MULTIPLE SCLEROSIS

A REAPPRAISAL

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SECOND EDITION

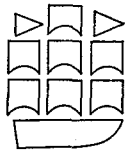

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TABLE 1, I *Collected incidence, prevalence and mortality data*

Place surveyed	Prevalence year	Prevalence rates			Population of survey area in thousands	Cases examined	Incidence rates¶			Age at onset			Crude death rate	Latitude‖
		M	F	P			M	F	P	M	F	P		
N. Ireland†	1951	46	57	51	1371	+	2·0	2·4	2·2	33	32	32	2·8	55°
Missoula	1957	—	—	59	43	+	—	—	1·9	36	29	—	1·3	47°
Boston Mass. (W)	1949			41	846	–	1·8	3·4	2·6	33	29	31	1·2§	42°
Denver Colo.	1949			38	416	–			2·2	34	30	32	1·1‡	40°
Winnipeg*	1949			35	314	+				31	29	30	1·4§	50°
	1962	27	44	35						27	26	26	1·6	
New Orleans* (W)	1949	8	12	10	485	+	0·3	0·6	0·4	33	29	30	0·3§	30°
(W)	1962	7	16	12	599	+								
South Africa (W)	1960	5	13	9	3078	+	0·3	0·8	0·6	—	—	31	0·4	(30°)
Northumberland	1958	—	—	50	2308	+	—	—	—	—	—	36	2·0‡	55°
San Francisco	1949			30	775								0·9‡	38°
Rochester Minn.	1965	60	107	88	33	+	2·3	4·1	3·2	—	—	32	2·1§	44°
Kingston Ont.	1949			57	30	+							1·5§	44°
Japan Kumamoto	1957	—	—	2	332	+	—	—	0·3	—	—	—		33°
Sappora	1957	—	—	2	426	+	—	—	0·3	—	—	—	0·1‡	43°
Fukuoka	1960	—	—	2	608	+	—	—	—	—	—	—		34°
Niigata	1960	—	—	4	230	+	—	—	—	—	—	—		38°
Queensland Cairns														(17°)
Townsville		—	—	5	237	+	—	—	—	—	—	—	0·7‡	(20°)
Mackay														(21°)
Downs				10	142	+	—	—	—	—	—	—		(28°)
Charleston S.C. (W)	1955	—	—	19	188	+	—	—	—	—	—	31	0·5‡	33°
Halifax N.S.	1955	—	—	32	198	+	—	—	—	—	—	31	1·2‡	45°
Denmark	1950	58	70	64	4252	+	—	—	(4·7)	31	30	31	2·0	56°
Switzerland	1957			51	5117	–							2·5‡	47°
Israel	1960			15	1735	+							0·5‡	32°
Orkneys and Shetlands	1954			118	40	+	—	—	—	—	—	—	5·9‡	59°
	1960			128	40	+	—	—	—	—	—	—	—	
North Scotland	1954			56	192	+							3·7‡	58°
Faeroes				37	35	+	—	—	—	—	—	—	—	57°
Cornwall	1958			63	339	–							2·4‡	50°
Stamford Lincs.	1949			44	41	+							1·9‡	52°
Gröningen (Dassel, 1960)	1959			56	472	+							1·8	53°
Iceland	1955	58	89	44	158	+	2·0	2·1	2·1†	—	—	27	0·7‡	65°
Hamburg	1960	—	—	57	1731	+	—	—	—	—	—	—	—	54°
Marseilles	1960	—	—	14	662	+	—	—	—	—	—	—	—	43°
W. Norway	1961	38	38	38	214	+	—	—	(1·9)	—	—	32	—	62°
S.E. Norway	1959	71	90	80	158	+	—	—	5·0	32	31	32	—	60°
Parma	1960			12									—	45°
Wellington N.Z.	1968	20	56	39	296	+	1·3	2·4	1·9				0·9	(42°)
Perth W.A.	1961	13	27	20	420	+	0·6	1·7	1·2	34	33	—	0·4	(32°)
Hobart Tas.	1961	20	46	33	116	+	—	—	2·2	36	32	—	1·5	(43°)
Newcastle N.S.W.	1961	17	21	19	143	+	—	—	1·2	27	32	—	—	(33°)
Mexico	1968	—	—	2	600	+	—	—	—	—	—	27	—	20°
West Australia (rural)	1961	5	24	14	187	+	0·6	1·5	1·1	35	32	—	0·3	(32°)

* Figures given are taken from the second survey.

† The published rates were based on part of the population only; here they have been recalculated using the whole population.

‡ Mortality rates based on published mortality returns.

§ Taken from Kurland (1952) Table 10.

‖ Parentheses indicate South latitude.

¶ Parentheses indicate calculated figures. (W) figures refer to white population.

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The Epidemiology of Multiple Sclerosis (continued)

I. THE DELINEATION OF HIGH AND LOW RISK ZONES

The 40 prevalence rates for the surveys selected in Table 1,I have been plotted on a world map in Figure 2,1a. Each survey is represented by a circle the diameter of which is proportional to the prevalence in that area. The general relationship of prevalence to distance from the equator in both hemispheres is well shown. The mortality data displayed in Figure 2,1b make a similar pattern with minor differences.

It is now possible to divide large areas of the world into zones according to the risk of developing multiple sclerosis. The definition of such zones is necessarily arbitrary and carries the risk that it may obscure certain features of the pattern.

In the following paragraphs the definitions used will be as follows. High risk zone: prevalence in excess of 40 per 100,000 and death rates in excess of 1·0 per 100,000. Low risk zone: prevalence rates less than 20 per 100,000 and death rates less than 0·5 per 100,000.

1. No population with a high risk of developing multiple sclerosis is known to exist between latitudes 40° N and 40° S. This area includes, in the Old World, the whole of Africa, the southern part of the Mediterranean basin, the Levant, the Middle East, the Indian subcontinent, South-East Asia, the whole of Australia except Tasmania,[1] and the bulk of Japan. In the New World it includes the southern United States, Central America and the Caribbean and South America apart from the southern parts of Chile and the Argentine.

2. Almost all populations that have been surveyed between 47° and 60° in Europe and north of 40° in North America have shown high risks. Exceptions are the surveys along the West coast of Norway and in the Faeroe Islands which have yielded prevalence rates in the upper part of the intermediate range (see Table 1, I).

In the Southern Hemisphere, surveys of communities south of 40° (Hobart, Tasmania and Wellington, N.Z.) have yielded figures (33 and

[1] Victoria, with a mortality rate of 1·0 per 100,000 is a borderline case.

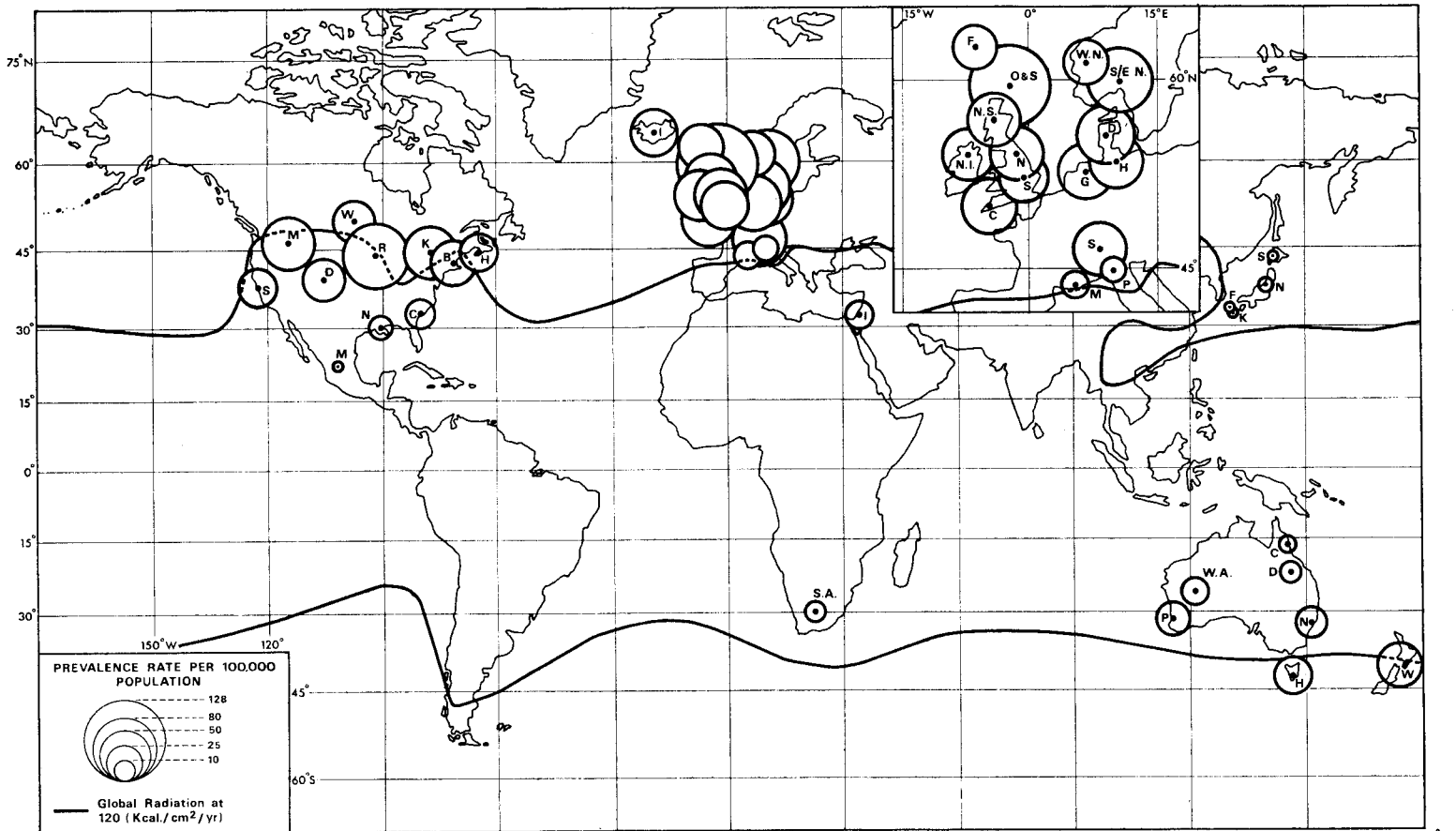

FIG. 2,1(a)
World distribution of multiple sclerosis – prevalence.

1963

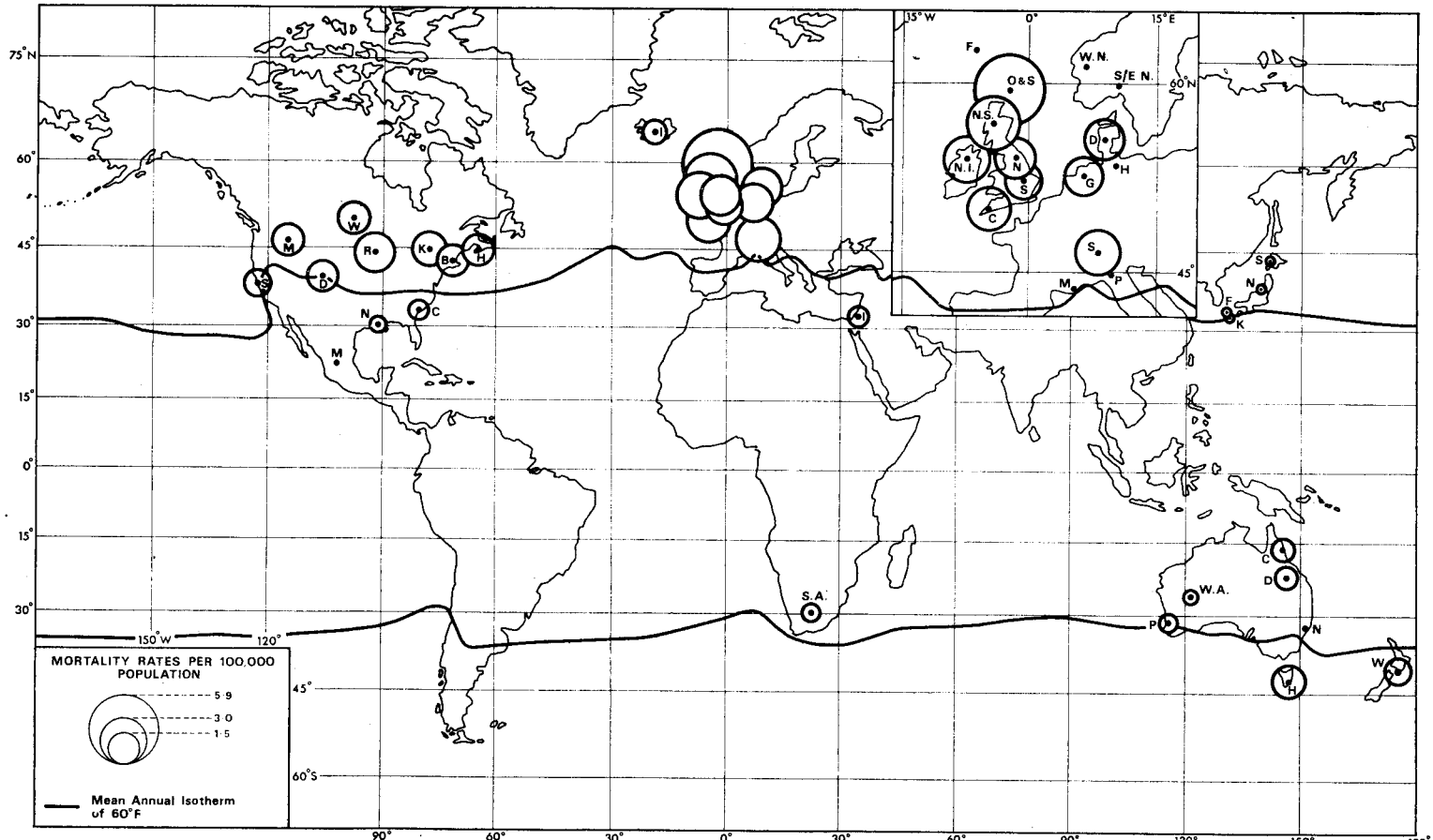

FIG. 2,1(b)
World distribution of multiple sclerosis – mortality. 1963

In conclusion it must be said that, contrary to the hopes expressed in the last edition of this book, recent work on the effect of migration on the risk of developing multiple sclerosis has so far failed to clarify the mechanism of the aetiological process. Indeed further work has if anything emphasised the apparent inconsistencies in the findings from different countries.

The evidence that emigrants from 'high' to 'low' risk areas carry with them at least part of the risk of their birthplace is strongest for South Africa. For Israel it is also strong and would probably be strengthened further if more data were available about the age composition of the various groups. For Australia and the United States no evidence in favour of a higher risk in immigrants to an area of low prevalence has appeared in spite of the publication of further surveys from Queensland, Western Australia and New Orleans. One simple explanation of this would be that these areas are in fact in the high risk zone and that the surveys have found only a small fraction of the cases. This seems unlikely particularly in view of the fact that each of these areas has been the site of two successive surveys. My own view is that a number of factors are probably involved including: relatively small numbers of immigrants from the high risk zone (New Orleans and Northern Queensland), stringent medical examination prior to entry to the country (all parts of Australia) and, in the case of Western Australia, a local prevalence, which is relatively closer to that of the high risk area (18) than Northern Queensland (6) or New Orleans.

No evidence has emerged to suggest that the risk of multiple sclerosis is increased for residents in the temperate zone by travel to the tropics—as in poliomyelitis. Nor is there any evidence that the disease in immigrants differs in severity or in character from that experienced by other groups. It would be interesting to have more detailed information about age of onset in cases of multiple sclerosis where symptoms commenced after migration.

Apart from some suggestive anecdotes referred to above there is at present no evidence to support the view that immigrants from low risk countries to countries where the disease is common have a higher risk than those who remain in the low risk zone. More information on this point is necessary.

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. 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, 1960), Winnipeg (Kurland, 1952; Stazio *et al.*, 1964; New Orleans (Kurland, 1952; Stazio *et al.*, 1967) and Perth, W.A. (Saint and Sadka, 1962; McCall *et al.*, 1968). 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.

Recently a meticulous study from Rochester, Minnesota has made available incidence and prevalence rates for a carefully observed community over a period of 60 years (Percy *et al.*, 1968). The high standard of ascertainment is due to the presence of the Mayo clinic in Rochester

TABLE 2,II

Incidence and prevalence of multiple sclerosis in Rochester, Minnesota 1905-65 (from Percy *et al.*, 1968)

	Incidence rate per 100,000	Prevalence rate per 100,000
1905 –1914	5·1	46
1915*–1924	3·6	41
1925*–1934	5·3	56
1935*–1944	2·3	71
1945*–1954	2·7	80
1955*–1964	3·2	88

* Point prevalence rates measured on Jan. 1st of these years.

and the excellent system of medical records which it maintains. Table 2,II shows that there has been no convincing change in incidence in this century. The increase in prevalence is probably due to lengthening of the period of survival due to more efficient treatment of complications. The high autopsy rate, and the very high proportion of cases in which the pathological findings confirmed the diagnosis (12 of 13 cases) are remarkable features of this survey.

Mortality data are less suitable for the study of time trends in multiple sclerosis than for any other surpose. 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 from 1931 for Canada and Australia. There has been little change over this period in the death rate for all persons in England, Australia,

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 and low risk zones (e.g. in the northern United States and in Italy). All the major rice-eating countries of the East are thought to have little multiple sclerosis, but rice is not widely used in other low risk areas such as South Africa, Italy or the southern United States. The production of oats is high throughout the high risk zone and little (3 per cent in 1953-5)[1] is exported for human consumption to the low risk zone. Exact data concerning the distribution of the use of oats in porridge, oat cakes, etc., are not available but it is doubtful whether it is eaten in Canada or the United States in any quantity except by Scots and their immediate descendants. Barley, rye and millets are not sufficiently widely eaten to be of interest.

The world pattern of production of the potato (*Solanum tuberosum*)

[1] This and other material in this section derived from the *Oxford Economic Atlas*.

that would produce a perpetual menstrual flow, while another patient stated that her husband could immediately tell the day of onset of her period by the marked improvement in her walking. On the other hand there is some evidence that menstruation may occasionally have the reverse effect. McFarland (1969) has reported the case of a female, aged 36, who for the previous 18 months had an exacerbation of symptoms exclusively during menstruation. Total urinary oestrogens were lower than usual with the onset of menstruation. Over a two-year period of treatment with an oestrogen-progestin compound, the patient remained free from symptoms during menstruation, total oestrogens became normal and her clinical status improved.

Abnormal Reaction to Foreign Substances

In 1938 Dr Foster Kennedy in a paper entitled *Allergy and its Effect on the Central Nervous System* described several cases in which neurological signs were associated with some form of allergic disorder, and instanced the case of a girl aged 20 in whom a diagnosis of multiple sclerosis had been based on recurrent attacks of retrobulbar neuritis over the previous two years. No attention had been paid to a history of urticaria, recurrent attacks of eczema and of asthma, the latter being brought on by contact with rabbits. She proved to be highly sensitive to *streptococcus viridans*. Following tonsillectomy there was no recurrence of retrobulbar neuritis nor other evidence of multiple sclerosis over a four-year follow-up period.

Kennedy was unwilling to accept multiple sclerosis as a diagnosis in these cases on the grounds that neurological signs tended to clear up with treatment of the underlying allergy. He considered, however, that oedema, which he assumed to be the basis of the temporary neurological symptoms in his cases, if often repeated might cause changes in nervous tissue similar to those met with in multiple sclerosis.

In the discussion which followed Kennedy's paper, Frantz (1938) described the following case:

> A girl with a history of urticaria since childhood provoked by eating chocolates and egg, in March 1937, aged 16, began to eat chocolate candies. The following month numbness in feet and legs spread to her arms and walking became unsteady. By June symptoms had cleared. In mid-October she awoke one morning with severe giddiness and numbness in the right arm; a few days later she saw double. On 3rd November, ataxia of both arms and a left extensor plantar response were noted. She was forbidden to eat chocolate or egg. On 25th November of the same year she was admitted to hospital with a three-day history of unsteadiness in walking; marked ataxia, bilateral extensor plantar responses and ankle clonus were present. Starvation for 24 hours followed by a gradual increase in diet coincided with rapid improvement, both plantar responses becoming flexor. While still

Ebbing, 1895). In our 1955 book (page 58) we described the case of a male, aged 30, who in the late evening, during a swim in water which was very cold, got into difficulties because his right leg suddenly went 'dead'. He was rescued by a passer-by. Next day as numbness was still present he was admitted to hospital and later discharged from the Army with signs typical of multiple sclerosis.

Lowering of body temperature by cold baths or cold air provides temporary relief (Boynton *et al.*, 1959; Watson, 1959) and may be used as an adjunct to physiotherapy in the treatment of spasticity.

Tobacco

We have previously commented on the fact that cigarette smoking may cause a temporary worsening of such symptoms as dysarthria, tremor, paraesthesiae, motor weakness and visual impairment in some multiple sclerosis patients—an observation originally made by Franklin and Brickner (1947) and recently by Wüllstein (1957; Courville *et al.*, 1964). Spillane (1955) has reported an adverse effect of smoking and intravenous nicotine in three out of 11 cases of spino-cerebellar ataxia and in one of five cases of multiple sclerosis showing ataxia. In 16 patients suffering from a variety of organic diseases of brain or spinal cord no such effect was produced.

From these few facts it is apparent that smoking may be harmful to some multiple sclerosis patients and that the temporary ill effects are not peculiar to this disease.

ASSOCIATED DISEASES

'With increasing interest in autoimmune disease and more careful examination, it is becoming clear that many patients show symptoms or signs of some other autoimmune condition than that of his or her primary diagnosis' (Burnet, 1962). Whether this quotation can be rightfully applied to multiple sclerosis must for the present remain an open question; nevertheless, it should encourage us to look beyond the nervous system in every patient suspected of this disease for evidence, past, present and in the future, of an abnormal antigen-antibody reaction in any other system. With the exception of periphlebitis retinae, uveitis and possibly allergic disorders, no special association of any disease with multiple sclerosis has yet been established, perhaps because of 'lack of interest'. Here is a field, only partially explored, which deserves more attention from clinician, epidemiologist and immunochemist in the hope that fresh light, albeit indirect, may be thrown on the nature and behaviour of the immune reaction in the