Annals of Epidemiology 37 (2019) 1–3

Contents lists available at ScienceDirect

Annals of Epidemiology

Commentary

Historical vignette: Leonard T. Kurland, FACE (1921–2001), the rise of neuroepidemiology, and the Rochester Epidemiology Project

David E. Lilienfeld, MD, MPH, MSEngin, MBA, FACE *, Walter A. Rocca, MD, MPH

Division of Epidemiology and the Department of Neurology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN

ARTICLE INFO

Article history:
Received 28 November 2018
Accepted 31 July 2019
Available online 2 August 2019

Keywords:
History
Rochester Epidemiology Project
Kurland
Neuroepidemiology
Amyotrophic lateral sclerosis
Multiple sclerosis

ABSTRACT

The creation of the field of neuroepidemiology was one of the two principal professional achievements of the American College of Epidemiology Fellow Leonard T. Kurland (1921–2001), the other being the establishment of the Rochester Project. In the former, Kurland established the role of the neuroepidemiologists in the development of the corpus of knowledge needed to control and prevent the occurrence of neurological conditions. Two examples of his endeavors in this regard were his work on the Guamanian focus of neurodegenerative diseases and his seminal investigations into the epidemiology of multiple sclerosis. He was also instrumental in the development of the Rochester, Minnesota community as a population laboratory within which epidemiologic investigations could be mounted. This pioneering achievement created a resource used by many generations of epidemiologists and clinicians to examine health and disease in the population.

The field of neuroepidemiology did not exist as such before Leonard T. Kurland began his career. Within a decade, he had established that area of scientific inquiry. This article is not only a tribute to the man but also to an exemplar from which the current generation of epidemiologists in training might benefit as they begin their professional careers (whether their interest is neurological disease or otherwise).

Leonard Terry Kurland was born on December 24, 1921. Raised in Baltimore, he attended Johns Hopkins University as an undergraduate and, subsequently, the University of Maryland School of Medicine. During both college and medical school, Kurland supported himself driving a taxi at night (as with many other details of this biography, Kurland personally communicated this information to the authors). After an internship at University of Maryland Hospital, Kurland completed the first year of a residency working in a tuberculosis sanitarium in suburban Baltimore in 1945.

In 1946, in the course of fulfilling his military obligations, Kurland entered the United States Public Health Service (USPHS) and was assigned to the Massachusetts state health department. During his time there, Kurland completed the MPH program in epidemiology at Harvard University (cum laude). He was then assigned to the newly formed National Institute of Mental Health. Although there had been earlier epidemiologic inquiries into individual neurological disorders, these conditions had not been subjected to the systematic application of epidemiologic methods to gain knowledge about their frequency and causes. Kurland immediately began to remedy that situation.

At the National Institute of Mental Health, Kurland began two major investigations: one into the epidemiology of multiple sclerosis and the other focused on amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease). Multiple sclerosis became the subject of his thesis while studying for his DrPH in epidemiology at the Johns Hopkins University School of Hygiene and Public Health, even as ALS developed into an ongoing interest during the remainder of his career. In addition, he conducted studies on epilepsy, cerebral palsy, neoplasms of the nervous system, myasthenia gravis, Parkinson's disease, developmental disorders of the nervous system, Minamata disease, dementia, glaucome, and uveitis, among others. His demonstration that the association between exposure to the swine flu vaccine and subsequent Guillain-Barre syndrome was smaller than it was initially estimated using evidence from series of referral patients exemplifies the role of the epidemiologist informing public health policy. Of particular note, though, is his research on ALS and on multiple sclerosis.

Amyotrophic lateral sclerosis

At the time Kurland began his work in multiple sclerosis, he became aware of a focus of ALS on the island of Guam in the western Pacific. Soon after World War II, a U.S. Navy physician (Harry M. Zimmerman, a Navy physician posted to Guam) reported his observation of a high number of autopsies conducted on members of the

* Corresponding author. Department of Health Sciences Research, Division of Epidemiology and the Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Tel.: +1 507 284 3568; fax: +1 507 284 1516.
E-mail address: lilienfeld2015@gmail.com (D.E. Lilienfeld).

https://doi.org/10.1016/j.annepidem.2019.07.017
1047-2797/

native Chamorro population with the finding of ALS [1,2]. In 1953, the Navy assigned Donald Mulder, a neurologist from the Mayo Clinic recalled to duty, and Kurland, still a USPHS officer (during periods of military conflicts—such as the Korean War—the USPHS operates as a branch of the Navy), to investigate further [3]. Thus would begin Kurland's 4 decades plus association with the Mayo Clinic.

Immediately after World War 2 and for some years thereafter, travel to and from Guam was controlled by the Navy; the island thereby provided a stable and closed population laboratory. Mulder and Kurland (Fig. 1) examined 40 cases of ALS, conducted a prevalence survey, and reviewed autopsy records [4].

They concluded that the cases were indeed ALS, and that the disease was common on Guam in contrast to the rarity reported in the medical literature. They also established that another neurodegenerative disease, Parkinsonism-dementia complex (a unique form of parkinsonism associated with a progressive dementia), was prevalent on the island [5]. The Chamorro natives referred to both conditions as "lytico-bodig," suggesting that each was part of a common pathophysiological process; this idea was confirmed during neuropathological investigations revealing a considerable number of neurofibrillary tangles in the brain in both conditions.

When Kurland moved to the National Institute of Neurological Diseases and Blindness (NINDB) in 1955 to found the Neuroepidemiology Branch, he continued his research activities on Guam [6].

During the next 3 decades, the NINDB would support an ongoing study of this neurodegenerative diseases focus, led first by Kurland and then from the mid-1960s onward, by Nobel laureate D. Carleton Gadjusek [7]. The hypotheses explored included the consumption of cycads, a staple of the Chamorro diet; a "slow" virus akin to that causing kuru; one or more genetic mutations; or combinations of two or more of these factors [8]. Although these hypotheses were subjected to considerable testing, none panned out. The search for the cause(s) of this focus of neurodegenerative disease remains elusive.

In the early 1980s, Bruce Schoenberg, one of Kurland's mentees and the then Chief of the Neuroepidemiology Branch at the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS, later renamed as the National Institute of Neurological Diseases and Stroke: NINDS), thought the Guam focus should be reinvestigated to see if the incidence for either of the two diseases had increased, decreased, or remained the same; he would then formulate testable hypotheses based on the results of that investigation. Building on his experience with dementia and parkinsonism case finding by door-to-door survey in the Copiah County Study in Mississippi, Schoenberg undertook a pilot survey on Guam (Kurland served as an advisor on the study and one of us [W.A.R.] assisted with the development of a computer database to store the clinical characteristics of the incident cases) [9]. Unfortunately, soon after completing the pilot study, Schoenberg died.

Fig. 1. Leonard T. Kurland (left) and Donald Mulder on Guam, circa 1953. Leonard T. Kurland, 1921–2001.

With Schoenberg's passing, in 1987, Kurland returned to working on the Guam focus, this time supported by the National Institute on Aging. He assembled a research team (including one of us [D.E.L.]) and these researchers tested several etiological hypotheses (genetic, viral, dietary) both epidemiologically and with laboratory investigations [10]. One of the team's findings was the suggestion of an olfactory deficit in the early stages of both parkinsonism and dementia [11]. They were unable to establish any evidence for the early hypothesis of cycad nuts as a source of a neurotoxin leading to these diseases. Although much knowledge was gleaned in these studies, an explanation for the Guam focus remains an enigma.

Multiple sclerosis

At the time Kurland began his studies on multiple sclerosis in the late 1940s, the etiology of the disease was little understood. Kurland examined the demographic characteristics and geographical distributions of multiple sclerosis around the world such as the increase in occurrence with ascending latitude (i.e., a north-south gradient in the risk of the disease) [12]. The etiological hypotheses he examined during his subsequent career included both viruses and bacteria, as well as nonmicrobial exposures such as trauma and geographical latitude. This work was recognized with the awarding to Kurland of the Charcot Award by the International Federation of the Multiple Sclerosis Societies.

Kurland's activities regarding the etiology of multiple sclerosis extended beyond conducting epidemiologic studies. Not only did he periodically critically review and summarize available literature on the epidemiology of the disease, but Kurland also synthesized nonepidemiologic findings into the totality of information about the disease and in doing so, explored ideas meriting further investigation [13]. Although the etiology of the disease is still unknown, the process of subjecting it to epidemiologic scrutiny began with Kurland's first studies in the late 1940s.

The Mayo Clinic

Building on his association with Mulder on Guam, Kurland completed additional training in neurology at Mayo Clinic. During this training, he discovered a unique opportunity for population-based research on neurological disease in Rochester, Minnesota (where Mayo is located), building on the unique medical records-linkage system at Mayo [14]. Thus, when in 1964, the chief of the biostatistics at Mayo, Joseph Berkson, retired, Kurland debunked from the NINDB to succeed Berkson, and he established an epidemiology program at Mayo. The Clinic had developed the Unit Medical Record system as a means of addressing the fragmentation of information among physicians attending a given patient [14]. With the Unit Medical Record, it became possible to follow-up patients throughout their lifetime with regard to the medical care they received from the Mayo Clinic and to ascertain the diseases that they developed. That capability made possible the Rochester Epidemiology Project, the creation of a population laboratory in Olmstead County, Minnesota [15].

The Rochester Epidemiology Project

Enticed by the potential of a system able to produce population incidence rates on multiple sclerosis, Kurland joined the Mayo Clinic in 1964 as chair of the Department of Medical Statistics and Epidemiology (now the Department of Health Sciences Research) and

director of the Mayo's medical record system. One of Kurland's first tasks was to develop an epidemiologic database that not only accessed the Mayo Clinic's records but also those of the Olmsted Medical Group (now known as the Olmsted Medical Center), a primary care-focused medical practice begun in 1949 and independent of the Clinic, as well as several general practitioners and other institutions in the region. In addition, the system was extended from the central city of Rochester to include all 100,000 or so residents of Olmsted County, Minnesota. Thus, the Rochester Epidemiology Project (REP) was born in 1966. It afforded a comprehensive view of the health of the population of Olmsted County for over 50 years. This work was made possible by grants from the National Institutes of Health, which has funded the REP continuously since 1966. As further evidence of Kurland's vision, it should be noted that the initial grant application included a genetic epidemiology component!

The power of the REP can be seen when one considers its unique ability not only to support epidemiologic studies of current Olmsted County residents but also of secular trends in disease incidence over a sustained period (generally, since 1966; before then, the data, while available, are considered less complete). Few databases exist elsewhere in the United States, if not the world, with data of similar richness giving the REP access to the complete (inpatient and outpatient) medical records of community residents. The passage of time merely increases the value of the database, as more person-years of experience are accrued within it. In that respect, it should not be surprising that the database has supported research resulting in more than 2800 publications (in approximately 500 of which Kurland was directly involved) on a host of acute and chronic diseases and diverse diagnostic tests and disease treatments. One of us (W.A.R.) has been the Co-Principal Investigator of the REP for more than a decade (since 2006).

Discussion

Leonard T. Kurland enjoyed a two-phase career as an epidemiologist: the establishment of neuroepidemiology as a specialty within both the epidemiology and the neurology communities, and the creation of the REP. Each of these major contributions was seminal in and of itself. Together, however, they underscore the key role that Kurland had in the construction of modern epidemiology during the middle of the 20th century. Although only his multiple sclerosis and Guam-focused work was discussed in detail previously, Kurland's contributions to neuroepidemiology include many other important studies (e.g., the characterization of Minamata disease—identifying methyl mercury intoxication as its cause; the establishment of one of the first population-based Alzheimer's disease registries; extensive research on the incidence, prevalence, and risk factors for epilepsy and convulsive disorder; and clarification of the association between the swine flu vaccine and Guillain-Barre' syndrome). He also trained many members of the next generation of neuroepidemiologists, including, for instance, Milton Alter and Bruce Schoenberg, among others [16–20]. Kurland's students include many of the leaders among today's neuroepidemiologists, not to mention investigators now active in other areas, such as cardiovascular epidemiology and the epidemiology of rheumatologic and auto-immune diseases. (Kurland was active in many epidemiologic studies outside of neurological diseases, such as a case-control study of Rauwolfia derivatives and breast cancer [21]. In doing so, he utilized the full armamentarium available to the epidemiologist, from population surveys to observational studies.)

Kurland was active in myriad other ways in the epidemiology community, for example, serving as President of the American Epidemiological Society. He was a Fellow of the American College of Epidemiology and a member of the United States Armed Forces Epidemiology Board, the Scientific Advisory Board of the U.S. Air Force, and the Congressional Office of Technical Assessment (providing the latter two agencies with an epidemiologic perspective key to their work). Of particular note is his service on the organizing Board of Directors of the American College of Epidemiology. Kurland was also chair of the Scientific Advisory Committee on Environmental Hazards (examining, for instance, Agent Orange and nuclear radiation) for the Veterans Administration, and participated in numerous review panels and professional organization committees. His work in the establishment of medical genetics as an area of epidemiologic activity is also notable.

Acknowledgment

The content is solely the responsibility of the authors and does not represent the views (official or otherwise) of the National Institutes of Health or any other organization.

Supported by National Institute on Aging grant R01-AG034676.

References

[1] Cmdr Lt, Zimmerman HM. Progress Report of Work in the Laboratory of Pathology During May 1945". In: Letter. 1. 1945.
[2] Kurland LT, Mulder DW. Epidemiologic investigations of amyotrophic lateral sclerosis. 1. Preliminary report on geographic distribution, with special reference to the Mariana Islands, including clinical and pathologic observations. Neurology 1954;4:365–78.
[3] Whisnant JP, Mulder DW. Kurland LT: 1921-2001. Ann Neurol 2002;51(5):663.
[4] Mulder DW, Kurland LT, Iriarte LL. Neurologic diseases on the island of Guam. US Armed Forces Med J 1954;5(12):1724–39.
[5] Reed D, Plato C, Elizan T, Kurland LT. The amyotrophic lateral sclerosis/parkinsonism-dementia complex: a ten-year follow-up on Guam. I Epidemiologic studies. Am J Epidemiol 1966;83(1):54–73.
[6] Source is Robert Kurland, Rochester, MN.
[7] Gibbs Jr CJ, Gadjusek DC. Amyotrphic lateral sclerosis-parkinsonism-dementia complex on Guam: A review and summary of attempts to demonstrate infection as the aetiology. J Clin Pathol Suppl (R Coll Pathol) 1972;6:132–40.
[8] Anderson W. From a Plague an Epidemic Comes. In: Ann Herring D, Swedlund AC, editors. Plagues and Epidemics: Infected Spaces Past and Present. London, UK: Berg; 2010. p. 251–67.
[9] Lavine L, Steele JC, Wolfe N, Calne DB, O'Brien PC, Williams DB, et al. Amyotrophic lateral sclerosis/parkinsonism-dementia complex in southern Guam: is it disappearing? Adv Neurol 1991;56:271–85.
[10] Waring SC, Esteban-Santillan C, Reed DM, Craig UK, Labarthe DR, Petersen RC, et al. Incidence of amyotrophic lateral sclerosis and of the parkinsonism-dementia complex of Guam, 1950-1989. Neuroepidemiology 2004;23(4):192–200.
[11] Doty RL, Perl DP, Steele JC, Chen KM, Pierce Jr JD, Reyes P, et al. Olfactory dysfunction in three neurodegenerative diseases. Geriatrics 1991;46(Suppl 1):47–51.
[12] Okinaka S, Reese HH, Katsuki S, Ueki K, Kuroiwa Y, Araki S, et al. The prevalence of multiple sclerosis and other neurological diseases in Japan. Acta Neurol Scand 1996;42:68–76.
[13] Rowland LP. NINDS at 50: Celebrating 50 Years of Brain Research. Bethesda, Maryland: National Institutes of Health; 2001. Department of Health and Human Services, Public Health Service.
[14] Kurland LT, Molgaard CA. The patient record in epidemiology. Sci Am 1981;245(4):54–63.
[15] Rocca WA, Yawn BP, St Stauver IL, Grossardt BR, Melton 3rd LJ. History of the Rochester Epidemiology Project: Half a century of medical records linkage in a US population. Mayo Clin Proc 2012;87(12):1202–13.
[16] Kurland LT, Faro SN, Siedler H. Minamata disease. The outbreak of a neurologic disorder in Minamata, Japan and its relationship to the ingestion of seafood contaminated by mercuric compounds. World Neurol 1960;1:370–95.
[17] Petersen RC, Kokmen E, Tangalos E, Ivnik RJ, Kurland LT. Mayo Clinic Alzheimer's Disease Patient Registry. Aging (Milano) 1990;2(4):408–15.
[18] Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. Epilepsia 1993;34(3):453–68.
[19] Safranek TI, Lawrence DN, Kurland LT, Culver DH, Wiederholt WC, Hayner NS, et al. Reassessment of the association between Guillain-Barré syndrome and receipt of swine influenza vaccine in 1976-1977: Results of a two-state study. Expert Neurology Group. Am J Epidemiol 1991;133(9):940–51.
[20] Rocca WA. Memoriam. Leonard T. Kurland (1991-2001). Neuroepidemiology 2002;21:262–4.
[21] O'Fallon WM, Labarthe DR, Kurland LT. Rauwolfia derivatives and breast cancer. A case/control study in Olmsted County, Minnesota. Lancet 1975;2:292–6.