MULTIPLE SCLEROSIS

Clues to its cause

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laboratory methods are devised, the diagnosis of MS must be based largely on clinical criteria for which a clinical method must be used.

Definition of MS under field conditions

A clinician who deals with individual patients may postpone a decision as to whether MS is the correct diagnosis until the clinical course makes the diagnosis obvious. However, the clinical investigator who studies MS in a population must make a decision at the time of initial contact with a patient; he may not see the patient again. The study of MS in populations is sometimes called field investigation because the investigator usually goes out into the community to collect facts about the disease. This type of investigator must have excellent clinical skills because the information upon which he must base his clinical judgements is often fragmentary. He must be able to weigh and sift clinical facts as astutely as the physician in the office, but the field investigator does so deprived of the luxury of time to observe the evolution of the disease process. To aid him in making a clinical decision the field investigator relies upon a rigid set of clinical criteria.

The clinical criteria used most widely in diagnosing MS under field conditions are those formulated by Allison and Millar (1954). More recently formulated criteria of the Schumacher *ad hoc* committee (1965) were designed for therapeutic trials and are not necessarily appropriate for field studies of MS with which this monograph is concerned.

Grading the probability of diagnosis of MS

A diagnosis of MS is made if the patient gives a history of remissions and exacerbations of neurological deficit attributable to a lesion in the central nervous system white matter and an examination reveals neurological deficits attributable to disseminated central white matter lesions. Cases that fit this description of having lesions scattered in time and place account for most but not all of those accepted as having MS. In practical situations encountered in the field, the history may be vague or not elicitable and the neurological findings may not always be clear cut. Yet, a decision to accept or reject the case must be made. To handle the dilemmas posed by circumstance in the field, a ranking system has been developed to indicate the degree of assurance that the diagnosis is correct.

Certain MS

A diagnosis of 'certain MS' is reserved for those patients with pathological proof of the diagnosis. Therefore, this category is rarely applicable in clinical field situations.

Early probable and latent MS

Included in this category are patients who show slight or no disability and few physical signs but who have a history of remitting symptoms and signs commonly associated with MS (*e.g.* transient blindness, diplopia, vertigo, ataxia, nystagmus, scotoma, pallor of optic discs, and numbness or weakness in one or more limbs).

Cases are eliminated from this category if they do not exhibit at least one physical sign typical of MS. Patients who are not available for examination are included only when there is documentary proof that typical signs and symptoms have occurred. It should be noted that cases of monocular optic or retrobulbar neuritis alone are not classified as MS as they lack the criterion of 'scattered lesions'.

The 'latent' cases are those among whom the history is suggestive of the presence of scattered lesions in the neuraxis and scattered deficit is confirmed by previous examinations. Yet, on follow-up examination little if any disability exists and few signs of residual central nervous system damage are found.

The 'early' cases are those with presenting complaints which are regarded as being common in MS (*e.g.* double vision, unsteadiness, paresthesia, weakness, visual impairment, sphincter disturbances). If such complaints are supported by findings indicating more than one lesion of the neuraxis, a diagnosis of MS is made even though the patient has no history of previous neurological symptoms.

Several advantages are gained in establishing a separate group of early probable and latent cases. Any field study of MS is bound to encounter cases of such recent onset that serious disability has not yet developed. The proportion of such early and latent cases among the total number reported might be regarded as a rough index of practitioner awareness of the diagnosis of MS. It is known that some patients have a mild course showing little disability and minimal signs, even several years after onset of symptoms. This is related to the tendency of the disease to undergo remission. Despite the lack of serious disability, the history and signs in these early and latent cases leave little doubt that an attack of MS has occurred.

An illustrative case of latent MS follows:

A woman aged 26 in 1951 lost vision in her right eye. Symptoms disappeared after one month. In 1956, at age 31, she had headaches, cramps in the legs, and a sense of inward shaking and 'walked as if drunk'. Nystagmus was then seen. On examination in 1957, six years after onset, she showed slight intention tremor on the left finger-to-no

test and increased tendon jerks in the upper limbs; she had no difficulty in carrying on all her usual activities.

Probable MS

This category includes patients in whom there is no reasonable clinical doubt as to the diagnosis and in whom some physical disability is found. The history is usually that of a remitting disease. On examination, definite physical signs that could be explained only by multiple lesions of the neuraxis are found.

Example: Between 1944 and 1945, this 26-year-old woman had numbness in one hand. In 1946, aged 28, vision became temporarily impaired in the left eye. At the age of 30, the right eye was similarly affected and, at the same time, paresthesia occurred in the left arm. The following year, walking became affected. In 1955, aged 37, she suffered from urinary bladder incontinence for a short time. On examination in 1957, increased emotional lability, pale optic discs, terminal intention tremor (greater on the right), and fine horizontal nystagmus on lateral gaze were noted. Spastic paraparesis was present, but there was no sensory loss.

Possible MS

This category includes patients showing physical disability and definite physical signs indicative of central nervous system disease and suggestive of MS. These patients usually have a progressive rather than a remittent course and do not have sufficient evidence of multiple lesions at varying levels; however, after clinical and laboratory studies, no other cause for the condition can be established.

Example: A 46-year-old woman began to drag her left foot. At that time, examination showed spastic ataxia with extensor plantar responses. Deep tendon reflexes were elicited with difficulty in the lower limbs. Sensation was intact. A myelogram was negative. Urinary bladder function was not affected. When examined at the age of 58, the cranial nerves were intact, but a spastic paraplegia with scissors gait was present. Tendon reflexes in the upper limbs were brisk and equal bilaterally. Tone was greatly increased in the lower limbs. The knee and ankle jerks were difficult to elicit. Extensor plantar responses were present. Vibration and postural joint sensibility were both impaired over the lower limbs and trunk.

Problems in differential diagnosis

Some problems in the differential diagnosis of MS are inevitable in any clinical study. The decisions regarding acceptance or rejection of patients with certain constellations of symptoms and signs must be standardized if the clinical series is to be reliable. The more commonly encountered diagnostic problems are discussed.

Spinocerebellar degeneration

In cases with prominent cerebellar signs and a progressive course, it is often difficult to rule out a primary spinocerebellar degenerative disease. These cases offer special problems in diagnosis and therefore are accepted only as 'possible' MS. Schut and Böök (1953) and Greenfield (1954) have shown that certain signs are more characteristic of the spinocerebellar degenerative disorders than MS; for example, skeletal deformities, onset in childhood, onset at approximately the same age among several members of the family, and coexistent cardiac anomalies. These findings weigh against accepting 'MS' as the diagnosis in some cases. An example of a case that offers such difficulties is given.

Example: A man, born in 1917. His father had been similarly affected and had died at the age of 52. His paternal grandmother had been confined to a wheelchair in the latter years of life, but no details regarding her illness were available. When he was 23 walking gradually became more difficult due to incoordination. A diagnosis of MS was suggested in 1956. In 1958, involuntary spasms of the neck developed. His speech became slurred. On examination in 1958, he had a facile mood and was almost euphoric. Titubation of the head with hyperextension spasms of the neck were present. Vision was normal. Dissociated nystagmus with the coarser component in the abducting eye on lateral gaze was pronounced. On extension of the arms, static tremor was evident. Tendon reflexes were increased in the left arm and a Hoffman response was present, but no increased resistance was obtained on passive movement. Brisk abdominal reflexes and hyperactive knee and ankle jerks with flexor plantar responses were found. Rapidly alternating movements were poorly performed and there was unsteadiness on the heel-to-shin and finger-to-nose tests. He walked with a wide-based gait, taking short, shuffling steps. Sensation was intact, and sphincters were controlled.

Because of the family history of the same disorder, the progressive course and the limitations of signs to the spinocerebellar systems, the case was not accepted as having MS.

An example of a patient with spinocerebellar signs accepted as MS is described in Ch. 1 § 2.

Progressive lateral or posterolateral signs

A history of progressive disability and signs of lateral column or posterior lateral column deficit on examination is not infrequently encountered among patients suspected of having MS. Since disorders other than MS may produce the same clinical picture, studies of gastric acidity, serum B_{12}, the vertebral column, cerebrospinal fluid, and spinal fluid dynamics to rule out other co

peans, but the difference probably reflects the higher proportion of young people in the Afro-Asian and native-born populations.

Our results suggest that the clinical manifestations of MS do not vary despite marked differences in prevalence. We have not been able to support the notion that clinical manifestations vary with geographical latitude. The inference to be drawn is that once affected, a patient is likely to run a similar clinical course whether he lives in a high- or in a low-prevalence area. Sutherland *et al.* (1962) came to the same conclusion on the basis of cases ascertained in Australia.

Diagnostic considerations

It is possible that the same etiological agent causes such radically different manifestations in alleged low-prevalence areas that clinicians have not come to appreciate that a particular clinical picture is allied to MS. Where the disease is rare, only cases with a clinical picture like that encountered in temperate regions would be recognized and diagnosed as MS. The five clinical entities other than MS included in the present survey may not have included the disease form common in low-prevalence areas. This hypothesis may, for example, explain the observations in Japan where MS is allegedly rare but neuromyelitis optica is common (Okinaka *et al.*, 1960).

Other factors which might affect the comparability of European and Afro-Asian groups should be considered. Some selection of clinical material might be caused by a difference in attitude toward medical care among Europeans and Afro-Asians. In one group, there might be a tendency to consult a physician even for mild complaints, but severely affected may be cared for at home, or vice versa. We feel that no such difference in utilization of medical facilities exists between the two groups in Israel.

Selection factors among immigrants

The patients ascertained in Israel in 1960 are immigrants for the most part (only 25 were born in Israel). One may question whether individuals who came to Israel are like individuals in the region of origin. When prevalence of the disease was examined by country of origin (Ch. 6 § 3), it appeared that rates in the immigrants resembled the rates in countries of origin where such data were available. It cannot, of course, be said with assurance that the disease in the immigrants is necessarily like that of individuals who remained behind. It is important to point out that medical status did not serve as a bar to admission to Israel and in many cases whole communities immigrated as a unit. It seems unlikely that selection of immigrants could account for the similarity in clinical picture between Europeans and Afro-Asians.

Afro-Asians, as a group, have a lower economic status than Europeans. However, economic factors in Israel are of negligible importance as a selecting factor for medical care, since a national health scheme keeps the cost of medical care down.

Analogy with poliomyelitis

Poskanzer *et al.* (1963a) have compared epidemiological characteristics of MS and poliomyelitis and have suggested the possibility that a polio-like infection sets the stage for MS. As in MS, a lower frequency of poliomyelitis is seen in tropical regions than in temperate regions. However, the few cases of poliomyelitis which do develop in tropical areas are clinically similar to those in temperate zones.

Environmental factors

The European and Afro-Asian groups differ in many cultural and ethnic characteristics. The geoclimatic factors to which the two groups were exposed before immigration to Israel also were dissimilar in many respects. Yet, clinical characteristics were similar in the two groups. It would appear that the cultural, ethnic, and geoclimatic variables exert little effect on clinical manifestations of MS. Nevertheless, the environmental variables should not be dismissed as being of no importance. Their study may yet disclose a clue to account for the striking difference in prevalence between the two groups.

2. Multiple sclerosis in Orientals

Reports of the frequency of MS in Japanese (Okinaka *et al.*, 1958), Chinese (Woods, 1929; Barlow, 1967; Schaltenbrand, 1943; Urban, 1949), and Koreans (Park, 1966; Barlow, 1967) suggest that this disease may be rare in Orientals. Moreover, the clinical manifestations of MS in Orientals have been reported to be unusual, with a higher frequency of both mild forms (retrobulbar neuritis) and severe forms (neuromyelitis optica) (Kuroiwa *et al.*, 1965) of demyelinating disease together with some unusual disorders (subacute myelo-optico-neuropathy) (Inone *et al.*, 1971) rather than the clinical types of demyelinating illnesses seen commonly in Caucasian populations (Müller, 1949; McAlpine and Compston, 1952; Leibowitz *et al.*, 1964a).

Verhaart (1951) observed 12 cases of demyelinating disease among Indonesian natives. Five of these twelve came to autopsy but characteristic lesions of MS were found only in one.

The question of whether MS in this racial group assumes an unusual clinical form is of considerable theoretical importance. If the clinical characteristics of MS indeed tended to differ in Orientals, then factors might be found which could ameliorate or modify the clinical expression of the disease in other population groups. Accordingly, additional opportunities were sought to evaluate the frequency and clinical manifestations of MS in Oriental populations. Such an opportunity presented itself in the State of Hawaii.

The Hawaiian study

In 1969, a state-wide study of MS in Hawaii was undertaken (Alter *et al.*, 1971). The method of case ascertainment was similar to the method used in Israel (Ch. 2). All sources of medical information in Hawaii were reviewed for persons diagnosed as or suspected of having MS or an allied disorder.

As a result of the intensive state-wide search, a total of 77 individuals with MS was identified. All 77 patients had resided in the State of Hawaii for at least two years prior to January 1, 1969, the date selected as 'prevalence day'. The clinical criteria used in accepting the 77 patients were the same as those used in other prevalence studies (see Ch. 1 § 1).

Age at onset

The mean age at onset of MS was 32.1 years in the Orientals and 29.6 years in the Caucasians. Among the nine Hawaiian-born Caucasians, the mean age at onset was 29.4 years. The distribution of age at onset by ethnic group is shown in Table 5.5. Considering the small number of cases, the distributions for Orientals and Caucasians in Hawaii were similar. In both groups, the majority of cases began in the third and fourth decades, and a similar percentage had onset after age 40. Among the Caucasians, a higher percentage had onset before age 20.

Table 5.5
Age at onset of MS in Hawaii by ethnic group (per cent of cases)

Age at onset (years)	Orientals	Caucasians		Mixed	Total
		Total	(Native)		
0–19	5	16	(44)	50	16
20–39	65	55	(12)	50	57
40+	25	23	(44)	–	22
Unknown	5	6	(–)	–	5
Total	100	100	(100)	100	100
Number of cases	20	53	(9)	4	77

Sex ratio

Whereas in many series of cases a slight excess of women has been reported (see Ch. 3 §1), there was a much larger excess in Hawaii. Among Hawaiian-born Caucasians, there were 8 women and 1 man. Among Orientals, the female to male ratio was 2.3:1, and among Caucasians as a group, it was 2.8:1. Considering the probable cases of MS, the ratio was 3.2:1. As the excess of women was evident in both Orientals and Caucasians, the two groups cannot be considered to differ in this respect. Migration of affected wives following husbands in military service assigned to Hawaii did not explain the excess since few of the affected women were married to military personnel. The sex ratios are summarized in Table 5.6.

Table 5.6
Sex ratios among various groups of patients with MS in Hawaii

Group	Number of patients	Number of females	Female:male ratio
Ethnic groups			
Orientals	20	14	2.3:1
All Caucasians	53	39	2.8:1
Native Caucasians	9	8	8.0:1
Mixed Caucasians	4	3	3.0:1
Probability of diagnosis			
Probable MS	59	45	3.2:1
Possible MS	18	11	1.6:1
Total	77	56	2.6:1

Initial symptoms

The initial symptoms of MS in the Orientals were tabulated (Table 5.7). An unusually high frequency of onset with optic nerve involvement was observed (55 per cent compared to 10–20 per cent in many other series consisting of Caucasians (see Ch. 4 §1).

Table 6.1 (continued)

Area	Author	Latitude	Prevalence per 100,000 population
EUROPE			
Bulgaria	Pernov (1964)	42°N	6
Czechoslovakia	Henner *et al.* (1964)		
Kladno	Henner *et al.* (1964)	50°N	73
North Bohemian region	Henner *et al.* (1964)	51°N	75
Paradubice, Přelouč, Hollice, Chrudim, Hlinska, and Časlav	Henner *et al.* (1964)	50°N	47
Prague	Henner *et al.* (1964)	50°N	85–90
South Bohemian region	Henner *et al.* (1964)	49°N	70
Denmark	Gram (1934)	56°N	29
	Hyllested (1956)		64
	Kurtzke (1966a)		74
	Hyllested (1969)		85
Faroes	Fog and Hyllested (1966)	62°N	54
England			
Carlisle	Brewis *et al.* (1966)	55°N	82
Cornwall	Hargreaves (1961)	50°N	63
Durham-Northumberland	Poskanzer *et al.* (1963b)	53°N	50
Newcastle	Miller *et al.* (1964)	53°N	25
Finland	Rinne *et al.* (1966)	62°N	19
	Rinne *et al.* (1968)		20
Turku	Panelius (1969)	60°N	43
France			
Arles	Behrend (1969b)	44°N	9
Bas-Rhin	French MS Society (1967)	49°N	41
Haute-Garonne	French MS Society (1967)	44°N	63
Marseille	Behrend (1966)	43°N	21
Montelimar	Behrend (1969b)	45°N	37
Orange	Behrend (1969b)	44°N	5
Vienne	Behrend (1969b)	46°N	32
Germany			
Cologne	Behrend (1969a)	51°N	74
Hamburg	Behrend (1966)	54°N	73
Magdeburg	Klein and Parnitzke (1963)	52°N	40
South Lower Saxony	Firnhaber (1972)	52°N	37
West Berlin	Iwanowski (1963)	52°N	85
West Lower Franconia	Bammer and Schaltenbrand (1960)	49°N	115

Table 6.1 (continued)

Area	Author	Latitude	Prevalence per 100,000 population
Hungary			
Budapest	Barlow (1962)	47°N	20
Iceland	Gudmundsson and Gudmundsson (1962)	65°N	44
	Kurtzke (1966a)		72
Italy			
Ferrara	Mapelli and Ramelli (1967)	45°N	13
Parma	Macchi *et al.* (1962)	45°N	12
Perugia	Paci and Borri (1969)	43°N	15
Sassari	Mapelli (1966)	41°N	20
Terni	Paci and Borri (1967)	43°N	13
Umbria	Paci and Borri (1969a)	43°N	15
Varese	Montanini *et al.* (1964)	46°N	19
Netherlands			
Groningen	Dassel (1960)	53°N	56
North Ireland	Allison and Millar (1954)	54°N	51
	Millar (1971)		80
Norway	Kurtzke (1966a)	63°N	36
Finmark County	Swank (1961)	71°N	11
Møre and Romsdal	Presthus (1966)	63°N	38
Oslo	Oftedal (1966)	60°N	80
Poland			
Bydgoszcz	Cendrowski (1965)	53°N	43
Krosno-district	Cendrowski (1965)	50°N	46
Poznań-district	Cendrowski *et al.* (1969)	52°N	78
Pruszkow	Cendrowski (1964)	52°N	28
Slupsk	Cendrowski (1965)	54°N	37
Warsaw	Cendrowski (1964)	52°N	28
	Miller *et al.* (1964)		25
Rumania			
Brasov	Seitan and Rosianu (1962)	46°N	46
Cluj	Duma and Morariu (unpubl. data)	47°N	43
Russia			
Lithuania	Briskman (1969)	56°N	32
Ukraine			
Cherkassy	Briskman (1969)	49°N	23
White Russia	Briskman (1969)	54°N	25
Scotland			
Northern mainland	Sutherland (1956)	57°N	62
Orkney	Sutherland (1956)	59°N	108

Table 6.1 (continued)

Area	Author	Latitude	Prevalence per 100,000 population
Outer Hebrides, Skye	Sutherland (1956)	58°N	38
Shetland	Sutherland (1956)	61°N	129
Sweden	Sällström (1942)	60°N	22
Älvsborgs District	Blomberg (1966)	59°N	73
Göteborg	Broman *et al.* (1972)	58°N	120
Stockholm	Sällström (1942)	59°N	18
Uppsala	Sällström (1942)	60°N	49
Switzerland	Bing and Reese (1926)	46°N	23
Basel	Georgi *et al.* (1961)	47°N	106
Bellinzona	Georgi *et al.* (1961)	46°N	15
Geneva	Georgi *et al.* (1961)	46°N	37
Lucerne	Georgi *et al.* (1961)	47°N	51
Valdis	Georgi *et al.* (1961)	46°N	19
Zürich	Georgi *et al.* (1961)	48°N	59
NORTH AMERICA			
Canada			
Manitoba			
Winnipeg	Westlund and Kurland (1953)	50°N	40
	Stazio *et al.* (1964)		36
Nova Scotia			
Halifax	Alter *et al.* (1960)	44°N	32
Ontario			
Kingston (city)	White and Wheelan (1959)	44°N	57
Kingston (area)	White and Wheelan (1959)		30
Mexico			
Mexico City	Alter and Olivares (1970)	20°N	2
United States			
Alabama	Peacock *et al.* (1969)	33°N	8
California			
San Francisco	Kurland and Newman (1953)	37°N	30
Colorado			
Denver	Kurland and Dodge (1953)	40°N	37
District of Columbia	Stazio and Kurland (1962)	39°N	27
Hawaii	Alter *et al.* (1971)	20°N	10
Louisiana			
New Orleans	Kurland (1952)	30°N	12
	Westlund and Kurland (1953)		6
	Stazio *et al.* (1967)		9
Massachusetts			
Boston	Ipsen (1950a)	42°N	51
	Kurland and Westlund (1954)		41

Table 6.1 (continued)

Area	Author	Latitude	Prevalence per 100,000 population
Duxbury	Deacon *et al.* (1959)	42°N	163
Minnesota			
Rochester	MacLean *et al.* (1950)	44°N	64
	Percy *et al.* (1971)		60
Mississippi			
Jackson	Breland and Currier (1967)	32°N	12
Montana			
Missoula	Siedler *et al.* (1958)	47°N	59
South Carolina			
Charleston	Alter *et al.* (1960)	32°N	14
Texas			
Houston	Chipman (1966)	30°N	7
West Indies			
Jamaica	Cruickshank and Montgomery (1961)	18°N	0.4

Table 6.2
Mortality due to MS in various communities

Area	Author	Period studied	Average annual mortality rate per 100,000 population
AFRICA			
Egypt	Barlow (1960)	1940	0.1
	Barlow (1960)	1947	0.02
Nigeria	Barlow (1960)	1938	0
Tanganyika	Barlow (1960)	1936	0
Union of South Africa	Goldberg and Kurland (1962) *	1950	0.1
(whites only)	Acheson (1961)	1950–59	0.09
Cape of Good Hope	Acheson (1961)	1950–59	0.07
Capetown	Barlow (1960)	1950	0.5
Natal	Acheson (1961)	1950–59	0.2
Orange Free State and Transvaal	Acheson (1961)	1950–59	0.06

same team carried out the research, as was the case in the Charleston–Halifax study (Alter *et al.*, 1960) and uniform diagnostic criteria are applied in accepting cases, the material available for review has been provided by the local practitioners. If these physicians had biases in diagnostic practices, the biases could be reflected in the medical records which the research team reviewed. It was desirable to compare rates of MS in diverse populations wherein the individuals were all cared for by the same clinicians. In such a situation, the effect of physician bias in producing differences in MS frequency among different populations would be minimized. The Israeli study (Chs. 2 and 6 §3) enjoyed this particular advantage in that the same group of physicians provided health care to individuals who had immigrated from many different parts of the world.

MS registries

Few methodological advances in population surveys have been made since the Charleston–Halifax study. There is, however, an easier and potentially superior method of obtaining information on frequency of MS in a region. This involves a population registry of MS. A registry has already been introduced in some countries, for example, Denmark (Hyllested, 1969), Northern Ireland (Millar, 1971) and Israel (Leibowitz *et al.*, 1969c) and, in time, may be adopted by others. An MS registry lists all cases diagnosed in the country. If MS is made a reportable disease and efforts are expended to assure that the reporting is complete and accurate, the MS registry will undoubtedly constitute the best source of information about the frequency of the disease in a region. Valid comparisons between regions would then merely require that uniform collection and classification practices be adopted for the registry.

Establishment of a registry is not without difficulty. Attention must be given to diagnostic criteria with assurance that patients added to the roster are, in fact, *bona fide* cases of MS. There must be at least periodic checks to assure that the sources of information are continuing to supply data and that interest is not flagging. The cost of maintaining a good registry should also be considered.

2. The geographic distribution of multiple sclerosis

The frequency of MS has now been reported for many regions of the world. Table 6.1 presents some of these data based on prevalence estimates. In Table 6.2, mortality data on MS are summarized and in Table 6.3, inci-

Table 6.1
Prevalence of MS in various communities

Area	Author	Latitude	Prevalence per 100,000 population
AFRICA			
Ethiopia	Hall (1961)	7°N	0
Union of South Africa	Kurtzke et al. (1970b)	31°S	9
ASIA			
India			
Bombay	Bharucha and Umarji (1961)	18°N	2
Iraq	Shaby (1958)	32°N	0.1
Israel	Alter *et al.* (1962)	31°N	15
Japan			
Fukuoka	Okinaka *et al.* (1960, 1966)	34°N	2
Kumamoto	Okinaka *et al.* (1960, 1966)	33°N	2
Niigata	Okinaka *et al.* (1960, 1966)	38°N	4
Sapporo	Okinaka *et al.* (1960, 1966)	43°N	2
Korea			
Seoul	Kurtzke *et al.* (1968)	38°N	2
Turkey	Mutlu (1960)	38°N	2.0
Aegean region	Mutlu (1960)	38°N	1.4
Black Sea region	Mutlu (1960)	40°N	1.6
Central Anatolia	Mutlu (1960)	39°N	1.8
Eastern Anatolia	Mutlu (1960)	39°N	1.8
Maramara-Thrace	Mutlu (1960)	41°N	3.7
Mediterranean region	Mutlu (1960)	36°N	0.1
South-East Anatolia	Mutlu (1960)	38°N	0.2
West Anatolia	Mutlu (1960)	39°N	1.9
AUSTRALASIA			
Australia			
New South Wales			
Newcastle	McCall *et al.* (1968)	33°S	20
Queensland			
Cairns	Sutherland *et al.* (1966)	17°S	7
Darling Downs	Sutherland *et al.* (1966)	28°S	12
Mackay	Sutherland *et al.* (1966)	21°S	6
Townsville	Sutherland *et al.* (1966)	19°S	7
South Australia	Rischbieth (1966)	30°S	38
Tasmania			
Hobart	McCall *et al.* (1968)	43°S	32
Western Australia			
Perth	McCall *et al.* (1968)	32°S	20
New Zealand	Sutherland *et al.* (1962)	39°S	23

Asian countries based on proportional hospital admission rates. These rates are all similar and uniformly low compared to rates in Western countries in the temperate zone (Table 6.1). Dr. Augustus Rose, a member of the National Advisory Board of the Multiple Sclerosis Society and Dr. Louis Rosner, head of the MS Clinic, University of California (Los Angeles) reported in personal communication to one of us (MA) that MS was also uncommon among Orientals living in the Los Angeles area. MS has been diagnosed in Taiwan (Hung and Lin, 1956; Hung, 1970) although it is rare there. Barlow (1967) has made available summaries in translation of reports of MS from North Korea and from China. Although the disease was considered uncommon in North Korea, eleven cases (five of which were acute) were collected in one and one-half years in a hospital in Pyongyan, North Korea. Five cases were collected from various medical centers in China according to the reports translated by Barlow (1967).

In Japan, MS appears to be rare in the entire country (Okinaka *et al.*, 1960, 1966). Frequency was below 4 per 100,000 in each of four communities studied (Fig. 6.10), although the northern community was above 43°N latitude, and a much higher rate was expected on the basis of MS rates in the United States communities at similar latitudes (*e.g.* Rochester, Minnesota).

The frequency of other neurological disease in Japan was also tabulated (Okinaka *et al.*, 1966). For example, the rate of amyotrophic lateral sclerosis (ALS) was 1.8 and 2.6 per 100,000, respectively, in Fukuoka and Niigata, rates which are similar to those reported in many other areas of the world (Kurtzke *et al.*, 1968). Kurtzke (1969b) postulated that the frequency of ALS

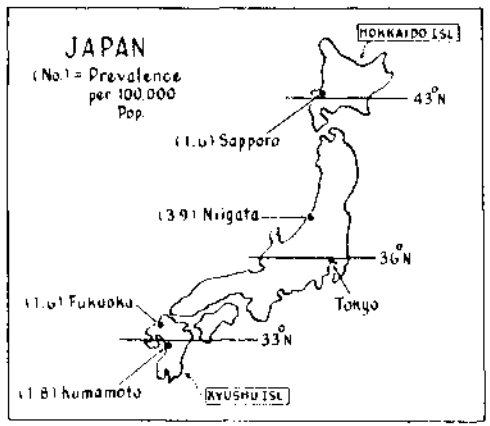

Fig. 6.10. MS prevalence rates in Japan. (Okinaka *et al.*, 1960.)

is uniform in many parts of the world (see Ch. 6 §1). The rate of ALS in Japan was within the expected range. Thus, there seems little basis, according to Kurtzke's (1969b) idea, for assuming that ascertainment of MS was incomplete.

Pacific Islands

Guam is a small Pacific island which had less than 40,000 inhabitants in 1963. It has been under intensive medical surveillance for several decades because of an unusually high rate of motor system disease. During the period of intensive surveillance, no MS has been recognized (Chen *et al.*, 1968). MS is also apparently rare in Fijians and the Indian population of Fiji (Sutherland *et al.*, 1962) as well as in the Dutch East Indies (Verhaart, 1951) and among Polynesians in the North Island of New Zealand (Hornabrook, 1962).

A state-wide study of MS in the Hawaiian Islands (Alter *et al.*, 1971) disclosed an MS prevalence rate of 9.9 per 100,000 population. Among the native-born population, it was 6.3 per 100,000 population. Age adjustment to the United States population in 1960 brought the rate up to 7.5 per 100,000 population. The age specific rates of MS for both the Oriental and white populations of this State were similar. The rates among other ethnic groups and among immigrants to Hawaii from other parts of the world are dealt with in Ch. 6 §§4,6.

India

A few studies in India have been carried out. These have been cited by Kurtzke (1964). Sathe (1955) found one example of a demyelinating disease in a Bombay hospital for paraplegics. Laha and Johri (1958) found 16 cases of MS in other hospitals and Datta (1960) found 8 cases. About 30 cases of MS in hospitals and an additional 15 cases in private practice were diagnosed in a five-year period by Bharucha and Umarji (1961). Since the population of Bombay was about 2.8 million, the frequency of MS in that community was estimated at about 2 per 100,000 population.

Alaska

A personal communication to one of us (MA) from the Public Health Hospital in Anchorage, Alaska indicated that MS was rare among Eskimos. None had been hospitalized at that facility although a suspected case lived in one of the villages. The Eskimo population is small and medically isolated so

showed a narrow range of 30 to 37. Similar data from southern areas is meager. McCall *et al.* (1969) observed no change in age at onset of MS among individuals who had lived all their lives in Western Australia as compared to individuals who had traveled abroad.

If residence in a low MS region influences the time of onset of MS, it apparently does not influence the clinical course. Once affected, individuals with MS tend to have as severe a clinical course in an environment with a low frequency of the disease as in an environment where the disease is common. In other words, the clinical course of the disease is not ameliorated where it is less common (Ch. 5 §§1–3).

Changing frequency of MS

In several communities information is available on the frequency of MS at different periods of time (Ch. 6 §5). Such studies are important in that they may indicate whether MS is changing in frequency. If either an increase or a decrease can be related to some change in the environment such as introduction of a sanitary water supply or a particular industry, then research efforts could be directed toward the environmental change, to determine which aspect was likely to be related to MS. The interpretation of frequency patterns for MS is discussed in some detail in Ch. 6 §5, where it is shown that the frequency of MS tends to be constant in a given locale. However, individuals who migrate from one prevalence zone to another at a young age show a different frequency from that of the place of origin. Instead, the young migrants show rates like those in the adopted country.

Seasonal trends

If MS were caused by some factor related to climate or temperature, one might detect a seasonal fluctuation in onset or in exacerbations of MS. Seasonal fluctuation in the frequency of MS has been investigated in several centers. Wüthrich and Rieder (1970), who studied data from Swiss University Clinics for Neurology and Ophthalmology in Basel, Bern, Lausanne, and Zürich, noted definite seasonal variation in bouts of MS. Using three-month seasonal averages, a maximum incidence of MS bouts in Basel occurred in the spring, and minimal incidence occurred in autumn. The difference between the first and second half of the year was significant even when data from each city were combined. No difference in seasonal trend was observed between the two sexes. When the four communities were compared, peak incidence in Bern was shifted forward by several months, compared to Basel; Lausanne was

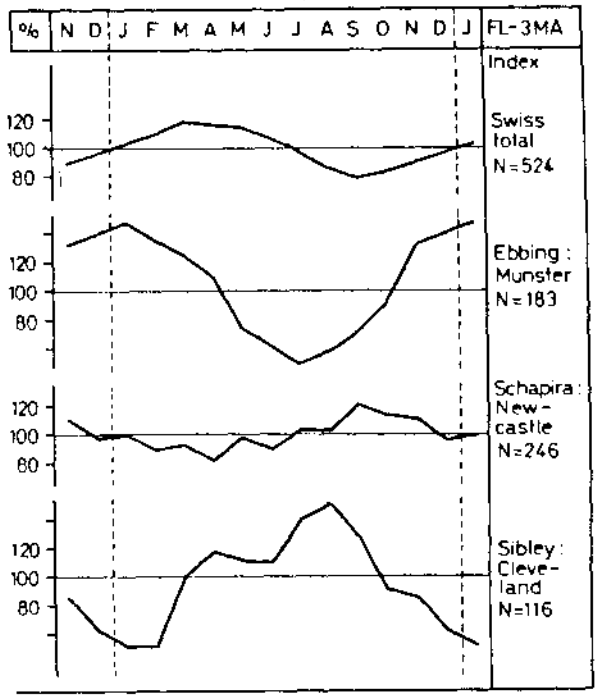

Fig. 7.6. Seasonal incidence of MS (per cent of mean annual, by month). (Wüthrich and Rieder, 1970.)

like Basel, and Zürich lay between the two extremes. The curve of Ebbing (1955) in seasonal frequency of MS in Münster was similar to that of Basel. Sibley and Foley (1965a) noted a summer peak (July-September) in onset and exacerbation of MS in Cleveland. Schapira (1959), on the other hand, was unable to show a significant seasonal fluctuation of MS in North-East England. It is still unclear, therefore, whether MS has a significant seasonal fluctuation in frequency in various parts of the world. There is little agreement even among those who accept the existence of seasonal fluctuations as to when peak frequency occurs (Fig.7.6). More studies of seasonal trends are warranted.

Gradient versus band theories of MS distribution

In order to resolve the question of whether a gradient model or a band model best describes the distribution of MS, additional data on MS frequency

Data on migrants to South Africa, Hawaii, and Israel were examined and all pointed to the fact that migration at or before age 15 years was associated with MS frequency like that of the adopted country, whereas migration after about age 15 years was associated with MS rates like those in the original homeland. Studies among migrant populations in Australia and the United States were also compatible with the notion that MS rates might be affected by age at immigration to the new environment. Other data, based on correlations between MS and childhood illness, conditions in the childhood home and clustering of cases, tended to support the notion that MS was acquired in childhood on or before age 15 years but not in infancy. If infancy were the 'critical age' for acquiring MS, then no change in MS frequency should have been found among those who migrated above and below age 15 years.

Although the migration data were consistent in pointing to the period at or before age 15 years as the 'critical age' for acquiring MS, numerous pitfalls in analysing migration data were recognized. Selection against (or in favor) of disabled individuals, variation in quality of medical care, the problem of the age of the migrants at the time of the analysis, and identification of an appropriate denominator population all affect the interpretation of rates of MS among migrants.

Is the frequency of MS changing?

Changes in environmental conditions might result in a change in MS frequency if the etiologic agent were closely linked to an environmental factor. Accordingly, the secular trend in MS was examined in the light of environmental changes. Various methods of estimating MS frequency were described, including proportional statistics from a practice or clinic, age cohort analysis, mortality rates, prevalence estimates, and incidence. Age cohort analyses of Israeli and British data were presented. Incidence estimates were regarded as the best measure, as incidence, which measures new cases of MS per unit population in a given period of time, is most sensitive to fluctuations in the etiologic factor. Data from Northern Ireland and Rochester, Minnesota, revealed no change in MS frequency in many decades and thus, were compatible with the observation of a stable incidence rate of MS in Israel over the last two decades.

Ethnic and genetic factors in MS

Comparisons of MS in Ashkenazim (largely Europeans) and Sephardim (largely Afro-Asians) born in Israel revealed remarkable similarity in prevalence of MS. Also, among Orientals and Caucasians native to Hawaii, similarity of MS frequency was demonstrated. In most clinical features too, Orientals and Caucasians, as well as Europeans and Afro-Asians with MS, resembled each other. In Poland, the rates of MS among Lithuanians, Jews, Gypsies, and Chinese were estimated to be similar. On the other hand, whites and blacks in the United States had similarities in the clinical features of MS, though blacks consistently had slightly lower MS frequency than whites in the same area. In general, blacks have a lower socio-economic status than whites and thus may not share identical environments. Ethnic aggregates in South Africa also had a difference in MS frequency, with the English-speaking group having a higher rate than the Afrikaans-speaking group and the latter, in turn, having a higher rate of MS than the colored groups. Among Bantu no MS had been found. As with whites and blacks in the United States, MS rates in South Africa parallel the socio-economic status. These data were interpreted as supporting the role of an environmental factor in the etiology of MS, although genetic predisposition to develop demyelinating disease was not, of course, excluded by the epidemiologic data. In fact, calculations of heritability, based on the number of affected parents and siblings in various series, pointed to an appreciable genetic component in the cause of MS. Genetic factors, causing differences in susceptibility among different populations, were considered to be one factor which accounted for differential distribution of MS and the occurrence of foci of MS in various parts of the world. Nonetheless, the role of an environmental factor in etiology was considered the more important.

Etiologic considerations based on epidemiology

The epidemiologic data available on MS were scrutinized and considered in the light of possible etiologies for MS. One interpretation of the geographic distribution of the disease (the gradient theory) pointed to the possibility that a geoclimatic factor is important. The amount of sunshine and the mean environmental temperature appear to be negatively correlated with MS frequency. Extra-terrestrial factors such as microwaves and cosmic radiation have also been mentioned as possibilities compatible with MS distribution. Plotting MS frequency against geomagnetic rather than geographic latitude provided a particularly good fit for Japan, which otherwise appeared to have a lower than expected rate of MS.

The interpretation that MS might be distributed according to frequency bands rather than along a gradient supported speculation that dietary fat or gluten or a metallic toxin might be important in the etiology of MS.

Considerable attention has been given to childhood illnesses as a factor

which might cause MS, either through delay in manifestation (*i.e.* long incubation period) or through establishing conditions in the nervous system favoring demyelination (*i.e.* delayed hypersensitivity). Data on acquisition of MS, derived from analysis of populations which have migrated, favor a factor acquired at or before age 15 years and are compatible with a childhood infection as a cause of MS.

The female preponderance of MS among patients with early onset was noted and discussed in the light of hormonal factors and pregnancy as a precipitating factor in central nervous system demyelination. The age at onset of MS was discussed in relation to the parts of the nervous system which seem more susceptible at different ages. Again hormonal factors were considered, as well as changes in vascular supply with age, to account for the fact that optic nerve lesions tend to manifest early whereas the spinal cord seems more prone to demyelination among older individuals.

Stability in the frequency of MS in a selected community where the secular trend was studied suggests that the factors associated with modernization of a region, such as introduction of packaged foods, automobiles, electrical appliances etc., are not relevant to the cause of MS. However, more fundamental changes such as those associated with conversion from agrarian to an industrialized society could not be excluded as relevant.

There is no unanimity regarding seasonal fluctuations in MS frequency, although some investigators showed that the rate of onset of MS varies significantly in different parts of the year. A seasonal fluctuation in MS frequency would, of course, support speculation that climatic changes are of etiologic importance, or it might raise questions about the relation of MS to certain insect vectors whose concentration varies during the year.

Geoclimatic vs *socio-cultural factors in etiology*

Variation in MS frequency in different areas allowed correlation with geoclimatic and socio-cultural factors in the same locales. A systematic analysis of correlations between MS frequency and 20 geoclimatic and socio-cultural variables in many countries revealed high coefficients for several factors. Amount of sunlight, for example, showed a correlation with MS frequency of −0.88. The consumption of steel (a measure of socio-economic development), the proportion of medical personnel and the percentage literacy in the population also showed high correlations (above +0.84). Thus, high correlations with MS frequency were found for both geoclimatic and socio-cultural variables. Available data could not resolve which was the more important in the cause of MS. The native-born population of Israel is living in geoclimatic conditions similar to those in the neighboring, Middle Eastern countries with low MS rates. On the other hand, socio-economic conditions in Israel are more similar to those in European countries with high MS rates. The finding of high MS rates among native Israelis would suggest that socio-economic rather than geoclimatic factors are important in the etiology of MS.

Clinical interviews comparing patients and controls

Another technique of identifying an etiologic variable involves comparisons of experiences and exposures between patients and controls prior to onset of MS. A number of such comparisons have been carried out. In the Winnipeg study, the comparison suggested that MS patients had had operations involving anesthetics prior to onset of MS significantly more often than controls. In a Minnesota study, MS patients reported fewer upper respiratory illnesses prior to onset than controls. In Poland, a similar study failed to implicate 'colds' or other respiratory illnesses as differentiating between patients and controls. Many other variables were compared. In particular, no association could be found between the type of sanitation facilities to which a patient had had access in childhood and risk of MS. Patients and controls had had similar sanitary facilities. However, in the town of Posnań the rate of MS was higher than in the countryside, and Posnań had better sanitation than the surrounding district. A study of US military personnel indicated a relationship between risk of MS and educational level, intelligence, residence in a large community prior to induction, and defective vision at induction. In a study of MS patients and controls in Israel, patients reported a higher level of sanitation in the childhood home than controls on each of three measures of sanitation: less crowding in the home, access to flush toilets, and piped drinking water. Since the childhood period seemed important with respect to when MS is acquired, and sanitation in the childhood home of MS patients was better on the average than controls, a hypothesis was formulated that the distribution of MS might be related to the level of environmental sanitation in a manner analogous to poliomyelitis.

The sanitation hypothesis

The hypothesis that a positive relationship exists between MS frequency and environmental sanitation was tested in a variety of ways.

In the first test, it was postulated that MS should increase in frequency in environments which improve their level of sanitation. Israel has experienced a radical transition in level of sanitation toward improved facilities after World

War I when Turkish rule was terminated. The improvement in sanitation has accelerated since the State became independent in 1948. At present Israel is like many of the more technologically advanced North American and European communities rather than like her Levantine neighbors. If level of sanitation were important in the etiology of MS, then native-born Israelis should have a high rate of MS like Europeans (and like European immigrants). The rate of MS in native-born Israelis was indeed high, as in European immigrants, and not low as in Afro-Asian immigrants. The high rate in native-born Israelis was especially noteworthy among the offspring of Afro-Asian immigrants. In the first test, the hypothesis was supported.

In a second test, it was postulated that MS should be rare in technologically advanced communities with poor sanitation facilities. Mexico City provided a population for this test. Although technologically sophisticated, Mexico City is characterized by many illnesses associated with poor sanitation. A study of MS in Mexico City revealed it to be rare (prevalence rate of 1.6 per 100,000 population). Indeed, Mexico City resembled Japan in being technologically sophisticated yet its people suffered from a high rate of illnesses associated with poor sanitation. Both Mexico City and Japan have low rates of MS. The second test also supported the hypothesis.

A third test postulated that MS would be less common among the economically disadvantaged than among those with higher socio-economic status in the same community. Several populations provided evidence in this test. In Britain, MS was most common among the highest socio-economic group. In the United States, Negroes, who tend to have lower socio-economic status than whites, consistently had a lower rate of MS than whites in the same community. In South Africa, the rate of MS in various groups tended to parallel the socio-economic status of the groups. The third test, too, lent support to the hypothesis.

A fourth test postulated that sanitation should be poor where MS is rare and superior where MS is common. Moreover, regions which do not appear to 'fit', so far as MS rate is concerned, when latitude is taken into account, should cease to be 'discrepant' if note is taken of the level of sanitation. Various measures of sanitation were used, and those related to poor water sanitation (*e.g.* enteric infections) correlated well with the distribution of MS. Those related to air pollution did not correlate, except for illnesses like tuberculosis, which are also measures of a poor standard of living. 'Discrepant' populations on the basis of latitude, such as Japanese, Eskimoes, Faroese, northern Scandinavians, were shown to have poorly developed sanitary facilities, particularly water sanitation. The fourth test of the hypothesis supported it and, moreover, suggested that water sanitation might be relevant to the etiology of MS.

The pathogenesis of MS is unknown, but a possible mechanism was suggested on the basis of conjecture which might fit many of the epidemiological facts. It was speculated that MS is due to an environmental infectious agent and the source of the agent is drinking water. The time of acquisition of the agent was regarded as crucial: if acquired in infancy or early in life and the nervous system is invaded, a relatively unmyelinated system is encountered and protective antibodies develop. If, on the other hand, the agent is acquired later in life, a well myelinated nervous system is encountered and demyelinating antibodies may develop. The demyelinating antibodies may produce symptoms in response to non-specific 'precipitating' factors such as febrile illness. The age at which the agent is acquired is determined by the sanitary level in the community. If sanitation is poor, the agent is acquired early: if sanitation is good, the agent is acquired later. Thus, MS frequency will be related to environmental sanitation.

If these speculations are valid, then the agent which causes MS may be most common in drinking water of environments where MS is rare. In any event, our reading of the epidemiological signposts point us in that direction. Laboratory skills are called for now to determine whether our reading was valid. Epidemiological methods serve mainly to point the way for more definitive investigations into the cause of MS.

MULTIPLE SCLEROSIS

Clues to its cause

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