Slow Viruses and Chronic Disease: the Contribution of Epidemiology

"The death rate is a fact, anything beyond this is an inference." —William Farr, 1874

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The term "slow virus" came into use about 25 years ago; it was coined by Sigurdsson, who applied it to a disease of sheep in Iceland. Although it is not an altogether satisfactory term, it has come to be widely used for a group of viruses having two main characteristics: long persistence in the host and the ability to produce chronic disease after a very long incubation period. Those human diseases so far identified have involved degenerative changes in the central system for the most part, but the range of conditions for which they are responsible has not yet been defined. Because certain neoplastic diseases appear to be of this type, and because there is some evidence that multiple sclerosis may also be caused by a slow virus, their potential importance is great.

Dr. Neal Nathanson entered the field of epidemiology through service with the Epidemic Intelligence Service of the Center for Disease Control. In 1957 Dr. Nathanson moved to Johns Hopkins University and in 1963 to the Department of Epidemiology at Johns Hopkins School of Hygiene and Public Health, where we were associated for more than 15 years. He became a virologist and increasingly turned his attention to the field of slow viruses. Recently he went to the Medical School of the University of Pennsylvania as chairman of the Department of Microbiology.—PHILIP SARTWELL, MD

THE CONCEPT OF SLOW VIRUSES was originally enunciated by Bjorn Sigurdsson in 1954 (*1*), based on his studies of several transmissible chronic infections of sheep in Iceland. Since that time, a considerable number of naturally occurring persistent or slow infections of animals have been described and much data accumulated on the microbiology and pathogenesis of these models (*2–4*). This presentation will not deal with these aspects of slow infection but will focus on the specific contribution which epidemiology can make to this field.

A number of human diseases have been clearly associated with persistent virus infections, and some of the best documented examples are listed in table 1. These instances are now sufficiently numerous to make slow infections an important consideration in the field of chronic disease.

Epidemiology has made certain specific contributions; the most important of them follow:

1. *Etiology* is often the key initial question raised about chronic diseases whose nature is obscure. In most

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Table 1. Selected list of chronic or recurrent diseases caused by slow or persistent virus infections

Disease	Agent	Reference No.
Kuru	Spongiform	5
Creutzfeldt-Jacob disease	Spongiform	6
Progressive multifocal leukoencephalopathy	J. C. virus	7
Subacute sclerosing panencephalitis	Measles virus	8
Rubella syndrome (fetus)	Rubella virus	9
Cytomegalovirus disease (fetus)	Cytomegalovirus	10
Chronic hepatitis	Hepatitis B virus	11
Recurrent herpes simplex	Herpes simplex virus	12
Herpes zoster	Herpes zoster virus	13

instances, the association with a slow infection is suspected and demonstrated by the methods of microbiology and pathology. However, in some diseases, epidemiologic studies have confirmed the infectious hypothesis and have documented the mode of transmission.

2. *Pathogenesis* is the salient problem, once etiology has been established, and it is often more complex than the proof of etiology. Epidemiology is not usually relevant in this quest, although the identification of specific risk factors may provide clues about pathogenesis.

3. *Prevention* is a goal in the study of slow infections and epidemiology may suggest approaches to the interruption of transmission, even if the mechanism of the disease is incompletely understood. Likewise, epidemiologic studies are essential to evaluate immunization where this approach is feasible. If intervention is possible, imaginative epidemiology can utilize the opportunity to develop important new information about the biology of slow infections.

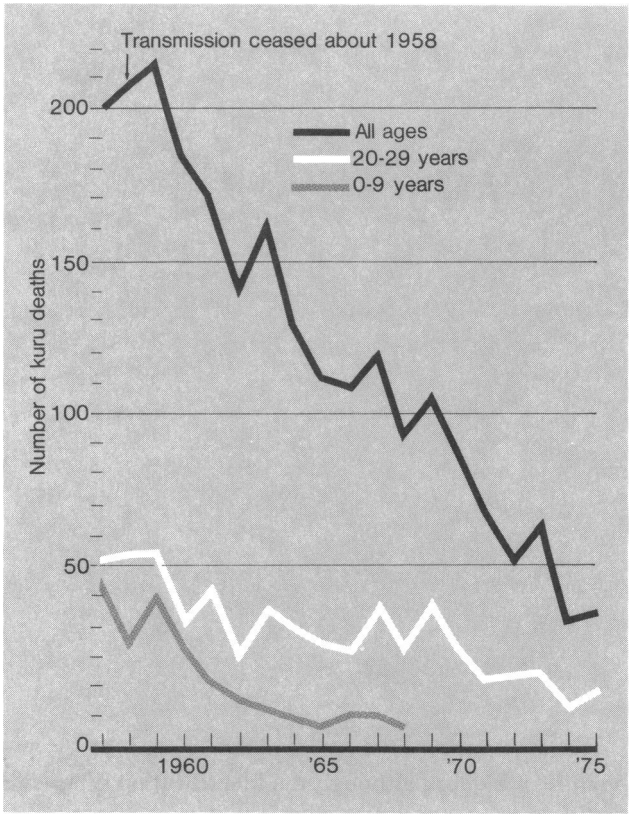
These points are illustrated in the next section, which cites specific examples from established slow or persistent infections of humans.

Chronic Diseases Caused by Slow Infections

Kuru. Kuru is a transmissible spongiform encephalopathy caused by an agent similar to that which causes scrapie in sheep. Kuru is limited to a small primitive population, the Fore linguistic group living in the eastern highlands of New Guinea, where it was a major cause of mortality.

In the original epidemiologic studies by Gajdusek (*5*) and colleagues, one striking observation was the age distribution which indicated that cases in childhood were equally divided among boys and girls, while

Figure 1. Deaths from kuru, 1957–75 among the Fore. Transmissions essentially ceased in 1957–58 due to proscription of the practice of ritual endo-cannibalism.



SOURCES: Nathanson and co-workers (*14*) after Gajdusek.

cases in adults were almost confined to females. Clearly, this peculiar distribution demanded explanation, and it appeared to offer a clue to causation. Initially, kuru was thought to be a genetic disease and complex genetic interpretations were devised to exploit the age and sex distribution. However, when the hypothesis of a transmissible agent was developed, the real meaning of the clue emerged. Transmission occurred during ritual endocannibalism, in which women and children consumed tissues of recently deceased relatives, accounting for the sparing of adult males.

A definitive test of this hypothesis was provided by the abolition of cannibalism, which was proscribed in 1956–58 by the Australian trust administrators. As figure 1 shows, during the 20 years after termination of cannibalism there was a remarkable linear decrease in annual kuru mortality. Not only did this intervention study confirm the method of transmission, but it also provided an estimate of the distribution of incubation periods of kuru. A crude reconstruction appears in figure 2, which suggests a mean of 7 years with a range of 2 to 20 years, assuming a log-normal distribution of incubation periods.

Thus, in kuru, epidemiologic studies have provided key evidence regarding etiology and pathogenesis.

Creutzfeldt-Jacob disease. The other transmissible spongiform encephalopathy of human beings is Creutzfeldt-Jacob disease. This rare disease occurs mainly as isolated sporadic cases. In one of the most complete ascertainment studies ever done, Brown and colleagues (*6,16*) estimated an annual incidence of 0.6 per million in France. Detailed investigation failed to reveal any direct contact between individual cases.

Since Creutzfeldt-Jacob disease is caused by an infectious spongiform agent similar in its properties to the agent of kuru, it seems likely that the disease is acquired by transmission. The alternative possible hypotheses concerning transmission of Creutzfeldt-Jacob infection follow:

1. Zoonosis: is scrapie transmitted by consumption of infected sheep?
2. Person-to-person: is the agent transmitted by persons who have inapparent infections?
3. Endogenous: is the disease initiated by activation of an endogenous agent?

Figure 2. Hypothetical estimate of the distribution of kuru incubation periods, based on data in figure 1, assuming a log-normal distribution after Sartwell (*15*)

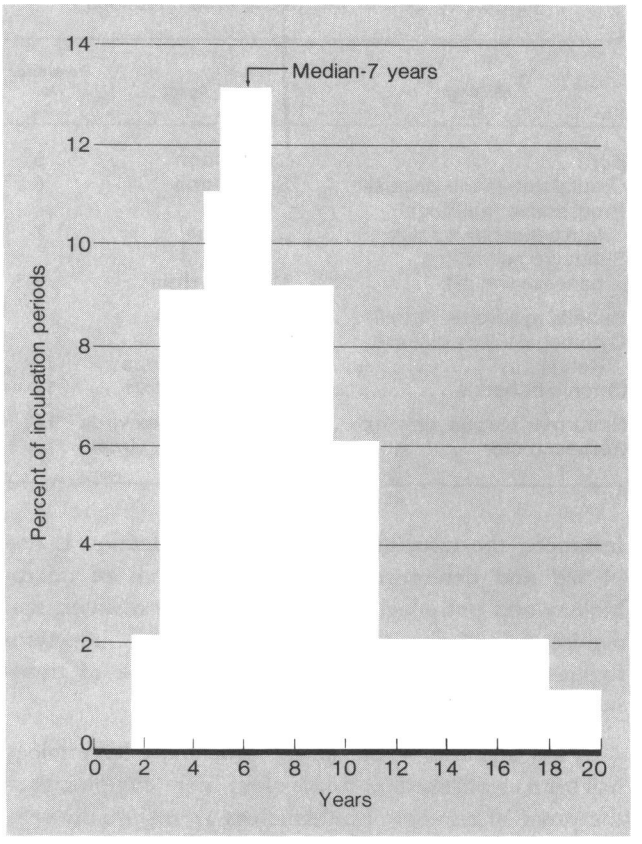


Table 2. Subacute sclerosing panencephalitis (SSPE) following natural measles or measles immunization, based on data of Modlin and co-workers (*18*) [1]

Primary measles infection	Populations (millions)	SSPE	Rate per million
Natural measles	29	168	5.8
Measles immunization .	60	34	0.6

[1] Cases of SSPE with onsets between 1960 and 1972, reported through 1974. Each case was assigned to a cohort, depending upon the year of measles case or measles immunization. Populations represent estimates for each year, 1960–72, of the number of cases of measles or numbers of susceptible children receiving initial measles immunization. Cohorts were then cumulated to provide data in this table.

Table 3. Selected list of chronic diseases which may be associated with a persistent or slow virus infection

Disease	Candidate agent	Reference No.
Multiple sclerosis	?	*20, 21*
Amyotrophic lateral sclerosis ..	?	*22*
Presenile dementia	? Spongiform	*5*
Glomerulonephritis	Hepatitis B virus, ? other virus	*11*
Hepatocellular carcinoma	Hepatitis B virus	*11*
Burkitt's lymphoma	Epstein-Barr virus	*23*
Nasopharyngeal carcinoma	Epstein-Barr virus	*24*

The apparent lack of contact between most cases suggests that Creutzfeldt-Jacob disease might be acquired as a zoonotic infection from consumption of infected lamb. However, the incidence of the disease in Australia is similar to that in other countries (*17*) although the sheep population is reported free of scrapie. Person-to-person transmission seems unlikely for two reasons: (*a*) even among the primitive Fore people with a very high incidence of kuru, direct transmission did not occur as evidenced by the consistent drop in incidence after cessation of ritual cannibalism and (*b*) the occurrence of subclinical infections (which could provide an unseen link between widely scattered overt cases) does not occur in most spongiform encephalopathies (*2*).

This reductionist argument forces consideration of the possibility that Creutzfeldt-Jacob disease is the consequence of activation of an endogenous agent. Although there is no evidence of such a phenomenon, it cannot be dismissed until an alternative explanation is found. At this time the transmission of Creutzfeldt-Jacob disease must be considered a major enigma and represents one of the more intriguing aspects of the biology of the spongiform agents.

Subacute sclerosing panencephalitis (SSPE). SSPE is a rare consequence of childhood measles (*8*). The link between this chronic fatal neurological disease and measles virus was suspected and proven by pathological and microbiological investigations. However, the pathogenesis remains mysterious, although epidemiology offers some clues. A systematic comparison of SSPE with uncomplicated measles (*8,18*) has shown that (*a*) patients with SSPE have often had their primary measles infections below 2 years, while the mean age for natural measles is about 6 years; (*b*) the interval from measles to onset of SSPE averages about 7 years; (*c*) males are affected at a rate which is more than two times that in females; (*d*) there are some geographic variations in incidence, the rates being higher in rural areas and in the southeastern part of the United States.

Although these facts do not explain the pathogenesis of SSPE, they do help to formulate certain questions and may provide clues. The following are remaining salient questions:

Does the viral genome persist during the 7-year incubation period, and if so, where?

Does age of primary measles influence the probability of CNS invasion or suggest that residual maternal antibody raises the risk of persistence?

How do the other risk factors influence the chance of viral persistence?

One related issue of great importance is the risk of SSPE in children immunized with measles vaccine. Since this vaccine is an attenuated variant which must replicate in order to immunize, it was far from clear whether it might carry a lesser or greater risk of SSPE. Similar conclusions were reached in both a retrospective case control study (*19*) and a prospective study. The prospective data are summarized in table 2, which indicates that the risk is about tenfold less following measles vaccine. Not only is this fortuitous result reassuring, but it also may provide one more clue about the pathogenesis of SSPE. Perhaps the (presumed) lesser virulence of the vaccine strain reduced the likelihood of neuroinvasion during primary infection. In any event, the vaccine is providing about 90 percent protection against this rare but fatal complication of measles infection.

Possible Viral Etiology of Multiple Sclerosis

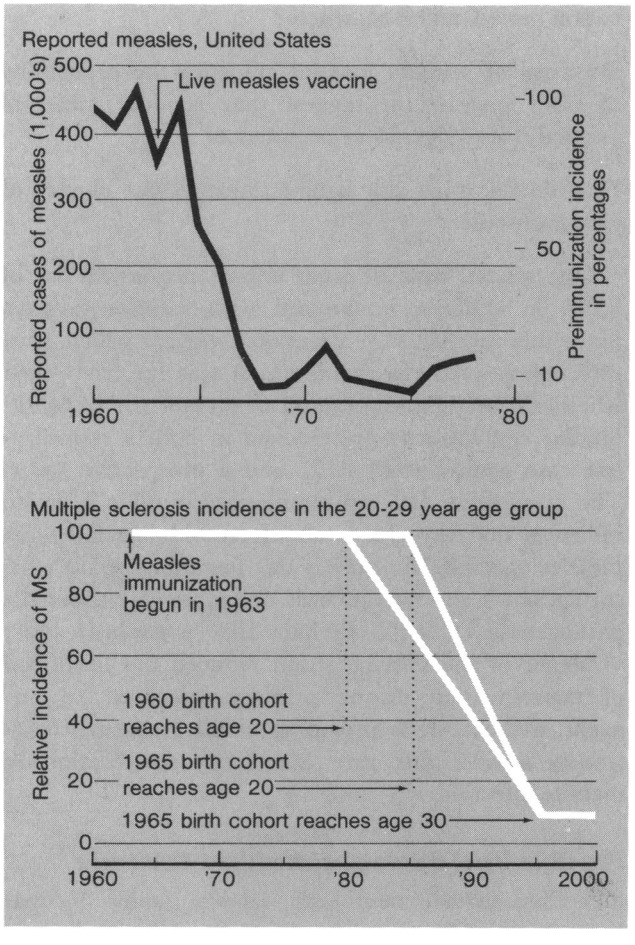
The four chronic neurologic diseases (table 1) that have recently been shown to be associated with slow or

persistent infection are all rare: kuru, Creutzfeldt-Jacob disease, subacute sclerosing panencephalitis, and progressive multifocal leukoencephalopathy. Slow infections are of potential relevance to public health because of their possible role in other chronic diseases of much greater prevalence. Selected examples are listed in table 3. At this time it appears likely that the three neoplasms in table 3 are caused by viruses, although co-factors may be essential for production of clinical tumors.

Among the neurological diseases listed in table 3, most attention has been devoted to multiple sclerosis (MS). The etiology of MS represents a major enigma in medicine, and it provides an excellent illustration of the uses of epidemiology in investigating a chronic disease which may be associated with slow infection.

The suspicion that multiple sclerosis may be caused by a virus infection rests most solidly upon naturally occurring animal diseases that are models of chronic neurological disease caused by a virus. Table 4 lists the salient clinical and pathological features of MS and indicates that all of these features are found in one or more of the four best-studied animal models (*25*). These models are visna, a retrovirus infection of sheep; distemper, a measles-like paramyxovirus infection of dogs; mouse hepatitis virus, a coronavirus infection of mice; and Theiler's virus, a picornavirus infection of mice.

Figure 3. Measles immunization with live virus vaccines only and reported measles, 1960–77, United States, after Center for Disease Control report (*27*). Lower panel shows the hypothetical effect of measles immunization on the incidence of multiple sclerosis in the age group 20–29 years, assuming that 90 percent of children born each year after 1965 were immunized with measles vaccine in infancy and that immunization provides complete protection against multiple sclerosis (*14*).



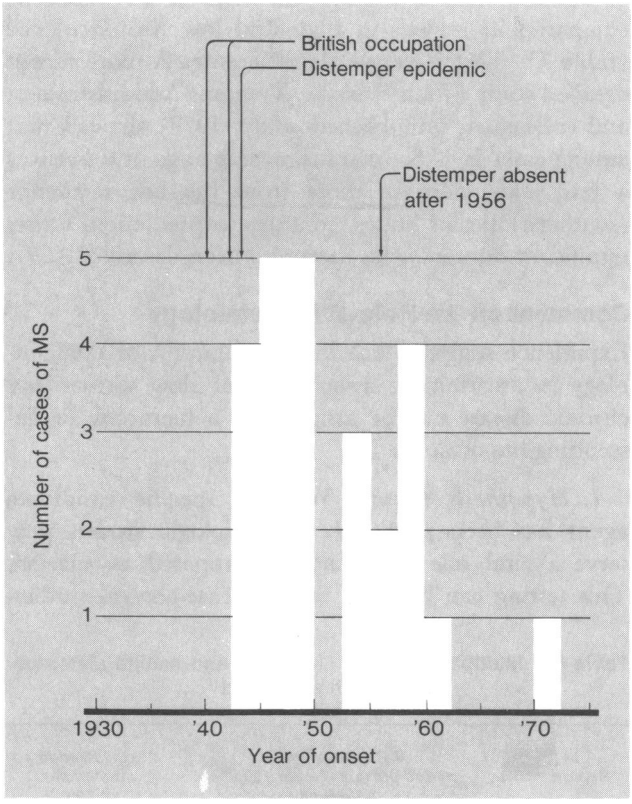
Epidemiologic data have been used to incriminate certain specific viruses as possibly associated with MS; once a "candidate" virus has been incriminated, epidemiology offers one approach to testing the putative association. Studies of measles and of distemper viruses illustrate this approach.

Measles. A possible association of measles with MS has been suggested repeatedly in the past 20 years (*20,21*), based on observations such as that persons with MS have slightly higher measles antibody titers than matched controls and that measles antibody is often found in the spinal fluid of those with MS.

Furthermore, epidemiologic studies have suggested an association. Analysis of measles and MS in Iceland (R. Tauxe, personal communication, 1979) is an interesting example. Since 1900 measles has occurred in intermittent epidemics in Iceland with almost total disappearance of the virus between outbreaks. Thus, different age cohorts of the Icelandic population have had measles at different ages, from birth to about 7 years. If these cohorts are grouped according to the age when they experienced measles and the subsequent incidence of MS calculated, there is an apparent sparing of the cohort born 1 year before epidemic measles (their rate is about half of that for other cohorts). Conversely, Alter and Cendrowski (*26*) found that persons with MS had had measles 2 or 3 years later than a group of matched controls.

The associations just cited can be regarded only as tenuous clues. The widespread use of measles vaccine, beginning in 1963 in the United States, offers a potential opportunity to make a definitive test of the possible relationship. The potential influence of immunization upon MS is diagramed in figure 3. Furthermore, the fact that epidemiologic studies, both case-control (*19*) and prospective (table 2), have shown that measles immunization has a dramatic effect upon SSPE, indicates that an effect upon MS is potentially demonstrable. Studies of this kind are now being proposed (R. Detels, personal communication, 1979) and even if the results are negative, they could at least serve to focus attention upon alternative agents.

Figure 4. Multiple sclerosis in the Faroe Islands by year of onset, showing the British occupation, 1940–43, and the introduction and disappearance of canine distemper



SOURCES: Nathanson and Miller (29) after Kurtzke and Hyllestad (30).

Table 4. Features of multiple sclerosis found in animal models of persistent central nervous system infection (4, 25)

Feature of multiple sclerosis	Frequency in animal models	Example	
		Virus or disease	Species
Long incubation	High	Distemper	Dog
Irregular progression ...	Low	Visna	Sheep
Focal central nervous system lesions	High	Mouse hepatitis	Mouse
Perivascular lesions	High	Theiler's virus	Mouse
Inflammation	High	Distemper	Dog
Primary demyelination ..	High	Mouse hepatitis	Mouse

Table 5. Hypothetical serologic profile for a multiple sclerosis "candidate" virus in the Faroe Islands for serums obtained in 1980

Cohort born	Percent of population with antibody	
	Candidate virus	Other virus
1910–19	70	70
1920–29	70	70
1930–39	70	70
1940–49	70	70
1950–59	50	60
1960–69	5	40
1970–79	5	20

Distemper. Distemper is a measles-like infection of dogs which can produce chronic neurological disease in its natural canine host. The hypothesis that distemper virus might be associated with MS has been raised by MS case-control studies (*28*); some studies indicated a history of more extensive contact with dogs among persons with cases than among the controls.

An unusual epidemiologic pattern of MS occurrence in the Faroe Islands has fueled interest in the putative distemper-MS association. Figure 4 sets forth incidence of MS in the Faroes and indicates that during the period 1945–60 there was an apparent "outbreak" of MS.

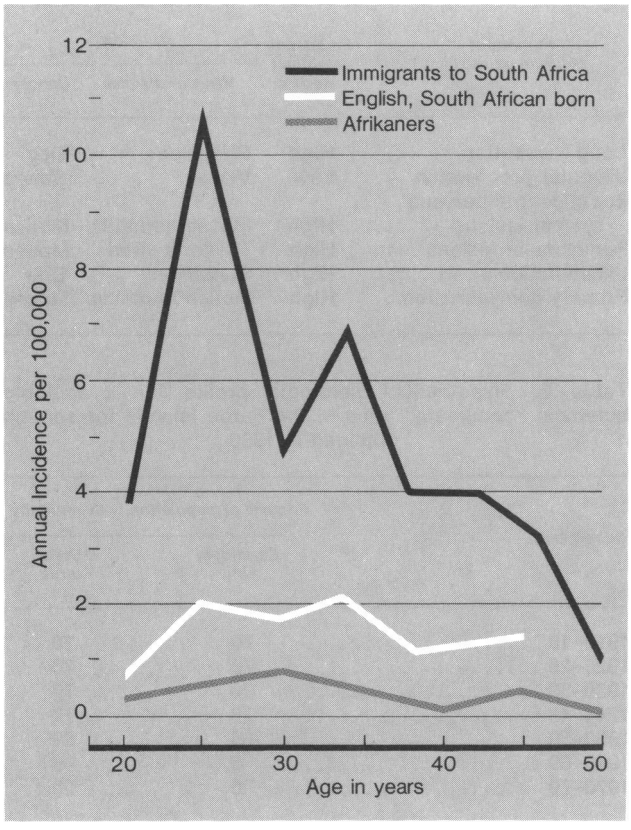
The unusual pattern of MS in the Faroes offers a special opportunity to search for a virus association. One possible approach is illustrated by a hypothetical data set constructed in table 5. The table is a summary of a cross-sectional serosurvey that could be used as a probe to search for a virus that was present in the Faroes in 1960 and which subsequently disappeared.

Returning to figure 4, an association with distemper was suggested because the cluster of MS cases in the Faroes had been preceded by an outbreak of distemper that was apparently introduced during the wartime British occupation (1940–43). An opportunity to test this suggested association was unexpectedly provided by observations in another relatively isolated population.

In Iceland, dogs are not immunized against distemper which does not exist as an enzootic infection. During the period 1900–80 distemper has occurred in Iceland only 3 times; in each instance a sharp outbreak was caused by inadvertent importation of an acutely infected dog. When these outbreaks are mapped (table 6), it is seen that two areas (Northwest and East) have scarcely been involved. Yet the rates of MS in these two regions were the highest recorded during 1946–65. This finding certainly suggests that MS can occur at a high rate in the relative or complete absence of distemper.

General epidemiologic patterns of MS. Another approach to the enigma of MS is to attempt to draw inferences from the general epidemiologic patterns of the disease. Although fraught with hazards, this approach deserves illustration because it has received

Figure 5. Average annual incidence of multiple sclerosis in white South Africans, 1945–54



SOURCES: Dean (*33*) and Kurtzke.

widespread attention and because it represents another potential contribution of epidemiology to the slow virus-chronic disease association (*29*).

One well-documented feature of MS is its geographic variation. Incidence is highest in the temperate zone and drops toward the equator. It was suggested by Poskanzer and co-workers in 1963 (*32*), by analogy with poliomyelitis, that this incidence gradient was compatible with a virus etiology if one assumed that the risk of MS was influenced by the age at infection so that incidence was highest in areas where the putative virus was acquired at an older age. The plausibility of this hypothesis is supported by analogy to several other human viruses: hepatitis A, hepatitis B, and Epstein-Barr virus (mononucleosis). Certain epidemiologic observations on MS are consistent with the poliomyelitis hypothesis. Among these are selected studies of migrant groups. For example, a comparison of native-born and immigrant white South Africans indicates that MS rates were considerably higher among the immigrants from England, a high incidence country (fig. 5). Furthermore, a similar pattern had been previously described for poliomyelitis in the same population (*34*).

However, the epidemiologic patterns predicted by the poliomyelitis hypothesis are not found with any consistency. For instance, when age at MS onset is compared in regions of high and low MS incidence (table 7), there is very little difference. A more recent detailed study (John Kurtzke, Veterans Administration, and colleagues, unpublished study, 1979) showed that among cases in U.S. veterans, average age at onset was a few years older in those from the low incidence (southern) tier of States, contrary to prediction. Other significant discrepancies have also been described (*29*).

Comment on the Role of Epidemiology

Experience suggests that the contribution of epidemiology in ascertaining associations of slow viruses and chronic disease can be assigned in a hierarchy of descending importance:

1. Hypothesis testing. When a specific candidate agent has been proposed, epidemiologic studies may serve a vital role in testing the proposed association. This testing can be done through case-control studies,

Table 6. Multiple sclerosis (1945–65) and canine distemper (1900–65) in Iceland [1]

Region	Multiple sclerosis period prevalence per 100,000 1945–65	Involved in distemper epizootic
Southwest	81	1921, 1941, 1966
Midwest	104	1921
Northwest	129	
North	102	1921, 1941
East	194	1941
South	80	1921, 1941, 1966

[1] After Nathanson and co-workers (*31*).

Table 7. Age of patient (mean or median) at onset of multiple sclerosis in areas of different prevalence [1]

Locale	Prevalence per 100,000	Age at onset (years)
New Orleans, La.	10	30
Western Australia	14	33
Newcastle-upon-Tyne	19	30
Perth, Australia	20	33
Hobart, Tasmania	33	34
Winnipeg, Canada	35	30
Denver, Colo.	38	32
Boston, Mass.	41	31
Northumberland County, England	50	36
Northern Ireland	51	32
Denmark	64	31
Norway	80	31

[1] After Acheson (*35*) and Nathanson and Miller (*29*).

through prospective population-based studies, or through intervention trials, depending upon individual circumstances.

2. *Special opportunities.* Unusually high or low incidence of the disease, including the clustering of cases in space and time, may provide important clues to etiology or aid in defining important risk factors. These distributions deserve study, both to document the reality of first impressions and to conduct imaginative explorations of explicit hypotheses.

3. *Descriptive population-based studies.* Because many chronic diseases such as MS are not reportable and because the diagnosis can readily be mistaken, population-based data on incidence and prevalence can be difficult and expensive to obtain. Therefore, once certain baseline rates have been roughly measured, further descriptive studies should be confined to carefully chosen populations. Thorough studies in a few areas may be more valuable than widespread collection of casual and incomplete data.

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