

MULTIPLE SCLEROSIS

A REAPPRAISAL

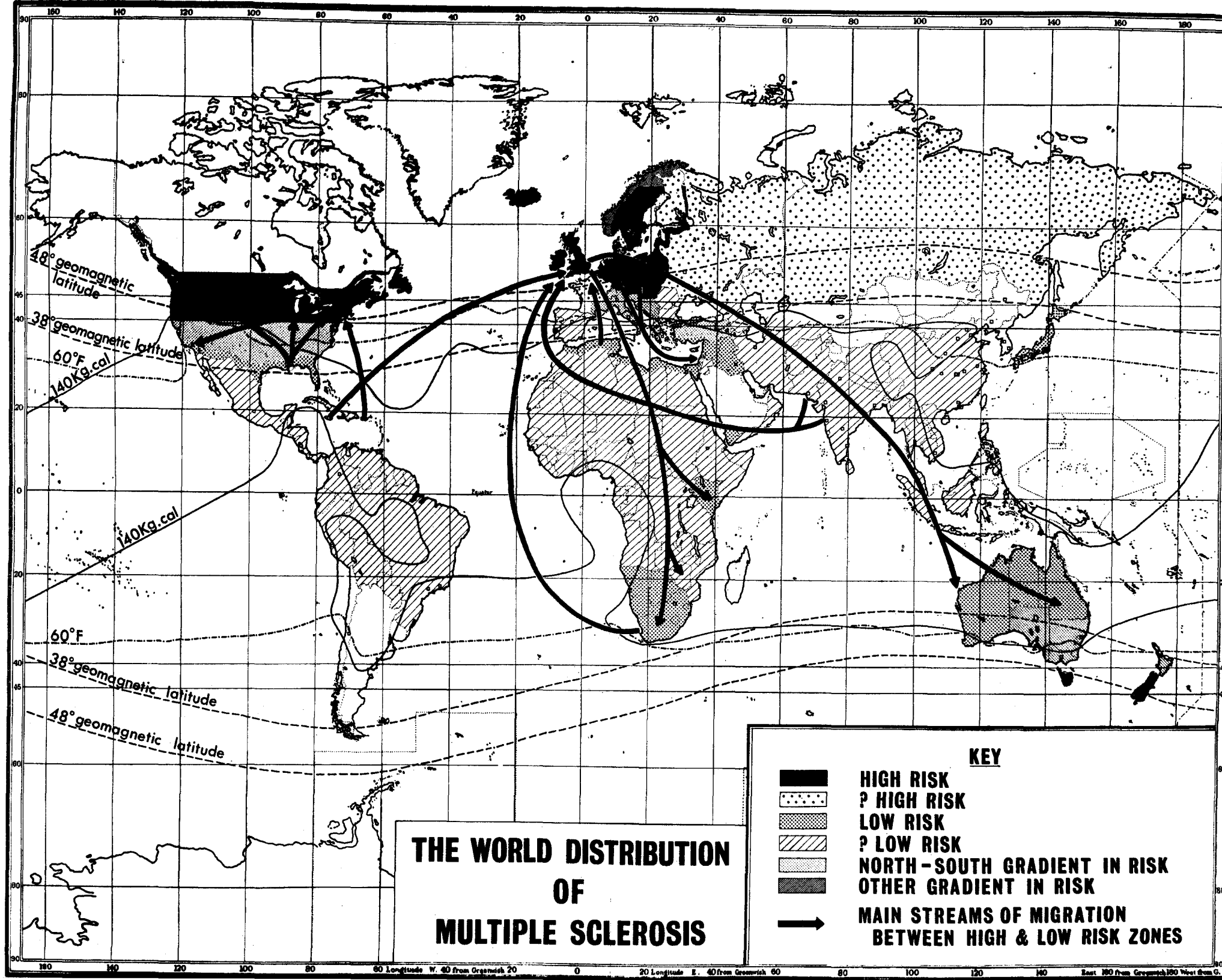
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



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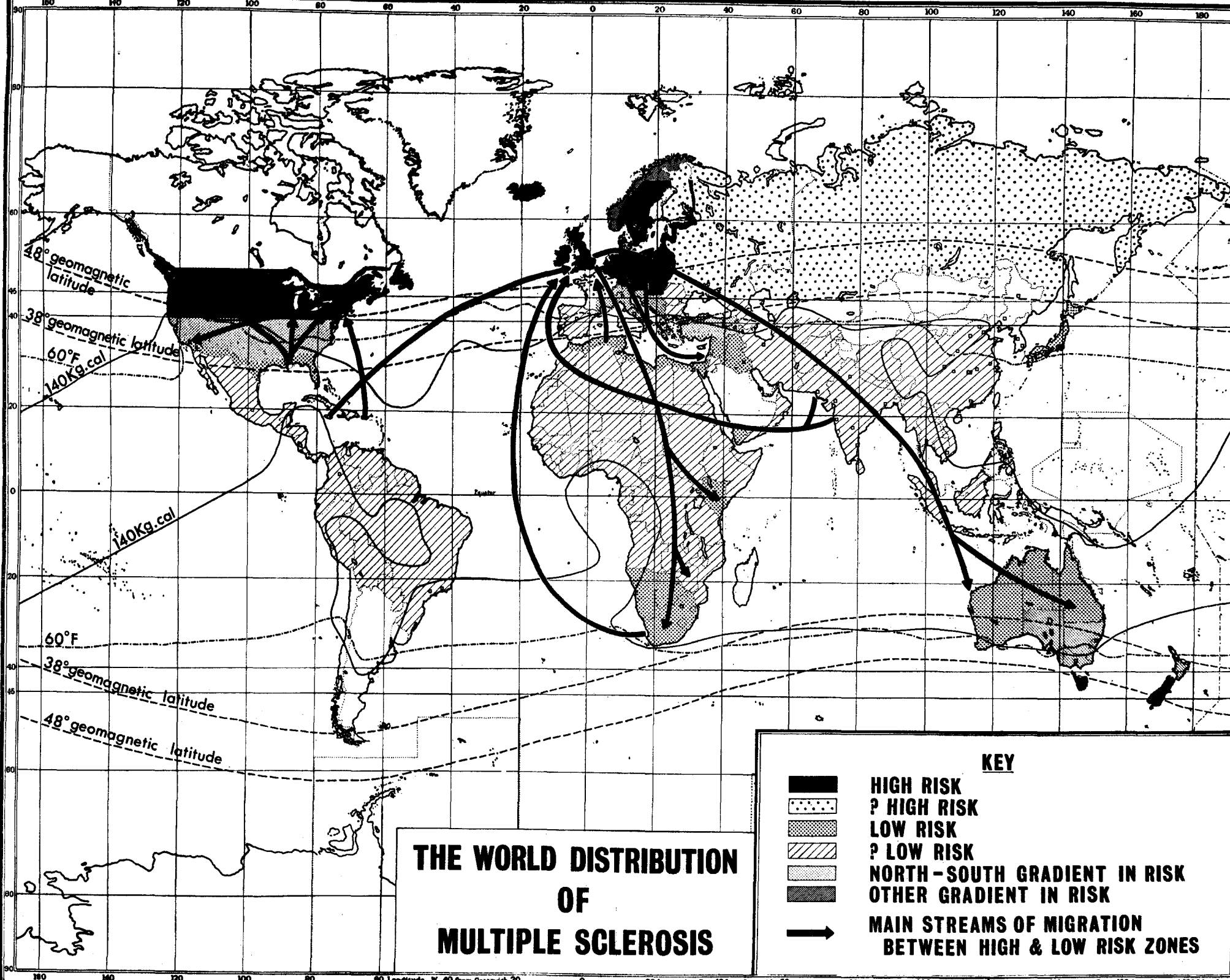
1968



**THE WORLD DISTRIBUTION
OF
MULTIPLE SCLEROSIS**

KEY

-  **HIGH RISK**
-  **? HIGH RISK**
-  **LOW RISK**
-  **? LOW RISK**
-  **NORTH-SOUTH GRADIENT IN RISK**
-  **OTHER GRADIENT IN RISK**
-  **MAIN STREAMS OF MIGRATION
BETWEEN HIGH & LOW RISK ZONES**



important factor. There is at present no evidence to suggest that persons emigrating from high to low risk areas incur a *higher risk than if they had remained at home* (cf. poliomyelitis, see Poskanzer, Schapira and Miller, 1963).

The evidence concerning the reciprocal situation (migration from low to high risk zones) is much less complete but there is at least a suggestion that a visit from low risk to high risk zone may increase risk. It would be interesting if the collection of further data showed that the longer the period of exposure, the higher the risk. These findings are not necessarily contradictory but may suggest that the required period of exposure may be short but that the incubation or latent period may be long. If this were so one would expect an excess of cases in immigrants from the high risk zone in low risk areas with appreciable immigrant populations; but in the reciprocal situation in the high risk zone immigrants from the low risk zone might be expected in due course to take on the risk of their new domicile.

III. IS MULTIPLE SCLEROSIS BECOMING COMMONER?

This is perhaps the most difficult question in a perplexing subject. To answer it with certainty for any given community, incidence rates by age and sex over a period of decades are required. At present no such information exists although eventually it will be forthcoming from Denmark where a national multiple sclerosis case register exists.¹ Prevalence data is available for the same community at two points in time for north Scotland (Sutherland, 1956; Allison, 1963), Switzerland (Bing and Reese, 1926; Ackermann, 1931; Georgi and Hall, 1960), Denmark (Gram, 1934; Hyllested, 1956), Boston (Ipsen, 1950; Kurland, 1952), Turkey (Mutlu, 1954, 1959), and Winnipeg (Kurland, 1952; Stazio *et al.*, 1963). In every case except Winnipeg the second estimate of prevalence has been higher than the first. This is consistent with an increase in incidence, a fall in fatality with a reciprocal lengthening of survival, or, perhaps more likely, fuller case ascertainment on the second occasion due to interest in the condition having been aroused by the first survey.

Mortality data are less suitable for the study of time trends in multiple sclerosis than for any other purpose. This is not only because they will only reflect changes in incidence after a considerable interval of time but because of the various revisions of coding procedures which have been introduced at different times in different countries. Crude death rates by sex are available from the beginning of the century for New Zealand and Switzerland, from 1921 for England and Wales and

¹ While this book was in press Dr Kurland kindly made available to the author the following unpublished average annual incidence rates for Winnipeg: 1940-4, 1.9; 1945-9, 1.4; 1950-4, 1.8; 1955-9, 1.4.

from 1931 for Canada and Australia. There has been little change over this period in the death rate for all persons in England, Australia, Canada and New Zealand but the rate in Switzerland increased steadily from 1905 to 1938, since when it has levelled off. According to Georgi and Hall (1960) the proportion of all autopsies in which multiple sclerosis has been found has also increased in Zurich and Basle but not elsewhere. It is of interest that in all nine countries for which WHO was able to collect data for the period 1931-54 (Canada, Ireland, Italy, Netherlands, England and Wales, Scotland, Switzerland, Australia and New Zealand) the risk of death from multiple sclerosis increased in women relative to men (Table 7). This may simply reflect increasing homogeneity of the data.

TABLE 7

Sex ratios between death rates from multiple sclerosis: then and now

Countries for which a 5-year mortality rate is available for 1931-5 or earlier	Female/male sex ratio	
	1931-5	1951-4
Canada	0.83	0.92
Ireland	0.50*	0.88
Italy	0.80	1.00
England and Wales	0.95†	1.47
Scotland	1.04	1.24
Switzerland	1.54†	1.81
Australia	0.73*	1.50
New Zealand	1.00†	1.09
Holland	1.21	1.31

* 1926-30.

† 1921-5

It is perhaps worth noting that where prevalence and mortality rates for the same locality depart from the expected line of correlation (Fig. 1) one possible explanation is that there has been either a rise or fall in incidence of multiple sclerosis in that locality in recent decades. If this were so it could be deduced that there had been an increase in incidence of multiple sclerosis in Iceland and a decrease in Northern Ireland and Scotland in the last two decades. However, local artifacts have already been mentioned which might have elevated the Scottish mortality rate and depressed the Ulster incidence and prevalence rates. Similarly an artifact might account for the discrepancy between the Icelandic mortality rate (0.7) and prevalence rate (44 per 100,000).

In conclusion it may be said that there is certainly no good evidence that multiple sclerosis has decreased in incidence in any part of the world. The evidence, such as it is, is consistent either with an increase in the incidence of the disease or at least with a maintenance of the same incidence over the last 50 years.

part of the spectrum is filtered out over large cities and no increased risk in cities such as was the rule in rickets has been found in multiple sclerosis (*vide supra*). Although a direct biological action of any other part of the spectrum seems unlikely, it is of some interest that Klüver (1954) has found that coproporphyrin III which fluoresces at 625 $m\mu$ is widely distributed in mammalian white matter.

If sunshine rather than temperature were a factor, experience at high altitudes should provide the necessary conditions for discrimination between these variables. In Denver, Colorado (5,280 feet), Kurland found the expected prevalence for that latitude and in Missoula County, Montana (3,223 feet), prevalence was also high. In Switzerland, on the other hand, a negative relationship can be demonstrated in Georgi and Hall's data between altitude and prevalence, but it is too irregular to suggest a direct effect. Thus no conclusive evidence of an influence of altitude on the risk of multiple sclerosis has been demonstrated.

In summary, the world pattern of multiple sclerosis does not fit the hypothesis that multiple sclerosis is due to the direct action of a climatic variable on the human body in the sense that frostbite, cold haemoglobinuria, rickets or carcinoma of the skin are directly related to climate. The frequency of 'chilling' must be correlated with coldness of winter, and we have seen that this is too much a correlate of distance from the ocean to fit well with the distribution of multiple sclerosis. Neither could a direct protective effect of solar radiation by itself account for the whole pattern of the disease. The possible ways in which climate might be related indirectly to the aetiology of multiple sclerosis are discussed below.

3. *Diet.*—If a constituent of the diet is implicated in the aetiology of multiple sclerosis it is likely to be one in which the pattern of production is conditioned by climate in such a way that it approaches the pattern of incidence of multiple sclerosis, but which is not sufficiently prized to be worth transporting over large distances to be consumed in other parts of the world. In theory such a substance might act as a protective factor in the diets eaten in the low risk zone or as a toxic factor in the diets of the high risk zone.

The species of fruit, cereals and vegetables produced vary in different parts of the world because of the sensitivity of plants to day length, temperature and precipitation. However, such a wide variety of subtropical fruit is now imported into countries in the high risk zone, including Iceland and Norway (e.g. citrus fruits and bananas), and both temperate (e.g. apples and pears) and subtropical fruits are so abundant in the northern United States and Canada, that it is unlikely that the lack of any constituent of fruit could be responsible for the high risk in these areas. Of the cereals (wheat, maize, oats, rye, rice, millets, barley) both wheat and maize are in common use in both high

history and to the findings in the cerebrospinal fluid. Multiple sclerosis is the usual cause of a spastic paraplegia in more than one member of a family. A history of this condition in a sibling or parent or near relative, especially if confirmed by a physician or by hospital records, would suggest the probability of multiple sclerosis in another member of the family provided the history, signs, and results of examination of the cerebrospinal fluid are compatible with that diagnosis.

The choice of subjects to be discussed under the heading of diagnosis will be limited to those which are most likely to cause difficulty.

X RETROBULBAR NEURITIS

Although this condition has such an intimate and characteristic relationship to demyelinating disease in general and to multiple sclerosis in particular, other causes of rapid loss of vision attended by defects in central vision must not be forgotten. The swelling of the optic disc (papillitis) occasionally met with in multiple sclerosis is usually unilateral and confusion with papilloedema is unlikely if due importance is attached to the accompanying rapid loss of vision in retrobulbar neuritis. When this is due to severe states of malnutrition, tobacco, toxic agents (including insecticides) or pernicious anaemia a pale disc may result. The onset of the defect, however, is seldom abrupt, pain in the eye and tenderness of the eyeball—frequent accompaniments of retrobulbar neuritis due to demyelination—are absent, and loss of central vision is usually bilateral and tends to be progressive. The cause is not likely to emerge until a full history has been taken and the results of examination of the cerebrospinal fluid, blood, and gastric contents have been made available (see under Subacute Combined Degeneration of the Spinal Cord, p. 156).

In young persons exudative choroiditis may cause rapid failure of central vision due either to involvement of the macula directly or to spreading oedema; clouding of the vitreous by inflammatory exudate may be a complication. Similarly a central serous retinopathy characterised by oedema without inflammation may cause objects to appear hazy or distorted. In both these states a central scotoma may occur and clear up in the course of a few weeks. The scotoma so produced may be positive, thus enabling the patient to draw it. When doubt exists as to the cause of a rapid failure of vision the importance of an ophthalmologist's opinion is obvious.

In our experience an attack of iridocyclitis is not a rare finding in the history of multiple sclerosis patients. Confusion with an attack of retrobulbar neuritis is unlikely, because the patient can usually remember not only pain but also the abnormal appearance of the affected eye and photophobia.

Rapid failure of central vision in one or both eyes may occasionally