures of severity. The register also included detailed mental tests of the "highest integrative functions" and comprehensive assessment of vision. All relevant findings were gathered before offering a neuroanatomical formulation, which preceded diagnosis. The final result for each patient was a hand-written report of approximately 20 pages. This was the format required in clinical protocols, with examination at admission and discharge from hospital. Students' examinations were supervised by a neurologist or resident. The hospital used these Cornell protocols from 1944 as the only format of neurological testing at patient admission and discharge.[2,6]

In the third year, students completed an obligatory four-week neurology rotation at one of Cornell's teaching hospitals, including the Bronx Hospital, where Kurtzke completed his rotation. As an elective, the third year of the programme also included an intensive course on functional neuroanatomy, taught by Louis Hausman (1890-1972), which included the construction of a 4:1 scale model of the brain. Kurtzke always kept the model he made in his office.[1,6]

During the fourth year, he completed two elective neurology rotations, a part-time rotation at Bellevue Hospital and a full-time rotation at the Bronx Hospital.[1] It was there that he conducted his first study on MS, dedicated to acute respiratory failure in these patients.[7] During the same period, he also participated in an epidemiological study on Colles fracture in New York.[8]

After completing a medical internship at Kings County Hospital in Brooklyn, he returned to the Bronx Hospital, where Wolff was director of training, for his neurology residency.[1,9] Unlike other centres, where residency positions were unpaid, the VA did pay a salary, which

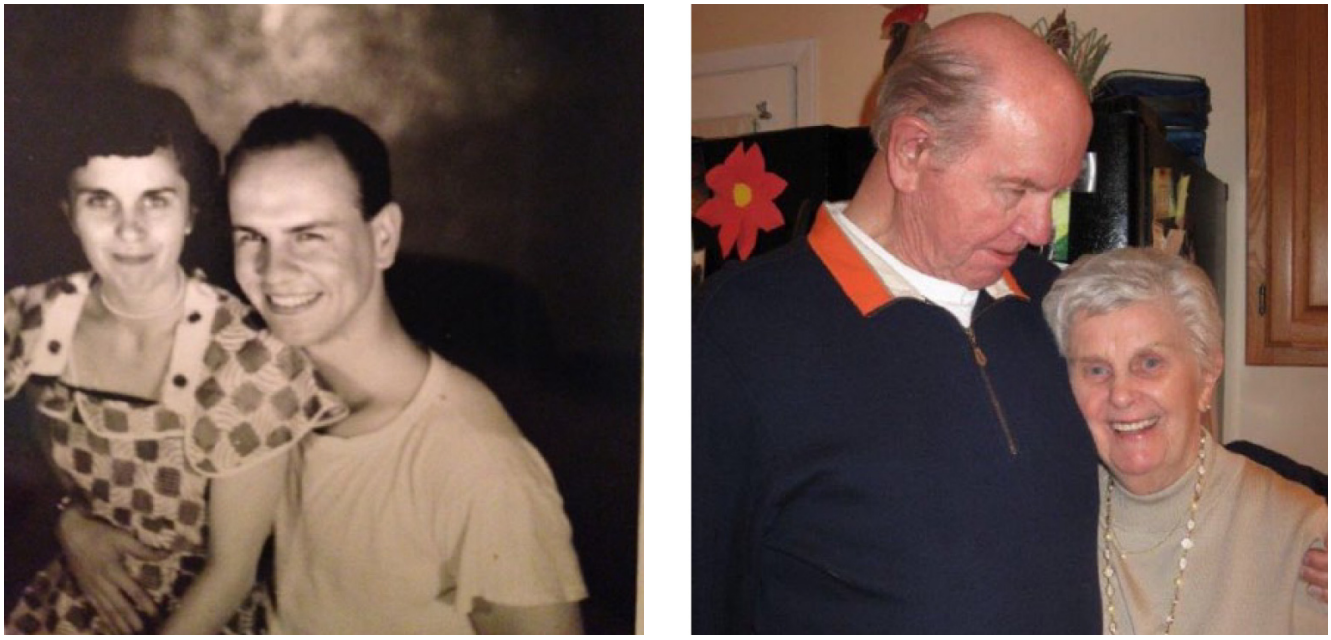

Figure 1. John Kurtzke and Margaret Nevin Kurtzke in the 1950s (left) and in the 2010s (right).[4]

Kurtzke desperately needed, as he was a father of two children (Figure 1).[4] He worked as a physician at the Department of Medicine and Surgery through a new programme called the career residency, as part of which he was required to serve two additional years as a full-time neurologist at a VA hospital after completing his residency training. In this position, he was considered to be on duty at all hours, seven days per week. Kurtzke was convinced that he would be able to continue at the Bronx Hospital, but this did not come to pass: in July 1956, he was assigned to the VA hospital of Coatesville, Pennsylvania, 50 miles from Philadelphia. At this neuropsychiatric hospital, with 1700 beds, he directed a new neurology department with 90 beds; the hospital was a neurological referral centre for veterans in the Philadelphia area. Years later, he recalled his experience of how the introduction of chlorpromazine revolutionised psychiatric care.[1,6] He was certified as a specialist in neurology in 1958.[3]

By 1963, the neurology department in Coatesville had grown to four neurologists, and had a two-year residency programme affiliated with Jefferson Medical College in Philadelphia, where Kurtzke was also an assistant neurologist. That year, he was invited to set up a neurology service at the Department of Veterans' Affairs Medical Center in Washington, DC, where a new hospital was under construction.[6] He worked as head of that department and as professor of neurology at Georgetown University until he retired in 1995, becoming a consultant neurologist and head of the neuroepidemiology research programme, as well as emeritus professor of the university.[3,5]

After his active military service in the US Navy Medical Corps from 1944 to 1946, he remained in the naval reserve until 1986, retiring with the rank of Rear Admiral and receiving various distinctions (Figure 2).[10] From 1966, he was also a consultant neurologist at the National Naval Medical Center, and professor of neurology at the Uniformed Services University (both in Bethesda, Maryland), remaining as a Distinguished Professor from 1992. He taught and mentored hundreds of neurologists during his time teaching in Washington and Bethesda.[3,5,10] Mitchell Wallin was one of his closest collaborators, and later his successor, in his neuroepidemiology research.

Figure 2. John Kurtzke, Rear Admiral of the Naval Reserve.[10]

Research on isoniazid in multiple sclerosis and the Disability Status Scale

Some months after John Kurtzke began his residency at the VA hospital in the Bronx, a nurse called his attention to a young paraplegic patient with MS and tuberculosis, who began moving his legs after starting treatment with isoniazid. After trialling the drug in more patients with the head of neurology, Louis Berlin (1915-1971), they decided that they should demonstrate the drug's efficacy in treating MS, but were aware that no acceptable method was available for evaluating their results; therefore, they needed to develop their own.[1] Clearly, to do so they would need an additional group against which to compare the effect of the drug, and a tool to measure the change. To that end, they used the detailed records of 220 veterans of the Second World War, and nearly 300 patients with MS hospitalised at their centre between 1944 and 1953, who underwent comprehensive examination at admission and discharge. All patients were at early stages of disease progression, generally having presented little or no deficits before the episode that led to their diagnosis. The challenge facing Kurtzke and Berlin was how to transfer these data to a classification system gathering all neurological findings in a format that reflected all stages of the disease, from asymptomaticity to severe disability, and which was sufficiently simple to administer. One method used at the time was that developed by the neurologist Leo Alexander (1905-1985) of Boston,[11] a complex system of 30 neurological signs and disabilities, some of which were duplicated, containing items that were judged arbitrarily and were of little value.[9,12,13]

Findings were classified within six mutually exclusive functional systems, according to the order of frequency in patients: pyramidal, cerebellar, brainstem, sensory, sphincter (bladder and bowel), and "other" (miscellaneous); each was scored from 0 to 5, except the latter, which was scored from 0 to 1. Some patients displayed improvements within one functional system and worsening in another; furthermore, the scores could not be added together. Therefore, they integrated the essence of each functional system, in terms of symptom presence and severity, into a scale measuring global neurological dysfunction, which Kurtzke named the DSS; scores were graded 0-10, with each step defined according to the frequency and severity of involvement of different functional systems. The scale was published in 1955, and was based on data from 315 patients. The article described in detail the different grades of the scale, and another published in 1956 described the characteristics of each of the six functional scales.[12,13]

With this first version of the scale, they evaluated the outcomes of isoniazid treatment in 30 patients and 175 historical controls admitted from 1945 to 1953, who had presented clinical activity in the two years prior to inclusion in the trial; their results were positive, and the research was published in 1954 in a journal on tuberculosis.[9,14] To confirm or reject these results, a multicentre, randomised, double-blind trial of 186 patients was subsequently conducted; 88 received isoniazid at 300 mg per day and 98 received placebo, and all patients were followed up for a minimum of 9 months. The study was conducted at 11 VA hospitals by the VAMS Study Group directed by Benedict Nagler (1928-2013), head of the central offices of the VA; Gilbert Beebe (1912-2003), of the National Research Council; and Leonard Kurland (1921-2001), head of the epidemiology section at the National Institute of Neurological Diseases and Blindness of the National Institutes of Health. Patients were assessed independently by neurologists from the VA, without the participation of John Kurtzke.[15] This kind of clinical trial had never previously been performed, either for MS or for any other neurological disease; the study was published in the *JAMA* in 1957. Though the study yielded negative results, it represented the introduction of the DSS. For Kurtzke, it also marked the start of a quarter-century of

collaboration in epidemiology research with the other promoters of the study.[1,6,16]

Army series

One consequence of the unsuccessful isoniazid trial by the VAMS Study Group was the fact that its members had access to detailed records of 16 million individuals who had served in the army during the Second World War. It was a unique opportunity to study the natural history of the disease in people of the age group in which it tends to appear; furthermore, they had data on unbiased controls, if patients with MS were paired with healthy individuals with whom they had coexisted during active service. Kurtzke and his colleagues spent years analysing the data from these records.[6]

Patient records were unusually extensive, with assessments at hospital admission and discharge. Furthermore, follow-up examinations subsequent to military service were very detailed. They reviewed all the available records from army, VA, and private hospitals, as well as an examination performed by neurologists across the country in cases in which recent data were not available. The research resulted in approximately 3000 neurological examinations covering the first 20 years of disease of 762 men diagnosed with MS in army hospitals from 1942 to 1951, which at the time employed excellent neurologists enlisted in military service. Each of the five neurologists in the group separately registered diagnoses at the time of diagnosis and after the global register,[17] coding the signs observed using the DSS and its functional systems. A total of 527 patients were diagnosed with MS (476 definite and 51 probable cases) and 146 received other diagnoses; insufficient data were available for 89 patients.[18,19]

The principles developed for the classification of MS in these veterans served as the basis for establishing a consensus position of an expert panel led by George Schumacher (1912-2008), another disciple of Harold Wolff, which also included Kurtzke and other researchers from the army series; the results were published in 1965. The panel classified definite MS as cases with objective evidence of the disease, affecting two or more central nervous system white matter areas, occurring in episodes separated by longer than 24 hours, or with clinical progression of around six months, in individuals aged 10-50 years at disease onset, which could not be explained by another cause.[20] These were considered the best and simplest criteria for determining clinical diagnosis. All subsequent diagnostic criteria, such as the Poser criteria[21] or successive versions of the McDonald criteria, met the requirements of the Schumacher panel.[19]

This research only included assessments of white men, excluding the small number of women and black men diagnosed with MS to prevent potential epidemiological biases; however, the group was so large that we may expect to make valid inferences for women, who only accounted for 2% of the group; this was addressed in a subsequent analysis.[6,22] For the epidemiological study, each of the 762 men initially diagnosed with MS was matched to a control according to age, sex, race, date of entry into military service, and survival of the war. Presence of MS showed a strongly positive relationship with level of education, socioeconomic status, and residence in urban areas. A north-south gradient in place of residence was also observed.[16,19,23]

The study group published eight major articles on the so-called army series. They all shared the main title "Studies on the natural history of multiple sclerosis," and the last five listed John Kurtzke as the lead author. The first two articles were published in 1966, and the last one in 1977.[5] The first article explained the study design, and the second was dedicated to optic neuritis in initial episodes.[18,24] The third presented an epidemiological analysis of the group.[23] The following articles studied the characteristics of disease onset, prognostic factors, and survival. Regarding prognosis, the authors observed that neurological status at five years after disease onset was predictive of progression over the next 13 years.[25]

Evolution of the DSS

In 1961, after assessing 408 patients (the 315 from the Bronx Hospital and a further 93 from Coatesville), Kurtzke expanded the combined methodology of the DSS and its functional systems to incorporate two additional functional systems frequently affected in these patients, the visual and the cerebral or mental systems, and increased the maximum scores for the majority of the different systems from 5 to 6, whereas the "others" category continued to be scored from 0 to 1. He also noted the need to include at least 200 patients with two years' follow-up in order for a therapeutic trial to establish the efficacy of a treatment.[17,26]

In a new revision of the DSS, published in 1965, he reviewed its structure in the light of preliminary data from the army series, restructuring the sensory functional system and making minor changes to the bladder/bowel functional system.[27] This revision coincided with the second therapeutic trial in MS, in which Kurtzke also participated; the trial was conducted at 10 university centres and sought to analyse the effect of ACTH in acute relapses, and reported positive results in 1970.[19,28]

At the time of diagnosis, the four most frequently affected functional systems in 527 patients with MS from the army series were, in order of frequency, the pyramidal, cerebellar, brainstem, and sensory systems, which were classified as major and were affected in the majority of patients at all disease stages. The four minor functional systems were bladder/bowel, visual, mental, and miscellaneous ("other") functions.[29] Subsequently, the authors described how each of the different functional systems could be described qualitatively as affected (1) or unaffected (0), generating an eight-digit binary number, without taking into account the severity of involvement of each functional system. Thus, a total of 256 different patterns of involvement were possible. A high percentage of patients presented simultaneous involvement of the four major functional systems, even at the time of diagnosis. As each functional system was designated independently of the others, taken together they encompassed all possible signs from the neurological examination, and could be calculated statistically. With this premise, the authors studied the specific patterns of 335 men with complete documentation from the group of 476 patients with definite MS from the army series. Half of all cases fitted one of the 14 most common patterns, and 96% were included in the 86 most frequent patterns, with concordance persisting throughout the series. The other 170 patterns were highly improbable. The frequency and severity of worsening of each functional system was correlated with an increase in DSS score, which globally presented a unimodal frequency distribution; however, in another patient series published 16 years later, a bimodal distribution was observed that differentiated two patient subgroups, those with poor prognosis and those with more benign forms.[17,30,31]

The use of the DSS in clinical trials demonstrated that patients' patterns of functional impairment may not be fully captured by the scale's 11 steps. The only way Kurtzke could see to solve this problem was to divide each step or grade in two, from 1.0 and 1.5 to 9.0 and 9.5, thus creating a 20-step scale, the EDSS, in 1983. Furthermore, he introduced new modifications to the scoring of sensory and sphincter function. This involved the use of more arbitrary definitions, as it was not feasible to revise the previous scores. This system of synthesising the clinical impairment of the central nervous system has remained unchanged ever since.[17,30]

Successive veteran cohorts

The experience with the army series inspired Kurtzke and his group to study a nationwide cohort of veterans of the Second World War and the Korean War, an undertaking that led to the publication of eight new studies between 1979 and 2000.[22,32] The series included 5305 veterans who had been diagnosed with MS by 1956, who were studied from the ninth or tenth year of clinical progression; once more, the authors used an unbiased pre-disease control group. This enabled them to study the disease in white and black men, and in white women, evaluating risk factors. As in the first army series, level of education was higher among patients with MS in all three groups, as was their socioeconomic status and the likelihood of living in urban rather than rural settings. White women presented a relative risk of developing MS of 1.79 with respect to white men; this represented a change, as the disease had previously predominated in men. White patients continued to display an excess with respect to other races, with a relative risk of 0.44 in black men and 0.22 in other ethnicities.[16,32]

To study the role of migration, relative risk of MS was compared among white men as a function of place or birth and place of residence prior to military service. Three tiers of relative risk of MS were observed according to place of birth: high risk in the north, low risk in the south, and medium risk in the area between the two, with variations as a result of migration. Thus, all ratios decreased with displacement from the northern to the middle or southern regions, and increased with northward migration.[6,33]

A new series of veterans who served in the Vietnam War subsequently contributed further information. The series included 5345 veterans who entered into service between 1960 and 1994, paired with controls at a ratio of 1:2. In the previous series, the relative risk of MS in white women with respect to white men had been 1.79; in this new series, it increased to 3.0 for all women. The relative risk of MS was lower in black men than white men (0.67),

but had increased in comparison to the last series (0.44). Geographical distribution according to state of residence at the time of entry into service also showed a north-south gradient, as had been the case in the Second World War and Korean War series, but had diffused over time. They concluded that these marked changes in geography, sex, and race in such a short time period strongly implied the participation of an environmental factor in causing or triggering the disease (Figure 3).[34]

Wallin and Kurtzke presented a third cohort of army veterans who served in 1990-2007, in the Gulf War era. It included 2691 patients, 66% of whom were men. This was the first cohort to include annual incidence data, with a rate of 9.6 cases per 100 000 population, a high level. The relative risk of MS was 3.5 in women with respect to men in the entire cohort (independently of race), and 1.2 in black men compared to white men. The results are even more impressive if we consider that the three cohorts amount to over 65 years of direct observation. Compared to white men, a significant, stable increase in the risk of MS was seen among women and black men. Thus, comparing with all men, the relative risk in women in the cohort increased from 1.79 in Second World War and Korean War veterans to 3.0 in veterans of the Vietnam War and 3.5 in Gulf War veterans. In black men, compared with white men, it increased from 0.44 to 0.67 and 1.2, respectively. The authors also describe the clinical characteristics of this third cohort, with 94% presenting relapsing-remitting MS and 6% presenting progressive forms. Progressive forms were more common in men and in black patients of both sexes. These changes observed in cohorts of veterans show an extraordinary concordance with the trends observed in other large series from recent decades. The latitude gradient in MS prevalence once again decreased in this most recent cohort.[35,36]

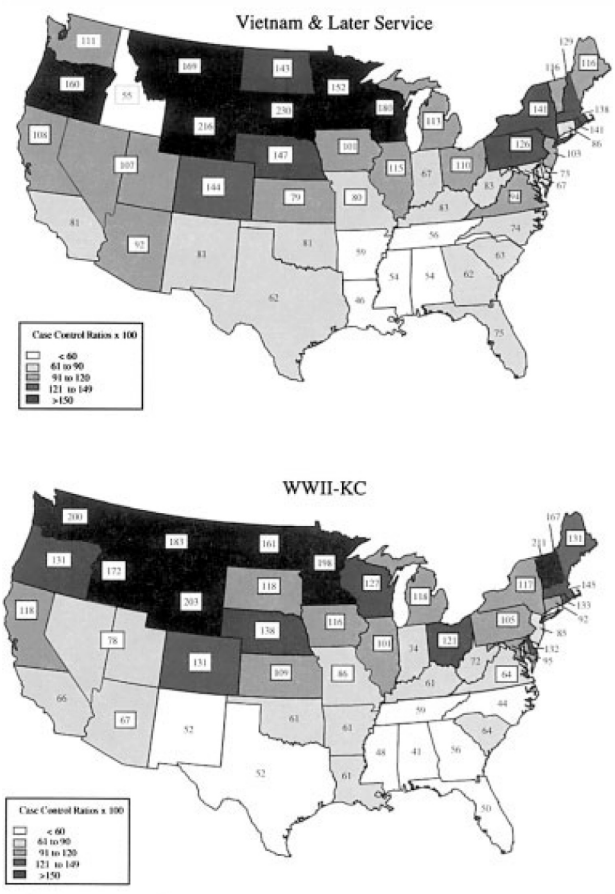

Figure 3. Adjusted case-control ratios (×100) for white male United States Army veterans with multiple sclerosis when they entered into military service. Above: cohort from the Vietnam era and later. Below: cohort from the Second World War and Korean War.[34]

Epidemics in the North Atlantic: the Faroe Islands

Epidemics related to MS may serve to characterise it as not only an acquired, but also as a transmissible disease. Thus, there is evidence of epidemics that may share common triggers in ethnically similar territories of various groups of islands of the North Atlantic. Definite epidemics were described in the Faroe Islands, with probable epidemics in Iceland[37] and the Shetland and Orkney Islands. The cases registered in Iceland between 1900 and 1975 provide data of at least one epidemic, starting in 1945, with mean annual incidence rates of 1.6 cases per 100 000 population in 1923-1944, 3.2 in 1945-1954, and 1.9 in 1955-1974. In the Shetland and Orkney Islands, where registers are available from 1911 to 1985, annual incidence rates from 1938 to 1970 suggest recurrent epidemics, with rates surpassing 14 cases per 100 000 population on numerous occasions, among the highest rates ever reported; they subsequently presented a sudden decrease to 3 cases per 100 000 population.[6,7]

In the 1960s, the Danish neurologists Mogens Fog (1904-1990) and Kay Hyllested (1918-1998), and the Northern Irish neurologist Sydney Allison (1899-1978) began a project to study the epidemiology of MS in the Shetland and Orkney Islands, where in 1962 the disease was

Figure 4. From left to right: John Kurtzke, Anne Heltberg, and Kay Hyllested in the Faroe Islands, June 1991.[6]

extremely prevalent (153 cases per 100 000 population), and in the Faroe Islands, where, though still high, it was considerably lower (54 cases per 100 000 population), with different patient age groups.[38,39]

From the early 1970s, John Kurtzke joined in the study of cases from the Faroe Islands, alongside Kay Hyllested and Anne Heltberg (Figure 4).[6] Between 1974 and 1999, he visited the islands nearly every summer, and at least one member of the group examined each inhabitant with suspected MS. To identify any possible known cases since 1900, they reviewed every imaginable source of medical information, finding no evidence of the disease prior to July 1943, the time of onset of the first case.[40,41] The first article of the series appeared in 1979,[42] and was followed by another six numbered publications and a vigorous defence of their data in 1988,[43] with a final summary in 2001.[44]

Four MS epidemic processes occurred among the Faroese population. Symptom onset in the first patient occurred in July 1943, marking the beginning of an epidemic of 21 cases among the Islands' population of 26 000. The disease exploded in the form of a type 1 epidemic, with a peak incidence of 10 cases per 100 000 population in 1945 and 1946, simultaneously in very separate populations on the islands. This first episode was followed by three successive type 2 epidemics, with 10, 10, and 13 cases, respectively. Age at exposure was 11-45 years, the patients' ages in 1941. Type 1 epidemics occur in a susceptible population exposed for the first time to a virulent infectious agent, whereas type 2 epidemics occur in populations in which the agent is already established. In type 1 epidemics, the ages of clinically affected patients define the age range of susceptibility to the infection.[44]

The authors attributed the first epidemic to the occupation of the islands by British troops for five years during the Second World War (April 1940-September 1945); the soldiers would have introduced a specific, persistent, probably asymptomatic infection that the authors name the primary multiple sclerosis affection (PMSA), which took two years to be transmitted to the native population, with person-to-person transmission (Figure 5).[6] A small percentage of individuals with PMSA infection would develop clinical MS years later. The creation of models of PMSA transmission through successive cohorts fit the data for the second and third epidemics, and predicted a fourth, with peaks at 13-year intervals. According to this hypothesis, the agent was transmissible, but clinical MS was not.[44] Patients in the successive epidemics lived mainly in the same cities as those in the first epidemic; the British soldiers had been stationed in the same places. Although the entirety of native Faroese population was at risk of PMSA, the age interval of those who acquired the disease was limited to the ages of greatest hormonal activity, a characteristic feature of susceptibility to the disease. The first epidemic was marked by a shorter incubation period and greater severity than that observed in endemic areas.[6,40,45]

In 2010, they studied the Danish records of all notifiable diseases in the Faroe Islands for the period 1900-1977, with a particular focus on identifying any excess during the Second World War. They concluded that the main candidate for PMSA was acute infectious gastroenteritis with faecal-oral transmission, which affected people of all ages and persisted throughout the conflict.[6,46] Until the end of his life, Kurtzke defended the hypothesis that PMSA may be a neurotropic enterovirus.[47] In the 1950s and 1960s, epidemiological similarities with poliomyelitis, caused by an enterovirus, were observed; however, Kurtzke considered these to be inconsistent.[6,48,49] Regarding the Epstein-Barr virus, he subsequently accepted its role as a trigger, but not a cause, of MS symptoms.[46]

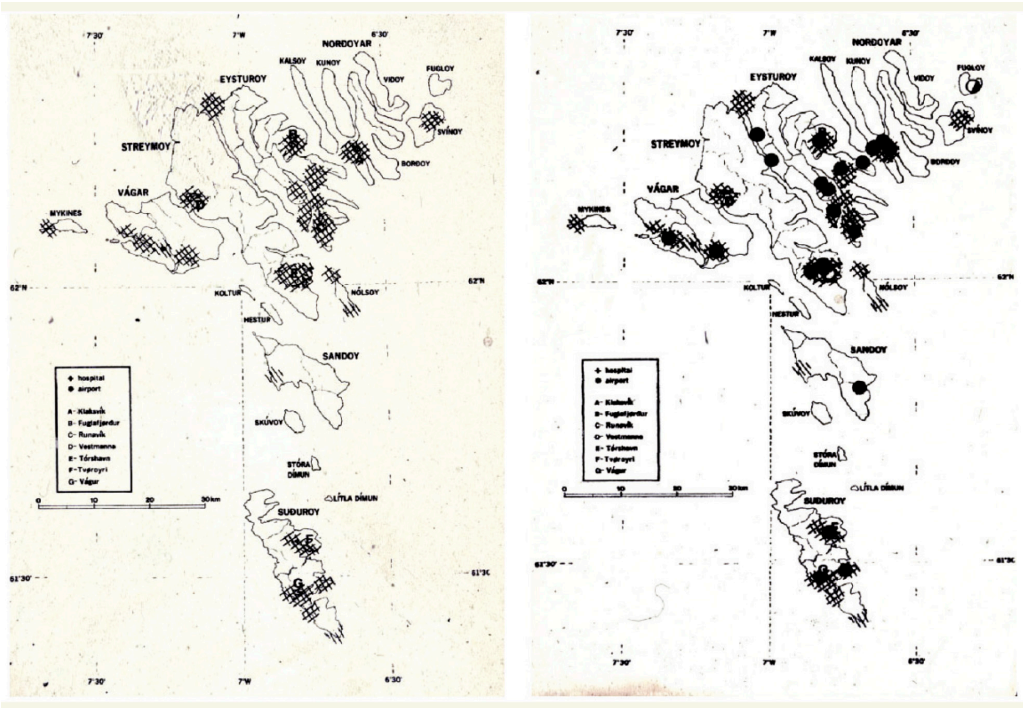

Figure 5. Multiple sclerosis in the Faroe Islands. Left: British military camps during the Second World War, cross-hatched for sites in Faroese villages, and diagonal-lined for sites outside villages. Right: places of residence of Faroese patients with multiple sclerosis (black points) are superimposed on the map of British troop encampments.[6]

Geographical distribution of multiple sclerosis

John Kurtzke was the most thorough researcher of the geographical distribution patterns of MS. From 1957 to 1963, he conducted a detailed review of all the prevalence studies he was able to find. At the time, good registries were available in the Nordic countries and Switzerland, where there were contiguous areas with high concentrations of cases. Above all, there was an area of high concentration of MS cases, which Kurtzke termed the "Fennoscandian focus." The geographic centre of this space seemed to be in the inland lakes area of central and southern Sweden, extending across the Gulf of Bothnia to south-western Finland, and west and south to Norway and Denmark.[6,49]

The first dissemination of MS in Europe may have been related to the Thirty Years' War of the 17th century, when Swedish troops occupied parts of Germany, north-west Switzerland, and north-east France. For a long time, it was believed that the existence of a north-south gradient may have reflected this southward propagation from Sweden. In the mid-19th century, there was considerable emigration from Sweden and Norway to the United States, and particularly the states of Minnesota and Wisconsin, the main focus of high MS prevalence at the time of the First World War; from there, it may have extended east and north along the Atlantic coast.[6]

The worldwide geographical distribution of MS was divided into three zones of high, medium, and low frequency. This distribution changed over the course of the 20th century, with slow growth from the apparently Scandinavian origin of the disease. In the 1960s and 1970s, prevalence was high, above 30 cases per 100 000 population, in northern and central Europe, southern Canada and the northern United States, south-eastern Australia, and New Zealand; medium rates (5-29 cases

per 100 000 population) were observed in southern European, North Africa, and the southern United States, and low rates in Asia and most of Africa and Latin America. From the early 21st century, high rates were observed in the majority of western European countries, Israel, Canada, the United States (with a reduction in the north-south gradient in the country), south-eastern Australia, New Zealand, and north-eastern Russia and the Russian Far East, and medium rates in North Africa, South Africa, Latin America, and Japan (Figure 6).[6,40,50,51]

Immigration. The examples of South Africa and France

Research into immigration from areas with different MS risk levels supports the idea that the disease is ordinarily acquired in early adolescence, when the immune system is not fully developed, with a long latency between acquisition of the disease and onset of symptoms; susceptibility extends to approximately 45 years of age.[3,51]

In 1971, Kurtzke and the British epidemiologist Geoffrey Dean (1918-2009) studied the case of European migrants to South Africa. A national MS prevalence study based on 1960 census data found a much higher rate of MS among migrants born in northern and central Europe compared to English-speaking white South Africans and other ethnicities. With regard to the potential effect of age at immigration, they noted that the risk of MS was less than three times that expected among those who emigrated before the age of 15-16 years. This was further evidence that MS is an acquired, exogenous disease of unclear nature. At that time, before his studies of the Faroe Islands, Kurtzke believed that the disease was acquired in endemic areas such as northern Europe around the age of 15 years, and remained latent until the number of lesions was sufficient to provoke symptoms. This would explain why immigrants over 15 years of age presented the prevalence rate of their region of origin, as the place of MS acquisition, whereas those migrating at a younger age showed prevalence matching the current place of residence.[48]

Kurtzke, Wallin, and Nicole Delasnerie-Lauprêtre studied MS in the so-called *pieds-noirs*, North Africans who emigrated to metropolitan France during the 1950s and 1960s. Migrants with disease onset after immigration had a prevalence rate 1.5 times greater than the overall rate for France. These higher rates than the native population are typical after a first exposure to an infectious disease. The remaining immigrants with MS, who had displayed the disease in North Africa, presented the mean prevalence rate of their place of birth. Migrants whose symptoms first manifested in France showed a minimum period of three years (mean, 13) before symptom onset, counting from the age of 11 years or the age of immigration, if they were older. This also suggests that, as in other studies, susceptibility to MS generally occurs between the ages of 11 and 45 years.[6,52]

Aetiology of multiple sclerosis

In 2017, after the death of John Kurtzke, an article was published that he had written with Mitchell Wallin on the contribution of genetics and the environment (nature vs nurture) to the aetiology of MS. The authors agreed that both factors played a role, but concluded that environmental factors were overwhelmingly the most influential. The initial geographic variations in Europe, the United States, and Australia, with subsequent diffusion from high-risk to low-risk areas over one or two generations, indicated too fast a rate of dissemination for genetic influences, latitude, or sun exposure and vitamin D to be the decisive aetiological factor. Furthermore, studies of migration and epidemics also supported the environmental hypothesis.[51]

They suggested that, though the disease had previously presented a preference for white men, it now presented a female predominance and the burden of other races was increasing. The authors recognised that Epstein-Barr virus infection, low vitamin D levels, and smoking had been demonstrated to be risk factors for the development of MS. Despite the discovery of more than 50 genetic loci for the disease by the time, they believed that these had a minimal contribution to overall risk, with the HLA loci being the most significant. They were aware of the disease's low prevalence in some ethnic groups and, based on studies of monozygotic twins, considered that the genetic loading for MS was 30% at most.[51]

Kurtzke defined MS as a primarily autoimmune disease triggered by undefined environmental factors in a predisposed host. After his studies in the Faroe Islands, he ventured to suggest the existence of a specific, generalised, and unidentified infection, which he named PMSA. It was a persistent infection with person-to-person transmission but which only led to clinical MS in a small percentage of individuals; therefore, development of the disease required prolonged exposure beginning between adolescence and the age of 45 years.[40] Until

Figure 6. Worldwide distribution of multiple sclerosis in 2003. Black: high-prevalence areas (> 30 cases per 100 000 population). Dotted: medium-prevalence areas (5-29 cases per 100 000 population). Diagonal lines: low-prevalence areas (< 5 cases per 100 000 population).[51]

two weeks before his death, at a National Institutes of Health symposium, he argued that the epidemiological evidence suggested that the disease may be explained by an infectious agent transmitted through the intestinal tract,[53,54] possibly a neurotropic enterovirus (Figure 7).[47,53]

Controversies about the Expanded Disability Status Scale

Over the years, several voices have signalled weaknesses in the EDSS; nonetheless, the latest version, published in 1983, remains unaltered today.[9] However, there has been controversy around Neurostatus, an evaluation system used in clinical trials whose most visible author is the Swiss neurologist Ludwig Kappos, who integrated the EDSS into his scale without the express authorisation of John Kurtzke. According to Kappos, Neurostatus originated in 1982, during the design of a prospective clinical trial conducted in Germany, comparing the effect of ciclosporin A and azathioprine in the treatment of MS. In that study, they used the EDSS, generously granted by Kurtzke a year before its official publication. The findings of the study were negative, but the authors used the follow-up data from over 2000 patients to modify the EDSS and its functional systems with a view to improving its reliability.[17,55,56] Kurtzke again defended his 1989 statement that the EDSS was like democracy, which had been called the worst form of government, except for all the others. He personally would only modify it to return to the old DSS.[9] Kurtzke's two scales, the DSS and EDSS, which he developed alone, were a product of his work at the VA, and have always belonged to the public domain, with no restrictions on their use.[19]

Epidemiology of other neurological diseases

From the 1950s, John Kurtzke defended the need for neurologists to have basic understanding of epidemiology and to perform population studies applied to clinical practice. He promoted the creation and development of a new discipline, neuroepidemiology, which used the common epidemiological research methods with characteristic aspects of neurological diseases, including conditions that are difficult to register and classify, as no

Figure 7. John Kurtzke with young attendees at a National Institutes of Health symposium in Washington, DC, November 2015, three weeks before his death.[53]

specific tests are available for their diagnosis.[3] In 1965, Kurtzke was one of the three founders of the Society of Neurological Epidemiology, alongside Leonard Kurland and Milton Alter (1929-2016). In 1967, they began using the term neuroepidemiology, and the society became a section of the American Academy of Neurology. In 1982, they founded the journal *Neuroepidemiology*, with Bruce Shoenberg (1942-1987) as the first editor.[57]

John Kurtzke's work was not limited to MS; rather, he also studied the epidemiology of other neurological diseases and syndromes including amyotrophic lateral sclerosis,[58,59] myasthenia gravis,[60] epilepsy,[61] Parkinson's disease,[62,63] brain tumours,[64] congenital malformations of the nervous system,[65] and spinal cord trauma.[66] He also participated in epidemiological studies and clinical trials on cerebrovascular disease[67-69] and Guillain-Barré syndrome.[70,71]

Furthermore, he was an experienced general neurologist and an extraordinary observer of neurological signs, for which he promoted a multidisciplinary approach.[54] On the latter subject, he spoke in Washington of his clinical collaboration with the neurologist Elmo Masucci (1920-1995).[1] He also concerned himself with care quality and the neurological training of medical professionals.[1,72-74]

Scientific output and acknowledgements

John Kurtzke remained active in academia until the last days of his life. Over a career of more than 60 years, he contributed to some 550 publications.[4-10] A search of the PubMed database in November 2024 returned 224 medical articles listing Kurtzke as the author or co-author.

He received numerous acknowledgements, including the John Dystel Prize for Multiple Sclerosis Research, which he was awarded by the National Multiple Sclerosis Society and the American Academy of Neurology in 1997, and the Charcot Award of the MS International Federation in 1999, as well as various distinctions from the VA and the US Navy. He was a guest lecturer at universities all over the world. He received an honorary degree from the University of Ferrara, in Italy, and was an honorary member of the neurological societies of Denmark, France, and Germany.[3-10]

Family life

In 1950, John Kurtzke married Margaret "Peggy" Nevin (1926-2023), a chemist who worked at Pfizer Laboratories in the research and development of such drugs as bacitracin[75] (Figure 1).[4] They had eight children (five girls and three boys), 21 grandchildren, and nine great-grandchildren. From 1963, the family lived in Falls Church, Virginia, near Washington, DC. Throughout his life, Kurtzke was a practising Catholic, dedicating his life to his scientific and professional career and to his large family. He continued working until the last day of his life, dying due to stroke on 1 December 2015. He was survived by his wife and six of his children.[4] His eldest son, John Francis Kurtzke Jr. (1951-2013), was a priest and mathematics lecturer.[76]

Conclusions

John Kurtzke was a distinguished figure in international neurology for several decades. In addition to being an excellent clinician, he was one of the founders of modern neuroepidemiology, with particular focus on the study of MS.

Based on his studies of large cohorts of war veterans, he described the natural history of the disease and created the EDSS, a scale for evaluating the clinical stage of MS which continues to be a valuable tool at the international level, four decades after it was published.

He proposed that the worldwide geographical distribution of MS be classified into three zones, with higher prevalence in areas further from the equator. After his studies on MS epidemics and immigration, he argued that the disease is mainly explained by environmental factors, with genetics playing a minor role, and proposed an infectious aetiology, probably involving a viral infection acquired at early stages after adolescence.

Our understanding of MS has evolved rapidly, and some of Kurtzke's opinions are now outdated, but the imprint he left on our knowledge of the disease is indelible.

Conflicts of interest and funding

This is an original article. This study was presented at the 77th Annual Meeting of the Spanish Society of Neurology. It has not been submitted to any other journal. The author has received no public or private funding for this study.

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