Update on the Epidemiology of Multiple Sclerosis

DANIEL R. WYNN, M.D.,* MOSES RODRIGUEZ, M.D., Department of Neurology; W. MICHAEL O'FALLON, Ph.D., Section of Biostatistics; LEONARD T. KURLAND, M.D., Dr.P.H., Section of Clinical Epidemiology

Neuroepidemiology has been important in providing clues about the cause and pathogenesis of multiple sclerosis. In this review, we update the incidence and prevalence rates of multiple sclerosis in Olmsted County, Minnesota, and examine the potential role of viruses, exposure to animals, toxins, trauma, and diet in the development of this disease. Diseases of probable autoimmune nature have also been linked to multiple sclerosis. These descriptive data may contribute to the formulation of testable specific hypotheses about the pathogenesis and treatment of multiple sclerosis and other demyelinating diseases.

In recent years, the incidence, prevalence, and mortality rates of numerous common and uncommon neurologic conditions have been estimated, and seasonal, regional, ethnic, and international differences in these rates have been described. Similarly, long-term sequelae, comorbidity, and survival characteristics of neurologic disease have been addressed. In many instances, these descriptive data have provided etiologic clues and have set directions for more specific hypothesis-generating and hypothesis-testing analytic studies.

INCIDENCE AND PREVALENCE

"The basic premise of epidemiology is that disease does not occur randomly but in patterns which reflect the operation of the underlying causes."1 The geographic pattern of multiple sclerosis (MS) has attracted considerable attention in recent decades, but such studies actually began soon after the formal description of the disease by Charcot,2 who commented that the disease was prevalent in France, not well recognized in Germany, and uncommon in England. These clinical impressions finally gave way to systematic comparative studies of the prevalence of MS.

In 1922, Davenport3 reported the distribution of MS in the United States based on diagnoses among Army inductees in World War I. He noted that the frequency of occurrence of MS was higher in urban than in rural areas and that the highest rates were among persons living near the Great Lakes and in Washington, Maine, Pennsylvania, Kansas, and Mississippi. In 1926, postal surveys of physicians in Switzerland by Bing and Reese4 and a subsequent survey by Ackermann5 suggested that MS was more common in the predominantly Germanic northern Swiss cantons than in the French and Italian cantons. Allison6 who conducted a survey in northern Wales in 1928, is credited with the first systematic
study of MS morbidity in a defined population in which diagnostic criteria were described and all the suspected cases were examined.

Many of the early reports were based on clinical impressions; nevertheless, some were useful in stimulating the intense population-based surveys that were needed to provide a geographic pattern of the distribution of the disease. In 1938, Steiner\(^7\) reported that he had noted no scarcity of MS in New York City, but during a 6-month period in New Orleans he had not seen a single clinical or autopsy case in a native-born person.

The next major development in the effort to clarify the distribution of MS was Limburg’s demonstration\(^8\) that MS death rates increased from south to north within the United States. Subsequent work by MacLean, Kurland, Kurtzke, Alter, Dean, Acheson, and others gradually developed the global topography of the disease with the general picture of a higher prevalence in the temperate zones than in the sub-tropics and tropics and some uncertainty about the disease prevalence nearer the poles.\(^9\)\(^10\)

Research at the Mayo Clinic has pursued the epidemiology of MS and has expanded to a systematic study of the population features of numerous neurologic disorders. The development of neuroepidemiology as a distinct discipline began with the presentation, by MacLean and associates\(^11\) in 1950, of the first population-based study of MS in the United States; they described the incidence and prevalence of MS and survival of affected persons in the population of Rochester, Minnesota. This study, based on the Mayo Clinic records system, showed that the prevalence of MS was more than twice that previously reported anywhere else, and the prognosis, based on community experience, was far more optimistic than estimates derived from hospital-based studies.

Two subsequent surveys of the frequency of MS have been done in Rochester. Percy and co-workers\(^12\) extended the earlier study by MacLean and colleagues\(^11\) by estimating prevalence ratios in Rochester at 10-year intervals from 1935 through 1964. In addition, they calculated the mean annual incidence rates for each decade from 1905 through 1964. Kranz and associates\(^13\) extended the incidence estimates through 1974 and the prevalence estimates through 1978. As has been observed in other communities where surveys have been repeated, Kranz and co-workers noted an increase in prevalence rate, from 46 per 100,000 as calculated by Percy and associates for 1915 to 108 per 100,000 for 1978. They noted a mean annual incidence rate of 3.6 per 100,000 population for the interval 1965 through 1974, similar to that calculated by Percy and colleagues for the 6 earlier decades, and concluded that the incidence rate of MS was stable in the Rochester population as also had been shown in a similar study in Winnipeg, Canada.

We recently reassessed the incidence and prevalence of MS in Rochester and in Olmsted County (of which Rochester is the county seat) for the 80-year interval 1905 through 1984.\(^14\) On Jan. 1, 1985, 152 prevalent cases of MS were identified in Olmsted County, of which 102 were in Rochester residents. Age- and sex-adjusted prevalence rates were 171 per 100,000 for Olmsted County and 177 per 100,000 for the city of Rochester. As noted in previous studies\(^12\)\(^13\) and by others elsewhere in repeated population-based studies of MS, the prevalence of MS has increased significantly in the past 10 years.

Previous increases in MS prevalence have been attributed to increased survival of MS patients, changes in population age structure, migration, and miscellaneous effects of restudy.\(^13\)\(^15\) Important effects of restudy include improved case-finding methods as a result of technologic advances in diagnosis and computerization of medical records, both of which increase completeness of case ascertainment. Another feature of importance in this population is the retention and availability of records since early in this century, increasing the likelihood that some cases previously regarded as “possible only” now were “probable” or “definite” because of information collected on such patients for several decades. Although these factors have likely contributed to the increased prevalence rates, they might be insufficient to explain the entire difference noted; therefore, an increase in disease incidence must also be considered.

An intensive reevaluation of all categories that might include MS cases for the 80-year period Jan. 1, 1905, to Jan. 1, 1985, identified 208 incident cases (57 males and 151 females) fulfilling current criteria for MS in the Olmsted County population. The age-adjusted incidence rates were 3.0 and 7.0 per 100,000 for males and females, respectively; the median age at onset was 34.3 years for males, 32.4 years for females, and 32.8 years overall. The median follow-up interval was 13.8 years for males, 14.1 years for females, and 14.0 years overall; 3,472 person-years of follow-up information was available for review. Autopsy information was available for 18 of the 41 persons (44%) who died during the study interval. The diagnostic criteria were those outlined by Poser
and associates\textsuperscript{16} from the Workshop on the Diagnosis of Multiple Sclerosis. More than 90\% of the patients were in the category "clinically definite MS A1." This high percentage of clinically definite cases probably is related to the availability of old medical records and the long period of follow-up.

These data suggest a trend toward an increasing risk for development of MS, a finding not previously noted in Rochester or other major centers.\textsuperscript{17} When grouped by place of residence—metropolitan Rochester or rural Olmsted County—the MS rates were comparable.

The increase in incidence may be real, although issues of improved case ascertainment, diagnostic improvements (especially in the milder cases), and improved study design must be considered. The increase in incidence may explain in large part the increases in prevalence noted now and previously in this community. Whether this implies a more general trend toward increasing risk of MS elsewhere awaits study in other communities.

**MIGRATION**

Since the demonstration by Limburg\textsuperscript{8} of an increasing frequency of MS from south to north within the United States, investigations in different parts of the world have supported the hypothesis that the risk of MS is related to distance from the equator.\textsuperscript{9,10} In an attempt to distinguish between the importance of environmental factors and possible genetic risk factors, the effect of migration on risk has been studied. The study of the incidence and prevalence of MS in migrant groups has been one of the most important natural experiments in the study of MS epidemiology.

Rozanski\textsuperscript{18} and subsequently Alter and associates\textsuperscript{19,20} reported the prevalence rate of MS among groups migrating to Israel. The prevalence rate was noted to be 5 to 10 times higher among northern European immigrants than among African or Asian immigrants or in the native population of Israel, even among those of northern European parentage. These findings suggested an environmental influence on the risk of developing MS.

In 1967, Dean\textsuperscript{21} noted that the prevalence rate among South Africans who were of European stock but were born and raised in South Africa was approximately 17\% of that among immigrants from England and Europe. Visscher and colleagues\textsuperscript{22,23} noted that the prevalence rate of MS is higher among Japanese-Americans than in the population of Japan, although this finding might be a reflection of differences in training and clinical practice. In addition, Kurtzke and Bui\textsuperscript{24} noted an increased risk of MS among persons who migrated from low-risk southern zones in the United States to high-risk northern zones as well as a decreased risk in those who migrated from north to south. Similar findings in France, Hawaii, Australia, England, and other locations have led to postulates of protective factors in subtropical zones and risk factors in temperate zones.\textsuperscript{9,10}

Migration after adolescence has been associated with a risk of MS characteristic of the country of origin, whereas migration earlier in life has been associated with a risk characteristic of the new environment.\textsuperscript{25,26} Studies of this important topic have been limited by the paucity of migrant groups suitable for study. The immigration policy of an admitting country may exclude disabled immigrants, or migration of patients may be relatively increased if it is thought that the climate of a particular country may favorably affect the course of the disease. As noted by Alter and co-workers,\textsuperscript{25} the migrant groups must be large enough to yield a sufficient number of cases for meaningful statistical analysis, medical facilities must be comparable for native and migrant populations, and the populations studied must be well defined demographically so that accurate incidence and prevalence figures can be generated.

Several racial groups have been reported to be maintaining low MS incidence rates although living in high-risk zones for MS.\textsuperscript{27,28} This result refutes a purely environmental interpretation, although those who migrated may have been the healthier members of the community and the level of medical care available in the adopted country may have been inadequate for the diagnosis and reporting of the disease when it did occur. Also, in some cases, the development of the disease may have led to their return to their homeland.

Before definite conclusions can be drawn, a substantial population of immigrants must be observed for most of a lifetime and comparisons in frequency must be made that take into account the age at migration and the duration of residence in the host country. Because hypotheses that implicate environmental factors assume, in part, that patients with MS and geographically matched control subjects have similar racial and genetic characteristics, ideally the migrant groups should be well defined or described genetically such that further characterization of the respective roles of heredity and environment can be made.

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What are the important risk factors for development of MS? Descriptive epidemiologic studies point toward a role for environmental factors in the development of MS, but what are these factors? The following have been topics of active research and ongoing controversy.

Infectious Agents.—The epidemiologic data accumulated for the past 25 years implicating an environmental influence in the development of MS provide indirect evidence that MS may be caused by an infectious agent. Of particular prominence have been the reports by Kurtzke and Hyllested of cases of MS among residents of the Faroe Islands. Between 1943 and 1963, 24 cases were identified. In this ongoing study, the 32 cases of MS diagnosed between 1943 and 1973 constituted three distinct periods of increased incidence. Kurtzke and Hyllested interpreted these data to indicate a point-source epidemic with an infectious common source associated temporally with the stationing of British troops in the Faroes during World War II. Based on their observations, they suggested that MS is a widespread systemic infectious disease that most frequently is asymptomatic and only rarely affects the central nervous system in a clinically detectable manner. Their hypothesis is based on two lines of evidence: (1) the pattern of onset of the cases between 1943 and 1960 and (2) contact between these patients and British troops during World War II.

Although these studies were performed well, some investigators have questioned their reliability. Suspicion has been raised about the completeness of case ascertainment, particularly in the period before 1943, during which no cases of MS are known; however, this was a time when medical expertise may have been less readily available. In addition, some uncertainty exists about the reliability of the use of retrospective methods for assignment of date of diagnosis. Just as the war brought turmoil to the Faroes, so it may have introduced unresolvable recall bias among patients, causing them to date the onset of their first symptoms to 1943, the midpoint of the stationing of British troops on the island. Evaluation of the association with the British garrisons is difficult without similar information from control subjects with some other progressive disease characterized by remissions and exacerbations.

The identity of the putative infectious agents remains unknown. Despite several observations that have raised hope, no associated infectious agent has yet been convincingly demonstrated. As detailed elsewhere in this symposium, viruses are known to cause several demyelinating diseases, in humans and in animals, with pathologic characteristics similar to those of MS. Of the proposed infectious agents, the morbilliform viruses measles and canine distemper virus (CDV) have received the most attention during the past decade.

In 1962, Adams and Imagawa noted an increased concentration of measles antibodies in patients with MS compared with control subjects. Measles antibodies also have been found to be increased in siblings of patients with MS. Several authors have noted an increase in measles antibody in the cerebrospinal fluid of patients with MS, in part attributable to increased production of antibodies within the central nervous system. An increase in MS risk has been reported when measles infection occurs later than usual in childhood; thus, the question is raised whether MS might be an age-dependent host response to measles virus.

Interpretation of these findings is difficult. Increased levels of antibody against viruses other than measles have been noted, although less consistently. The titer of measles virus antibody found is relatively low, and in some patients with MS, this antibody may even be absent. In a carefully performed seroepidemiologic study of MS in the Shetland and Orkney Islands—an area of very high MS incidence and prevalence—no association was noted between MS and measles or 17 other viruses.

In 1977, Chan suggested that MS may be attributable to exposure to a virus passed in canine urine. Cook and Dowling subsequently reported three cases in which MS apparently developed in sisters after a family dog suffered from an acute encephalopathy. In a subsequent case-control study, an increased relative risk was noted for contact with dogs before the onset of MS. Additional reports suggested a temporal relationship between epidemics of CDV and MS. The findings from these studies were interpreted to suggest that CDV is the putative agent in MS.

Several factors suggest a relationship between CDV and MS. Canine distemper encephalitis (CDE) and MS are characterized by demyelination and inflammatory infiltration. Optic neuritis may be the sole clinical manifestation of either disease. Patients with MS and dogs with CDE have increased cerebrospinal fluid γ-globulin levels and may have antitymulin antibodies. CDV may remain latent for years before producing neurologic disease (old dog encephalitis).
Despite these seemingly promising findings, a relationship among MS, increased exposure to dogs, and CDV has not been confirmed in case-control studies by other investigators. Other factors that also suggest that MS may not be related to CDV have been noted. For example, although neurotropic strains of CDV may exist that could infect humans, none has been found. In only a single unconfirmed case has viruslike material been noted in the brain of patients with MS, whereas intracytoplasmic and intranuclear inclusions are common in CDE. CDE and old dog encephalitis frequently affect the gray matter extensively and are associated with prominent neuronal degeneration, whereas MS is primarily demyelinative and is associated with only minor neuronal degeneration. CDV is ubiquitous throughout the world; the distribution of MS does not parallel this, and MS occurs in areas where dogs are uncommon. With widespread vaccination against CDV, CDE presumably has declined, whereas the incidence of MS has not. In immunoprecipitation studies of serum specimens from patients with MS, antigens unique to CDV have not been identified.

Many important methodologic problems arise in the analysis of Cook and Dowling’s data. Much of their data is retrospective and subject to the problems of case-control studies. Of prime importance is the selection of a group of control subjects for those variables that may be confounding but are not causal. To help ensure comparability, multiple control groups are desirable. Why other investigators have been less successful in detecting a relationship between MS and exposure to pets is unclear.

Attempts have been made to correlate MS with prior infections. Gay and associates noted a fourfold increase in chronic sinusitis in patients with MS compared with age- and sex-matched control subjects; in this study, MS and chronic sinus infection were significantly associated with the timing of attacks of MS, with the age at which patients suffered their attacks, and with the seasonal pattern of attacks. These findings raise the question of whether MS may be a delayed response to an upper respiratory pathogen or an allergic antigenic challenge. Indeed, Sibbrey and colleagues noted minor respiratory tract infections preceding 27% of MS exacerbations, although a suitable basis for comparison is not evident.

A similar seasonal fluctuation of MS has not been observed consistently in other communities. Kranz noted no significant relationship between MS and infections or tonsillectomy. Several investigators have looked for but found no consistent patterns of childhood illnesses. Therefore, multiple modes of infection may act as nonspecific triggers for the immune system in initiating the onset or in eliciting an exacerbation of MS.

Trauma.—The role of trauma in precipitating, aggravating, or causing MS remains highly controversial. In 1877, Charcot proposed a link between the onset of MS and exposure to cold, falling, illness, or stress. Subsequently, Mendel suggested that, in the absence of other etiologic factors, trauma could be considered as a cause of MS that develops within a year after severe trauma, particularly if the trauma involves the skull or the spine. In support of this hypothesis, cases occurring after major or minor injury have been reported. Von Hoesslin reported trauma in 59 of 516 cases of MS (11.4%), McAlpine noted injury in 5.6% of 142 patients with MS, Adams and co-workers noted accidental or surgical trauma in 41 of 389 cases of MS (10.5%), and Bobowick and colleagues noted an increase in the recall of trauma by patients with MS in comparison with their discordant twin siblings.

Bamford and associates recently pointed out that most of the data relating to the etiologic controversy were derived from retrospective and uncontrolled studies. Nevertheless, McAlpine reported that trauma to a limb or any part of the body, including operation, could occasionally precipitate the disease in a predisposed person or could cause a relapse. In a retrospective and prospective study, Bamford and colleagues noted a suggestion of an increase in electrical injury preceding clinical exacerbations in patients with MS. Kurland and Westlund noted no significant difference between patients with MS and control subjects in regard to a history of trauma to the spine or trauma to the head sufficient to cause unconsciousness.

Pathologic studies have suggested a role for trauma in the pathogenesis of MS. Brain and Wilkinson speculated that cervical spondylosis renders the spinal cord more susceptible to MS lesions. In patients with MS, Oppenheimer found twice as many plaques in the cervical cord as in other areas of the nervous system and thus suggested that mechanical stress may play a role in determining the site of MS lesions. Gonsette and co-workers and Riechert and associates examined the brains of five patients with MS who died after thalamotomy and noted fresh demyelinating lesions adjacent to or surrounding the needle tracks in four of them. These studies, however, provided no information about injuries that were not
followed by clinical MS or details about the severity of the trauma. Poser\textsuperscript{81} recently postulated that alterations in the blood-brain barrier associated with trauma may result in exacerbation or recurrences of previously symptomatic plaques, in the appearance of symptoms from silent lesions, or in the formation of new plaques in areas of selected vulnerability. In addition, he suggested that, in patients whose MS develops after injury to the nervous system, MS plaques may form in areas of old trauma. Unfortunately, Poser's hypothesis is based on anecdotal reports only, and statistically valid data are lacking.

Thus, the answer to this important clinical and medicolegal question remains uncertain. Most authorities agree that no available evidence supports the theory that trauma causes MS. Because of the unpredictable course of the disease, however, demonstrating a convincing relationship or lack of such a relationship between clinical worsening of MS and traumatic events has proved difficult. We are in the process of evaluating a large cohort of patients with head trauma in Olmsted County to determine whether the occurrence of MS was increased subsequently in comparison with what would be expected based on the local incidence rates of MS.

**Heavy Metals.**—A recent report by Stein and colleagues\textsuperscript{82} of an increased incidence of MS among workers exposed to zinc in a manufacturing plant raises the question of a role of heavy metals and other toxins in MS. In that study, 11 cases of MS were diagnosed among workers within a 10-year period, an incidence 2 to 4 times greater than that predicted by using population-based incidence data from Rochester,\textsuperscript{12} Denmark,\textsuperscript{83} and a study by the National Institute of Neurological and Communicative Disorders.\textsuperscript{84} Although expected case numbers and relative risks within the factory were estimated by using three comparison groups, no comparisons were made with other MS populations in the local community to assess the suitability of using such incidence data. Because of the lack of prior incidence estimates in this population and the apparent increase in incidence, such population data would be helpful. Our recent finding that the incidence of MS is higher than previously reported in Rochester emphasizes the need for up-to-date local rates.

These findings may be important because abnormalities of zinc balance may affect immunoregulation.\textsuperscript{85-87} A decrease in erythrocyte zinc levels during clinical exacerbations of MS was described recently,\textsuperscript{88} but Stein and associates\textsuperscript{82} failed to find specific abnormalities of zinc in blood samples from patients with MS. All plant workers were noted to have increased blood zinc levels. If, however, an increased blood zinc level leads to a substantial alteration in immune function, one might expect to find an unusually high prevalence of other immunologically based disorders among workers. Such an increase was not noted.

Reports of clusters of patients with MS in small populations have stimulated new theories about etiologic factors. In 1947, four of seven workers investigating swayback, a demyelinating disease in sheep, were found to have MS within 3 months of one another and within 1 year of their common exposure to pathologic material from the sheep.\textsuperscript{89} Swayback was subsequently presumed to be related to copper deficiency and excessive exposure to lead.\textsuperscript{90} Follow-up studies found no increase in lead exposure among the workers and no convincing evidence of deficiency of copper or any other trace element; thus, the occurrence of the cluster was unexplained. Similar small clusters, all without final explanation, have occurred in Mansfield, Massachusetts,\textsuperscript{91} Mossyrock, Washington,\textsuperscript{92} Nova Scotia, Canada,\textsuperscript{93} and elsewhere. A cluster of MS in the seacoast village of Duxbury, Massachusetts,\textsuperscript{94} was found to be due to migration of persons whose cases had begun elsewhere. A recent cluster of cases of MS on Key West, Florida, was thought to be associated with both canine distemper and environmental pollution, but confirmation of these cases as MS is still awaited.\textsuperscript{94,95}

Clusters of MS and other diseases can be expected to occur by chance. Only independent evidence of prior or subsequent clustering in the same population can be interpreted as indicative of an association. With such clusters, the main concern is to ensure that the diagnosis is correct and that the earliest symptoms of the disease occurred during residence in the community, not before migration into the area. When these conditions are present in a cluster, opportunities are available for extensive study to identify possible risk factors.

**Diet.**—The relationship of diet to the cause of MS remains controversial. In 1950, Swank\textsuperscript{96,97} first suggested that MS was related to a high-fat diet. This hypothesis was based on (1) a correlation of diet and the geographic distribution of MS, on a global scale, and the observation that populations in Norway\textsuperscript{98} and Switzerland who were consuming more animal fat had higher rates of MS, (2) a view that the disease has become more common during the past century, (3) a reported high attack rate among persons changing suddenly from a low-fat to a high-fat diet, (4) the
supposed decrease in the disease in occupied countries during World War II, and (5) the alleged therapeutic effects of a low-fat diet.

Agranoff and Goldberg noted a high correlation between consumption of milk and MS. Dean noted that, although this correlation may exist in Europeans and North Americans, Afrikaans-speaking white South Africans, whose diet is rich in animal fat, have a low incidence of MS. Dean thought that these findings implicated an infectious, possibly viral, cause, but the high rate among northern Europeans who migrate to South Africa after the age of 15 years could imply the importance of early dietary exposure.

In the Winnipeg case-control study, no obvious association was found between MS and diet. Although some investigators have reported a beneficial effect of a low-fat diet, others have obtained equally salubrious results with high-fat diets.

Dietary fat is of particular interest in MS because the myelin sheath of nerves is composed predominantly of lipids. The results of this research have been incomplete and contradictory; thus, no consensus exists about the pathogenesis of MS or its treatment.

Disease Associations.—In the continuing search for clues about the cause of MS, attempts have been made to determine whether it is linked with other diseases. Of particular interest has been a question about associations between MS and autoimmune diseases and neoplasia.

Anecdotal reports and small series of cases have suggested an association between MS and myasthenia gravis, systemic lupus erythematosus, ankylosing spondylitis, ulcerative colitis, scleroderma, diabetes mellitus, or cancer. Dietary fat is of particular interest in MS because the myelin sheath of nerves is composed predominantly of lipids. The results of this research have been incomplete and contradictory; thus, no consensus exists about the pathogenesis of MS or its treatment.

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