The geographic pattern of multiple sclerosis has eluded a sound explanation. Studies have eliminated a number of erroneous concepts, but clarification of cause and control still remains to be achieved. However, etiologic hypotheses should be consistent with the known geographic distribution.

GEOGRAPHIC AND CLIMATIC ASPECTS OF MULTIPLE SCLEROSIS

A Review of Current Hypotheses

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MULTIPLE sclerosis is a neurological disease of unknown cause and is often progressive and fatal. It has an unusual geographic distribution which has defied an explanation that might elucidate its cause or lead to effective treatment or prevention. The disease has been the subject of numerous intensive mortality and morbidity analyses which provide excellent illustrations of survey technics in chronic disease epidemiology.

An essential preceding step to effective field studies is the clear description of the clinical syndrome. Unfortunately, in multiple sclerosis there is no specific laboratory or clinical procedure to confirm the diagnosis of multiple sclerosis cases, nor do we have assurance that what we count as cases are the same disease entity. Because there are many neurological diseases of genetic and unknown etiology which resemble multiple sclerosis, the diagnosis is often reached only after the patient has had more than one episode and other possibilities have been excluded. The error of diagnosis is greatest early in the disease; yet the early cases are the very ones which might facilitate identification of some predisposing or disease precipitating experience. Since early symptoms often develop insidiously and may remit and recur, the precise season or even the year of onset may be uncertain. Furthermore, a delay of months or even years from onset to diagnosis is not uncommon and further complicates the recognition of significant events which may have preceded the onset of the disease.

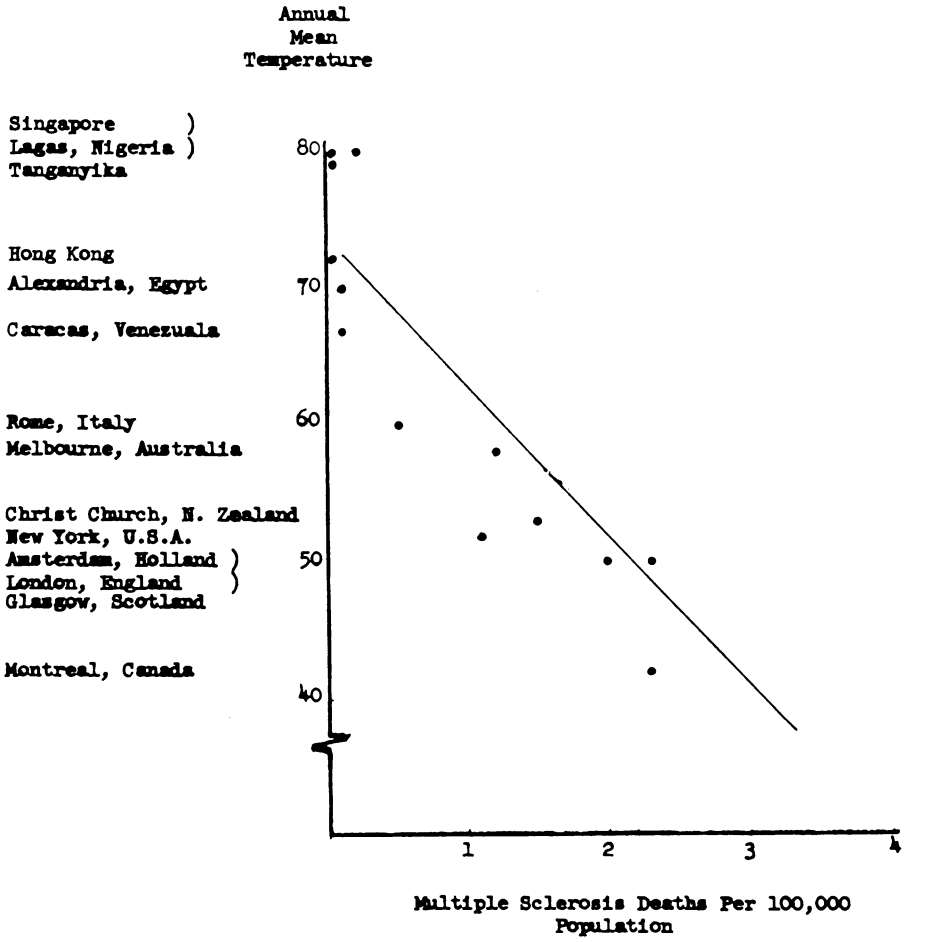
Since incidence rates are relatively small and difficult to obtain accurately, most geographic comparisons have been limited to prevalence rates. These are statistically more stable but may be biased if severity of the illness or longevity of the patients differ geographically or if there is appreciable migration of patients into or out of the community under study. In spite of these difficulties, many epidemiological surveys have been undertaken to clarify the basic issue of whether genetics or environment is the major causative influence.

In view of the early clinical impression that multiple sclerosis selectively occurred in people of northern European origin or extraction,[1] a first step in the series of epidemiologic investigation was to examine the geographic pattern

of multiple sclerosis mortality. Figure 1, based on Limburg's study in 1948,[2] reveals an inverse relation between crude mortality rates for multiple sclerosis and the mean annual temperature of the major city of each country. Mortality studies with age-adjusted rates showed a similar pattern. Although it appears that the colder the climate the higher the crude death rate, alternate explanations such as the relative amount of neurological diagnostic services cannot be ignored.

Because of the nonuniformity of many international mortality reporting sources, it seemed more profitable to map the geographic pattern over a wide area which had similar coding, classification systems, language, and medical standards. Figure 2 shows the distribution of the average annual age-adjusted multiple sclerosis mortality rates per 100,000 population for the United States and Canada. The high rates are associated with the northern United States and Canada.

Figure 1—Crude Death Rate for Multiple Sclerosis for Selected Countries by Annual Mean Temperature



Modified from Limburg, C. Multiple Sclerosis and the Demyelinating Diseases. Williams and Wilkins, 1950, Chapter II.

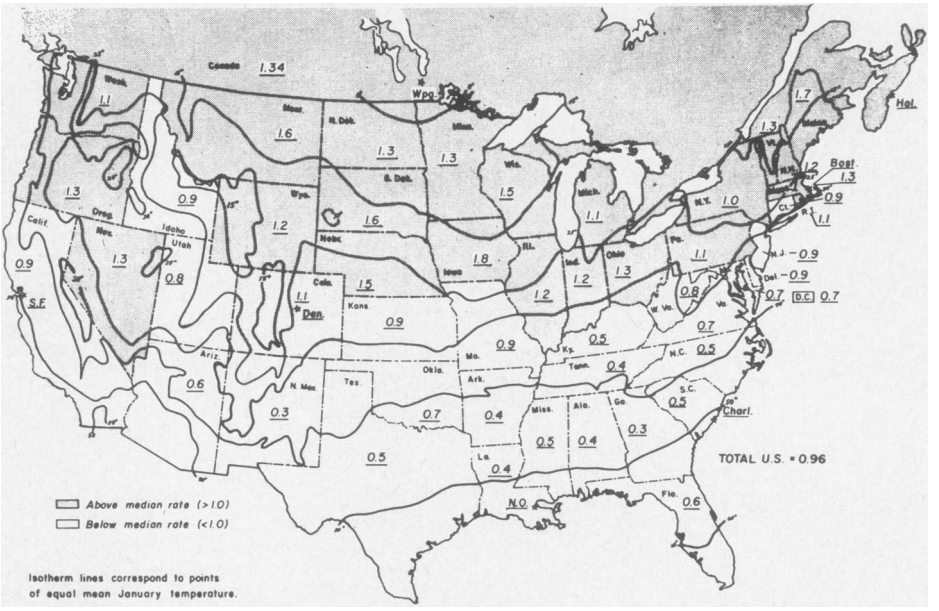


Figure 2—Average Mortality Rates/100,000 Population, Canada and the United States, for White Population, 1949-1951

The next step was to determine the morbidity and mortality of multiple sclerosis in detail in several large, widely separated communities in which the standards of medical practice were high. These studies were completed in Boston, Winnipeg, New Orleans, Denver, and San Francisco.[3]

All available diagnostic sources including hospitals, clinics and practitioners serving the respective communities were studied to discover cases of multiple sclerosis and allied disorders. Duplicates were consolidated, the latest diagnosis and living or dead status was determined, and the prevalence rates were computed for a date about one year prior to the study to partially compensate for the long delay from onset to diagnosis. Table 1 shows that multiple sclerosis prevalence was much greater in the northern cities than in New Or-

Table 1—M. S. Prevalence Ratio for White Population, U. S. and Canadian Communities (NINDB Study)

Community	Latitude °N.	Temp. Mean Jan. °F.	Prevalence Ratio per 100,000 Population	
Winnipeg	50	−3.5	42	(40)
Boston	42	28	41	
Denver	40	31	38	
San Francisco	37	50	30	
New Orleans	30	55	13	(6)

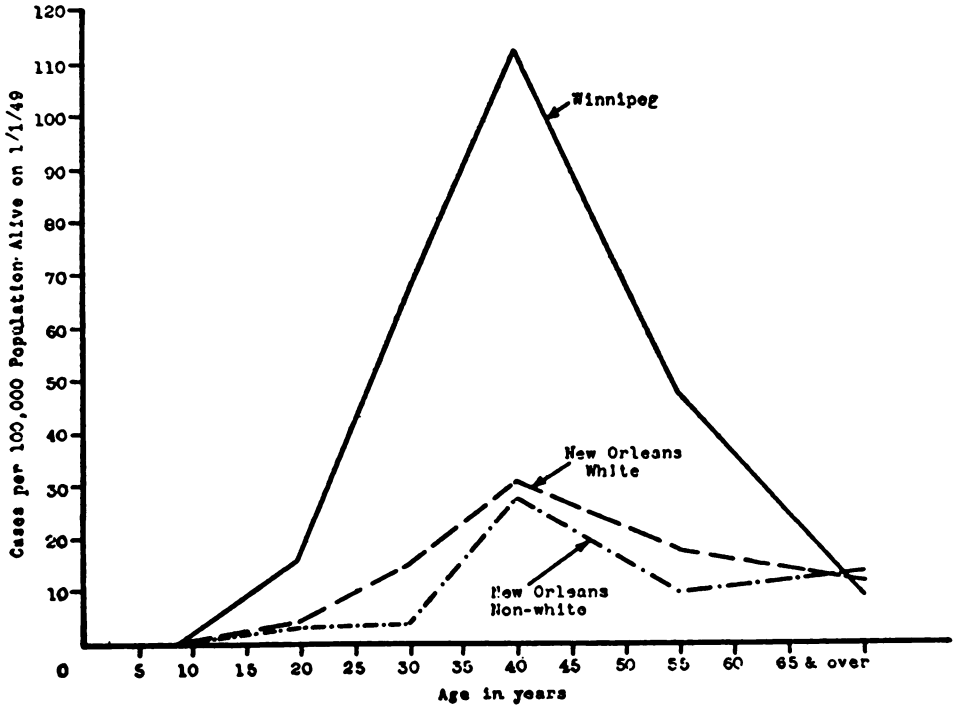
[ ] Preliminary result.
( ) Final result after detailed neurological examination of patients.

leans. Although there appears to be a north to south gradient, there was no obvious focalization of cases within these cities. There were so few conjugal or familial cases that ordinary transmissibility or a common source of exposure seemed unlikely. In spite of the differences in prevalence, the clinical features of the disease were similar in all cities; however, the mean age of onset appeared to progressively decrease as the prevalence rate increased. In New Orleans and Winnipeg,[4] the two cities whose latitude and multiple sclerosis prevalence differed the most, a particularly intensive reevaluation was made, including an additional examination of the patients.

All patients uncovered by the earlier study, plus those found by a review of all sources, were interviewed and examined by a neurologist. The numbers in parenthesis in Table 1 show that the agreement with the over-all result of the earlier survey was good, but that the previous estimate of a 3.6 to 1 ratio between Winnipeg and New Orleans was conservative. The review following neurologic examination revealed a ratio of 6.6 to 1. The discrepancy occurred because many cases in New Orleans which had been counted were not acceptable when examined.

Figure 3 shows multiple sclerosis prevalence rates by age in Winnipeg and by age and race in New Orleans. This is a

Figure 3—Multiple Sclerosis Prevalence* Ratios per 100,000 Population.† Winnipeg by Age, New Orleans by Age and Color, January 1, 1949



* Based on probable cases known to be living in New Orleans or Winnipeg on January 1, 1949.
† New Orleans population estimated, 1947; Winnipeg population from 1946 census.

graphic illustration of the difference in the rates, at all ages, between the two cities. There was no statistically significant difference between Caucasians and Negroes in New Orleans.

A further follow-up study in Winnipeg by Stazio is now in progress and preliminary results are available.[5] There was no indication of any change in the annual incidence rates for the 20 years prior to 1961. About 30 per cent of the 1951 cases were no longer acceptable as multiple sclerosis and an additional 20 per cent, mostly cases which had been symptomatic but undiagnosed in 1951, were now included. The over-all result in prevalence was not appreciably affected, but there is a discrepancy in a sizable proportion of the individual cases. Inaccuracies of about 40 per cent underreporting and 18 per cent overreporting for multiple sclerosis as the primary cause of death was also noted.

In order to elucidate any etiological or associated factors, numerous characteristics of the Winnipeg patients prior to the onset of the disease were compared with a representative, matched sample of the Winnipeg population.[4]

No statistically significant difference was found in the comparison in regard to: areas of Europe from which the individuals or their ancestors had migrated, place of birth, birth order, education, occupation, urban or rural residence, source of food and water, exposure to animals, vaccinations and inoculations received prior to onset, previous illness, back injuries, and head injuries.

Ethnological differences appeared to be of little significance. In Winnipeg there was no difference in prevalence for persons of English, French, or Ukrainian descent. In the earlier study in Boston, the rate among Caucasians and Negroes was similar and was considerably higher than the corresponding rates among Caucasians and Negroes in New Orleans.

In recent years, other population surveys have been completed in Ireland, Scotland, Denmark, Canada, and the United States.[1,6-8] These surveys also attempted to enumerate all the living, medically attended multiple sclerosis patients in a specified population. In most instances, patients were examined by the investigator or a neurologic consultant and the diagnostic criteria of multiple sclerosis which were expressed or inferred are believed to be sufficiently alike to justify a comparison.

The results of these and many other investigations could be summarized as follows: multiple sclerosis is found in many parts of the world and among all major racial groups. In the northern hemisphere it is more prevalent among the people of northern Europe, Great Britain, Canada, and the northern United States where the rates range from about 35 to 65 per 100,000 population. In these areas the rates are in the high to moderately high range, and it is difficult to see any pattern which would suggest a difference in risk for the northern Europeans as compared to those in Canada and the northern United States. The rates are generally higher (within the same geographic latitude) in the smaller communities, but this is probably due to the greater intensity of the study which is possible in such homogeneous populations. Among the people of the tropics and subtropics, the rates are considerably lower than in the temperate zones.

The one area in the northern hemisphere which does not show the north to south gradient is Japan.[9] An effort was made to conduct a survey, using the same technics as used in the United States, in two Japanese communities of over 300,000 population separated by 10° latitude. The results failed to show a variation in multiple sclerosis prevalence rates which were approximately 2 per 100,000 in each city. This may be an accurate picture, but the low rates may also be due to a number of limitations and difficulties inherent in the

study. Neurology has only recently developed as a separate medical discipline in Japan and case finding is always influenced by the mode of medical diagnosis and the differences in neurologic training of physicians. We prefer to consider these rates as minimal values until further surveys now in progress are completed.

Data on the southern hemisphere are limited but Acheson[10] has studied mortality rates of multiple sclerosis in Australia, New Zealand, and South Africa and found a relationship to latitude similar to that in the northern hemisphere. Dean[11] had first observed that multiple sclerosis is far more common among European immigrants to South Africa than among persons of European stock born and raised in South Africa.

Dean's more recent studies[12] show that multiple sclerosis does occur in South African born persons who have not been overseas, but the rate is very low—about 2 per 100,000. This area is about the same distance from the equator as New Orleans and the rates compare quite well with those of similar latitudes in the northern hemisphere. Among the immigrants from European countries the prevalence of multiple sclerosis is nearly as high as in the country of their origin. Dean's most interesting finding is that the prevalence of multiple sclerosis in South African born persons who visit Europe is about seven and a half times greater than in South African born persons who do not leave Africa.

The phenomenon of mass migration offers unique opportunities for investigating the question of geographic influence on multiple sclerosis. First Rozanski[13] and later Alter[14] took advantage of the unusual population composition of Israel to study this question.

A large segment of the Jewish population of Israel has been exposed to the influences of diverse climatological and geographic conditions. They have gathered as one population in Israel where immigration is not limited by any medical restrictions, and where the doctor-patient ratio is the highest in the world.

The findings are far more suggestive of an association with a geographic factor than a racial one. The prevalence rate among northern European immigrants was five to ten times higher than among Jews of Oriental, southern European, and Mediterranean origin. Among those persons born in Israel, the rates were low, regardless of the national origin of their parents. Both Alter, et al.,[14] and Dean[12] have computed a minimum latent period (from presumed exposure in the "high risk" temperate areas to the onset of symptoms after migration) of about 9 to 12 years among immigrants to Israel and South Africa. Although this procedure introduces several gross assumptions, it is the first reasonable effort to approach the question of an "incubation period" in such a chronic disease. The present mechanism does not enable one to determine the upper limit of such a latent interval.

The geographic pattern showing a more frequent distribution of multiple sclerosis further away from the equator has been accepted by most investigators. It is still uncertain, however, which of the many possible factors related to latitude may be relevant to the etiology of multiple sclerosis. Various meteorological and climatological influences such as "colder" winter temperatures or diminished sunshine appear to correlate with multiple sclerosis distribution. Whether these act directly on the patient or indirectly through plants, animals, or vectors in his environment is a purely speculative matter at this time.

Dietary deficiencies and excesses, including fat, lead, and copper, which may vary in different regions, have been investigated. There is no convincing evidence that any of these play a direct role even though Swank,[15] a proponent of the theory that a high fat diet causes multiple sclerosis, claims to have "as-

Table 2

City	Degrees North Latitude	Multiple Sclerosis Cases per Million Population	Average Annual Sunshine Hours
Seattle	48	31	2,049
San Francisco	38	12	2,935
Los Angeles	34	4	3,217

From Acheson, Bachrach and Wright.[16] Some Comments on the Relationship of the Distribution of Multiple Sclerosis to Latitude, Solar Radiation and Other Variables. Acta psychiat. et neurol. scandinav. 35:132–147, 1960.

tonishing results" with his low fat regimen. Viruses and allergic-hyperallergic reactions have been sugested in the continuing research efforts, but clear, reproducible evidence has not followed theory. Ichelson's[16] report of "successful" culture of spirochetes from the spinal fluid of multiple sclerosis patients has once again stimulated the search for a microorganism, but others have demonstrated that Ichelson's spirochetes were contaminants in her culture medium.

A more recent attempt to identify meaningful variables correlated with latitude was made by Acheson, Bachrach, and Wright.[17] They studied the distribution of multiple sclerosis in men discharged from Veterans Administration Hospitals with a diagnosis of this disease, between 1954-1958. This study was concerned with the birthplace of the patients whereas previous studies have been concerned with the residence of the patients either at death or following the onset of the disease.

A multiple-regression analysis was done using the following variables: multiple sclerosis rate per million for the mean year of birth of the patients (1920), degrees north latitude of birthplace, average hours of sunshine, average annual degree day (an index of severity of winter), and average daily December solar radiation. The highest correlations of multiple sclerosis prevalence were with average total annual hours of sunshine and with average daily December solar radiation. The fact that the correlation between multiple sclerosis and sunshine was a negative one indicates that if sunshine exerts an effect it must be preventive or protective rather than harmful.

The best illustration of the possible importance of sunshine is shown in Table 2 selected from Acheson's data. The rates of multiple sclerosis per million (by birthplace) decrease from north to south in three principal cities on the Pacific coast. The main difference in climate along this coast lies in sunshine (and precipitation) rather than in severity of winter.

Further speculation concerning the direct protective qualities of solar radiation comes from the work of Schneider.[18] He identified a strain of mice which are, genetically, 100 per cent susceptible to the development of experimental allergic encephalomyelitis (EAE), when inoculated with a suspension of brain tissue and adjuvant. When such animals were subjected to a flux of approximately 3,000 foot candle from a bank of high output fluorescent lamps, EAE was reduced 50-75 per cent. Schneider thinks the near infra red wave length is responsible for this phenomenon. One drawback is that other investigators have noted that heat and stress may also have a similar effect. This relationship between multiple sclerosis and solar radiation remains uncertain. If one assumed

that the latent period from "exposure" to onset or exacerbation were constant, a seasonal variation in incidence would be expected. However, several investigations have not revealed any such variation.[19]

In view of the difficulties in explaining the geographic distribution of multiple sclerosis, Barlow[20] has sought a new association. He plotted several sets of mortality and morbidity data for multiple sclerosis against the geomagnetic latitude of the location from which the data were obtained. The geomagnetic latitudes relate to the earth's magnetic field and are skewed with respect to parallels of geographic latitude.

The plotted rates versus geomagnetic latitude showed a consistent rapid rise in multiple sclerosis between the geomagnetic latitudes of 40° and 50°, and a leveling off above 50°. According to Barlow, the distribution of multiple sclerosis and particularly the low rate area of Japan are better correlated with geomagnetic than geographic latitudes. One of the phenomenon known to be related to geomagnetic latitude is cosmic radiation, and Barlow thought it appropriate to examine the various cosmic ray parameters. He found that altitude was a more important parameter of cosmic ray intensity than latitude. At sea level the latitude change between 0° and 50° is only 14 per cent, while from sea level to 6,500 feet there is a 70 per cent increase. The present difficulty with the cosmic ray hypothesis is that, while the number of high energy particles observed at very high altitudes varies with latitude, these particles appear to be filtered out by the atmosphere and no material increase in their effects can be observed at sea level.

The epidemiological approach with its emphasis on the host-environment relationship does not mean we have satisfied ourselves that no genetic factor is involved. The results of studies in Great Britain, Ireland, Scandinavia, Germany, and the United States[6-8] have been interpreted as showing that familial incidence is higher than would be expected by chance.

In Sutherland's[8] series, seven out of 545 sibs (1.3 per cent) of 127 patients were said to be affected; while in Hyllested's[6] series 44 of 11,924 sibs (0.4 per cent) were considered affected. The difficulty is that these findings do not differentiate between the effects of an environmental exposure common to members of the same family and a genetic disease.[21] Concordance with respect to multiple sclerosis has been studied in identical twins and found to be low.[22] This is one of the most serious arguments against a purely hereditary basis for multiple sclerosis. Aside from the tendency to a slightly higher rate in females and a slight tendency to a familial aggregation of cases, the occurrence of multiple sclerosis in a community appears to be on an almost random basis within the young adult group.

A very practical question which is often asked is: Should patients with early multiple sclerosis be advised to migrate to a warmer latitude where the prevalence is low? Multiple sclerosis is a disease marked by remissions and exacerbations; in general, the more frequent the exacerbation, the more rapid the progression. The cause of the exacerbation is no better understood than the etiology of the disease. Long-standing clinical attitude has been to recommend that patients move to a low prevalence area in the hope that exacerbations would be fewer; however, there is no evidence that such a change has a beneficent effect. No patient group which has migrated from one area to another has been carefully evaluated. The only comparative study was on life expectancy in New Orleans and Winnipeg.[4] Although the life expectancy of patients who could be identified in the two communities seemed to be equal, the data were limited and the results thus indecisive. In the absence

of any specific treatment, and until a decisive study is made, it seems that migration to a warm latitude might be worth trying if it would cause no economic or emotional hardship, and if the patient recognizes that the benefits are uncertain.

There are many other areas yet to be explored. The similarity of the geographic distribution of multiple sclerosis to that of rheumatic fever remains a point of interest and speculation. The cause of rheumatic fever is unknown, but a hypersensitive reaction to streptococci is suspected. It has been suggested that multiple sclerosis may also be a manifestation of an allergic hypersensitivity possibly triggered by a virus infection. The analogy between the tissue-specific type of hypersensitivity reactions reported in various animals inoculated with kidney and heart tissue and that of demyelination produced in animals inoculated with brain substance might also be cited as evidence of an isoallergic factor in multiple sclerosis. However, the sequence of events that could initiate such an allergic reaction in humans (liberation of tissue antigen from the CNS stimulating antibody formation, which in turn react with the original tissue) is as yet completely unknown.

Multiple sclerosis may be a syndrome in which a specific agent prevalent in the temperate zones is rare or absent in the subtropics and tropics, accounting for the differential incidence geographically. Another possibility is that clinically recognized cases of multiple sclerosis represent only a small segment of the total spectrum of the disease process and that, for reasons still unknown, the proportion of subclinical cases is less in the temperate than in the other zones.

Efforts continue to be made to isolate a virus from multiple sclerosis patients. A new area in this field has been opened by the studies on scrapie, a chronic neurological wasting disease of sheep.[23] Under natural conditions this disease seems to be genetically determined. Experimentally the disease has been successfully transmitted after an incubation period of months or even years to sheep, goats, and mice by the inoculation of brain homoginate from affected animals. This possible dual mechanism of a genetic and an infective agent (so-called provirus) could provide better understanding of etiologic mechanisms of human disease.

Summary and Conclusions

Multiple sclerosis has a remarkable geographic pattern with the highest prevalence and mortality rates in the temperate zones of both hemispheres and with decreasing rates in the subtropics and tropics. This difference is associated with geography rather than with race or national origin. No specific exogenous or genetic basis for the geographic pattern has been identified, but it is speculated that some climatologic condition influences the frequency of the disease. It is unknown whether this effect is a direct one on the patient or an indirect effect on the animal or plant life in his environment. Migratory populations have been especially useful in this research and indicate that the rate among those migrating from a high to a low risk area exceeds that of the population into which they have immigrated. In the studies of migrating populations, the average minimal latent period from presumed exposure in their prior home to the onset of symptoms has been estimated to be about 9 to 12 years.

It will be essential to clarify many of the features referred to above. Communities on the same latitude, but having different climates with respect to temperature and sunshine, should be compared. Similarly investigation of communities having different altitudes could be rewarding.

It may well be that the causes of

multiple sclerosis are determined by several factors, including a genetic predisposition, and the importance of each factor may vary in different geographic areas. It is still reasonable to expect that future etiologic hypotheses should be consistent with the known geographic distribution.

REFERENCES

1. McAlpine, D.; Compston, N.; and Lumsden, C. Multiple Sclerosis and the Demyelinating Diseases. Baltimore, Md.: Williams and Wilkins, 1955.
2. Limburg, C. "The Geographic Distribution of Multiple Sclerosis and Its Estimated Prevalence in the United States." Chap. II in Multiple Sclerosis and the Demyelinating Diseases. Baltimore, Md.: Williams and Wilkins, 1950.
3. Kurland, L. T., and Westlund, K. Epidemiological Factors in the Etiology and Prognosis of Multiple Sclerosis. Ann. New York Acad. Sc. 58:682–701, 1954.
4. Westlund, K., and Kurland, L. T. Studies on Multiple Sclerosis in Winnipeg, Manitoba and New Orleans, Louisiana. Am. J. Hyg. 57:380–407, 1953.
5. Stazio, A. Personal communication.
6. Hyllested, K. Disseminated Sclerosis in Denmark. Prevalence and Geographical Distribution. Copenhagen, Denmark: J. Jorgenson, 1956.
7. Millar, J., and Allison, R. Familial Incidence of Disseminated Sclerosis in Northern Ireland. Ulster M. J. 23:29–91, 1954.
8. Sutherland, J. Observation on the Prevalence of Multiple Sclerosis in Northern Scotland. Brain 75: 635–654, 1956.
9. Okinaka, S.; McAlpine, D.; Miyagawa, K.; Suwa, N.; Kuroiwa, Y.; Shiraki, H.; Araki, S.; and Kurland, L. T. Multiple Sclerosis in Northern and Southern Japan. World Neurology 1:22–42, 1960.
10. Acheson, E. Multiple Sclerosis in British Commonwealth Countries in the Southern Hemisphere. Brit. J. Prev. & Social Med. 15:118–125, 1961.
11. Dean, G. Disseminated Sclerosis in South Africa. Brit. M. J. 1:842–845, 1949.
12. ————. (Personal communication.)
13. Rozanski, J. Contribution to the Incidence of Multiple Sclerosis Among Jews in Israel. Monthly Rev. Psychiat. & Neurol. 123:65–72, 1952.
14. Alter, M.; Halpern, L.; Bornstein, B.; Silberstein, J.; and Kurland, L. T. Multiple Sclerosis in Israel. A.M.A. Arch. Neurol. & Psychiat. 7:253, 1962.
15. Swank, R.; Lerstad, O.; Strom, A.; and Backer, J. Multiple Sclerosis in Rural Norway. New England J. Med. 246:721–728, 1952.
16. Ichelson, R. Cultivation of Spirochete from Spinal Fluid of Multiple Sclerosis Cases and Normal Controls. Proc. Soc. Exper. Biol. & Med. 95:57, 1957.
17. Acheson, E.; Bachrach, C.; and Wright, F. Some Comments on the Relationship of the Distribution of Multiple Sclerosis to Latitude, Solar Radiation and Other Variables. Acta psychiat. et neurol. scandinav. 35:132–147, 1960.
18. Schneider, H., and Lee, J. The Effect of High Intensity Fluorescent Illumination on Experimental Allergic Encephalomyelitis. Federal Proc. 46th Ann. Meeting 21:270, (Mar.-Apr.), 1962.
19. Kurland, L.; Mulder, D.; and Westlund, K. Multiple Sclerosis and Amyotrophic Lateral Sclerosis —Etiologic Significance of Recent Epidemiologic and Genetic Studies. New England J. Med. 252: 649–653, 1955.
20. Barlow, J. S. Correlation of the Geographic Distribution of Multiple Sclerosis With Cosmic Ray Intensities. Acta psychiat. et neurol. scandinav. 35: 108–131, 1960.
21. Reese, H., and Kurland, L. T. Multiple Sclerosis— An Unsolved Problem in Medicine: A Review of Present Investigation into Etiologic Factors and Pathogenic Mechanisms. Medicine in Japan 741–748, 1959, Vol. V.
22. Muller, R. Genetic Aspects of Multiple Sclerosis. A.M.A. Arch. Neurol. & Psychiat. 70:733–740, 1953.
23. Parry, H. Scrapie: A Transmissible and Hereditary Disease of Sheep. Heredity 17:75–105, 1962.

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