Clinical studies of multiple sclerosis in Israel¹

Part II A comparison between European and Afro-Asian patients²

MILTON ALTER, URI LEIBOWITZ, AND LIPMAN HALPERN

From the Department of Neurology, Hadassah University Hospital, Jerusalem, Israel, and the Department of Neurology, University of Minnesota Hospital, Minneapolis 14, Minnesota, U.S.A.

The prevalence of multiple sclerosis decreases from a high rate in temperate latitudes to low rates in latitudes near the equator. This general trend has been noted both in the northern and southern hemispheres (Davenport, 1922; Ulett, 1948; Kurland and Westlund, 1954; Acheson and Bachrach, 1960; Alter, Allison, Talbert, and Kurland, 1960; Alter, Halpern, Kurland, Bornstein, Leibowitz, and Silberstein, 1962; Acheson, 1961; Sutherland, Tyrer, and Eadie, 1962; Saint and Sadka, 1962; Dean, 1961; Spota and Brage, 1951). In view of the decline in prevalence with geographical latitude it becomes pertinent to inquire whether a systematic variation in the clinical manifestations of multiple sclerosis also exists. For example, is the disease also milder where it is less common; is prognosis worse where there is a high prevalence; are certain symptoms peculiar to a particular geographic locale?

There are only a few studies in which the possible relationship between clinical characteristics of multiple sclerosis and prevalence has been explored. Westlund and Kurland (1953) reported that the prevalence of multiple sclerosis in Winnipeg, Canada, was six times higher than in New Orleans, Louisiana, a community more than one thousand miles farther south, but no appreciable clinical difference was discerned between patients in the two communities. However, the validity of the clinical comparison may be questioned as different neurologists had examined the patients in each community. Later, Kurland and Westlund (1954) suggested that age at onset of illness tended to be younger in communities with higher prevalence. Alter *et al.* (1960) compared clinical features of patients identified in Halifax, Nova Scotia, and Charleston, South Carolina. The prevalence of multiple sclerosis was two and one-half times lower in the southern community. The comparison revealed that in the southern com-

munity there was a slightly lower average age at onset, a higher percentage of relapsing cases, a higher exacerbation rate, and a higher percentage of severely disabled patients. Alter *et al.* (1960), in another study, compared Negro patients born in the northern part of the United States with Negroes born in the southern part. The study revealed some clinical differences between the two groups. Among the northern-born Negroes, average age at onset was earlier, there were proportionately more females, retrobulbar neuritis as an initial symptom occurred more commonly, and a relapsing course was reported by a higher proportion. All Negroes included in the study, however, had been diagnosed at the Neurological Institute of New York and the possibility existed that the southern-born Negroes included in the study were not representative of southern Negroes in general. On the basis of the studies cited it would seem that clinical manifestations of multiple sclerosis may differ in regions of different prevalence but additional supporting evidence is needed.

In Israel, an unusual opportunity was afforded to examine the question anew. Israel's population contains representatives from every continent and many different countries, including regions of high and low prevalence of multiple sclerosis. The inhabitants number approximately two million and may be divided into three groups of about equal size: native-born Israelis, European immigrants, and Afro-Asian immigrants. Before 1949, the majority of immigrants were European; between 1949 and 1954 Afro-Asian immigration increased sharply; since 1954, immigration was from both Europe and Afro-Asian countries and was relatively small. Immigration from America has also been small (Statistical Abstract of Israel, 1961). An extensive network of medical facilities staffed by well-trained personnel exists throughout the country. The major population centres have modern hospitals with departments of neurology. All segments of the population have access to the same medical facilities. A national health insurance scheme makes the cost of medical care

¹This study was supported by grant no. 265 from the National Multiple Sclerosis Society.

²Part I of this study, 'A clinical analysis based on a country-wide survey', by U. Leibowitz, L. Halpern, and M. Alter was published in the *Archives of Neurology* (10, 502-512) in 1964.

nominal. Political factors tend to isolate Israel from her neighbours so that medical care is customarily obtained within the country and all affected are easily accessible. Immigration policies of the state were such that individuals with chronic illnesses were not excluded. These unusual and perhaps unique conditions make Israel an ideal area for study of patients from a cross-section of many areas of the world.

A country-wide survey of multiple sclerosis was completed by 1961 by Alter *et al.* (1962). The survey revealed that multiple sclerosis was more than six times as prevalent in Europeans as in Afro-Asians. The present study compared clinical characteristics between the Afro-Asians and the European group. As native-born Israelis had a prevalence similar to that of the Afro-Asians, Israeli patients were grouped with Afro-Asians in the clinical comparison.

CASE FINDING METHOD

In order to identify patients with multiple sclerosis living in Israel, medical records of all hospitals, referral clinics, and facilities for caring for the chronic sick were reviewed for the period 1955-59. Physicians with a private neurological practice were questioned and mortality data at the Central Bureau of Statistics were studied. At each source of information, patients were listed who had been diagnosed as having multiple sclerosis or one of five clinically similar conditions, *i.e.*, primary lateral sclerosis, non-traumatic paraplegia, optic or retrobulbar neuritis, cerebellar ataxia, and myelopathy. After scrutiny of case notes, patients who clearly had a disease other than multiple sclerosis were discarded. Patients who died or left Israel before 1 January 1960 were also excluded. Of the 580 who remained, 520 were re-examined by us. A modification of the diagnostic criteria formulated by Allison and Millar (1954) was applied and two categories of cases were accepted: probable and possible multiple sclerosis. Of the 520 in the provisional list, 282 patients were finally accepted as having multiple sclerosis and were living in Israel on 1 January 1960. Additional details regarding diagnostic criteria and case selection are reported in an earlier communication (Alter *et al.*, 1962).

In the present study, 13 of the 282 accepted cases were excluded because of inadequate clinical information. The remaining 269 were divided into two groups as follows: 208 of European origin (including one patient born in Argentina) and 61 from Afro-Asian countries. The two groups were compared for a number of clinical characteristics. It is well to emphasize that the diagnostic criteria and method of case selection were the same for each group.

RESULTS

PREVALENCE The prevalence of multiple sclerosis in Israel on 1 January 1960 was 15 per 100,000 population. If the European and Afro-Asian groups were considered separately, prevalence rates were 31.3 and 5.1 per 100,000 population respectively. Age-specific rates for the two populations are listed in Table I. Although the age composition of the two populations differ in that a much higher percentage of Afro-Asians are under 20, it is important to note that the prevalence is higher for Europeans in each age-group category. Difference in prevalence cannot, therefore, be attributed to differences in the age composition of the two populations.

TABLE I

NUMBER OF PATIENTS, NUMBER IN GENERAL POPULATION, AND AGE SPECIFIC PREVALENCE RATE BY DECADES AND AREA OF ORIGIN (ISRAEL, 1960)

Age	Origin					
	Europe			Afro-Asia		
	No. of Patients	Population	Rate per 100,000	No. of Patients	Population	Rate per 100,000
>20	0	71,641	—	8	708,603	1.1
20—29	15	69,805	21.5	23	194,806	11.8
30—39	43	134,480	32.0	10	120,344	8.3
40—49	68	158,636	42.9	11	70,641	15.6
50—59	64	130,910	48.9	8	55,025	14.5
60—69	13	64,938	20.0	—	28,533	—
70—79	3	34,171	8.8	1	16,308	6.1
Unknown	2			0		
Total	208	664,581	31.3	61	1,194,260	5.1

AGE OF PATIENTS ON PREVALENCE DAY AND AT ONSET OF SYMPTOMS The age of patients in each group was determined on 1 January 1960. The mean age of Europeans was 46.9 years while that of Afro-Asians was 34.6 years. It has already been pointed out that the Afro-Asian population was younger on the average than the European. Therefore, it is not surprising that the mean age of Afro-Asian patients on prevalence day was also younger.

The mean age at onset of illness was 34.2 years among Europeans and 27.4 years among Afro-Asians. Although the difference is statistically significant ($p < 0.001$), it probably reflects the difference in age composition of the two populations and should not be accepted as necessarily indicating a tendency for earlier onset among the low prevalence group.

Since prevalence of multiple sclerosis was considerably higher among Europeans than among Afro-Asians, it was of interest to determine whether longer residence in the European environment affected the age at onset of the disease. A correlation was obtained between age at onset and 'exposure'.

The 'exposure' period for patients with onset while still in Europe was the number of years from birth to onset. For Europeans with onset in Israel, exposure equalled the years from birth to immigration. Exposure for Afro-Asians was the number of years from birth to immigration. The regression line for Europeans did not differ significantly from that plotted for Afro-Asian immigrants ($T = -0.426$). When patients with onset under 20 years of age were considered, the slopes of regression lines for Europeans and Afro-Asians still were not significantly different. It would appear that residence in a high prevalence environment did not influence age at onset of illness more than residence in a low prevalence environment. Comparison of risk of developing multiple sclerosis as a function of length of 'exposure' would have been of interest. The risk, however, could not be derived owing to lack of data on age at immigration for the general population.

DURATION OF ILLNESS In order to assess whether multiple sclerosis has a longer average duration for a group with high prevalence than for a group with low prevalence it would be advisable to follow the patients from onset to death. An attempt at long term follow-up has been made by Allison (1950) for patients identified in Britain. Another approach utilizes life-table methods (Kolb, 1950; MacLean and Berkson, 1951). Life-table methods were not feasible in Israel because of lack of accurate life table data. Instead, the duration from onset to prevalence day (1 January 1960) was compared. A mean duration of 12.7 years was found for Europeans while for Afro-Asians the mean duration was 7.2 years. Here again, the fact that Afro-Asian patients were on the average younger than European patients may account for the apparent shorter duration of illness. The difference, in any event, is not statistically significant.

CLINICAL TYPES Virtually any combination of symptoms and signs may be found in a particular patient with multiple sclerosis. Nevertheless, among the patients encountered in the survey, all could be classified at the time of examination into one of the following clinical types:

Disseminated type 1 Patients with exacerbations and remissions of neurological deficit were classified as 'disseminated-recurrent' multiple sclerosis if examination gave evidence of scattered central nervous system lesions. Such patients were classified as disseminated-recurrent type even if they had entered a progressive phase.

2 Progressive, in which some patients insisted that their course was steadily progressive. On examina-

tion, however, evidence of disseminated lesions of the kind common in multiple sclerosis was found.

3 Recurrent optic neuritis, *i.e.*, patients whose sole symptom was attributable to unilateral optic or retrobulbar neuritis were excluded. However, if one eye and then the other was affected, after an interval of at least three months, evidence of 'scattering' was at hand and the patients were classified as the disseminated-optic neuritis form of multiple sclerosis. Patients with bilateral, simultaneous optic neuritis were difficult to classify because conditions other than multiple sclerosis are perhaps more commonly the cause. Hierons and Lyle (1959) showed that both optic nerves are occasionally affected simultaneously in patients who later develop neurological signs compatible with multiple sclerosis. We were inclined, however, to consider patients who had only one attack of bilateral simultaneous optic neuritis as having insufficient evidence to warrant the label of multiple sclerosis.

4 Spinal-optic: some patients presented with involvement of both optic nerves and spinal cord. If single such episode had occurred it was difficult to decide whether Devic's disease or multiple sclerosis was the correct diagnosis. We were reluctant to accept a patient as having multiple sclerosis unless the subsequent course included additional attacks.

5 Spinal recurrent: some patients had several attacks, all of which were limited clinically to the spinal cord. On examination, evidence of neurological deficit was also limited to the spinal cord.

Spinal progressive type A proportion of patients had a slowly progressive paraparesis. On examination spasticity of lower limbs and often posterior column impairment was found. After careful study to rule out other conditions which could produce the same clinical picture, *e.g.*, cord compression, multiple sclerosis remained as a likely diagnosis.

Spino-cerebellar type In another form of multiple sclerosis, cerebellar ataxia was the most

TABLE II
NUMBER AND PERCENTAGE OF PATIENTS BY CLINICAL TYPE AND AREA OF ORIGIN (ISRAEL, 1960)

Type	Origin	
	Europe ¹	Afro-Asia
	No. of Patients	No. of Patients
Disseminated		
Recurrent	100 (50%)	34 (56%)
Progressive	25 (12%)	4 (7%)
RBN recurrent	5 (2%)	—
Spinal-optic	3 (1%)	2 (3%)
Spinal recurrent	14 (7%)	4 (6%)
Spinal progressive	43 (22%)	14 (23%)
Spino-cerebellar	11 (6%)	3 (5%)
Total	201 ¹ (100%)	61 (100%)

¹Seven European cases, clinical type unknown

prominent sign. Frequently, pyramidal signs were an associated finding. Cerebellar ataxia due to multiple sclerosis had to be differentiated carefully from the hereditary spino-cerebellar degenerative disorders. A family history of similar cases with onset at about the same age and the presence of cardiac and skeletal anomalies influenced us against accepting certain ataxic patients as having multiple sclerosis.

After classifying the patients into the above more or less arbitrary groups, European and Afro-Asian patients were compared. Table II shows a remarkable correspondence between the European and the Afro-Asian groups as regards the distribution of clinical types.

PRESENTING SYMPTOMS The presenting symptoms could be allotted to one of the following nine categories:

Motor Complaints of weakness, paralysis, dragging a leg, and stiffness are included.

Sensory Numbness, tingling, pins and needles, electrical sensation, loss of sensation, and pain are examples.

Combined sensory and motor If both motor and sensory complaints occurred at the onset, the patient was tabulated separately in this category.

Visual Loss of vision, blurring, a cloud or veil over one eye are representative.

Diplopia This category is self-explanatory.

Cerebellar and/or vestibular Complaints of imbalance, unsteadiness, staggering, drunken walk, trembling of a limb; also, symptoms of turning, dizziness, and light-headedness are included.

Sphincter disturbance Urgency, hesitancy, incontinence, precipitancy were listed here.

Mixed If complaints referable to more than one of the above categories occurred, the patients were tabulated in the 'mixed' category.

Miscellaneous Complaints which did not fit in any of the above groups were listed here, *e.g.*, a seizure, mental or emotional aberration.

The various presenting symptoms and percentage affected in each group are given in Table III. Again a remarkable similarity between Europeans and Afro-Asians is apparent.

CLINICAL COURSE In many series, about two-thirds of patients have a clinical course characterized by remissions and exacerbations while one-third have a chronic-progressive or static course (Brown and Putnam, 1939; Alter *et al.*, 1962; Carter, Sciarra, and Merritt, 1950; Lazarte, 1950). The proportion of relapsing cases in Israel conforms to the general experience. Of European patients, 62% reported a remitting-relapsing course whilst 66% of Afro-Asians had remissions and exacerbations. Thus, no appreciable difference in the percentage of exacerbation cases was discernible between high and low prevalence groups.

EXACERBATION RATE Typically, multiple sclerosis progresses in fits and starts. The frequency of exacerbations and remissions may reflect the severity of the illness. Therefore, a comparison of European and Afro-Asian patients in this regard was of interest. 'Exacerbation' had first to be defined: a neurological symptom or sign not previously present or re-appearance of a symptom or sign after it had been absent for at least three months. Minor fluctuations in status such as increased fatigue or slight change in ability to balance or coordinate were not accepted as constituting 'exacerbation'. By way of illustration, a patient without eye symptoms who began to have visual impairment or a patient with previously normal visual fields who showed a scotoma was regarded as having an exacerbation provided the change occurred after a quiescent period of at least three months. An episode of paraesthesia or demonstration of a Babinski response in a patient who previously had flexor plantar responses is another example. If such a change occurred within less than three months of another episode, the change was regarded as part of the earlier attack. The three-month interval was set quite arbitrarily but some cut-off point applied systematically in all patients was necessary. Since examinations were not performed regularly on patients it is obvious that a change of neurological status of which the patient was not aware would be missed in the tabulation. Therefore, computation of exacerbation rates may well contain an error of indeterminate size. There is no reason to believe, however, that such an error would be greater for one group than for the other.

'Exacerbation rate' is the number of exacerbations per person-year duration of illness (McAlpine and

TABLE III

NUMBER AND PERCENTAGE OF PATIENTS BY PRESENTING SYMPTOM AND AREA OF ORIGIN (ISRAEL, 1960)

Symptom	Origin	
	Europe ¹	Afro-Asia
	No.	No.
Motor	83 (41%)	18 (29%)
Sensory	27 (13%)	8 (13%)
Combined motor-sensory	12 (6%)	9 (15%)
Visual	29 (14%)	8 (13%)
Diplopia	6 (3%)	1 (2%)
Cerebellar-vestibular	14 (7%)	8 (13%)
Sphincter	4 (2%)	1 (2%)
Mixed	25 (12%)	7 (11%)
Miscellaneous	3 (2%)	1 (2%)
Total ¹	203 ¹ (100%)	61 (100%)

¹Five European cases, presenting symptom unknown

Compston, 1952; Brown and Putnam, 1939; Alexander, Berkeley, and Alexander, 1958). When all 164 exacerbating cases were considered together, a rate of 0.28 per person-year of illness resulted, *i.e.*, approximately one every three to four years. Europeans showed 0.25 and Afro-Asians 0.49 exacerbations per person-year of illness. Lest the inference be drawn that the exacerbation rate tended to be higher in Afro-Asians, it must be stressed that the average duration of illness was shorter for Afro-Asians than for Europeans. It has been shown by other investigators (McAlpine and Compston, 1952; Müller, 1949, 1951) that the exacerbation rate tends to be greater in the earlier years of illness. Since Afro-Asians included more cases with shorter duration, it would be expected that the exacerbation rate among them would be higher than for Europeans.

In order to circumvent the difficulty inherent in the above comparison, patients with disease of equal duration were compared (Table IV). When inequalities in duration of illness were controlled, the exacerbation rate was almost identical for each group.

TABLE IV

NUMBER OF PATIENTS AND RATE OF EXACERBATION PER PERSON-YEAR OF ILLNESS BY DURATION OF ILLNESS AND AREA OF ORIGIN (ISRAEL, 1960)

Years	Europe		Afro-Asia	
	No. of Cases	Rate of Exacerbation	No. of Cases	Rate of Exacerbation
During the whole course of the disease	124	0.25	40	0.49
During the years 1-5 ¹	104	0.40	19	0.39
During the years 6-10 ²	72	0.10	4	0.13

¹In patients who were ill five years at least

²In patients who were ill 10 years at least

It is to be noted, too, that the exacerbation rate tended to decrease appreciably with longer duration, and thus additional support is provided for the contention that exacerbations are concentrated in the early years of illness.

The European patients with an exacerbating course were divided into those who had spent the first five years after onset of illness in Europe and those who had spent the first five years after onset of illness in Israel. Of the 33 patients in the former group, an exacerbation rate of 0.35 per person-year of illness was found. The exacerbation rate for the 53 patients in the latter group was 0.45 per person-year of illness. Thus, the exacerbation rate for the first five years of illness was approximately the same for European patients whether they lived in Europe or in Israel, after onset of illness. Migration of Euro-

pean individuals to Israel before the onset of illness did not ameliorate the clinical course when measured in terms of the exacerbation rate. It is appreciated that the exacerbation rate does not necessarily reflect the severity of the clinical course. Conceivably, one patient might suffer more attacks but recover more completely than another patient. Moreover, a single episode resulting in paraplegia might be considered more severe than several which left a small scotoma, or slight ataxia as a residual effect. Accordingly, disability was also compared.

DISABILITY In grading disability, a modification of Hyllsted's (1961) criteria was used. Thus a 'moderately' disabled group (grades 1-3) and a 'severely' disabled group (grades 4-6) were established. In analysing the data for all patients, 51% were moderately disabled and 49% severely disabled on examination. However, 48% of the European group was moderately disabled as compared with 61% of the Afro-Asian group; 52% of Europeans were severely disabled as compared with 39% of Afro-Asians. Here, again, one must not conclude that the Afro-Asians necessarily had a less disabling form of multiple sclerosis. Recall that the mean duration of illness was shorter for the Afro-Asian group, and that disability may be expected to increase with greater duration of illness.

When disability for Europeans and Afro-Asians was compared for groups with equal duration of illness (Table V), disability was not consistently greater in either group; indeed, the difference in

TABLE V

NUMBER OF PATIENTS AND NUMBER AND PERCENTAGE SEVERELY DISABLED BY DURATION OF ILLNESS AND AREA OF ORIGIN (ISRAEL, 1960)

Duration of Illness (yr.)	Europe		Afro-Asia	
	Total No.	No. Severely Disabled	Total No.	No. Severely Disabled
0-5	44	14 (32%)	32	12 (37%)
6-10	44	23 (52%)	15	5 (33%)
11-15	52	31 (60%)	6	4 (67%)
16+	65	38 (59%)	8	3 (38%)
Total ¹	205 ¹	106 (52%)	61	24 (39%)

¹ Three European cases, duration unknown

ability for each five-year duration period was not significant. The degree of disability might conceivably be influenced by the length of 'exposure' to the European environment. Therefore, the percentage of severely disabled European patients was assessed for varying lengths of residence in Europe (Table VI). No trend was discerned, so that longer residence in

TABLE VI

NUMBER OF EUROPEAN PATIENTS AND NUMBER AND PERCENTAGE SEVERELY DISABLED BY AGE AT IMMIGRATION TO ISRAEL

Age at Immigration ¹ (yr.)	No. of Cases ²	No. of Severely Disabled
0—9	5	3 (60%)
10—19	37	20 (54%)
20—29	64	24 (38%)
30—39	45	25 (56%)
40—49	32	17 (53%)
50 +	21	16 (76%)
Total ²	204 ²	105 (51%)

¹Age at immigration equals years of 'exposure' to European environment

²Four cases, age at immigration unknown

Europe apparently was not associated with a higher proportion of severely disabled individuals.

DISCUSSION

Although the prevalence of multiple sclerosis is considerably higher among Europeans than among Afro-Asians in Israel, there is remarkable similarity in the clinical characteristics of the disease in the two groups. The clinical types, presenting symptoms, course of illness, exacerbation rate, and degree of disability on examination were almost identical. Mean age at onset and mean duration of illness were less for Afro-Asians than for Europeans, but the difference probably reflects the higher proportion of young people in the Afro-Asian population.

Our results suggest that the clinical manifestations of multiple sclerosis do not vary despite marked differences in prevalence. We have not been able to support the notion that clinical manifestations vary with geographical latitude. What does the apparent constancy of the clinical picture imply as regards possible aetiological factors?

The relation between prevalence and geographical latitude has been interpreted to mean that an environmental factor influences the frequency of the disease and is presumably of aetiological importance (Kurland and Westlund, 1954). It would be reasonable to expect that in areas of low prevalence the effect of the aetiological agent on patients would be ameliorated. Accordingly, later onset, lower exacerbation rate, and less disability for a given duration of illness might have been expected among Afro-Asians. On the other hand, it could be argued that the 'attenuated' aetiological agent would only affect the most susceptible, and, therefore, only more severe cases would be apparent in areas of low prevalence. The finding of an almost identical clinical picture in the high and low prevalence group is unexpected and difficult to explain. 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 a similar conclusion on the basis of cases ascertained in Australia. Moreover, exacerbations of the disease may not necessarily require re-exposure to a detrimental factor, for otherwise number and rate of exacerbations would have been higher in Europeans.

It is possible that the same aetiological 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 multiple sclerosis. Where the disease is rare only cases with a clinical picture like that encountered in temperate regions would be recognized and diagnosed. The five clinical entities other than multiple sclerosis 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 multiple sclerosis is allegedly rare but neuromyelitis optica is common (Okinaka, McAlpine, Miyagawa, Suwa, Kuroiwa, Shiraki, Araki, and Kurland, 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 exists between the two groups in Israel.

The patients ascertained in Israel are immigrants for the most part (25 are 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 (Alter *et al.*, 1962), 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 were transported as a unit. It seems unlikely, though, 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.

It should be mentioned that some authors suspect genetic rather than environmental factors to be of

aetiological importance (Myrianthopoulos and Mackay, 1960). Perhaps the environmental factor postulated to be of aetiological significance is uniformly distributed but genetically susceptible individuals are concentrated in temperate zones. On this assumption, the clinical characteristics for susceptible groups would be expected to be similar. The gradual decline in prevalence from temperate zones to the tropics would be difficult to reconcile with the notion of varying concentrations of genetically susceptible individuals. Migration and difference in racial strains in temperate and tropical regions would be expected to produce clumping of susceptible individuals and abrupt changes in prevalence rather than a gradual decline toward the equator.

Several factors suggested as being of aetiological importance may be re-examined in the light of our clinical findings. Acheson and Bachrach (1960) suggested that different exposure to light among individuals in tropical and temperate regions might play a role in the pathogenesis of multiple sclerosis. If the effect of light were purely quantitative, the clinical manifestations of the disease would not be expected to be similar in high and low prevalence areas. Individuals who dwell in regions with ample sunlight should have milder disease than those whose exposure to light is less. In order to reconcile this suggestion of Acheson and Bachrach (1960) with our clinical observations, we would have to postulate that the affected individuals in the low prevalence environment had had less exposure to light than was characteristic of unaffected individuals of their area, *e.g.*, that individuals who develop the disease remain indoors more. While such a difference seems unlikely, *a priori*, it could be tested by appropriate questioning of patients.

The same arguments could be advanced against the idea that temperature or dietary fat or radiation were of pathogenic importance in multiple sclerosis. The affected individual in the low prevalence environment would have to share in common with the affected of the high prevalence environment not only the kind, but also the degree, of exposure to the pathogenic agent.

Poskanzer, Schapira, and Miller (1963) have compared epidemiological characteristics of multiple sclerosis and poliomyelitis and have suggested the possibility that a polio-like infection sets the stage for multiple sclerosis. As in multiple sclerosis, a lower frequency of poliomyelitis is seen in tropical regions than in temperate regions. The few cases of poliomyelitis which do develop in tropical areas are clinically similar to those in temperate zones. Here the analogy between poliomyelitis and multiple sclerosis applies well. However, the thesis that a virus of any kind, let alone a polio-like virus, might be of patho-

genic significance in multiple sclerosis suffers from the lack of pathological support.

Adams and Imagawa (1962) have suggested that a common infection like measles might damage the nervous system in certain individuals, releasing antigenic material. Later the material could give rise to auto-immune reactions characterized by demyelination. However, a recent study by Reed, Sever, Kurtzke, Huebner, and Kurland (1963) of titres in blood and spinal fluid against a large number of viral agents failed to provide evidence for an infectious-allergic aetiology of multiple sclerosis. Efforts to culture a slow growing virus like that which produces visna in sheep from patients with multiple sclerosis likewise failed (Thormar and von Magnus, 1963).

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 multiple sclerosis. Nevertheless, the variables should not be dismissed as being of no importance. Their study may yet provide a clue to account for the striking difference in prevalence between the two groups.

SUMMARY

Israel's population includes immigrants from every continent and many different countries of the world. A country-wide survey completed in 1961 disclosed 282 patients with multiple sclerosis. Of these, 208 were of European origin and 61 were of Afro-Asian origin, including 25 native Israelis. The prevalence of multiple sclerosis was more than six times higher in Europeans than in Afro-Asians.

Despite the large difference in prevalence, the clinical characteristics of the disease were remarkably similar in the two groups. No significant differences could be discerned when presenting symptoms, course of illness, exacerbation rate, and disability on examination were compared. A similar percentage of disseminated, spinal progressive, and spino-cerebellar types was found in each group. Apparent earlier age at onset of illness for Afro-Asians was attributed to the fact that the Afro-Asians have a lower mean age in the general population than Europeans. The duration of residence in the European environment ('exposure') did not influence age at onset nor subsequent disability.

Various factors which have been suggested as being of aetiological importance were discussed in the light of the clinical observations of the present

study. It appears that once an individual is affected with multiple sclerosis, domicile does not influence the clinical manifestations appreciably.

REFERENCES

- Acheson, E. D. (1961). *Brit. J. prev. soc. Med.*, **15**, 118.
 —, and Bachrach, C. A. (1960). *Amer. J. Hyg.*, **72**, 88.
 Adams, J. M., and Imagawa, D. T. (1962). *Proc. Soc. exp. Biol. (N. Y.)*, **111**, 562.
 Alexander, L., Berkeley, A. W., and Alexander, A. M. (1958). *J. Amer. med. Ass.*, **166**, 1943.
 Allison, R. S. (1950). *Brain*, **73**, 103.
 —, and Millar, J. H. D. (1954). *Ulster med. J.*, **23**, suppl. no. 2.
 Alter, M., Allison, R. S., Talbert, O. R., and Kurland, L. T. (1960). *Wld Neurol.*, **1**, 55.
 —, Halpern, L., Kurland, L. T., Bornstein, B., Leibowitz, U., and Silberstein, J. (1962). *Arch. Neurol. (Chic.)*, **7**, 253.
 Brown, M. R., and Putnam, T. J. (1939). *Arch. Neurol. Psychiat. (Chic.)*, **41**, 913.
 Carter, S., Sciarra, D., and Merritt, H. H. (1950). *Proc. A. Res. Nerv. Ment. Dis.*, **28**, 471.
 Davenport, C. B. (1922). *Ibid.*, **8**, 51.
 Dean, G. (1961). *Proc. roy. Soc. Med.*, **54**, 10.
 Hierons, R., and Lyle, T. K. (1959). *Brain*, **82**, 56.
 Hyllested, K. (1961). *Acta psychiat. scand.*, **36**, 553.
 Kolb, L. C. (1950). *Res. Publ. Ass. nerv. ment. Dis.*, **28**, 28.
 Kurland, L. T., and Westlund, K. B. (1954). *Ann. N.Y. Acad. Sci.*, **58**, 682.
 Lazarte, J. A. (1950). *Proc. A. Res. Nerv. Ment. Dis.*, **28**, 512.
 MacLean, A. R., and Berkson, J. (1951). *J. Amer. med. Ass.*, **146**, 1367.
 McAlpine, D., and Compston, N., (1952). *Quart. J. Med.*, **21**, 135.
 Müller, R. (1949). *Acta med. scand.*, suppl. 222.
 — (1951). *Arch. Neurol. Psychiat. (Chic.)*, **66**, 561.
 Myrianthopoulos, N. C., and Mackay, R. P. (1960). *Acta genet. (Basel)*, **10**, 33.
 Okinaka, S., McAlpine, D., Miyagawa, K., Suwa, N., Kuroiwa, Y., Shiraki, H., Araki, S., and Kurland, L. T. (1960). *Wld Neurol.*, **1**, 22.
 Poskanzer, D. C., Schapira, K., and Miller, H. (1963). *Lancet*, **2**, 917.
 Reed, D., Sever, J., Kurtzke, J. F., Huebner, R., and Kurland, L. T. (1963). *Trans. Amer. neurol. Ass.*, **88**, 119.
 Saint, E. G., and Sadka, M. (1962). *Med. J. Aust.*, **2**, 249.
 Spota, B. B., and Brage, D. (1951). *Pren. méd. argent.*, **38**, 772.
 Statistical Abstract of Israel, No. 12 (1961). The Government Printer, Israel.
 Sutherland, J. M., Tyrer, J. H., and Eadie, M. J. (1962). *Brain*, **85**, 149.
 Thormar, H., and von Magnus, H. (1963). *Acta neurol. scand.*, **39**, 209.
 Ulett, G., (1948). *Dis. nerv. Syst.*, **9**, 342.
 Westlund, K. B., and Kurland, L. T. (1953). *Amer. J. Hyg.*, **57**, 380, 397.