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Epidemiological study of multiple sclerosis in Israel[1]

Part II Multiple sclerosis and level of sanitation

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The frequency of multiple sclerosis has been found to increase with increasing latitude. This peculiar geographical distribution has given rise to various hypotheses implicating an environmental factor in the aetiology of the disease (Dean, 1949; Westlund and Kurland, 1953; Kurland and Westlund, 1954; Kurland, Mulder, and Westlund, 1955; Acheson, Bachrach, and Wright, 1960; Mutlu, 1960; Alter, Halpern, Kurland, Bornstein, Leibowitz, and Silberstein, 1962; Kurland and Reed, 1964). Recently, Poskanzer, Schapira, and Miller (1963) have discussed the possibility of an infectious aetiology and have suggested that multiple sclerosis may be an occasional manifestation of a widespread subclinical infection. They think that an enteric infection should be considered because of many similarities in the epidemiological pattern of poliomyelitis and multiple sclerosis. They postulate further that the prevalence of clinically apparent multiple sclerosis might be correlated with the level of sanitation, a situation analogous to that observed in poliomyelitis. Thus, in areas where the sanitary level is high, infection may be acquired later in life, when the individual is more susceptible to the process which produces multiple sclerosis. Conversely, where sanitation is poor, infection may be acquired early when the individual is less susceptible. Although supporting evidence is meagre, these postulates are attractive because they are compatible with the known geographical distribution of the disease. In temperate areas where sanitation is generally on a high level, multiple sclerosis is common; in tropical regions the sanitary level is generally poorer and multiple sclerosis is rare.

There are some clinical observations suggesting that the central nervous system of older individuals may be less resistant to the pathological process of multiple sclerosis. Thus, the disease is extremely rare before age 15 and patients with late onset of multiple sclerosis have fewer remissions and develop severe disability more rapidly than patients with earlier onset of the disease (Müller, 1949; Müller, 1951; McAlpine, 1946; McAlpine, 1957; Papac, 1957; Leibowitz, Alter, and Halpern, 1964).

The postulate that sanitary level is related to aetiology would derive additional support if it could be shown that patients with multiple sclerosis tend to have a higher level of sanitation before the onset of the illness than controls from the same area. In the present communication, tests of this hypothesis are presented.

SUBJECTS AND METHOD

A nation-wide survey was carried out to identify all patients with multiple sclerosis living in Israel on 1 January 1960. A list of cases was compiled by reviewing medical records for the period 1955 through 1959 at all hospitals, chronic care centres, and referral clinics with neurological facilities. In addition, physicians with neurological practices were questioned. From each source, cases diagnosed as having multiple sclerosis or one of five clinically similar disorders, *e.g.*, primary lateral sclerosis, nontraumatic paraplegia, myelopathy, cerebellar ataxia, and optic neuropathy, were identified. The initial list included 1,000 patients. After carefully reviewing all documentary medical evidence, a total of 420 patients could be excluded from further consideration because of their having a disease other than multiple sclerosis which would account for the neurological signs and symptoms. The remaining 580 individuals constituted a provisional list of cases of multiple sclerosis. Of the latter, 520 were successfully located and personally examined by one of the project's neurologists (U.L., M.A., or L.H.). After examination 282 cases were accepted as having multiple sclerosis according to the criteria of Alter *et al.* (1962).

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In 1963, an effort was again made to contact the patients with multiple sclerosis in order to carry out a study of exposure of these patients to a variety of factors of possible aetiological importance in multiple sclerosis. It was possible to locate and interview 241 patients from the original group of 282 identified in the nation-wide survey.

The interview consisted of a series of 146 pre-coded and several open-end questions, including items on demographic and personal variables—socio-economic status, medical history (including obstetrical and surgical information), personal habits, outdoor exposure, physical and mental strain, emotional and physical trauma, personality characteristics, diet, and sanitary level in the childhood home. The final questionnaire incorporated the experience of two pre-tests based on 10 patients and 20 controls.

The controls were chosen by a cluster random sampling procedure from the 1961 population registry of the three major population centres of Israel. The controls selected were individually matched with patients on the basis of age, sex, and region of birth in a ratio of four controls to one patient.

As the study was concerned with factors of aetiological importance, the enquiries in the questionnaire pertained to events before the onset of multiple sclerosis. An 'age at onset' was assigned to each control to correspond with the age at onset of multiple sclerosis of the patient with whom the control was matched.

The results of the survey have already been reported (Antonovsky, Leibowitz, Smith, Medalie, Balogh, Kats, Halpern, and Alter, 1965). No statistically significant differences between patients and controls were obtained on demographic variables, socio-economic status, medical history, diet, and several other items. On the other hand, patients tended to have lived longer in metropolitan centres, patients more frequently reported serious injuries and periods in hospital before the onset, female patients more often reported having general anaesthesia before the onset, patients were more frequently exposed to dogs as pets in childhood, patients had serious emotional trauma more often before onset and tended to have personalities in which aggressive reactions were inhibited. In addition, patients differed significantly from controls with respect to sanitary level of the childhood home. In the present report, the results of the inquiry about sanitary level of the childhood home are elaborated.

The items in the questionnaire relevant to sanitary level included source of drinking water, type of toilet facilities, and degree of crowding, all referring to the childhood home when the respondent was about 10 years old. The childhood period was emphasized because of evidence that an experience or exposure in early life may determine the risk of developing multiple sclerosis (Poskanzer *et al.*, 1963; Kurtzke, 1965b).

Additional items pertinent to sanitary level included frequency of certain infections from birth to age 15 and from age 15 to age at onset of multiple sclerosis; size of community of birth and of later residence; and socio-economic status. Socio-economic level was based on occupational and educational criteria and was determined both for the period when the respondent was 10 years old and at the onset of multiple sclerosis.

RESULTS

The source of drinking water in the childhood home of patients and controls is compared in Table I. Those having piped water were considered to have the highest sanitary level while those who drank well water, river, lake, spring, and rain water were considered to have a less sanitary supply. Comparison of respondents in the highest versus the lower sanitary categories revealed a significantly higher percentage of patients in the highest category.

TABLE I

SOURCE OF WATER SUPPLY OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS AT AGE 10

Source of Water	*% Patients*	*% Controls*	*Sanitary Level*
Piped water in house	52	45	High
Well	32	42	
River, lake, spring	7	9	
Rain water	2	1	Low
Other source	6	3	
No answer	1	0	
Total	100%	100%	
Number of cases	241	964	

$\chi^2 = 4{\cdot}704$, $p < 0{\cdot}05$, 1 d.f.

Toilet facilities available to patients and controls in the childhood home are compared in Table II.

TABLE II

TYPE OF TOILET FACILITY AVAILABLE TO PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS AT AGE 10

Facilities	*% Patients*	*% Controls*	*Sanitary Level*
Flush toilet in dwelling unit	40	34	High
Non-flush toilet in dwelling unit	6	6	
In building, not in dwelling unit	5	5	Low
In yard or none	48	55	
No answer	1	0	
Total	100%	100%	
Number of cases	241	964	

$\chi^2 = 4{\cdot}233$, $p < 0{\cdot}05$, 1 d.f.

Flush lavatories within the dwelling were considered to represent the highest sanitary facility. Non-flush indoor lavatories were categorized as less sanitary and outdoor facilities or lack of toilet facilities the least sanitary. An analysis of responses again revealed a significantly higher percentage of patients than controls in the highest sanitary category.

A crowding index was derived by dividing the number of people living in the respondent's house when the respondent was aged 10 by the number of rooms in the house, excluding the kitchen. As shown in Table III, a higher percentage of patients than controls lived in less crowded houses. The difference between patients and controls was statistically significant when a comparison was made between the percentage reporting less than two persons per room and those with two or more per room.

TABLE III

CROWDING INDEX OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS AT AGE 10

Crowding Index	% *Patients*	% *Controls*	*Sanitary Level*
Less than 1·0 persons per room	6	6	
1·0—1·9 persons per room	34	27	High
2·0—2·9 persons per room	30	31	
3·0—3·9 persons per room	14	16	Low
4·0 or more persons per room	15	19	
No answer	1	1	
Total	100%	100%	
Number of cases	241	964	

$\chi^2 = 4{\cdot}532$, $p < 0{\cdot}05$, 1 d.f.

TABLE IV

SCALE OF SANITARY LEVEL BASED ON TOILET FACILITY, WATER SOURCE, AND CROWDING INDEX FOR PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS AT AGE 10

Sanitary Level Class	% *Patients*	% *Controls*	*Sanitary Level*
Class 1 less than 2·0 persons per room; flush toilets; piped drinking water	23·2	15·7	High
Class 2a less than 2·0 persons per room; no flush toilets; piped drinking water	7·9	5·9	
Class 2b 2·0 or more persons per room; flush toilets; piped drinking water	14·9	15·7	Intermediate
Class 3a less than 2·0 persons per room; no flush toilets; no piped drinking water	9·9	12·3	
Class 3b 2·0 or more persons per room; no flush toilets; piped drinking water	9·1	10·9	
Class 4 2·0 or more persons per room; no flush toilets; no piped drinking water	32·9	38·6	Low
No answer	2·1	0·9	
Total	100%	100%	
Number of cases	241	964	

$\chi^2 = 8{\cdot}703$, $0{\cdot}01 < p < 0{\cdot}02$, 2 d.f.

The items on crowding, toilet facilities, and water source were combined and arranged in a scale designed to reflect gradation in sanitary level. The data are shown in Table IV. Combining the four middle groups in the scale into an 'intermediate' sanitary level, and comparing patients and controls on high, intermediate, and low levels, patients again had a significantly higher sanitary level than controls.

The specific birthplace of each respondent was recorded and its population size at the time of the respondent's birth was determined as precisely as possible by using published demographic reports. Patients and controls did not differ significantly on size of birthplace (Table V). Respondents were also asked about the size of communities in which they resided most of the time until the onset of the disease. A higher percentage of patients than controls reported residing mainly in metropolitan centres of over 500,000 population ($\chi^2 = 7{\cdot}671$, $p < {\cdot}01$, 1 d.f.; Table XIIA).

TABLE V

SIZE OF BIRTHPLACE OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS

Population of Birthplace at Time of Birth	% *Patients*	% *Controls*
500,000 or more	15	18
100,000—499,999	20	23
25,000—99,999	22	17
5,000—24,999	21	20
Less than 5,000	8	6
Place not located or population unknown	14	16
Total	100%	100%
Number of cases	241	964

The difference in sanitary level between patients and controls cannot be attributed to a rural-urban difference in place of major residence, since similar proportions of patients and controls lived in rural areas. The difference cannot be due to a difference in the proportions dwelling in urban versus metropolitan residences, as differences in sanitary level between patients and controls appeared to be restricted to those dwelling in towns. As shown in Table VI, differences in sanitary level between patients and controls existed only among the respondents who reported living in metropolitan areas; similarly the differences in the percentage living in metropolitan areas appeared only among respondents with a high sanitary level.

Place of residence may be related to socio-economic status. There is, therefore, a possibility that a difference in socio-economic status between patients and controls may account for the higher sanitary level of patients. However, no consistent overall difference was found between patients and

TABLE VIA

SANITARY LEVEL AT AGE 10 OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY SIZE OF PLACE OF LONGEST RESIDENCE[1]

Place of Longest Residence	*Low Sanitary Level*	
	% Patients	*% Controls*
Metropolitan	13 (60)[2]	25 (162)
Non-metropolitan	41 (175)	42 (793)

TABLE VIB

SIZE OF PLACE OF LONGEST RESIDENCE OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY SANITARY LEVEL AT AGE 10

Sanitary Level	*Metropolitan Residence*	
	% Patients	*% Controls*
High	33 (156)	21 (582)
Low	10 (79)	11 (373)

[1]'Low sanitary level' refers to class 4 and 'high sanitary level' to all others in Table IV.

[2]The numbers in parentheses represent the base totals of the percentages, *e.g.*, 13% of 60 metropolitan patients had a low sanitary level.

controls in socio-economic level as reflected by education of a parent or of a respondent or the occupation of the head of the household when the respondent was 10 years old or at the time of onset. The analysis of socio-economic status has been described in greater detail elsewhere (Antonovsky, Leibowitz, Medalie, Smith, Halpern, and Alter, 1966).

An implication of the observation that patients had a higher sanitary level than controls is that infectious diseases related to sanitation might be less common in patients. Inquiry was made about eight different infectious diseases. No significant differences between patients and controls emerged. Questions about infections referred to the childhood period as well as to the period between age 15 and the onset (Table VII).

TABLE VII

INFECTIOUS DISEASES TILL AGE 15 AND FROM AGE 15 TILL AGE AT ONSET AMONG PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS

Disease	*Till Age 15*		*Age 15 till Onset*	
	Patients (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)
Diphtheria	10	9	2	2
Typhus	2	3	4	2
Hepatitis	7	9	5	5
Pneumonia	7	10	4	5
Typhoid fever	7	7	4	6
Tuberculosis	1	1	0	1
Pertussis	31	30	1	1
Nephritis	2	3	2	2
Number of cases	241	964	241	964

TABLE VIII

INCIDENCE OF 'OTHER SERIOUS ILLNESSES' FROM AGE 15 TILL ONSET

	Disease Groups	*No. of Other Illnesses Reported*	
		Patients	*Controls*
1	Viral, bacterial, and parasitic infections	24	63
2	Ophthalmological complaints	14	2
3	Neurological complaints	20	21
4	Peptic ulcer	1	18
5	Renal, urinary tract	1	10
6	Diabetes	—	9
7	Liver, gall bladder	—	9
8	Cardiovascular	—	18
9	Skin	1	8
10	Respiratory	9	34
11	Gastro-intestinal (excluding peptic ulcer)	11	43
12	Inflammations, focal infections	3	8
13	Endocrine (including gynaecology)	4	18
14	Malnutrition, deficiency disease	—	1
15	Bones, joints, muscles	6	21
16	Venereal	2	1
17	Other	9	18
	Total	105	302
	Number reporting other serious illnesses	70	222

Respondents were also asked about 'other serious illnesses' from age 15 till the onset of multiple sclerosis. Of the 105 illnesses reported by patients, 24 were classified as 'viral, bacterial, or parasitic infections'. Of the 302 illnesses reported by controls, 63 were so classified (Table VIII). The infectious diseases constitute about the same proportion of illnesses reported for both patients and controls (23% and 21%, respectively).

COMPARISONS OF SUBGROUPS An analysis of sanitary level was made for various subgroups of patients and controls using the indices of source of drinking water, toilet facilities, and crowding in the childhood home. Table IX contains the relevant data for three groups with different regions of origin, namely, Eastern Europe, Central Europe, and Afro-Asian countries. In each of the subgroup comparisons, the percentage of respondents in the lowest sanitary category was compared. A lower percentage of patients than controls appeared in the lower sanitary level category in eight of the nine comparisons, *i.e.*, relatively more patients were in the higher sanitary categories. The difference was particularly striking in the Central European group which, incidentally, had the highest prevalence of multiple sclerosis of any group studied in Israel (Alter *et al.*, 1962).

Patients and controls were also compared, controlling for age at interview (Table X). In the oldest age group, a lower percentage of patients than controls had a poor sanitary level. The comparison in the 40-to-54-year-old category pointed in the same direction. In the youngest group, however, patients did not have a higher sanitary level than controls.

TABLE IX

SANITARY LEVELS AT AGE 10 OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY REGION OF BIRTH[1]

Lower Sanitary Category	*Eastern Europeans*		*Central Europeans*		*Afro-Asians*	
	Patients (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)
No flush toilet in dwelling unit	69	74	40	55	59	64
No piped water in dwelling unit	55	62	32	48	44	50
3·0 or more persons per room	29	36	16	30	41	40
Number of cases	125	500	50	200	32	128

Patients born in Israel (18), in southern Europe (11), or in western Europe (5) and their controls are excluded from these tabulations.

TABLE X

SANITARY LEVEL AT AGE 10 OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY AGE IN 1962

Lower Sanitary Category	< 39 *Years*		40-54 *Years*		55+ *Years*	
	Patients (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)
No flush toilet in dwelling unit	53	51	61	69	65	77
No piped water in dwelling unit	39	31	47	58	49	68
3·0 or more persons per room	41	36	28	29	18	45
Number of cases	66	271	104	400	71	293

TABLE XI

SANITARY LEVEL AT AGE 10 OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY DURATION OF ILLNESS

Lower Sanitary Category	*Duration of Illness*					
	< 9 *Years*		10-19 *Years*		20+ *Years*	
	Patients (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)	*Patients* (%)	*Controls* (%)
No flush toilet in dwelling unit	53	61	66	67	58	72
No piped water in dwelling unit	42	46	51	57	44	59
3·0 or more persons per room	32	35	30	34	20	40
Number of cases	93	372	93	372	55	220

A comparison was made between patients with different durations of illness and their controls (Table XI). In every comparison, controls had a lower sanitary level, the difference being particularly large between patients with longest duration of illness and their controls.

In sum, analyses by subgroup revealed that the evidence supporting the hypothesis that patients had a higher sanitary level than controls was strongest for the European immigrant group, the groups which were older at the time of interview, and those with a long duration of illness.

Region of birth, age, and duration of illness are all interrelated in the Israeli patient population. Older people are more likely to be ill longer and to be Europeans. On the other hand, younger people are more likely to be ill for a relatively short time and are more likely to be Afro-Asians. The direct relationship between age and duration of illness is, of course, inherent. The relationship between those variables and region of birth is a function of the different age structures of the European and Afro-Asian populations in Israel. Before 1948, 90% of the immigrants were European-born. Since then, Afro-Asian immigration has increased sharply, and constituted 55% of the immigrants until 1962. This is reflected in the median ages of the various ethnic groups. In 1963 the median age of European-born people in Israel was 46·5 years; of Asian born, 33·2 years; and of African-born, 26·1 years (Statistical Abstract of Israel, 1964). Among the patients in the present study, 19% of the Europeans were under 40 years of age at the time of the interview compared with 43% of the Afro-Asians. Hence, the observation that European immigrants, older patients, and those ill longest all showed similar patterns of response on the sanitary questions is more easily understood.

The size of the community of longest residence was also determined for groups from different regions of origin. In the European but not in the Afro-Asian group, a higher percentage of patients than controls lived mainly in large metropolitan communities (Table XIIB). Further analysis revealed that patients who were ill longer (Table XIIC) and also

TABLE XII

TYPES OF MAJOR RESIDENCE UNTIL ONSET OF PATIENTS WITH MULTIPLE SCLEROSIS AND CONTROLS BY REGION OF BIRTH, DURATION OF ILLNESS, AND AGE IN 1962

	Mostly Metropolitan	*Mostly City*	*Mostly Small Town or Village*	*Other*	*Total (%)*	*Number*
A All respondents						
Patients	25	49	24	2	100	241
Controls	17	57	25	1	100	964
B By region of birth						
Eastern European patients	30	44	23	3	100	125
Eastern European controls	17	55	26	2	100	500
Central European patients	26	46	26	2	100	50
Central European controls	18	46	35	1	100	200
Afro-Asian patients	9	57	34	0	100	32
Afro-Asian controls	25	52	22	1	100	128
C By duration of illness						
<9 years, patients	24	53	23	0	100	93
<9 years, controls	14	64	20	2	100	372
10-19 years, patients	23	49	25	3	100	93
10-19 years, controls	19	53	25	3	100	372
20+ years, patients	31	39	26	4	100	55
20+ years, controls	20	45	35	0	100	220
D By age in 1962						
−39 years, patients	11	56	33	0	100	66
−39 years, controls	13	64	22	1	100	271
40-54 years, patients	32	45	21	2	100	104
40-54 years, controls	20	53	24	3	100	400
55+ years, patients	28	48	20	4	100	71
55+ years, controls	18	52	29	1	100	293

those who were oldest at the time of interview (Table XIID) had lived mainly in large cities more often than their controls.

DISCUSSION

The data presented in this report suggested that risk of developing multiple sclerosis may be higher in individuals with a high level of sanitation in the childhood home. It may be argued that the indices used to measure sanitation reflect the influence of another variable which is more directly related to the aetiology of the disease. It is known, for instance, that socio-economic status is related to sanitary level. However, as was shown elsewhere (Antonovsky *et al.*, 1966), no consistent differences in socio-economic status as measured by occupation and education were found between patients with multiple sclerosis and controls in Israel. Data indicating that patients with multiple sclerosis were similar to controls in the general population as regards socio-economic status have also been presented by Westlund and Kurland (1953) based on a study in Winnipeg, Canada. The Israeli and Canadian observations strengthen the likelihood that differences in sanitary level and not socio-economic differences have some relevance to the aetiology of multiple sclerosis.

The analyses by subgroup showed that the differences between patients and controls on sanitary level were greatest among the Europeans, the older age groups, the groups with a long duration of multiple sclerosis, and the groups with metropolitan residence. But, as all these variables were interrelated in the Israeli population, it is uncertain whether such subgroup differences would be found in other populations.

For respondents 55 and older in 1962, the period of reference as regards sanitary level at age 10 ended in 1917; for those 40 to 54 in 1962 the reference period was 1918-1932; and for those 39 or less in 1962, the period was 1933 or later. It is plausible to assume that during the first four decades of this century sanitary conditions in the general environment improved. Indeed, a generally higher level of sanitation in the younger as compared with the older respondents in the Israeli series supports this assumption. It was also shown that patients who were youngest at the time of interview differed least in sanitary level from their controls (Table X). Thus, with improvement of the general level of sanitation, it is possible that differences in an individual's level of sanitation become less important as a factor in affecting the risk of developing multiple sclerosis. A certain sanitary level in the general environment may represent a 'threshold'

below which the risk of developing multiple sclerosis may change sharply. Inspection of curves of the distribution of multiple sclerosis in fact suggests that the prevalence of the disease increases sharply above 45° north latitude (Kurtzke, 1965a). Although it is unknown whether the general level of sanitation follows a similar gradient, it is known that sanitation, in general, increases with latitude.

In recalling the poliomyelitis analogy it should be noted that a high risk of developing paralytic poliomyelitis occurs after migration from an area with a high level of sanitation and a high prevalence of paralytic poliomyelitis to an area with a low level of sanitation and a low prevalence of paralytic poliomyelitis (van Rooyen and Morgan, 1943; Paul, Havens, and van Rooyen, 1944; Seddon, Agius, Bernstein, and Tunbridge, 1945; McAlpine, 1945; Illingworth, 1945; Caughey and Porteous, 1946; Sabin, 1947; Paul, 1948, 1949). Similarly, in an environment with generally poor sanitation, the prevalence of multiple sclerosis may be low and the risk of developing multiple sclerosis may be increased for individuals whose personal home sanitary level is high and for those who migrated from an environment with high sanitary level.

In Israel, the immigrants from Europe have a prevalence rate six to 10 times higher than native-born Israelis. However, immigrants from Afro-Asian countries to Israel have a prevalence rate which is as low as that of native-born Israelis (Alter *et al.*, 1962).

Table VI demonstrated that the differences between patients and controls on the sanitary items appeared among the respondents with metropolitan residence, who have, in general, a higher level of sanitation. This seems to contradict the above results. An explanation of this apparent discrepancy could again be sought in the poliomyelitis analogy. During the three decades before the beginning of vaccination, there was a definite shift toward an older age in the distribution of acute cases of poliomyelitis (Dauer, 1948; MacLean, 1950). This was interpreted as being due to improvement of hygiene and sanitation, progressively delaying the first exposure to the polio virus. On the other hand, comparison of the age distribution of cases in urban and rural areas showed an older age of infection in rural communities (Aycock, 1929; Howe, 1949). This was explained as being due to delayed exposure in sparsely settled areas. Thus, it may be that improvement of sanitation caused the age shift in urban communities while low density of the rural population caused even greater shift, despite no better sanitary conditions. In fact, these urban-rural differences have recently become less marked as the distinctions between rural and urban life have lessened (Howe, 1949). Similarly, the present results on multiple sclerosis may indicate that a higher sanitary level was connected with a higher risk of multiple sclerosis, especially in the big cities one generation ago. In small communities early exposure was prevented by other factors, *i.e.*, sparse population, and individual differences in sanitation played a minor role in this respect. During the last decades, together with improvement of sanitation in both urban and rural communities and the gradual obliteration of other urban-rural differences, the size of place of residence as well as the level of sanitation in the individual household became less important.

In view of the low rate of multiple sclerosis in the Afro-Asian population of Israel (Alter *et al.*, 1962; Alter, Leibowitz, and Halpern, 1964) and the postulated relationship between level of sanitation and prevalence of multiple sclerosis, it would be expected that the level of sanitation reported by Afro-Asians would be lower than that reported for Europeans. Yet, the percentage of Afro-Asians in lower sanitary level categories was less than that of Europeans on two of the three indices used (Table IX). However, Afro-Asians are, in general, younger and no more rural than Europeans in the Israeli population (Table XIIB). Therefore, general sanitation was being reported for a more recent period in time by Afro-Asians than by Europeans. The sanitary level of Europeans should perhaps have been compared with that of Afro-Asians of an older generation in order to determine whether the apparent higher level of sanitation among Afro-Asians as compared with Europeans reflects recent improvement in sanitation in the Afro-Asian environment. If the hypothesis implicating sanitary level in the aetiology of multiple sclerosis were correct, then an improving level of sanitation in Afro-Asian communities would cause the prevalence of multiple sclerosis to rise toward that of European communities. There is some evidence (Poskanzer *et al.*, 1963; Kurtzke, 1965b) that the 'incubation period' of multiple sclerosis is very long, perhaps even decades. Thus, improvement in sanitation may be reflected in an increasing rate of multiple sclerosis only after a generation has passed. If prevalence of multiple sclerosis in developing countries which now have low rates increased after improvement of sanitation, support for the hypothesis that sanitary level is somehow related to aetiology would be obtained. Countries like Japan, India, and North African countries are of particular interest as regards changing prevalence of multiple sclerosis in view of the reported low prevalence now current and the fact that sanitary facilities are being improved. It is noteworthy that in Japan, which is reported to have a low prevalence of multiple sclerosis (Okinaka,

McAlpine, Miyagawa, Suwa, Kuroiwa, Shiraki, Araki, and Kurland, 1960), human waste is used as fertilizer.

There are few follow-up surveys in which the possibility of changing prevalence can be used to test the sanitation hypothesis. A 10-year follow-up study of multiple sclerosis in Winnipeg, Canada (Stazio, Kurland, Bell, Saunders, and Rogot, 1964) showed a stable prevalence rate. However, Winnipeg may not be a suitable community in which to test the hypothesis. Having reached a high level of sanitation decades ago, sanitary level in Winnipeg may not have changed sufficiently in the last decades to be reflected in a change in prevalence of multiple sclerosis. The possibility of changing prevalence might more profitably be explored in areas with poor sanitation and a low rate of multiple sclerosis in which improved sanitary facilities are currently being developed.

The specific aetiological agent(s) in multiple sclerosis is unknown. Our observations on water source, lavatory facilities, and crowding are compatible with the suggestion that an enteric pathogen may be involved in the aetiology of multiple sclerosis, although another infectious agent, such as a respiratory pathogen, is, of course, not ruled out. It is commonly accepted that frequent respiratory infections are characteristic of temperate latitudes and there is epidemiological evidence (Andrewes, 1964) that respiratory infections increase with the onset of cold weather. Infections with streptococcus and complications therefrom are also reported to be more common in temperate than in tropical countries (McCarty, 1958). A respiratory infection deserves consideration as a possible factor in the aetiology of multiple sclerosis.

The results of the inquiry about infections and other illnesses (Tables VII-VIII) do not support the hypothesis, and may imply that patients and controls did not differ in relation to histories of infectious disease. However, there are many pitfalls in the retrospective approach used in the present study. If infection is, indeed, an aetiological factor, then the infection of importance may be so minor that it was not recalled by the respondents. Alternatively, the infection may have been experienced with equal frequency by patients and controls but patients represent individuals with increased susceptibility to demyelination provoked by the infection.

Another difficulty with the notion that multiple sclerosis has an infectious aetiology akin to poliomyelitis is the apparent lack of fluctuation in seasonal and annual incidence rates (Schapira, 1959). This difficulty may be overcome in part by the assumption of a long incubation period for multiple sclerosis (Poskanzer *et al.*, 1963; Kurtzke, 1965b) which would tend to reduce annual and seasonal fluctuations. It is also conceivable that the observations implicate some non-infectious factor such as water treatment rather than an infectious agent.

Recent observations on the 'slow virus' infections of animals, *e.g.*, visna (Sigurdsson, Palsson, and van Bogaert, 1962), scrapie (Parry, 1962), and aleutian mink disease (Symposium on slow virus diseases, 1965) may be pertinent. These agents have long incubation periods. The mechanism of transmission of slow virus disease is not yet completely understood but the diseases are observed in aggregations of animals which may imply that a degree of crowding and a certain concentration of the agent may be necessary for successful transmission. Recently, Kurtzke (1965a) has provided evidence that multiple sclerosis also occurs in clusters, or 'dense multiple sclerosis areas', a condition resembling the distribution of the above-mentioned diseases.

In view of the observations on differences in sanitary level between patients and controls as revealed in the Israeli study, it is worthwhile to attempt confirmation and to give additional attention to the possibility that multiple sclerosis may have an infectious aetiology.

SUMMARY

A questionnaire designed to elicit information of possible relevance to the aetiology of multiple sclerosis was administered to 241 patients with the disease and to matched controls in an Israeli population. The items in the questionnaire pertaining to sanitary level formed the basis of this report. Inquiry was made about sanitary level because of the observation that multiple sclerosis is more common in temperate zones, which tend to have high sanitary levels, than in tropical areas, where sanitation is generally poorer. It was postulated that if sanitary level had any relevance to aetiology, patients with multiple sclerosis would report a higher sanitary level before the onset of illness than controls from the same area. Indices used to measure sanitary level included source of drinking water, toilet facilities, and degree of crowding, all pertaining to the childhood home when the respondent was about 10 years old. The childhood period was emphasized because of evidence that a childhood experience or exposure may determine the risk of developing multiple sclerosis. On all three indices a higher percentage of patients than controls had higher sanitary levels.

The differences in sanitary level were not attributable to a difference in socio-economic status as measured by occupation and level of education.

The relation between sanitary level and multiple sclerosis suggested by the present report was dis-

cussed in the light of various theories of aetiology. The results are compatible with an infectious aetiology having a long incubation period. However, inquiry about experience with eight specific infections and with 'other serious illnesses' failed to show a difference between patients and controls. Assuming infection is of aetiological importance, either it was not recalled by the respondents or, if equally common in patients and controls, patients were more susceptible to demyelination as a complication of the infection.

A relation between sanitation and prevalence of multiple sclerosis was reminiscent of similar observations on poliomyelitis. As in poliomyelitis, multiple sclerosis might be the occasional complication of a widespread infection. In environments with a high sanitary level, infection may be postponed until an age when the central nervous system is more susceptible to the process which provokes demyelination.

It would be possible to confirm the Israeli observations that high sanitary level of the childhood environment is related to aetiology by determining the prevalence of multiple sclerosis in areas with low sanitary level now and after sanitary facilities are improved.

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